

Examination of Fear Extinction in Chronic Cannabis Use, Anxiety Disorders, and their Co-occurrence

by

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Abstract

Comorbid cannabis use and anxiety are common, but the relationship is not well understood. The main active ingredient of cannabis is $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC). Acute THC intoxication has been shown to improve between and within-session fear extinction, while chronic THC intoxication impairs fear extinction and discrimination. The current project aimed to determine if chronic cannabis use was associated with worse fear discrimination, extinction (within-session extinction), and extinction retention (between-session extinction) in the anxiety disorder population. 46 participants from three groups (i.e. clinically significant anxiety and cannabis-naïve, chronic cannabis users, or cannabis-naïve healthy controls) completed a 2-day fear differential conditioning paradigm. Results suggest that chronic cannabis-users have an impaired ability to extinguish within-session fear-based responding as compared to the other two groups. There was no evidence of significant group differences in extinction retention or fear discrimination. Findings have important clinical implications as they suggest that chronic cannabis use may impair one's ability to extinguish fear-based learning, a primary mechanism of exposure-based therapy, which may be a potential barrier to therapy effectiveness.

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Examination of Fear Extinction in Chronic Cannabis Use, Anxiety Disorders, and their Co-occurrence

Anxiety disorders are impairing for the individual and society, making them an important area of clinical concern (Hoffman et al., 2008). Anxiety disorders are defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition Text Revision (DSM-5-TR; American Psychological Association, 2022) as disorders that share features of excessive fear, anxiety, and related behavioral disturbances that are excessive or persistent beyond what is developmentally appropriate. Anxiety disorders are highly prevalent, with an estimated 28.8% of the general population having been diagnosed with an anxiety disorder in their life (Kessler et al., 2005), and are associated with significant socioeconomic and individual burdens (Andlin-Sobocki et al., 2005; Hoffman et al., 2008; Ruscio et al., 2017). Anxiety disorders are in part due to deficits in fear-based learning and extinction. Those experiencing anxiety and related disorders show elevated amygdala activation to fear (Ball et al., 2017), diminished fear extinction (Wen et al., 2022), and elevated fear generalization (Dymond et al., 2015; Grant et al., 2015; Haddad et al., 2012). Thus, treatments for anxiety disorders may be improved through a better understanding of fear learning and extinction processes.

Data suggest a strong rate of concurrence between anxiety and cannabis use, with those experiencing anxiety symptoms often turning towards substances, including cannabis, to relieve and mitigate symptoms, but co-morbidity remains poorly understood (Ouellette et al., 2022). Patients with anxiety often report high rates of cannabis use and patients who use cannabis often have high rates of anxiety, making it difficult to determine causality (Crippa et al., 2009). Existing literature has shown associations between more cannabis use and greater anxiety symptoms, which could be explained via self-medication, heavy-cannabis use induced anxiety,

or a third variable responsible for heightened anxiety and heavy cannabis use (Lev-Ran et al., 2012; Xue et al., 2021).

Cannabis users who report use to reduce anxiety symptoms generally believe that cannabis successfully helps them minimize their symptoms (Sexton et al., 2016). However, literature has suggested a discrepancy between the perceived benefit of cannabis for anxiety and actual measures of symptom improvement (Bonn-Miller et al., 2013; Turna et al., 2019). Bonn-Miller and colleagues (2013) found that social anxiety motives for cannabis use were associated with heightened cannabis use problems and greater perceived helpfulness. Additionally, in an online survey study, Turna and colleagues (2019) found that 92% of individuals reported cannabis to be beneficial in reducing anxiety symptoms, despite continuing to endorse moderate anxiety symptoms. These findings indicate a potential discrepancy between perceived benefit and actual symptom improvement. However, they could alternatively suggest that individuals with more severe psychopathology are using greater amounts of cannabis but only seeing moderate improvements in symptoms.

Beyond self-reported symptom improvements, Lev-Ran and colleagues (2012) found that among anxious individuals, regular cannabis users experienced a reduced quality of life compared to occasional cannabis users. Further, Fergusson & Boden (2008) found that cannabis use frequency was related to worse quality of life, including lower relationship and overall life satisfaction. In prospective studies, cannabis has been found to worsen anxiety symptoms and in some cases lead to increased odds of developing an anxiety condition (Kedzior & Laeber, 2014; Xue et al., 2021). This literature suggests a discrepancy between people's anxiolytic beliefs about cannabis and the long-term effects of chronic cannabis use on anxiety symptoms, life satisfaction, and treatment outcomes. While the data is fairly consistent in suggesting that higher

frequency cannabis use for anxiety disorders is related to worse outcomes or no improvements in symptoms, it is possible that cannabis is beneficial in improving anxiety symptoms and that lower QoL and worse anxiety symptoms are due to an unidentified third variable (e.g., more severe vulnerability predicts proneness to worse anxiety and frequent cannabis use.) Despite reports of reduced quality of life and increased rates of anxiety, cannabinoids (i.e., one of a group of substances found in the cannabis plant) are being explored as treatments for anxiety and related disorders; in part due to evidence that cannabinoids may be able to enhance fear extinction.

Fear Extinction

Pavlovian fear conditioning (Pavlov, 1927) is the process through which an innocuous stimulus is paired with an aversive unconditioned stimulus (US). Through the repeated pairing of the innocuous stimulus with the aversive stimulus, the subject comes to exhibit a conditioned fear response to the innocuous stimulus (i.e. conditioned stimulus or CS) (Myers & Davis, 2007). Fear extinction is the process through which a feared conditioned stimulus ceases provoking the conditioned fear response after repeated exposure to the conditioned stimulus in the absence of the aversive unconditioned stimulus. Fear extinction recall (i.e., between-session extinction) is the retrieval of the extinction memory during re-exposure to the conditioned stimulus after a delay.

In recent years, there has been extensive research on the mechanisms of fear extinction. Numerous brain mechanisms have been implicated in fear extinction, including the amygdala, hippocampus, and prefrontal cortex, which are believed to be central to fear conditioning (Myers & Davis, 2007). The amygdala is believed to be essential to the acquisition and expression of fear. Rat studies have supported its involvement through pharmacological manipulation and

single-unit recordings (Furmark et al., 1997; Myers & Davis, 2007). Neuroimaging studies on humans have corroborated rat studies by finding evidence of increased amygdala activation during fear conditioning (Furmark et al., 1997). Lesion studies offer further evidence as lesions of the amygdala disrupt both acquisition and expression of fear (Walker & Davis, 2000). The hippocampus also plays a role in fear conditioning, in that it contextualizes fear so only specific situations are paired with an aversive stimulus. Further, the hippocampus is related to inhibitory avoidance, in that one avoids the specific conditions which are related to the aversive stimuli (e.g., if someone experiences a tornado while at a movie theater, they may associate the tornado with the theater and thus routinely avoid movie theaters) (Myers & Davis, 2007). Lastly, the medial prefrontal cortex (mPFC) is believed to be essential to the retention or expression of fear extinction. Microstimulations in the mPFC during extinction training have been shown to increase retention of extinction and reduce freezing (Milad et al., 2004; Milad & Quirk, 2002). These brain regions play an important role in our processing, interpretation, and reaction to fear. As discussed above, a primary component of anxiety disorders is impairments to fear-based learning and extinction. As such, fear extinction has been adapted as a central component of some empirically based treatments, specifically Exposure-Based Therapy (EXP) which is a component of Cognitive-Behavioral Therapy (CBT).

Exposure Therapy (EXP)

EXP is considered the frontline treatment for fear and anxiety-related disorders (Carpenter et al., 2018; Craske et al., 2022). EXP for anxiety disorders has substantial empirical support, as compared to other active treatments and controls (Carpenter et al., 2018; Craske et al., 2022; Watts et al., 2015). The basic principle of EXP is anxiety symptom reduction through fear extinction (Ouellette et al., 2022), with the premise that repeated exposure to a feared

stimulus in the absence of avoidance behavior and the feared outcome will produce fear reduction. Ball and colleagues (2017) explored whether brain activation during fear extinction predicted EXP effectiveness. Extinction learning was measured through subjective ratings. Individuals with greater extinction learning, greater activation in the ventral medial prefrontal cortex (vmPFC), and less activation in the amygdala, insula, and periaqueductal gray reported greater anxiety reduction at a two-week post-exposure follow-up (Ball et al., 2017). Additionally, Forcadell and colleagues (2017) found that individual differences in fear extinction learning and extinction recall, assessed using a 2-day fear differential conditioning paradigm, were associated with better exposure therapy outcomes. These findings support fear extinction as a mechanism of EXP.

EXP is generally effective with 40 – 60% of individuals with anxiety seeing improvements in symptoms, however, there is substantial treatment response heterogeneity (Cuijpers et al., 2014; Hollon et al., 2006). Little is known about how baseline predictors might affect CBT response or fear extinction efficacy specifically. Research on the effects of cannabis use on CBT outcomes is sparse and inconsistent. Bedard-Gilligan and colleagues (2018) found that cannabis use was related to less symptom improvement, treatment adherence, and treatment retention among individuals in a 10-week prolonged exposure treatment for PTSD. Ouellette and colleagues (2022) explored whether cannabis use frequency and cannabis-related problems at baseline predicted CBT outcomes. Participants received 12, 2-hour weekly sessions that included psychoeducation and exposure to anxiety-inducing situations that were tailored to the presenting anxiety disorder. Cannabis use frequency was found to be related to worse CBT outcomes for anxiety and related disorders, however individuals who used cannabis frequently still saw a statistically significant improvement in symptoms. Cannabis-related problems was not

related to CBT outcomes (Ouellette et al, 2022). Understanding the impact of cannabis on treatment is of large clinical concern, as cannabis is the most commonly used illicit substance among individuals with psychiatric diagnoses (Kessler et al., 1996). Below we will explore how cannabis may impact and alter brain regions associated with fear extinction.

Cannabis and Fear Extinction

Cannabinoid type-1 (CB1) receptors are components of the endocannabinoid system (ECS) and are densely expressed in numerous brain regions, many of which are associated with anxiety and emotional learning, including the hippocampus, amygdala, and prefrontal cortex (Kendall & Yudowski, 2017; Papini et al., 2017). The ECS helps regulate numerous aspects of the body, including the central nervous system, digestive, and reproductive tracts. Δ^9 -tetrahydrocannabinol (Δ^9 -THC) is a cannabinoid and is the main psychoactive ingredient of cannabis. Δ^9 -THC binds to the CB1 receptors, just like endocannabinoids, and acts as a partial agonist (i.e. it binds and activates the CB1 receptor, but is unable to induce maximum activation). Manipulation of the endocannabinoid system, through Δ^9 -THC administration, can affect the function of many of the brain regions mentioned above, resulting in changes in learning and memory which can impact fear extinction and retention (Papini et al., 2015, 2017).

Recently, there has been substantial interest in the involvement of the ECS in fear conditioning. This interest stems from evidence that cannabinoids appear to modulate memory. Specifically, the CB1 receptors modulate synaptic plasticity, which is a key neurochemical process in learning and memory (Myers & Davis, 2007; Papini et al., 2017). Marsicano and colleagues (2002) studied fear acquisition and extinction in mice that did and did not have CB1 receptors. The CB1-deficient mice were able to acquire and retain fear but showed deficits in short-term and long-term extinction. The intact CB1 receptor group was given a CB1 antagonist,

which resulted in the same deficits seen in their CB1-deficient siblings (Marsicano et al., 2002). These findings highlight the necessity of the CB1 receptor for fear memory extinction.

Numerous studies have explored the acute effects of cannabinoid modulation in both rats and humans. In rats, Cannich and colleagues (2004) found that the ECS, measured through calcineurin expression and kinase phosphorylation, modulated the extinction of aversive memories in rats. These findings suggest that acute administration of THC may enhance fear extinction (Cannich et al., 2004; Papini et al., 2017). These findings have been replicated using human subjects. Klumpers and colleagues (2012) were the first to test whether synthetic cannabinoids could enhance fear extinction in humans. Cannabis-naïve healthy humans consumed THC or a placebo 2 hours prior to a fear-potentiated startle paradigm. The THC group demonstrated greater within-session extinction of skin conductance response (SCR). However, there were no differences in the retention of fear extinction (i.e., between-session extinction), measured through SCR, or startle response, measured using electromyography through the orbicularis oculi muscle under the right eye, between conditions. Subjective shock expectancy and fearfulness ratings, collected for each startle cue, were consistent with the physiological data. Rabinak and colleagues (2013) ran a similar experiment using individuals with less than 10-lifetime experiences with cannabis. In this study, THC promoted between-session extinction of SCR as compared to the placebo but did not improve within-session extinction of SCR (Rabinak et al., 2013). Further, Diggs and colleagues (2022) found that THC promoted enhanced within-session fear extinction, as measured by the electroencephalography-recorded late positive potential (LPP), in young occasional cannabis users who underwent a 2-day fear conditioning paradigm. The LPP is believed to be a neurophysiological measure of attention and processing, making it a promising indirect indicator of fear and safety learning (Diggs et al, 2022). These

initial findings are promising, as they suggest that THC promotes fear extinction, but results are inconsistent (e.g., within-session extinction vs. extinction retention, startle vs. skin conductance response) across studies.

Even fewer studies have explored the impact of long-term, repeated exposure (i.e., chronic) to cannabis on Pavlovian fear conditioning. Lin and colleagues (2008) tested the effects of repeated cannabinoid exposure on fear extinction in rats. CB1 receptor agonists were administered once per day for seven days. On day eight, the rats were run through a fear conditioning paradigm. Rats exhibited impaired fear extinction and were unable to experience any acute benefits of cannabinoid administration (Lin et al., 2008). Results suggest that endocannabinoids play an important role in fear extinction, but long-term exposure may mitigate their efficacy. Lin and colleagues (2008) looked at repeated CB1 receptor agonism in animals, but Papini and colleagues (2017) were the first to assess this in humans by looking at chronic cannabis users (i.e., those who used cannabis for at least 5 days a week for 90 days). Chronic cannabis users without psychiatric comorbidity and healthy controls were run through a 2-day differential fear conditioning paradigm. Chronic cannabis users experienced reduced within- and between-session extinction as compared to healthy controls. Chronic cannabis users also experienced a reduced ability to differentiate between fear and safety stimuli during conditioning. Both animal and human studies suggest that, in contrast to acute administration in infrequent/minimal users, chronic cannabis use impairs rather than facilitates fear extinction.

The Present Study

To reiterate, those experiencing elevated anxiety symptoms often turn to cannabis to relieve their symptoms and users report believing that cannabis is effective in doing so. However, co-occurring anxiety and chronic cannabis use appear to complicate the clinical

picture, potentially reducing the efficacy of EXP by impairing the mechanism associated with fear extinction. To our knowledge, Papini et al. (2017)'s study is the only previous work to assess the impact of chronic cannabis use in humans on fear extinction. Importantly, while Papini and colleague's recruitment of chronic cannabis users and controls with no psychiatric comorbidities tightened inferences about results being specific to cannabis, it did not inform our understanding of how chronic cannabis use impacts fear extinction in a population where fear extinction deficits are already present (i.e. those with anxiety disorders). This has important clinical implications given patient perceptions that cannabis use is an effective anxiety treatment and data showing that frequent cannabis use is related to worse CBT outcomes in patients with anxiety disorders. As such, I replicated Papini and colleagues' 2-day differential fear conditioning paradigm between chronic cannabis users (CAN) and controls (CTRL). However, I expanded the scope of the study by altering the groups (i.e., adding an anxiety only (ANX) group) to examine the relationship between chronic cannabis use and fear extinction in those with an anxiety disorder. These additional groups allow me to examine differences between chronic cannabis users, non-users, and non-users with co-occurring anxiety on fear extinction, fear extinction recall, and subjective discrimination of fear and safety stimuli.

Hypotheses

Aim 1. Papini et al. (2017) found that chronic cannabis users (CAN) experienced an impaired ability to extinguish within-session SCR responding as compared to a control group (CTRL). There were no differences in within-session extinction of US expectancy. Cannabis-users also displayed less between-session extinction of the SCR as compared to controls, with no differences in between-session extinction of the US expectancy. Lastly, the cannabis-users displayed significantly lower US expectancy differentiation, but not SCR differentiation, between

fear and safety stimuli (i.e., fear discrimination) as compared to healthy controls. In the current study, we aimed to replicate this finding.

Consistent with previous research, I expected that CAN would show greater impaired between and within-session fear extinction of the SCR and greater deficits in differentiating fear and safety stimuli as compared to the CTRL group. I did not expect to find any differences in within- and between-session extinction of US expectancy. Conversely, I expected that CAN would show lower US expectancy fear differentiation, but no differences in SCR differentiation, as compared to controls.

Aim 2. Investigate how non-users with an anxiety disorder (ANX), chronic cannabis users without an anxiety disorder (CAN), and healthy controls (CTRL) in between- and within-session fear extinction and fear discrimination.

I hypothesized that we would see impaired fear discrimination and within and between session fear extinction of the SCR among CAN as compared to ANX and CTRL. I did not expect to see any differences in within- and between-session extinction of US expectancy across groups. In terms of fear discrimination, I expected that CAN would show significant differences in US expectancy differentiation as compared to the CTRL and ANX groups, but no differences in SCR fear differentiation.

Method

Participants

46 participants were recruited from Auburn University and the surrounding community setting. All participants met the following inclusion criteria: (1) English fluency, (2) 18 – 64 years old. Participants were divided into one of three groups. Group one (ANX) consisted of

participants who meet criteria for a current anxiety or fear-related disorder per the SCID-5 and were naïve to cannabis, having smoked less than 20 times in their life. Fear and anxiety-related disorders include Generalized Anxiety Disorder, Panic disorder with and without Agoraphobia, Social Anxiety Disorder, Post-Traumatic Stress Disorder, Specific Phobia, and Obsessive-Compulsive Disorder. Group two (CAN) consisted of participants who chronically used cannabis. Participants were permitted to have other current diagnoses or historical diagnoses so long as they did not fit the exclusion criteria below. Diagnostic information was collected using the Structured Clinical Interview for DSM-5 Disorders (SCID-5). The last group was the control group (CTRL); participants were naïve to cannabis and reported minimal anxiety concerns. The CTRL group had no history of other psychopathology per the SCID-5. In addition, CTRL and ANX groups were required to test negative on a urine test that verified no recent use of substances, including THC. To maintain safety and internal validity, participants were excluded for any of the following: (1) other non-subscribed substance abuse, with the exception of alcohol and nicotine, (2) past-year moderate or severe Alcohol Use Disorder (i.e. ≥ 4 criteria) assessed with the SCID-5 to reduce the impact of co-occurring substance abuse, (3) currently receiving cognitive-behavioral therapy for cannabis and anxiety related problems, (4) history of seizure, psychotic, or cardiovascular disorder, (5) allergies to lotions/cosmetics, (6) current regular use of psychotropic medication (e.g., antipsychotic, mood stabilizer, antidepressant, anticonvulsant, or benzodiazepine.) A brief 5 – 10-minute online screening questionnaire was administered to interested participants prior to scheduling their first in-person visit to assess the inclusion criteria and exclusion criteria 1 and 3 – 6. Exclusion criteria 2 was assessed during a screening interview conducted in-person or over the phone. The screener questionnaire reduced the burden on participants by weeding out ineligible participants prior to inviting them to a longer in-person

visit. Participants with an Overall Anxiety Severity and Impairment Scale (OASIS; Campbell-Sills et al., 2009) were prioritized during recruitment to increase the likelihood of participants meeting for an anxiety or fear-related disorder.

The study was advertised to the SONA subject pool and in the community to those who would like to participate in a study looking at anxiety and learned responses. Fliers were posted around Auburn University and the surrounding area to recruit students from the student body. Online postings via Facebook and Instagram also facilitated the recruitment of people from a wider demographic area. Interested participants e-mailed the lab to receive a link to the consent form and screener questionnaire to determine eligibility. Eligible participants were invited to complete a screening interview in-person or over the phone. Participants still eligible following the screening interview were scheduled for the lab visits. Participants from the SONA pool received 0.5 credits for participating in the online screener, 1.5 additional credits for the eligibility interview, 3.5 credits for lab visit 1, and 1 credit for lab visit 2. Thus, SONA participants earned a total of 6.5 credits. Community participants received \$100 for their participation. Credit and/or payment were provided at the completion of the study to increase participant adherence. We did not have any participants stop part way through study participation.

Self-Report Measures

Participants completed a short demographics questionnaire, assessing age, biological sex, gender, sexual orientation, ethnicity, marital status, the highest level of education completed, average household income, current medications, and lifetime experience of mental health treatment and diagnoses (see Appendix A). Participants also completed the following measures throughout the course of the study (see Table 1 for information on when each measure will be

administered). Surveys were not administered at Lab Visit Day 2 to streamline procedures and decrease potential difficulties with adherence.

The Overall Anxiety Sensitivity and Impairment Scale (OASIS; Campbell-Sills et al., 2009) was used to screen for clinically significant anxiety symptoms during the screening survey. The OASIS is a 5-item self-report measure of frequency and severity of impairment (i.e., work/school/home) in anxiety disorders (see Appendix B for full measure). Questions further assess avoidance behavior and social interference. The instructions orient participants to a wide range of anxiety symptoms (i.e., worry, panic attacks, and flashbacks). Respondents can choose from 5 response options, labeled 0 – 4. A response of 0 indicates little to no anxiety symptoms or impairment, while 4 corresponds to severe symptoms or impairment. The response scores are summed to obtain a total score. Scores of 8 or higher are shown to indicate clinically significant anxiety symptoms (Campbell-Sills et al., 2009). The OASIS has been shown to have excellent reliability and validity in clinical and non-clinical samples. The five OASIS items display strong loadings onto a single factor and show good internal consistency (Cronbach's $\alpha = .84$) (Campbell-Sills et al., 2009). Additionally, the OASIS shows excellent convergent validity and correlates highly with measures of anxiety (BSI-A), panic (PDSS), social anxiety (SPIN), posttraumatic stress (PCL-C), and generalized anxiety (GADSS) with correlations ranging from .40 to .60 (Campbell-Sills et al., 2009; Norman et al., 2006). The OASIS did not correlate with measures of other constructs, such as the Alcohol Use Disorders Identification Test (AUDIT), showing good discriminant validity. The OASIS has also been shown to have excellent 1-month test-retest reliability (Campbell-Sills et al., 2009).

Drug Use Frequency (DUF) measure assesses the usual frequency of use for nicotine/tobacco, alcohol, cocaine/crack, amphetamines, opioids, hallucinogens, and sedatives

over the past year (see Appendix C). Respondents can answer 0 (never), 1 (one time), 2 (monthly or less), 3 (two or four times a month), 4 (two or three times per week), or 5 (four or more times per week). The DUF shows good concurrent validity with the Timeline Followback (TLFB) and knowledgeable informants (i.e., spouses) (O’Farrell et al., 2003).

The Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU Inventory; Cuttler & Spradlin, 2017) measures frequency, age of onset, and quantity of cannabis use (see Appendix D). It uses photos as well as questions to help facilitate the assessment of quantity, type, method, and typical THC levels of cannabis. Each question contains different response options, and it uses skip logic based on affirmative and negative responses. The DFAQ-CU was tested in a cannabis-user population and was found to have excellent internal consistency, with Cronbach Alpha coefficients ranging from .69 to .95. This measure was also found to have high convergent (Marijuana Smoking History Questionnaire, Timeline Followback), discriminant (AUDIT), and predictive validity (Cannabis Abuse Screening Test). These results support that the DFAQ-CU is a psychometrically sound measure for measuring the age of onset, frequency, and daily sessions of cannabis use.

The Enhanced Cannabis Timeline Followback (ECTLFB; Petrilli et al., 2023) asks respondents to retrospectively estimate their drug, marijuana, and cigarette use. In the current variation, respondents were asked to retrospectively report on their substance use over the past four weeks. Participants were asked to identify the types of cannabis (i.e., strong cannabis, weak cannabis, hash/resin) and other substances they used over the past 30 days. The use of visuals aided recall. For each type of cannabis, participants were asked to report on their methods of use (e.g., joint, vape, bong) and quantity of use. They were also asked whether they generally share their cannabis with others or consume it all by themselves, and how many sessions a cannabis

method generally lasts. These questions were intended to capture detailed information about the participant's typical use patterns. In part 2, participants were given a calendar of recent events and asked to recall their use on each day over the past 30 days. Participants were prompted to think about events and dates of marijuana purchase prior to recalling specific use sessions. Participants reported their number of sessions, method of use, and quantity of use per day.

Clinical Interviews

The Structured Clinical Interview for the DSM-5 (SCID-5) is a semi-structured diagnostic interview that can be used in clinical and research settings. The SCID-5 has been shown to have excellent validity and reliability, as assessed via interrater test-retest, joint interview, and face-to-face versus telephone application (Osório et al., 2019). Interrater test-retest showed a 73 – 97 % agreement between the interview and clinical diagnosis. It also showed excellent specificity and sensitivity (>0.70). The substance-abuse portions of the SCID, including cannabis, have been shown to have good concurrent validity with frequency of use and quantity of use, with those using greater amounts and more frequently meeting more criteria (Kranzler et al., 1996). There is also evidence for excellent discriminant validity in that the SCID can differentiate drug abuse from alcohol abuse/dependence. The cannabis-use portion also has excellent predictive validity and has been found to be able to differentiate between patients with a current diagnosis and those who previously met for cannabis use or another previous disorder (Kranzler et al., 1996).

Fear Extinction Paradigm

The fear extinction paradigm was administered across two consecutive days. Across all phases of the paradigm, colored squares (i.e., red, yellow, blue) were presented for 4 seconds at 6

-18 second intervals. The order was pseudorandomized to ensure no consecutive presentation of the same color during habituation and no more than two consecutive presentations of the same color during additional phases. Visual stimuli were presented on a laptop computer and auditory stimuli were delivered through headphones.

Day 1 consisted of a habituation phase. Participants underwent four nonreinforced trials for each of the three to be conditioned stimuli. SCR was measured during this phase to measure a baseline unconditioned physiological response and to allow the participant time to adapt to the task procedures. Following habituation, participants underwent a conditioning phase. Study staff informed the participant that they may or may not hear loud sound-bursts paired with a shock. Two of the visual conditioned stimuli from the habituation phase (CS+; blue and yellow squares) were coterminated with an aversive white noise burst and co-occurring shock (US; 500 ms, 100 dB) at a 35% reinforcement rate. The third conditioned stimulus (CS-; red square) was not paired with the aversive stimuli (US). The conditioning phase consisted of 61 total stimuli presentation, where the reinforced CS+ trials were pseudorandomly intermixed with the unreinforced CS+ and CS- trials. There was 23 presentations of each CS+ (15 unreinforced, 8 reinforced) and 15 presentations of the CS-. Participants received a 10-minute break. Following the break, participants underwent an extinction training. Participants were reminded that they may or may not hear loud sound bursts and receive a co-occurring shock. Extinction training consisted of 30 trials, 15 nonreinforced trials for the CS- and 15 nonreinforced trials for one of the CS+ (i.e., blue square). The other CS+ (i.e., yellow square) remained unextinguished.

On Day 2, approximately 24 hours following extinction training, participants returned to the lab for assessment of between-session extinction. Study staff reminded participants that they may or may not hear loud sound-bursts with a co-occurring shock. Participants received 10

nonreinforced trials for each of the CSs. This session was used to assess whether there was a spontaneous recovery of the conditioned responses. See Appendix E for a visual of the task described above.

This protocol was adapted from prior studies (Papini et al., 2017; Rabinak et al., 2013), which utilized a white noise burst as the aversive US. In this study, I chose to alter the aversive US by pairing the white noise burst with a shock. I made this change based on research suggesting that those from racial minorities may produce a smaller SCR response to the aversive US (Kredlow et al., 2018; Webb et al., 2022). To account for this, some research suggests pairing an audio and physiological aversive stimuli to increase the fear response and therefore the SCR among these populations (Alexandra Kredlow et al., 2017).

Equipment

For the electric shock, electrodes were placed on the ring and index finger between the first and second knuckle with a small amount of signal electrode green gel. The electrodes were attached to a STMISOLA shock apparatus. Each electrical shock lasted only 200ms and the maximum stimulation level was 7mA. This is considered a mild shock and is in the ampere range used by physical therapists and chiropractors, but of a much shorter duration. This level of stimulation presents no risk of physical injury. The shock intensity was calibrated during the work-up procedure so that the stimulation level did not exceed an intensity the participant could tolerate. In line with prior work (Kaye et al., 2016), each startle probe was a 50ms, 102db burst of white noise with near instantaneous rise time - 10,000 times lower than Occupational Safety and Health Administration (OSHA) guidelines for maximum daily acoustic energy exposure for adults.

Skin conductance response (SCR) and heart rate were measured using auxiliary adaptors. For SCR, Ag-AgCl electrodes were filled with electrolyte paste and placed on two palmar locations on the participant's non-dominant hand.

Procedures

All study procedures were approved by the local institutional review board prior to starting data collection. Prior to scheduling in-person appointments, participants were asked to complete an online screener questionnaire (~10 minutes). They could complete this online questionnaire from any computer.

Eligible participants were invited to a screening interview (in-person or over the phone according to participant preference) to assess for psychiatric diagnoses through the SCID-5. Due to the distressing nature of the fear conditioning procedure, participants were also asked to complete the 9th question on the Beck Depression Inventory to assess for current suicidal ideation or intent (see Appendix F). Those with positive responses completed a CSSR and a coping card with a clinician. Participants who reported current intent were excluded from the study (CSSR of 4 or greater). Interviews were conducted by graduate clinicians and results were reviewed in frequent supervision meetings by a licensed clinical psychologist. Participants were assigned to one of three groups based on their diagnoses: CAN, ANX, or the control condition.

Eligible participants were scheduled for 2 to 3-hour baseline appointment. This appointment was conducted in an experimentation room. This room was divided in half using a divider to separate study staff from the participant, to ensure that study staff could monitor psychophysiology equipment without the participant being able to view their activity or responses. Study staff observed the participant throughout the tasks using a small camera. The participant's half of the room consisted of a chair, a laptop, and a cabinet. At this appointment,

participants were instructed to provide a urine and saliva sample, and study staff tested these samples for drugs. Participants were provided with a BUA-approved urine cup that they carried to the bathroom in a cardboard box. After the sample had been deposited in the cup, the participant was asked to wipe the edges of the container with a moist sanitary wipe, provided to them in the box. Once the cup had been returned to the study staff, the staff waited five minutes before looking at the results of the polysubstance test on the side of the urine cup. Positive results were indicated by one line, while negative results were indicated by two lines. To assess recent THC use, which cannot be tested using the urine drug test, participants were provided with a NarcoCheck test and asked to allow their mouth to fill with saliva while keeping the tab of the test in their mouth. Saliva tests have been shown to be effective in detecting whether cannabis was smoked in the last 4 to 6 hours (Niedbala et al., 2001; Anizan et al., 2013; Arkell et al., 2019), and the NarcoCheck has been used in similar studies to detect recent THC use (Feinstein et al., 2019; Beckham et al., 2023). Study staff waited a few moments before reading the results. As with the urine drug test, positive results were indicated by one line and negative results by two lines. CTRL and ANX participants were excluded for a positive urine or saliva drug test. CAN participants were excluded for positive tests of any substance other than THC for the urine drug test and excluded for any positive test on the saliva drug test.

Participants completed a battery of surveys (~ 30 minutes) while study staff attached SCR and shock equipment (see Equipment section above). Study staff started the white noise machine to minimize extraneous noise before having the participant complete day 1 of the fear conditioning paradigm (see task description above). Before the task begins, research staff walked the participant through a shock work-up, in which participants were asked to select a shock level that was highly annoying, but not painful (a self-reported rating of 100). Research staff increased

the shock in 10 volts intervals until the participant rated the shock a 50 (0 being no annoyance and 100 being highly annoying, but not painful), then the voltage was increased in 5-volt increments until the participant reached a rating of 100. Study staff checked in throughout the study to ask if the participant had questions.

Participants were scheduled to return to the lab 24 hours following the fear condition paradigm (i.e., Day 2) for a 30-minute lab visit. During this visit, participants completed the second part of the fear conditioning paradigm to assess for between-session extinction. Participants were debriefed before receiving course credit or money for their participation.

Results

Forty-six participants (Control $n = 20$, Anxiety $n = 14$, Cannabis $n = 12$) completed both days of the 2-Day Fear Differentiation Paradigm. The control group contained a larger proportion of males, with 12 males (60%) and 8 females. The anxiety group contained more females ($n = 12$, 85%). The cannabis group contained 8 males (67%) and 4 females. A wide array of ages were represented in this study. The control ($M = 20.05$) and anxiety ($M = 20.93$) groups were relatively matched on age, whereas the cannabis ($M = 35.00$) group was significantly older ($p < 0.00$). Primary diagnoses were recorded for all participants and can be found in Table 3. Diagnostic descriptives of current and lifetime diagnoses as captured via the SCID-5 can be found in Table 4. In general, the anxiety group was primarily composed of individuals with a primary diagnosis of generalized anxiety disorder, current, ($n = 3$) or social anxiety disorder, current ($n = 6$). Of the cannabis group, 10 participants met current *DSM-IV-TR* diagnostic criteria for cannabis use disorder (mild $n = 3$, moderate $n = 4$, severe $n = 3$).

Sample size. This study was a replication of Papini and colleagues's study which utilized 20 subjects per group. To be consistent with this past study, the current study aimed to include 20 subjects per group. With this number of participants, the study would have been significantly powered at 0.99 to find a statistically significant effect for between- and within-session extinction. A power analysis for detecting a significant omnibus group effect was conducted using four groups, an expected sample size of 80, and an expected effect size of 0.76 for between-session extinction or 0.78 for within-session extinction. The expected effect sizes were taken from Papini and colleagues' findings. Recruitment rates were significantly less than expected ($n = 46$) due to difficulty recruiting chronic cannabis users. Given this, the current study was significantly underpowered.

Preliminary Analyses. Raw SCR data was inspected for excessive motion and/or poor contact with skin. Poor quality SCR data was excluded from calculations. SCR data was pre-processed and analyzed using LedaLab (Benedek & Kaernbach, 2010). In Ledalab, raw data were downsampled to 10Hz and a 1st order low-pass 5Hz filter was applied. Data were then subjected to continuous decomposition analysis and the average phasic driver value in μS between 1 and 6 seconds of stimulus presentation was used to quantify SCR amplitude (as recommended by Benedek & Kaernbach, 2010).

Within-session and between-session SCR extinction values as well as subjective fear discrimination values during conditioning were computed for each participant according to Papini and colleagues (2017). 1 participant's US expectancy data was excluded due to non-responses to most items in the habituation and extinction phase. Within-session extinction was calculated by dividing the mean response of the later CS + E trials in fear extinction (trials 8 – 15) by the mean response of CS + E trials in late conditioning (trials 8 – 15). Papini and

colleagues suggest using the later portions of conditioning and extinction phases due to the low reinforcement rate (35%). This ratio (i.e., mean CS + E fear extinction / mean CS + E fear conditioning) was converted into a percentage by multiplying the score by 100 and subtracting it from 100. The final percentages show the amount of within-session extinction, with 0% indicating no extinction and 100% indicating complete extinction.

Similarly, between-session extinction was calculated by dividing the Day 2 first trial of the CS + E or CS = U by the Day 1 mean response to the CS + E or CS + U in late conditioning. This ratio was converted to a percentage using the same method discussed above, with 0% meaning no between-session extinction and 100% indicating complete between-session extinction. Papini and colleagues suggest using trial 1 on Day 2 to differentiate between-session extinction learning from the additional extinction that could occur on Day 2 from nonreinforced trials.

Subjective fear discrimination was calculated by dividing the mean response of the CS- from the mean response to the CS+ stimuli during late conditioning. This ratio was converted to a percentage using the same method as above, with 0% indicating no differentiation between stimuli and 100% indicating full differentiation. This ratio was calculated during late conditioning due to the low reinforcement rate (35%), allowing participants enough time to learn the pairings.

Hypothesis 1 & 2.

Consistent with Papini et al. (2017), we hypothesized that the CAN group would have greater difficulty extinguishing fear-based learning as compared to the CTRL and ANX groups. Between and within-session extinction values were calculated for each participant, using the

procedure described above, and a one-way ANOVA in SPSS (Version 29) was used to assess differences between groups.

Differential Conditioning. Data was checked to assess whether SCRs to the CS+ were more than an orienting response, meaning that responses to the CS+ were greater than participant's SCR during habituation where the stimuli had not yet been conditioned. A mixed analysis of variance tested whether there were differences in SCR between late habituation and late conditioning, and whether there were group differences in acquisition. There were no evidence of group differences, $F(2, 43) = 0.733, p = 0.486$, or a stimulus x group interaction, $F(2, 43) = 0.720, p = 0.525$. There was a main effect of stimulus, $F(1, 43) = 5.451, p = 0.016$, in which there were greater SCRs to the CS+ and CS- as compared to habituation (both $ps < 0.03$), but no difference between the CS- and CS+ ($p = 0.840$). These analyses suggest that participants acquired SCR responses to both the CS+ and CS- that were greater than the SCRs measured during the last three trials of the habituation phase. Further, SCR responses were acquired equally across groups and across both the CS+ and CS-.

There were no significant group differences between cannabis (16% +/- 6%), control (11% +/- 5%), and anxiety (13% +/- 5%) groups in their SCR fear differentiation between CS – and CS+, $F(2, 43) = 0.211, p = 0.811$. Nor were there differences between the cannabis (23% +/- 9%), control (31% +/- 7%), and anxiety (37% +/- 8%) groups in US expectancy differentiation of CS+ and CS-, $F(2, 42) = 0.620, p = 0.543$.

Within-Session Extinction. There was evidence of group differences in US expectancy to the CS+E (see Figure 1), $F(2, 42) = 3.258, p = 0.048$, between the cannabis (20% +/- 7%), anxiety (46% +/- 7%), and control (36% +/- 6%) groups. Post-hoc tests were conducted using Tukey's HSD test. The comparisons revealed significant differences between the cannabis and

the anxiety groups ($p = 0.039$), in which the cannabis group displayed less extinction of US expectancy to the CS+E as compared to the anxiety group. There were no group differences between cannabis users and controls ($p = 0.237$). There was no evidence of significant differences in the extinction of SCR to the CS+E (see Figure 2), $F(2, 43) = 1.329$, $p = 0.275$, across the cannabis (35% $\pm$ 11%), anxiety (59% $\pm$ 10%), and control (43% $\pm$ 8%) groups. However, results followed a similar pattern in which the cannabis group displayed a lower extinction of SCR responding as compared to the anxiety and control groups.

Between-Session Extinction. There was no evidence of differences in SCR to the CS+E (see Figure 2), $F(2, 43) = 1.199$, $p = 0.311$, between the cannabis (0% $\pm$ 6%), anxiety (13% $\pm$ 6%), and control (7% $\pm$ 5%) groups. There was also no evidence of group differences in US expectancy to the CS+E between the cannabis (28% $\pm$ 7%), anxiety (39% $\pm$ 6%), and control (28% $\pm$ 5%) groups (see Figure 1), $F(2, 43) = 1.062$, $p = 0.355$.

There were no differences in US expectancy to the CS+U between the cannabis (17% $\pm$ 6%), anxiety (24% $\pm$ 6%), and control (14% $\pm$ 5%) groups, $F(2, 42) = 1.029$, $p = 0.366$. There was no evidence of differences in SCR to the CS+U between the cannabis (7% $\pm$ 8%), anxiety (21% $\pm$ 8%), and control (12% $\pm$ 6%) groups, $F(2, 43) = 0.835$, $p = 0.441$.

Supplemental Analyses. Calculation methods for within and between session extinction values differ greatly. Lonsdorf, Merz, and Fullana (2019) cite sixteen unique ways to calculate extinction values that are commonly used in the literature. Given that over 50% of participants did not experience any reduction in fear responding between sessions (i.e., 0% between-session extinction), we recalculated between-session fear extinction using an alternative method. This was calculated by averaging the SCR to the first two trials of the Day 2 recall phase for each CS+. This number was divided by the largest SCR value during the second half of the Day 1

conditioning phase. The second half was selected to allow participants time to acquire fear-based responding to the CS+, given the low reinforcement rate (35%). This ratio was multiplied by 100 to create a percentage of maximum responding and then subtracted from 100 to create a measure of extinction retention. Extinction retention of the CS + E was not significantly different between the cannabis (15% +/- 9%), anxiety (26% +/- 8%), and control (20% +/- 7%) groups (see Figure 3), $F(2, 43) = 0.399, p = 0.674$. Nor was extinction retention of the CS + U between the cannabis (20% +/- 10%), anxiety (23% +/- 9%), and control (27% +/- 8%) groups, $F(2, 43) = 0.144, p = 0.866$. Despite these non-significant results, extinction retention values are significantly higher than those calculated using the alternate method (i.e., the method used by Papini et al. (2017)).

Discussion

Of the existing literature, only one study has assessed the relationship between chronic cannabis use and fear extinction. The current study built on this research by assessing group differences between cannabis users and non-users, either with or without a co-occurring anxiety disorder. Impairments in fear extinction and fear generalization (Grant et al., 2015) have been well-documented in anxiety and related disorders, however, there is limited evidence on how fear responding may differ between cannabis users and anxious non-users. Given that fear extinction is a primary mechanism of exposure therapy in CBT, understanding the relationship between chronic cannabis use and anxiety will allow us to better understand how cannabis may alter treatment effectiveness. Some researchers believe that cannabis may be able to enhance the extinction of fear by increasing activation in the amygdala, hippocampus, and vmPFC, areas associated with learning and memory. Preliminary evidence supports that acute cannabis use may improve lab-based fear extinction (Clayson & Larson, 2012; Diggs et al., 2022; Klumpers et al., 2012), however chronic cannabis has been shown to impair fear extinction and fear

generalization (Lin et al., 2008; Papini et al., 2015). Evidence has shown high rates of co-occurrence between cannabis use and anxiety (Crippa et al., 2009; Ouellette et al., 2022), making it essential that we understand how cannabis use may alter the clinical picture.

The current study expanded on Papini et al. (2017)'s work by assessing group differences in fear extinction between controls, chronic cannabis users, and an anxiety group. The 2-Day Fear Differentiation Task was intended to capture information about fear differentiation, fear generalization, within- and between-session fear extinction in SCR and US expectancy ratings. The analysis suggests that the unconditioned stimulus (i.e., the shock and white noise burst) was successful in eliciting SCR values greater than those exhibited during the habituation phase, suggesting that all groups acquired the expected fear responding to both the CS+ and CS-. Additionally, there were no differences in acquisition between the CS+ and CS-. This is consistent with Papini et al. (2017) and suggests that, in this particular paradigm, the typical CS+ and CS- differentiation was not achieved. Difficulties differentiating CS- and CS+ are likely due to the low reinforcement rate, which kept the threat signal value of the CS- ambiguous to participants. Groups displayed non-significant differences in fear differentiation in SCR and US expectancy between CS+ and CS-, indicating that all three groups displayed similar fear discrimination. Fear differentiation percentages were generally low (SCR: 11 – 16%, US Expectancy: 23 – 37%), suggesting that across groups, participants displayed an inability to differentiate between harmful and safe stimuli. This is likely due to the pairing of the aversive shock with the white noise burst, which was the only difference between the conditioning paradigm used in this study compared to the Papini et al. (2017) task. Papini et al. (2017) solely utilized a white noise burst of the same length and intensity without the addition of the shock, and on average saw higher rates of differentiation (SCR: 36 – 39%, US Expectancy: 25 – 48%).

Differences in differentiation may have impacted between- and within-session extinction values, given that elevated fear responding across groups may suggest that they will have difficulties extinguishing fear-based responses.

Within-session extinction is a measurement of one's ability to extinguish fear-based responding with continuous presentation of conditioned and safe stimuli without the presentation of the aversive stimuli. Papini et al. (2017) found evidence of impaired within-session extinction of the SCR to the extinguished conditioned stimuli (i.e., CS + E) among cannabis users as compared to controls. We did not find evidence of significant differences in within-session extinction of the SCR to the CS+E between controls and cannabis users. However, group means suggest a similar pattern of responding in which cannabis users displayed lower extinction values than either the control or anxiety groups. Inconsistent with Papini et al. (2017), we found evidence of group differences in within-session extinction of US expectancy, in which cannabis users showed an impaired ability to extinguish fear-based responding as compared to the other two groups. As you may recall, existing research has shown that chronic cannabis users, as compared to acute cannabis users, may experience impairments in fear-based learning (Papini et al. 2017; Lin et al., 2008). The current study provides further evidence that chronic cannabis use may impair fear extinction, specifically within-session extinction. Of note, the largest difference in within-session extinction of US expectancy and SCR was seen between the cannabis and anxiety groups, in which the cannabis users displayed lower rates of within-session extinction. Anxiety disorders have consistently been found to be linked to impairments in fear-based extinction, which is unsurprising given the nature of these disorders (Michael et al., 2007; Blechert et al., 2007; Orr et al., 2000). In the present study, anxious individuals were found to better extinguish fear-based learning as compared to the cannabis group. The anxiety group was

not significantly different from controls, but did have unexpectedly higher average extinction values. It could be that we had a higher functioning group of anxious individuals, better able to adapt to fear-based stimuli, or it could be the case that cannabis users experience significant difficulty extinguishing fear-based learning, or an unknown third variable.

Between-session extinction assesses one's ability to recall extinguished fear-based responding following a 24-hour period. Papini et al. (2017) found that cannabis users displayed less SCR between-session extinction to the CS+E as compared to controls. They found no difference in US expectancy across groups. In the current study, we did not find evidence of any significant group differences. However, the means suggest that cannabis users generally displayed reduced between-session extinction as compared to the anxiety and control groups. In the current study, there were also no differences in extinction generalization across groups. Papini et al. (2017) also found no evidence of differences in extinction generalization between chronic cannabis users and controls.

It is important to note that across the combined sample, participants generally displayed lower percentages of within- and between-session extinction as compared to past research. Papini et al. (2017) solely utilized a white noise burst rather than a combination of a shock and white noise burst. We utilized the combination of methods with the hopes of eliciting a better SCR response across racial groups. The addition of the shock may have made it difficult for participants to extinguish fear-based responding, resulting in a "global fear". This hypothesis is further supported by fear differentiation rates, which were generally lower in the current project than in Papini et al. (2017), indicating that participants had difficulties differentiating safe and harmful stimuli no matter their group. Further, a majority of participants experienced a complete return of fear-based responding between sessions (i.e., their day 2 SCR was significantly higher

than their day 1 responses, resulting in a 0% between-session extinction rate). This suggests that a majority of participants, no matter their group, had difficulty extinguishing fear-based learning. Given that the tasks were matched on everything except the unconditioned stimuli, these differences are likely due to the additional aversive stimuli.

The results from the current study have some important clinical implications. They suggest that chronic cannabis use may impair within-session fear extinction compared to cannabis-naïve individuals with an anxiety disorder. Given that fear extinction is a primary mechanism of Exposure-Based Therapy (EXP) for anxiety disorders and cannabis use is common in this population, this finding may suggest that therapy clients will experience reduced benefit from therapy. If this is the case, then chronic cannabis users may wish to abstain from cannabis use while participating in EXP to experience its complete effects. It may also be the case that cannabis users have been generally resistant to manualized treatment, such as EXP, and thus have sought out cannabis as an alternative treatment. If this is the case then perhaps there is a third variable, external to cannabis use, which results in these differences in fear-based responding.

As with every study, this project had its limitations. As reviewers may recall, Papini et al. (2017) recruited 20 participants per group. Power analysis for the current project also suggested that a sample of 80 participants, 20 per group, would sufficiently power us to find a significant effect. Due to difficulties with recruitment, among other barriers, this study was significantly underpowered. The cannabis group contained 12 participants, and the anxiety group contained 14 participants, which was significantly below the expected recruitment numbers. This may have significantly impacted results. Additionally, the project originally started with four groups: healthy controls, cannabis-naïve individuals with an anxiety or fear-related disorder, chronic

cannabis users without a current or past anxiety or fear-related disorder, and chronic cannabis users with a co-occurring anxiety or fear-related disorder. Due to difficulties recruiting cannabis users, the cannabis groups were combined during analyses to ensure that we had enough participants to compare across groups. Thus, the cannabis group was a conglomerate of chronic cannabis users with or without a current anxiety or fear-related disorder. This may have significantly impacted the performance of the cannabis group as compared to the other groups, as we do not have a literature basis to suggest how co-occurring anxiety and fear-related disorders and chronic cannabis use may impact fear-based responding. Similar to the limitations discussed above, matching participants based on demographic variables became difficult given the limited number of eligible participants. Given this, the cannabis group is older and more diverse than the other groups, increasing the likelihood of confounds. Future studies should further explore the impact of concurrent cannabis use and anxiety on fear-based learning, as this question was not adequately explored in the current project.

This study was the first to assess differences in fear extinction between chronic cannabis users and an anxiety group. Additionally, this study added to the limited research on the impact of chronic cannabis use on fear extinction. Findings provide evidence that chronic cannabis use is associated with fear-based responding and thus may complicate the clinical picture. Moreover, these findings suggest the need for additional research into the effects of chronic cannabis use on fear responding, especially given the increased prevalence of cannabis use among clinical populations.

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Appendix

Table 1. Surveys and Interviews Administered per Time Point

Measure	Screening Survey	Eligibility Interview	Lab Visit: Day 1	Lab Visit: Day 2
Overall Anxiety Sensitivity and Impairment Scale (OASIS)	X		X	
Drug Use Frequency (DUF)	X			
The Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU Inventory)	X			
Enhanced Cannabis Timeline Followback (TLFB)			X	
Structured Clinical Interview (SCID)		X		

Note. “X” indicates that the survey/interview will be administered at the listed timepoint.

Table 2. Demographics

Group	Cannabis Group (CAN)	Anxiety Group (ANX)	Control Group (CTRL)
# of Participants (N)	12	14	20
Mean Age	35.00	20.93	20.05
Ethnicity/Race	White (Non-Hispanic): 8 Hispanic: 1 Black: 2 Asian/Pacific Islander: - Other: 1	White (Non-Hispanic): 9 Hispanic: 1 Black: - Asian/Pacific Islander: 4 Other: -	White (Non-Hispanic): 15 Hispanic: 2 Black: 1 Asian/Pacific Islander: 2 Other: -
Sex	Male: 8 Female: 4	Male: 2 Female: 12	Male: 12 Female: 8

Table 3. Diagnostic Information for Anxiety and Cannabis Groups

<i>Primary Diagnosis</i>	<i># of Participants</i>
Anxiety Group (ANX)	
Social Anxiety Disorder	6
Generalized Anxiety Disorder	3
Specific Phobia	1
Unspecified, Otherwise Specified Anxiety Disorder	1
Post-Traumatic Stress Disorder	1
Other Specified Trauma- and Stressor-Related Disorder	1
Obsessive-Compulsive and Related Disorder	1
Cannabis Group (CAN)	
Generalized Anxiety Disorder	2
Other Specified Trauma- and Stressor-Related Disorder	1
Cannabis Use Disorder, Mild	2
Cannabis Use Disorder, Moderate	4
Cannabis Use Disorder, Severe	3

Table 4. Overall Diagnosis Information (Current and Historical Diagnoses)

<i>Diagnoses</i>	<i># of Participants</i>	
Anxiety Group (ANX)	Current Diagnosis	Historical Diagnosis
Social Anxiety Disorder	6	1
Generalized Anxiety Disorder	6	1
Specific Phobia	2	0
Unspecified, Otherwise Specified Anxiety Disorder	1	0
Post-Traumatic Stress Disorder	1	1
Other Specified Trauma- and Stressor-Related Disorder	2	0
Obsessive-Compulsive and Related Disorder	1	0
Major Depressive Episode, Single Episode	0	2
Major Depressive Episode, Recurrent	1	2
Persistent Depressive Disorder	0	1
Hypomanic Episode	0	1
Bipolar II	1	0
Alcohol Use Disorder, Mild	1	0
Cannabis Group (CAN)		
Social Anxiety Disorder	1	1
Generalized Anxiety Disorder	2	0
Specific Phobia	0	1
Agoraphobia	1	0
Unspecified, Otherwise Specified Anxiety Disorder	1	0
Post-Traumatic Stress Disorder	0	1
Other Specified Trauma- and Stressor-Related Disorder	1	1
Major Depressive Episode, Single Episode	0	3
Major Depressive Episode, Recurrent	1	1
Persistent Depressive Disorder	0	1
Cannabis Use Disorder, Mild	2	0
Cannabis Use Disorder, Moderate	4	0
Cannabis Use Disorder, Severe	3	0

*Historical diagnosis means that the disorder is currently in remission.

Figure 1. The percentage reduction in US expectancy to the CS + E from late conditioning to extinction. Higher percentages indicate greater extinction.

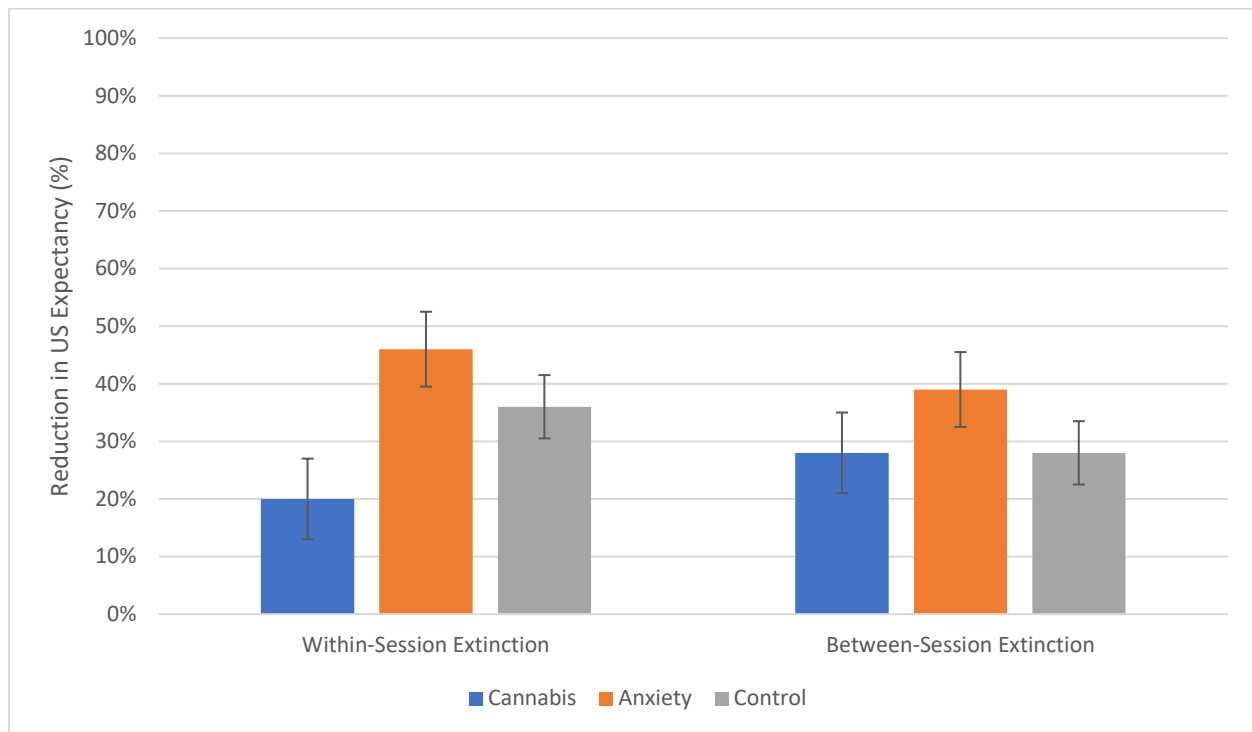


Figure 2. Percent reduction in SCR to the CS + E from late conditioning to extinction. Higher percentages indicate greater extinction.

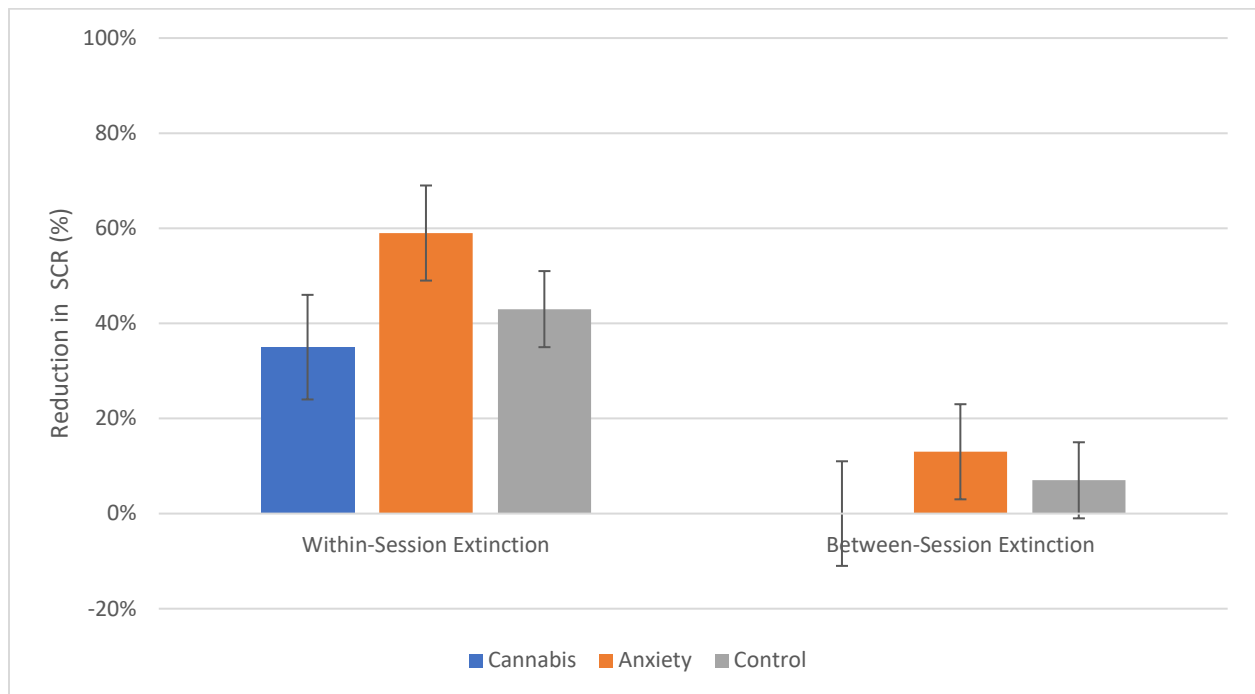
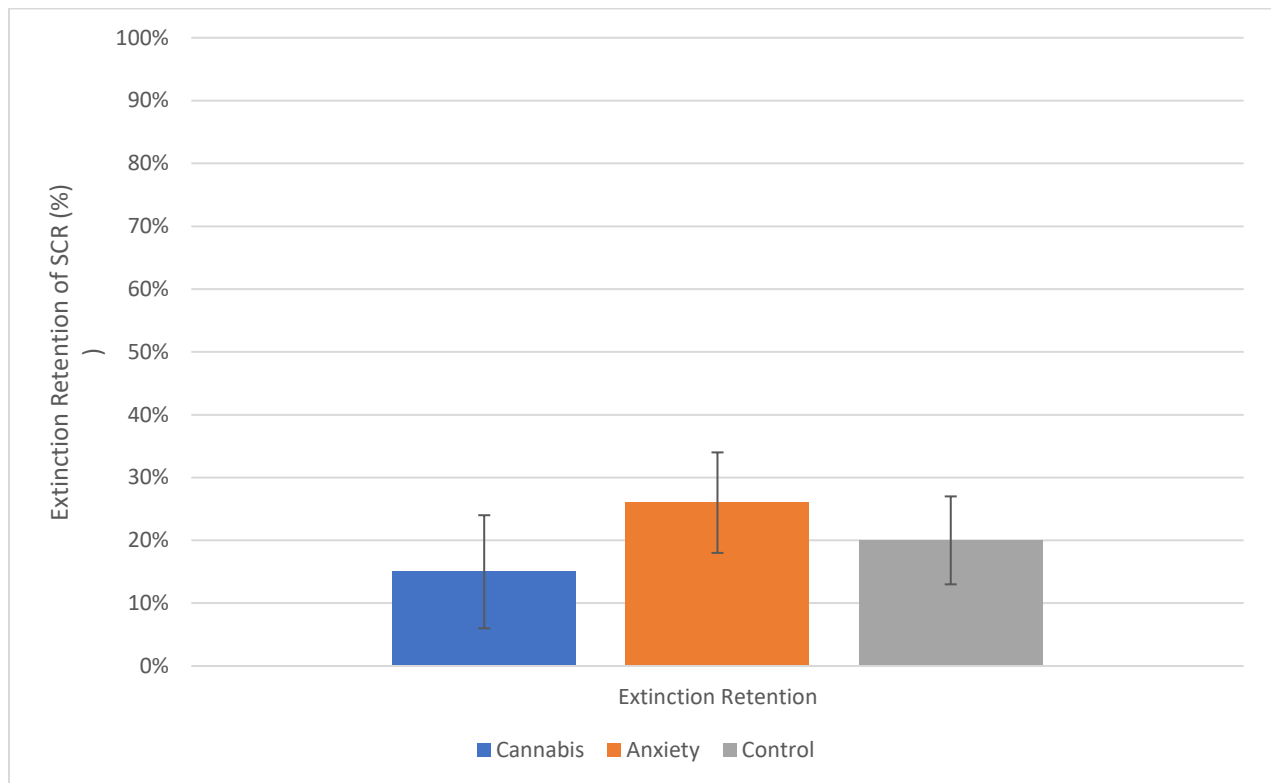


Figure 3. This was a supplemental analysis look at the percentage of extinction retained during Day 2 extinction recall. Higher percentages indicate greater retention (i.e., greater learning of extinction).



Appendix A. Baseline Demographics Questionnaire

Baseline Questionnaire Battery

Demographics

Study # _____

Age: _____

Biological Sex: Male / Female

Gender: Male / Female / Transgender / Other (Please specify: _____)

Sexual Orientation: Heterosexual / Homosexual / Bisexual / Other (Please specify: _____)

Predominant Ethnicity:

___ Black (not Hispanic)

___ White (not Hispanic)

___ Hispanic

___ Asian or Pacific Islander

___ American Indian or Alaskan Native

Other (please specify): _____

What is your marital status?

___ Married

___ Single/Never Married

___ Divorced

___ Separated

___ Widowed

What is your highest level of education completed?

___ Less than High School

___ High School Diploma

___ Some College

___ Bachelor's Degree

___ Post-Graduate Degree

What is the average household income of your family?

___ \$0-\$9,999

___ \$10,000-\$19,999

___ \$20,000-\$29,999

___ \$30,000-\$39,999

___ \$40,000-\$49,999

___ \$50,000-\$59,999

___ \$60,000-\$69,999

___ \$70,000-\$79,999

___ \$80,000-\$89,999

___ \$90,000-\$99,999

___ \$100,000 or more

Please list any medications you are currently taking: _____

FOR FEMALES ONLY:

Do you take birth control medication? Yes \ No

If YES, please write the medication's name, dose amount, and dose frequency:

Are you currently menstruating? Yes \ No

If YES, skip to next page.

If NO, enter the date range when you were last menstruating (if needed, you can use the calendar at the end of the packet for assistance remembering): _____ - _____

Appendix B. The Overall Anxiety Sensitivity Index (OASIS)

Overall Anxiety Severity and Impairment Scale (OASIS)

The following items ask about anxiety and fear. These symptoms may include panic attacks, situational anxieties, worries, flashbacks hypervigilence of startle. Include all of your anxiety symptoms when answering these questions. For each item, circle the number for the answer that best describes your experience *over the past week*.

1. In the past week, how often have you felt anxious?

- 0 = *No* anxiety in the past week.
- 1 = *Infrequent* anxiety. Felt anxious a few times.
- 2 = *Occasional* anxiety. Felt anxious as much of the time as not. It was hard to relax.
- 3 = *Frequent* anxiety. Felt anxious most of the time. It was very difficult to relax.
- 4 = *Constant* anxiety. Felt anxious all of the time and never really relaxed.

2. In the past week, when you have felt anxious, how intense or severe was your anxiety?

- 0 = *Little or None*: Anxiety was absent or barely noticeable.
- 1 = *Mild*: Anxiety was at a low level. It was possible to relax when I tried. Physical symptoms were only slightly uncomfortable.
- 2 = *Moderate*: Anxiety was distressing at times. It was hard to relax or concentrate, but I could do it if I tried. Physical symptoms were uncomfortable.
- 3 = *Severe*: Anxiety was intense much of the time. It was very difficult to relax or focus on anything else. Physical symptoms were extremely uncomfortable.
- 4 = *Extreme*: Anxiety was overwhelming. It was impossible to relax at all. Physical symptoms were unbearable.

3. In the past week, how often did you avoid situations, places, objects, or activities because of anxiety or fear?

- 0 = *None*: I do not avoid places, situations, activities, or things because of fear.
- 1 = *Infrequent*: I avoid something once in a while, but will usually face the situation or confront the object. My lifestyle is not affected.
- 2 = *Occasional*: I have some fear of certain situations, places, or objects, but it is still manageable. My lifestyle has only changed in minor ways. I always or almost always avoid the things I fear when I'm alone, but can handle them if someone comes with me.
- 3 = *Frequent*: I have considerable fear and really try to avoid the things that frighten me. I have made significant changes in my life style to avoid the object, situation, activity, or place.
- 4 = *All the Time*: Avoiding objects, situations, activities, or places has taken over my life. My lifestyle has been extensively affected and I no longer do things that I used to enjoy.

4. In the past week, how much did your anxiety interfere with your ability to do the things you needed to do at work, at school, or at home?

- 0 = *None*: No interference at work/home/school from anxiety
- 1 = *Mild*: My anxiety has caused some interference at work/home/school. Things are more difficult, but everything that needs to be done is still getting done.
- 2 = *Moderate*: My anxiety definitely interferes with tasks. Most things are still getting done, but few things are being done as well as in the past.
- 3 = *Severe*: My anxiety has really changed my ability to get things done. Some tasks are still being done, but many things are not. My performance has definitely suffered.

- 4 = *Extreme*: My anxiety has become incapacitating. I am unable to complete tasks and have had to leave school, have quit or been fired from my job, or have been unable to complete tasks at home and have faced consequences like bill collectors, eviction, etc.

5. In the past week, how much has anxiety interfered with your social life and relationships?

- 0 = *None*: My anxiety doesn't affect my relationships.
- 1 = *Mild*: My anxiety slightly interferes with my relationships. Some of my friendships and other relationships have suffered, but, overall, my social life is still fulfilling
- 2 = *Moderate*: I have experienced some interference with my social life, but I still have a few close relationships. I don't spend as much time with others as in the past, but I still socialize sometimes.
- 3 = *Severe*: My friendships and other relationships have suffered a lot because of anxiety. I do not enjoy social activities. I socialize very little.
- 4 = *Extreme*: My anxiety has completely disrupted my social activities. All of my relationships have suffered or ended. My family life is extremely strained.

Appendix C. The Drug Use Frequency (DUF) measure

Drug Use Frequency Form

What was your usual frequency of nicotine/tobacco use in the past year?

- 0 – Never
- 1 – One Time
- 2 – Monthly or less
- 3 – Two to four times per month
- 4 – Two to three times per week
- 5 – Four or more times per week

What was your usual frequency of alcohol use in the past year?

- 0 – Never
- 1 – One Time
- 2 – Monthly or less
- 3 – Two to four times per month
- 4 – Two to three times per week
- 5 – Four or more times per week

What was your usual frequency of cocaine/crack in the past year?

- 0 – Never
- 1 – One Time
- 2 – Monthly or less
- 3 – Two to four times per month
- 4 – Two to three times per week
- 5 – Four or more times per week

What was your usual frequency of amphetamines (e.g., meth, Adderall) in the past year? (If applicable, indicate whether you used the drug as prescribed by a doctor or if you did not use it as prescribed by a doctor).

- 0 – Never
- 1 – One Time
- 2 – Monthly or less

3 – Two to four times per month

4 – Two to three times per week

5 – Four or more times per week

What was your usual frequency of opioids (e.g., Vicodin, Oxycodone, Percocet, morphine, heroin) in the past year? (If applicable, indicate whether you used the drug as prescribed by a doctor or if you did not use it as prescribed by a doctor).

0 – Never

1 – One Time

2 – Monthly or less

3 – Two to four times per month

4 – Two to three times per week

5 – Four or more times per week

What was your usual frequency of hallucinogens (e.g., MDMA/Molly/Ecstasy, LSD, Mushrooms, etc.) in the past year?

0 – Never

1 – One Time

2 – Monthly or less

3 – Two to four times per month

4 – Two to three times per week

5 – Four or more times per week

What was your usual frequency of sedatives (e.g., Valium, Xanax, Klonopin, etc.) in the past year? (If applicable, indicate whether you used the drug as prescribed by a doctor or if you did not use it as prescribed by a doctor).

0 – Never

1 – One Time

2 – Monthly or less

3 – Two to four times per month

4 – Two to three times per week

5 – Four or more times per week

Appendix D. The Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU)

DFAQ-CU Inventory

Instructions: Please read each of the following questions and mark the response alternative that best describes your use of cannabis. *Note that the term cannabis is being used to refer to marijuana, cannabis concentrates, and cannabis-infused edibles.*

1. Have you ever used cannabis?

0 = No

1 = Yes

**If response = 0 then skip to end of questionnaire*

2. Which of the following best captures when you last used cannabis?

1 = over a year ago

2 = 9 – 12 months ago

3 = 6 – 9 months ago

4 = 3 – 6 months ago

5 = 1 – 3 months ago

6 = less than 1 month ago

7 = last week

8 = this week

9 = yesterday

10 = today*

11 = I am currently high*

**If response = 10 (today) or 11 (I am currently high) then answer 2b below*

2b. How high are you right now?

0 = I am not at all high

1 = I am a little bit high

2 = I am moderately high

3 = I am very high

4 = I am extremely high

3. Which of the following best captures the average frequency you currently use cannabis?

0 = I do not use cannabis

1 = less than once a year

2 = once a year

3 = once every 3-6 months (2-4 times/yr))

4 = once every 2 months (6 times/yr)

5 = once a month (12 times/yr)

6 = 2 – 3 times a month

7 = once a week

8 = twice a week

9 = 3 – 4 times a week

10 = 5 – 6 times a week

11 = once a day

12 = more than once a day

4. Which of the following best captures how long you have been using cannabis **at this frequency**?

1 = less than 1 month

7 = 2 – 3 years

2 = 1 – 3 months

8 = 3 – 5 years

3 = 3 – 6 months

9 = 5 – 10 years

4 = 6 – 9 months

10 = 10 – 15 years

5 = 9 – 12 months

11 = 15 – 20 years

6 = 1 – 2 years

12 = more than 20 years

5. Before the period of time you indicated above, how frequently did you use cannabis?

0 = I did not use cannabis

7 = once a week

1 = less than once a year

8 = twice a week

2 = once a year

9 = 3 – 4 times a week

3 = once every 3-6 months (2-4 times/yr.)

10 = 5 – 6 times a week

4 = once every 2 months (6 times/yr.)

11 = once a day

5 = once a month

12 = more than once a day

6 = 2 – 3 times a month

6. How many days of the past week did you use cannabis?

0 = 0 days

4 = 4 days

1 = 1 day

5 = 5 days

2 = 2 days

6 = 6 days

3 = 3 days

7 = 7 days

7. Approximately how many days of the past month did you use cannabis? _____

8. Which of the following best captures the number of times you have used cannabis in your entire life?

1 = 1 – 5 times in my life

6 = 501 – 1000 times in my life

2 = 6 – 10 times in my life

7 = 1001 – 2000 times in my life

3 = 11 – 50 times in my life

8 = 2001 – 5000 times in my life

4 = 51 – 100 times in my life

9 = 5001 – 10,000 times in my life

5 = 101 – 500 times in my life

10 = More than 10,000 times in my life

9. Which of the following best captures your pattern of cannabis use throughout the week?

- 0 = I do not use cannabis at all
- 1 = I only use cannabis on weekends
- 2 = I only use cannabis on weekdays
- 3 = I use cannabis on weekends and weekdays

10. How many hours after waking up do you typically first use cannabis?

- | | |
|-----------------------------------|---------------------------------|
| 0 = I do not use cannabis at all | 5 = 1 – 3 hours after waking up |
| 1 = 12 – 18 hours after waking up | 6 = within 1 hour of waking up |
| 2 = 9 – 12 hours after waking up | 7 = within ½ hour of waking up |
| 3 = 6 – 9 hours after waking up | 8 = immediately upon waking up |
| 4 = 3 – 6 hours after waking up | |

11. How many times a day, on a typical weekday, do you use cannabis? _____

12. How many times a day, on a typical weekend, do you use cannabis? _____

13. What is the primary method you use to ingest cannabis?

- | | |
|---------------------------------|---|
| 0 = I do not use cannabis | 4 = Bong (water pipe) |
| 1 = Joints | 5 = Hookah |
| 2 = Blunts (cigar sized joints) | 6 = Vaporizer (e.g., Volcano, Vape pen) |
| 3 = Hand pipe | 7 = Edibles |
| | 8 = Other _____ |

14. Which of the following other methods to ingest cannabis do you use **regularly** (at least 25% of the time use you cannabis)? [Mark all that apply]

0 = None
1 = Joints
2 = Blunts (cigar sized joints)
3 = Hand pipe
4 = Bong (water pipe)

5 = Hookah
6 = Vaporizer (e.g., Volcano, Vape pen)
7 = Edibles
8 = Other _____

15. What is the primary form of cannabis you use?

0 = None****

A = Marijuana***

B = Concentrates (e.g., Oil, Wax, Shatter, Butane Hash Oil, Dabs)**

C = Edibles*

D = Other _____

16. What other forms of cannabis do you use **regularly** (at least 25% of the time you use cannabis)?
[Mark all that apply]

0 = None****

A = Marijuana***

B = Concentrates (e.g., Oil, Wax, Shatter, Butane Hash Oil, Dabs)**

C = Edibles*

D = Other _____

*****If response to questions 15 and 16 = 0 (None) then skip to question 29*

****If responses to questions 15 or 16 = A (Marijuana) then answer questions 17-21*

***If responses to question 15 or 16 = B (Concentrates) then answer questions 22-26*

**If responses to question 15 or 16 = C (Edibles) then answer question 27*

Note: If you use more than one form of cannabis then complete all of the associated questions listed above.

****If responses to questions 15 or 16 = A (Marijuana) then answer questions 17-21 below.*

Please use the image below to refer to various quantities of marijuana. The image is not to scale; the dollar bill is included to help provide size perspective.



For questions 17 to 19 below, clearly indicate the number of grams of marijuana you use with a number between 0 – 100. Do NOT include other forms of cannabis you may use (such as concentrates). You may use up to 3 decimals to indicate amounts under 1 gram.

Note: 1/8 of a gram = 0.125 grams, 1/4 of a gram = 0.25 grams, 1/2 of a gram = 0.5 grams, 3/4 of a gram = 0.75 grams. 1/8 of an ounce = 3.5 grams, 1/4 of an ounce = 7 grams, 1/2 ounce = 14 grams, 1 ounce = 28 grams

17. In a typical session, how much marijuana do you personally use? _____

18. On a typical day you use marijuana, how much do you personally use? _____

19. In a typical week you use marijuana, how much marijuana do you personally use? _____

20. On a typical day you use marijuana, how many sessions do you have? _____

21. What is the average THC content of the marijuana you typically use? Leave blank if you do not know.

1 = 0 – 4%

5 = 20 – 24%

2 = 5 – 9%

6 = 25 – 30%

3 = 10 – 14%

7 = greater than 30%

4 = 15 – 19%

***If response to questions 15 or 16 = B (Concentrates) then answer questions 22-26 below*

22. In a typical session you use cannabis concentrates, how many hits do you personally take? ____

23. On a typical day you use cannabis concentrates, how many hits do you personally take? _____

24. How many hits of cannabis concentrates did you personally take yesterday? _____

25. On a typical day you use cannabis concentrates, how many sessions do you have? _____

26. What is the average THC content of the concentrates you typically use? Leave blank if you do not know.

1 = 0 – 9%

5 = 40 – 49%

2 = 10 – 19%

6 = 50 – 59%

3 = 20 – 29%

7 = 60 – 69%

4 = 30 – 39%

8 = 70 – 79%

9 = 80 – 90%

10 = greater than 90%

***If response to questions 15 or 16 = C (Edibles) then answer question 27 below*

27. When you eat edibles how many milligrams of THC do you personally ingest in a typical

session? _____

28. What is your current age? _____

29. How many years in total have you used cannabis? _____

30. How old were you when you FIRST tried cannabis? _____

31. Has there been any time in your life when you used cannabis regularly (2 or more times per month for 6 months or longer)?

0 = No

1 = Yes*

**If response = 1 (Yes) then answer questions 31b and 31c below*

31b. How old were you when you FIRST STARTED using cannabis regularly (2 or more

times/month)? _____

31c. Has there been any time in your life when you used cannabis on a daily or near daily basis for 6 months or longer?

0 = No

1 = Yes*

**If response = 1 (Yes) then answer question 31ci below*

31ci. How old were you when you FIRST STARTED using cannabis on a daily or near daily basis? _____

32. Which of the following best captures the average frequency that you used cannabis before the age of 16?

0 = more than once a day

1 = once a day

2 = 5 – 6 times a week

3 = 3 – 4 times a week

4 = twice a week

5 = once a week

6 = 2 – 3 times a month

7 = once a month

8 = once every 2 months (6 times/yr.)

9 = once every 3-6 months (2-4 times/yr.)

10 = once a year

11 = less than once a year

12 = never

33. Do you have a physician's recommendation to use cannabis for medicinal purposes?

0 = No

1 = Yes*

2 = Yes, but I use it for both medicinal and recreational purposes*

**If response = 1 or 2 (Yes) then answer questions 33b and 33c*

33b. Which medical condition(s) do you use cannabis for?

33c. What percentage of the time do you use cannabis for recreational (rather than

medicinal) purposes? _____

DFAQ-CU Scoring

Daily Sessions Items: 20, 25

Frequency Items: 2, 3, 6, 7, 8, 9, 10, 11, 12

Age of Onset Items: 30, 31b, 31ci, 32

Marijuana Quantity Items: 17, 18, 19

Concentrate Quantity Items: 22, 23, 24,

Edibles Quantity Item: 27

Note: Standardize (z-transform) scores prior to calculating the mean of each of the 6 factors (daily sessions, frequency, age of onset, marijuana quantity, concentrate quantity, edibles quantity).

Screening/Characterization Items: 1, 2b, 4, 5, 13, 14, 15, 16, 21, 26, 28, 29, 31, 31c, 33, 33b, 33c

Contact us at: DFAQCU@gmail.com if you would like a Qualtrics version of the DFAQ-CU shared to your Qualtrics account.

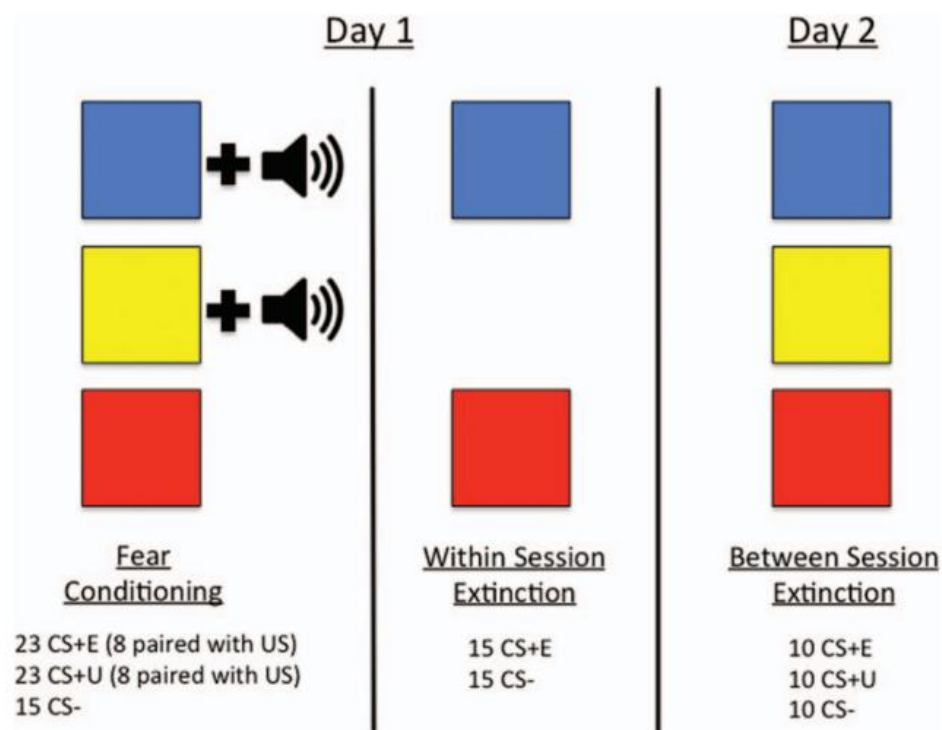
Appendix E. The 2-Day Fear Differential Task from Papini et al. (2017)'s paper

Figure 1. Fear conditioning and extinction paradigm. US = unconditioned stimulus (sound blast); CS + E = conditioned stimulus that underwent extinction; CS + U = conditioned stimulus that remained unextinguished; CS- = conditioned stimulus that was never paired with the US. See the online article for the color version of this figure.

Appendix F. Beck Depression Inventory – Screener for SIBeck Depression Inventory – II

Instructions: Please read the statements below carefully, and then pick out the **one statement** that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement.

9 - Suicidal Thoughts or Wishes

- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.