TRAUMA CUE-INDUCED AFFECT, CRAVING, AND AUTOMATIC COGNITIONS IN CANNABIS USERS WITH TRAUMA HISTORIES

By

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DEDICATION

For Cammy. And little me.

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ABSTRACT

There is an elevated prevalence of cannabis use among trauma-exposed individuals. Moreover, posttraumatic stress disorder (PTSD) and cannabis use disorder (CUD) are highly comorbid. Frequent pairing of trauma cues with cannabis use may lead to classically conditioned cannabis craving on future trauma cue exposure. Similarly, through strong memory associations formed between trauma cues, negative affect, cannabis use, and relief outcomes, trauma cue exposure should theoretically elicit both negative affect and automatic cannabis-relevant cognitions (e.g., cannabis approach bias) that promote cannabis use. Theoretically, these conditioning processes should be particularly strong in those with PTSD and could serve as mechanisms underlying PTSD-CUD comorbidity. In this dissertation, I conducted a scoping review and four experimental studies to test predictions arising from these classical conditioning and associative learning models among trauma-exposed substance/cannabis users. Study 1 mapped existing research on experimental trauma/substance cue exposure in substance users with trauma histories/PTSD, identifying gaps, methodological challenges, and common responses elicited by trauma cue reactivity paradigms (CRPs). Four subsequent empirical studies focused on testing effects of trauma cue exposure, PTSD, and their interactions on relevant cognitive and affective outcomes in cannabis users with trauma histories. Study 2 showed a single-session trauma CRP (semi-structured personalized trauma interview) elicited greater cannabis craving and negative affect (particularly in those with more PTSD symptoms) compared to a neutral interview. Study 3 investigated effects of trauma cue exposure (semi-structured interview) and PTSD symptom severity on cannabis approach bias, revealing a positive association between PTSD symptoms and this automatic cognitive bias. Study 4 tested another trauma CRP (online expressive writing); trauma vs. neutral writing and likely PTSD were both independently associated with greater negative affect and cannabis expectancy craving. Study 5 examined effects of trauma cue exposure (expressive writing) and likely PTSD on the accessibility of cannabis-related information in memory; trauma (vs. neutral) writing elicited greater cannabis accessibility. Collectively, my studies contribute to understanding mechanisms underlying co-occurring PTSD-CUD, suggesting contributions from both trauma cue-elicited automatic and controlled cognitive processes, as well as conditioned negative affect. My dissertation also contributes methodologically by validating two single-session CRPs (interview; expressive writing) for future use in this field.

LIST OF ABBREVIATIONS AND SYMBOLS USED

α	Cronbach's alpha
AAT	Approach avoidance task
APA	American Psychological Association
ApBM	Approach Bias Modification
CBM	Cognitive Bias Modification
CI	Confidence interval
CRP	Cue reactivity paradigm
CUD	Cannabis use disorder
CWAT	Cannabis word association task
H1	Hypothesis 1
H2	Hypothesis 2
H3	Hypothesis 3
H4	Hypothesis 4
M	Mean
N	Sample size
PTSD	Posttraumatic stress disorder
p	P-value
r	Correlation
SD	Standard deviation
SE	Standard error
SUD	Substance use disorder

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Reflecting back to the ninth grade, I was driven by a desire to understand why I turned to cannabis excessively following trauma - a notion that seemed more than mere coincidence to my adolescent mind. The following year, I remember discussing the doctoral level Psychology program at Dalhousie University with my school guidance counsellor, who laughed when I enthusiastically pulled up the Psychology Doctoral program website. Whether consciously or not, her doubt in me fueled my determination to be where I am today, writing this dissertation. Far above my ego, though, I owe a huge debt of gratitude to my childhood self -- inherently curious and seeking understanding amidst adversity. She is the true catalyst for my journey, and to her I give endless thanks. To my mom, Ryan, Kyle, Sam, Moon, Emma, Raven, Tristan, Curt, Brady, Princess Parmesan and Lady Gouda (my cats lol), and most notably, my late friend Cameron: I can't thank you enough. Life doesn't provide enough opportunities for me to acknowledge how much I value your friendship. Please take this immortal, though bound-to-be-forgotten, dissertation declaring my affection for you as such. I couldn't have done it without you.

CHAPTER 1. INTRODUCTION

My dissertation examines the role of trauma cue-induced craving and automatic cognitive biases as mechanisms potentially contributing to comorbid posttraumatic stress disorder (PTSD) and cannabis use disorder (CUD). It includes three published, one in press, and one under review manuscripts. The first is a scoping review of the existing cue reactivity literature examining conditioned affect, craving, and other relevant cognitive outcomes among trauma-exposed substance users that may serve as mechanisms to explain substance use in this population. This review informed the subsequent four empirical manuscripts included in the present dissertation, given that the review identified: 1) a lack of CRP research with cannabis as the substance of interest; 2) affect and craving as common outcomes in this body of research; 3) sparse examination of automatic cognitions in these populations; and 4) existing barriers in using the CRP methodology when studying trauma-exposed individuals or those with PTSD. Thus, the second study experimentally tested the use of a single-session CRP (i.e., a semi-structured, personalized trauma interview) in eliciting trauma (vs. neutral) cue-induced craving and affective outcomes in cannabis users with trauma histories. The third study utilized this same single-session CRP and a cannabis approach-avoidance task to quantify cannabis (vs. neutral) approach bias in the same population, under trauma (vs. neutral) cue conditions. The fourth manuscript assigned cannabis users with trauma histories to complete either a trauma or neutral expressive writing task as an alternative CRP to test differences across writing conditions on participants' cannabis craving and negative affect and to pilot the use of the expressive writing task as a CRP. The final manuscript tested the effect of the expressive writing trauma (vs. neutral) CRP on automatic

cannabis-related cognitions. Studies 2 and 3 were conducted with a single lab-based sample and Studies 4 and 5 were conducted with a single online sample. Prior to presenting the manuscripts, I will briefly introduce and discuss: the prevalence and nature of comorbid PTSD-CUD; the psychological theories of conditioning that inform my dissertation; and an overview of the current scientific literature using CRPs in a population of trauma-exposed substance users. Finally, I will discuss the specific objectives of each study in my dissertation, prior to moving on to the studies themselves in their specific chapters.

Comorbid Posttraumatic Stress, Substance, and Cannabis Use Disorders

Globally, the range of trauma exposed individuals who go on to develop posttraumatic stress disorder (PTSD) is reported to be between 5.6-19.5% (Atwoli et al., 2015; Koenen et al., 2017). Other trauma exposed individuals may experience subthreshold PTSD symptoms; though not meeting criteria for a full PTSD diagnosis, subthreshold PTSD symptoms may nonetheless be very distressing (McLaughlin et al., 2015). Rates of lifetime PTSD have been shown to be higher among those living in war-affected, low-to-middle income countries (Hoppen et al., 2021). Further, the probability of being diagnosed with lifetime PTSD among those with trauma histories was associated with being young, of the female sex, unmarried, as well as having less education and lower income (Koenen et al., 2017). In the North American context of the present dissertation, nearly 90% of American adults (Kilpatrick et al., 2013) and 64% of Canadian adults (Government of Canada, 2022) have experienced at least one traumatic event in their lifetime. Far fewer go on to develop PTSD. Indeed, following trauma exposure, only 8.3% of Americans and 8% of Canadians went on to meet clinical criteria

for PTSD at some point in their lifetimes (Government of Canada, 2022; Kilpatrick et al., 2013).

The diagnosis of PTSD involves the enduring experience of distressing symptoms after exposure to a traumatic event. As defined in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition – Text Revised* (DSM-5-TR; American Psychiatric Association [APA], 2022), trauma involves exposure to death or threat of death, serious injury or threat of injury, and actual or threatened sexual violence. Traumatic events leading to PTSD may include incidents of violence (i.e., combat-related, interpersonal), natural disasters, and other forms of severe human suffering (APA, 2022). Accidents or illnesses resulting in serious injury or death, either witnessed or experienced, as well as the unexpected death of a loved one, accounted for over half of traumatic experiences in one global survey by the World Mental Health Consortium - a finding consistent across countries (Benjet et al., 2016).

PTSD is the only diagnosis in the DSM-5-TR (APA, 2022) that requires exposure to an environmental trigger to make the diagnosis – i.e., the 'Criterion A' traumatic event. In addition to trauma exposure, four clusters of symptoms characterize a PTSD diagnosis. Re-experiencing the traumatic event (Criterion B) involves sudden, involuntary, and recurrent memories, dreams, or flashbacks relating to the traumatic event, sometimes triggered by external reminders or 'cues.' Symptoms of avoidance (Criterion C) are marked by efforts to evade unwanted memories, thoughts, or reminders of one's traumatic experience. Hyper-arousal (Criterion D) refers to disruptions to one's sleep, hypervigilance, aggression, or reckless behaviors. Finally, negative cognitions and mood (Criterion E) are defined as persistent negative thoughts about the self, others, and the

world; a decreased interest in activities one used to enjoy; distorted feelings of self-blame surrounding the traumatic event; and an inability to remember important parts of the traumatic experience (APA, 2022). These symptoms must be present for at least one month (Criterion F) and must provoke distress and/or cause functional impairment to one's daily life (Criterion G) to warrant a diagnosis of PTSD (APA, 2022). Substance use disorder (SUD) is another DSM-5-TR (APA, 2022) defined disorder, which may develop following the use of a substance or drug. Importantly, the DSM-5-TR does not consider the amount of substance used when determining the diagnosis of an SUD, but rather the degree of negative consequences stemming from the substance use, such as substance cravings and excessive time spent using or pursuing use of the substance (APA, 2022).

The craving response associated with SUD is evidenced across all substances, but the processes of craving and cue reactivity for cannabis and alcohol exhibit many similarities and some differences. For example, neurobiologically, both substances involve common pathways in the brain's reward system, particularly the mesolimbic dopamine pathway, which reinforces substance use and craving (Vergara et al., 2018). Psychological factors such as stress, coping mechanisms, and emotional regulation similarly influence cravings for both cannabis and alcohol, with individuals using either substance to manage negative emotions (Tiffany & Wray, 2015). However, the pharmacological properties of cannabis and alcohol differ, with cannabis affecting the endocannabinoid system and alcohol influencing GABAergic and glutamatergic neurotransmission, leading to unique subjective experiences and physiological responses (Nair et al., 2015). Patterns of use and socio-cultural factors further differentiate the two, with alcohol often consumed in social settings and cannabis used in varied contexts,

including medicinally. Overall, the literature suggests that while there are common elements in craving and cue reactivity across substances, drug-specific nuances exist (Araujo et al., 2015).

While many Canadians drink alcohol (76% had at least one drink in the past year; Government of Canada, 2019a) and some use cannabis (21% used at least once in the past year) and other substances (such as sedatives [11%], stimulants [1%], and other illegal drugs [3%]; Government of Canada, 2019a) for both medical and non-medical reasons, only 4.1% meet criteria for an SUD (Government of Canada, 2023a). In contrast to the demographics associated with PTSD in the U.S. listed above, having an SUD was associated with being Black, middle-aged, and male (Vasilenko et al., 2017). Moreover, those who identified with two or more races as well as Alaskan Natives and Native Americans were more likely to have an SUD compared to Black, White, Hispanic, Asian, or Native Hawaiian respondents (Ali et al., 2023). While previous versions of the DSM distinguished between substance abuse (the milder form of SUD) and substance dependence (the more severe form of SUD), in the DSM-5-TR (APA, 2022) these two disorders were collapsed into a single diagnostic entity (i.e., SUD). In the DSM-5-TR (APA, 2022), severity is determined based on the number of symptoms present: two or three symptoms constitutes mild SUD; four or five symptoms indicates moderate SUD; and six or more symptoms reflects severe SUD (APA, 2022).

PTSD and SUD often co-occur at rates that far exceed chance. For example, in a U.S. study, nearly half (46.4%) of individuals with PTSD also fulfilled criteria for an SUD compared to 37% of trauma-exposed individuals without PTSD (Pietrzak et al., 2011). Indeed, this pattern of elevated PTSD-SUD comorbidity has been documented

across numerous substances. For example, one study found those with (vs. without) cocaine use disorder were 2.18 times more likely to have PTSD in their lifetimes (Saunders et al., 2015). Similarly, individuals with AUD were 1.3 times more likely to be diagnosed with PTSD at some point in their lifetime (Grant et al., 2015) and individuals with PTSD were more likely to develop AUD than those without PTSD (Ouimette & Read., 2014). Such patterns also extend to nicotine, with one study demonstrating those with PTSD were twice as likely to be smokers compared to those without PTSD (Kearns et al., 2018). The clinical significance of PTSD-SUD comorbidity is underscored by evidence indicating a more severe symptom profile (Berenz et al., 2012), a more challenging course (Ouimette et al., 2006), diminished response to treatment (Hien et al., 2021), and higher relapse rates (Jacobsen et al., 2001) among individuals with both disorders compared to those with either disorder in isolation (Berenz & Coffey, 2012). Evidently, such findings strongly underscore the intricate relationship between PTSD and SUDs across various substance types, and its strong clinical relevance.

This pattern of comorbidity further extends to cannabis use and cannabis use disorder (CUD; Kevorkian et al., 2015; Walsh et al., 2014). Importantly, the legalization of cannabis in Canada in 2018 presented an opportunity for many to access cannabis for various purposes, including potential self-medication for conditions like PTSD, without a prescription. Indeed, while nearly a quarter of cannabis users in Canada use cannabis daily (Government of Canada, 2024), rates of those who meet criteria for CUD is generally much lower (Wu et al., 2016). For example, in 2019 – 2020, 11.9% of U.S. Veterans reported past month cannabis use, with this percentage increasing to 20% among younger (under 44 years) Veterans (Hill et al., 2021). In a Canadian context, 23%

of Veterans reported starting to use cannabis after exposure to a traumatic event and 42% began using cannabis after leaving the Canadian Armed Forces (Sterniczuk & Whelan, 2016). Cougle et al. (2011) found those with PTSD (compared to those without PTSD) were 3.3 times more likely to use cannabis in their lifetime, with demographic variables controlled. Statistical significance was maintained even after controlling for other substance use and mental disorders, with an adjusted 1.99 times greater likelihood of cannabis use among those diagnosed with (vs. without) PTSD (Cougle et al., 2011). While cannabis use, even daily use, does not necessitate adverse cannabis use outcomes or CUD, this association does point to a particular vulnerability or susceptibility among individuals with PTSD who use cannabis.

Among members of the public, 17.6% of individuals diagnosed with PTSD in the U.S. will also be diagnosed with CUD at some point in their lifetime (Hasin et al., 2016). Indeed, one study showed those with a PTSD diagnosis were 2.6 times more likely than trauma-exposed individuals with subclinical PTSD to have CUD (Walsh et al., 2014). The number of lifetime traumatic events experienced, however, was not associated with CUD. Interestingly, a similar insight from Kevorkian et al. (2015) suggests that the severity of PTSD largely contributes to the likelihood of adverse cannabis use outcomes among those with trauma histories. Specifically, they observed that mere exposure to trauma was linked to cannabis use in general, but that it was cannabis users diagnosed with PTSD who were at a higher risk of developing CUD (Kevorkian et al., 2015). Importantly, their findings remained significant when controlling for demographics (i.e., age, gender, race, ethnicity), other DSM-5-TR disorders, including depression, anxiety (including panic, social, and agoraphobia), AUD, and personality disorders (Kevorkian et

al., 2015). Similarly, Metrik and colleagues (2022) identified a longitudinal association between a PTSD diagnosis and a CUD diagnosis one year later. Indeed, such results highlight the robustness of the association between PTSD, cannabis use, and adverse cannabis use outcomes and are consistent with early conclusions by Stewart (1996) that it is PTSD rather than trauma exposure per se that increases risk for substance use disorder.

Despite the above-listed implications of adverse cannabis use outcomes among those with PTSD, some individuals with PTSD may be prescribed cannabis for the treatment of PTSD or may choose to self-medicate their PTSD with cannabis (Asselin et al., 2022). Indeed, many individuals with PTSD attest anecdotally that cannabis effectively treats their PTSD (Shishko et al., 2018). In Canada, the use of medicinal cannabis is authorized to treat PTSD in both Veterans (Mejia et al., 2023) and among members of the general public (Health Canada, 2016). Importantly, Veterans Affairs Canada will reimburse Veterans who use medicinal cannabis for up to three grams per day (Government of Canada, 2019b). However, the risk-to-benefit ratio of this policy has been challenged given the association of cannabis use with several mental and physical health issues among Veterans (Turna & MacKillop, 2021).

Of the little longitudinal research on cannabis use among those with PTSD that exists, some potentially beneficial effects have been observed. For example, Bonn-Miller and colleagues' (2022) work identified cannabis users (vs. non-users) as 2.5 times more likely to have recovered from clinically significant PTSD by the end of the one-year study period. However, without proper medical supervision and guidance, individuals may inadvertently exacerbate their symptoms via cannabis use. Indeed, most longitudinal research points to cannabis use as a predictor of worsened PTSD symptom severity or

unrelated to improvements in PTSD symptoms over time (Metrik et al., 2022; Wilkinson et al., 2017). Despite the common usage of cannabis for PTSD symptom management, there is a lack of double-blinded, randomized controlled trials supporting the use of cannabis for the treatment of PTSD (McKee et al., 2021). Moreover, many studies which tout the efficacy of cannabis in managing PTSD symptoms are observational or case studies (Shishko et al., 2018) or are without randomization or comparators (Rehman et al., 2021). Indeed, very little high-quality research exists to support the use of cannabis for the treatment of PTSD (McKee et al., 2021). For these reasons, some experts caution against the use of cannabis in this population (Bedard-Gilligan et al., 2022).

In addition to comorbid PTSD-CUD being an understudied area compared to other PTSD-SUD comorbidities (e.g., alcohol use disorder; cocaine use disorder), these substances may impact the trauma-exposed (compared to those without trauma histories) differentially. Perhaps due to the severe effects of alcohol and cocaine, these areas were primarily studied to address their more immediate and pronounced health risks, such as overdose, severe withdrawal symptoms, and long-term physiological damage (Rehm et al., 2011; Sanvisens et al., 2021). Alcohol's depressant effects can temporarily alleviate anxiety but often lead to exacerbated depressive symptoms, disrupted sleep, and increased risk of physical dependence and withdrawal (Brady & Back, 2012; Rehm et al., 2011). Cocaine, as a powerful stimulant, may momentarily mitigate anhedonia but significantly heightens anxiety, paranoia, and hyperarousal (Sanvisens et al., 2021), complicating PTSD treatment and increasing addiction potential (Brodnik et al., 2020). In contrast, cannabis' unique interaction with the endocannabinoid system offers a distinct profile of effects, and many trauma-exposed individuals attest cannabis is nothing but

beneficial in addressing PTSD symptoms. Indeed, cannabis is generally thought of as one of the safer illicit substances (Leos-Toro et al., 2020). However, like alcohol and cocaine, cannabis can also pose risks of dependency and cognitive impairment (Kroon et al., 2020) as well as liver damage (Choi et al., 2020). Indeed, more research into cannabis-PTSD comorbidity is needed to fully elucidate cannabis' therapeutic potential and pitfalls.

Processes of Adverse Substance Use Outcomes in Trauma-Exposed Individuals

There are several theories that have been proposed and experimentally tested that may help explain these high rates of PTSD-CUD comorbidity and shed light on the mechanistic underpinnings of the links of trauma exposure with subsequent cannabis use. Those relevant to the current dissertation are described in this section of the general introduction. These are: a) the self-medication hypothesis (Khantzian, 1997); b) two-factor avoidance theory (Stasewicz & Maisto, 1993); c) classically conditioned craving (Romero-Sanchiz et al., 2022); and d) the negative reinforcement model (Baker et al., 2004). I will briefly describe each theory generally and discuss how they apply to trauma-exposed individuals who use substances generally, and cannabis specifically. Then, I will explain how these theories converge by describing how research has applied these works in the context of addiction. First, the self-medication hypothesis, first proposed by psychiatrist Edward Khantzian in 1985 and revised in 1997, posits that individuals with SUDs will use substances to alleviate distressing symptoms of an underlying psychiatric condition. According to Khantzian (1997), substance use serves as a form of self-medication – i.e., a coping mechanism employed by individuals to manage various forms of psychological pain or discomfort. The temporary symptom relief provided by drugs or

alcohol reinforces their continued use, gradually leading to the development of addiction over time (Khantzian, 1997). In the context of PTSD-SUD, some individuals may resort to substance use to numb distressing emotional and/or physical symptoms of PTSD or to escape from intrusive memories and trauma reminders. While Khantzian's (1997) self-medication hypothesis offers valuable insights into the complex relationship underlying emotional distress and substance use, it is not without its criticisms. Khantzian's theory was initially criticized for oversimplifying the myriad social, environmental, and genetic factors that contribute to the development and perpetuation of SUDs (Lindgren et al., 2019). Moreover, as a psychodynamic theory, it fails to articulate a testable mechanism underlying self-medication. In contrast, application of operant conditioning theory can explain how someone with PTSD might learn to self-medicate their symptoms, placing them at increased risk for developing an SUD. Applying B. F. Skinner's operant conditioning theory (1963) to substance use, it has been suggested that the act of consuming substances can be reinforced by the removal or reduction of negative states or emotions (see Baker et al., 2004). Indeed, negative reinforcement learning focuses specifically on the immediate relief provided by substance use (e.g., reduction of anxiety) and the consequent reinforcement of the substance use behavior due to the removal of the aversive state (Baker et al., 2004). In the context of PTSD-SUD, the aversive state motivating relief-oriented substance use could be PTSD symptoms or the negative emotions that accompany trauma cue exposure.

Similarly, two-factor avoidance theory first proposed by Mowrer (1947) for anxiety disorders and adapted by Stasiewicz and Maisto (1993) for SUD, also highlights the role of negative affect as a pivotal factor in both the initiation and maintenance of

substance use. When applied to understanding the mechanisms underlying comorbid PTSD-SUD, two-factor learning theory adds to the operant conditioning theory (described above) by explaining how trauma reminders can come to elicit the negative emotions through classical conditioning. For example, if a traumatic mugging took place in a subway, through the pairing of the formerly neutral subway with the naturally fear-eliciting mugging, the survivor may come to experience conditioned negative emotions to subways. Through operant conditioning, the survivor comes to learn that substance use allows for escape from/avoidance of the aversive negative emotions evoked by trauma reminders (e.g., subway) reinforcing their future substance use in the context of trauma cue exposure (e.g., cannabis use prior to any subway travel). However, over time, the avoidance of trauma-related negative affect becomes a driving force behind continued substance use, perpetuating the cycle of addiction (Stasiewicz & Maisto, 1993).

Another pertinent theory in elucidating the relationship between trauma/PTSD and SUD involves the role of classical conditioning in the development of conditioned craving—an intense urge to use the substance triggered by exposure to conditioned cues. It has long been recognized that stimuli associated with drug use, frequently paired with substance consumption, can engender a conditioned craving response through classical conditioning processes (Drobes & Tiffany, 1997). Similarly, individuals with a history of trauma/PTSD and substance use may experience the frequent pairing of trauma cues (e.g., intrusive memories, exposure to trauma reminders) with substance consumption, as expounded by the two-factor learning theory (Stasiewicz & Maisto, 1993). This repeated association can lead to robust associations being formed between trauma cues and substance use (Blume, 2001). Consequently, trauma cues themselves become conditioned

stimuli capable of eliciting a conditioned craving response (Romero-Sanchiz et al., 2022). Moreover, it is crucial to recognize that the operant/two-factor theory must first establish the conditions necessary for explaining the initial pairing of trauma cues and substance use. Therefore, classical conditioning of craving to trauma cues does not develop independently but rather functions as an additional process within the broader learning framework which may also contribute to substance use maintenance. Thus, it is important to understand how operant conditioning mechanisms lay the groundwork for the frequent pairing of trauma cues and substance use, paving the way for the subsequent development of conditioned craving responses.

What unites these theories is their connection to learning theory, particularly in their reliance on the mechanisms of classical and operant conditioning to explain the maintenance of comorbid PTSD-SUD. In terms of classical conditioning, negative emotions such as fear become classically conditioned responses to stimuli that were initially neutral. Through traumatic experiences, these formerly neutral stimuli, when paired with the negative emotions elicited by trauma, acquire the ability to evoke strong negative emotions on their own. This process involves associating the neutral stimuli (a trauma reminder) with the traumatic event itself, leading to the transformation of these formerly neutral stimuli into conditioned stimuli capable of eliciting negative affect independently (Stasiewicz & Maisto, 1993). In the context of operant conditioning, substance use may serve as a coping mechanism to avoid reliving traumatic memories or to numb the emotional pain associated with the trauma. If substance use effectively reduces or removes this aversive negative affect, it is negatively reinforced. This negative reinforcement strengthens the learned association between substance use and relief from

trauma-related negative affect, making future substance use more likely in similar situations (e.g., when a trauma reminder is present; Baker et al., 2004).

Baker et al. (2004) also emphasized the role of interoceptive (i.e., internal bodily state) cues associated with negative affect, in this learning process. Indeed, within the framework of operant conditioning, these interoceptive or internal bodily state cues also serve as trauma reminders or triggers for negative emotions. Interoceptive cues can thus play a pivotal role as antecedents to behavior, signaling to individuals that the expected reward (i.e., relief from the internal negative feelings) will be attained if the behavior (i.e., substance use) is performed in the presence of the reminder (Baker et al., 2004). In this context, negative affect, or the internal interoceptive cues associated with it, could function as negative discriminative stimuli (Baker et al., 2004). These cues serve as signals indicating that the desired relief outcome will be achieved if substance use occurs at that moment. Thus, individuals learn to associate the presence of negative affect with the prospect of relief through substance use, with the relief outcome reinforcing the behavior in response to such cues.

Importantly, both theoretically (e.g., Baker et al., 2004; Khatzian, 1997; Stasiewicz & Maisto, 1993) and empirically (McHugh et al., 2017; Read et al., 2017; Romero-Sanchiz et al., 2022), research in this area suggests that individuals high in PTSD may be particularly susceptible to these conditioning processes. Indeed, the conditioned responses elicited by trauma cues, such as heightened cravings (Romero-Sanchiz et al., 2022) or a slowing of cognitions (Read et al., 2017), are likely to be more pronounced among those with severe PTSD symptoms due to their heightened emotional reactivity to trauma cues (Baker et al., 2004; McHugh et al., 2015).

Experimental Applications of Learning Theory in Recent Research on Substance Users with Trauma Histories

Experimentally, conditioned responses to trauma cues are studied in a research context using a CRP. This approach involves exposing individuals to specific stimuli in a controlled laboratory setting, aiming to provoke reactions rooted in learning and motivation (Reynolds & Monti, 2013). A typical trauma CRP involves exposure to visual and/or audio cues that describe the participant's personalized trauma experience. The established protocol for developing a personalized trauma CRP follows a two-session format. In the initial session, participants engage in a semi-structured interview (Sinha & Tuit, 2012) to recollect details of their most traumatic experience. Subsequently, these details are distilled into a standardized personalized audiovisual cue, which serves as the CRP during the second session (e.g., Coffey et al, 2002; 2006; 2010). Outcomes measured following trauma cue exposure are often affective and cognitive outcomes such as negative affect, cannabis craving, and other relevant cognitive outcomes.[1] As described above, through conditioning, substance users with trauma histories (particularly those with PTSD) may experience negative emotions and/or substance craving when exposed to cues related to their traumatic experiences. Trauma cue reactivity research is a new body of work relative to the long history of testing conditioned craving to substance cues; thus, some methodological gaps exist which have perhaps interfered with researchers conducting robust and adequately powered trauma CRP experiments. Given avoidance symptoms such as avoiding thoughts and reminders of the trauma are a

[1] Variations in methodology and common outcomes in PTSD-SUD CRP research are further discussed in Chapter 2, as the primary goal of Study 1 (Chapter 2) was to scope the CRP research literature conducted with trauma-exposed, substance using samples, and identify notable gaps in this body of literature to inform Studies 2 – 5.

requirement for a PTSD diagnosis (APA, 2022), a significant issue is the high participant drop-outs observed between initial interviews and subsequent CRP sessions (e.g., Coffey et al., 2006). Moreover, due to these considerable attrition rates and the substantial time and resources required for conducting CRP studies, researchers have difficulty in obtaining sufficiently large sample sizes during in-lab data collection, which is crucial for detecting the interactions theorized to exist between PTSD symptoms and trauma cue exposure (i.e., trauma cue effects theorized to be larger in those with PTSD diagnoses/greater PTSD symptoms). Additionally, acquiring results in a more condensed timeframe (e.g., single session) would reduce overall participant distress and minimize the resources needed to conduct this type of research.

Despite the above-listed challenges inherent in studying this population with this methodology, researchers using trauma CRPs have successfully added to the empirical literature supporting the role of conditioning processes involving trauma cues in PTSD-SUD comorbidity. Specifically, in support of two-factor learning theory predictions (Stasiewicz & Maisto, 1993), research has shown exposure to cues that are reminders of traumatic experiences (vs. reminders of emotionally neutral experiences) elicit negative affect (e.g., Tull et al., 2013). This negative affect, in line with Khatzian's (1997) self-medication hypothesis, serves as a motivating factor for individuals with more severe PTSD symptoms to use cannabis to cope (Atasoy et al., 2023). Theoretically, this coping-motivated use was initially learned through operant conditioning processes (Stasiewicz & Maisto, 1993). The frequent pairing of trauma cues with substance use then sets the stage for classically conditioned craving to develop in response to trauma reminders. Indeed, in a proof-of-concept study, exposure to trauma (compared to neutral) cues in a sample of

cannabis users with trauma histories has been shown to elicit cannabis craving, particularly among those with more severe PTSD (e.g., Romero-Sanchiz et al., 2022). Indeed, research has demonstrated strong trauma (vs. baseline or neutral cue exposure) cue-elicited substance craving and negative affect among cocaine (Tull et al., 2013), cannabis (Romero-Sanchiz et al., 2022), and alcohol users (Coffey et al., 2010). Importantly, interactive effects with PTSD symptoms have been elucidated in recent literature – specifically, Berenz and colleagues (2021) identified PTSD symptoms as a moderator of trauma-cue induced negative affect, suggesting that individuals with more severe PTSD would logically exhibit more pronounced emotional distress when confronted with trauma cues. Therefore, the central importance of negative affect and substance craving following exposure to trauma cues, particularly among those with PTSD, remains evident.

Dual Cognitive Processes and Automaticity: Clinical and Research Applications

While experimental trauma CRPs, informed by operant and classical conditioning theories, provide insight into the learning processes underlying PTSD-SUD comorbidity, cognitive dual-process models of addiction (e.g., Wiers & Stacy, 2006; Wiers et al., 2013) expand upon these principles by introducing two distinct cognitive processes – specifically, automatic processes and controlled processes – that both may be relevant to understanding this comorbidity. Automatic processes are fast, reflexive, and impulsive reactions, driven by learned associations and triggered automatically. Such automatic processes may be activated by trauma cue exposure (Read et al., 2017) and drive addictive behaviors (Wiers & Stacy, 2006) just as do more controlled cognitive processes like trauma cue-induced craving. For example, an individual may be conditioned to

associate substance use following exposure to a trauma reminder with relief from the emotional distress elicited by the trauma reminder. Thus, through learning, strong memory associations are formed between trauma cues, negative affect, substance use, and relief such that substance use becomes automatized in response to trauma cue exposure. The automatic response to these cues may lead the individual to seek immediate relief through substance use, without conscious forethought or controlled consideration of the long-term consequences. This conditioned automaticity leads to individuals finding themselves using the substance, without feeling they had even made a conscious (deliberative) decision to use (Romero-Sanchiz et al., 2022).

Several cognitive processes exist that are theoretically contributing to these processes of automaticity (Wiers & Stacy, 2006). These include attentional bias (i.e., automatic allocation of attention toward substances); interpretive bias (i.e., the tendency to interpret ambiguous information as related to substances); memory bias (i.e., tendency to retrieve substance-related information in memory), and memory accessibility (i.e., ease with which substance-related associations come to mind). Each of these biases operates differently and can impact behavior in various ways (Field & Wiers, 2012; Nelson et al., 1998). Moreover, lab-based paradigms for assessing these automatic cognitive processes generally fall into two categories: reaction time tasks, such as the Approach Avoidance Task (AAT; Cousijn et al., 2011) or the Stroop task (Read et al., 2017), and writing response tasks, such as associative memory tests (Ames et al., 2007; Neighbors et al., 2020; Pilin et al., 2022). In the context of PTSD-SUD research, theoretically, these automatic processes can be experimentally manipulated using trauma CRPs.

On the other hand, controlled cognitions are more deliberate, involving some degree of active decision making and consideration of desired consequences (Wiers et al., 2013). In the context of PTSD-SUD research, substance craving is considered a relatively deliberate cognitive process of which the individual is typically aware. In PTSD-SUD research, experiencing an increase in substance cravings following trauma cue exposure (relative to neutral cue or pre-cue baseline) is an example of this type of controlled cognitive process typically tapped through self-report.

The above-described conditioning processes at both controlled and automatic levels were integrated into Baker and colleagues' (2004) negative reinforcement theory of addiction. Specifically, Baker emphasizes the role of negative reinforcement, where substance use is reinforced by the removal of (e.g., negative reinforcement; avoidance) or expectation of a reduction of negative affective states (e.g., positive reinforcement; approach; expectancy craving). This aligns with the automatic processes described in the dual process model (Wiers et al., 2013), where impulsive reactions to cues associated with substance use are driven by learned associations and triggered automatically. Indeed, in the population of interest outlined in the present dissertation, these learned associations between substance use and relief from negative affect following a trauma reminder can lead to engagement in substance use without awareness that one has made the decision to use (Wiers & Stacy, 2006). This alignment underscores the multifaceted nature of addiction, wherein both deliberate decision-making processes and automatic responses to trauma reminders contribute to the reinforcement and perpetuation of substance use behaviors.

By comprehending the conditioning processes that occur within the context of comorbid PTSD-CUD, clinicians can tailor their interventions to address the underlying mechanisms driving both conditions. Classical conditioning, for instance, elucidates how trauma-related cues can become associated with substance use, leading to heightened cravings and the perpetuation of substance use behaviors (Stasiewicz & Maisto, 1993). Indeed, the classical conditioning of negative affect in response to trauma cues can come to activate automatic cognitive processes, perhaps driving impulsive substance use through associative learning. With this knowledge, clinicians may be better equipped to employ evidence-based interventions that target the specific conditioning processes. Furthermore, understanding the mechanistic relationship between PTSD and cannabis use is imperative for preventing relapse and promoting long-term recovery (Hill et al., 2024). By directly addressing both the cognitive and affective mechanisms that underlie both PTSD and SUD, clinicians can raise awareness among individuals with PTSD about the conditioning processes that drive their substance use (for example, learning about automatic cognitive processes) and can empower them to take an active role in their recovery. Moreover, with this knowledge, clinicians can better equip their clients with the specific targeted skills and coping strategies necessary to navigate challenging situations without resorting to substance use.

Patterns of altered cognitions among alcohol users with PTSD (Read et al., 2017) have been shown in the literature, but the effects of trauma exposure on automatic cognitions, particularly in a cannabis-using population, is underexplored. Moreover, very few studies exist examining the more controlled mechanisms (i.e., cannabis craving) that may underlie cannabis use, that may be activated in response to trauma cue exposure

(Romero-Sanchiz et al., 2022). Indeed, with both the automatic and controlled mechanisms of comorbid PTSD-SUD understudied in CUD/cannabis dependent/cannabis using individuals specifically, and the existing literature pointing to an increased risk of CUD for those with PTSD (Kevorkian et al., 2015), it is important to understand the mechanisms underlying heightened CUD risk among individuals with PTSD symptoms, particularly those mechanisms that may be activated by exposure to trauma reminders.

My dissertation had two main aims. First, I wanted to address methodological barriers that exist in trauma CRP research focused on trauma-exposed populations. Second, I wanted to use these improved trauma CRP methods to replicate and extend to cannabis users with trauma histories prior findings on the role of trauma cue-elicited affective and automatic and controlled cognitive processes as mechanisms that may contribute to CUD risk in trauma survivors and those with PTSD. While I have described background statistics and theory relevant to both trauma-exposed cannabis users and individuals with diagnosed PTSD and CUD, the population used across all studies in the present dissertation were cannabis users with trauma histories. While any observed main effects of trauma exposure are relevant to the population of cannabis users with trauma histories, I used PTSD (either as a continuous variable or using a categorical cut-off) to allow me to comment on affective and cognitive processes/mechanisms that may be unique to (i.e., PTSD main effects), or where cue effects may be particularly relevant to (i.e., PTSD x cue exposure interactions), cannabis users with higher PTSD severity or probable PTSD diagnoses.

Summary

Populations exposed to trauma face a heightened risk of developing CUD, a complex phenomenon influenced by various factors, including learning and conditioning processes. Within the framework of classical conditioning, trauma-related cues become associated with cannabis use, fostering the development of trauma cue-elicited cannabis craving and substance-seeking behaviors. Additionally, operant conditioning mechanisms may reinforce substance use as individuals seek relief from distressing symptoms (e.g., negative affect) associated with trauma exposure. By understanding the interplay between trauma exposure and PTSD symptoms on outcomes influenced by conditioning, clinicians can better identify and address the needs of trauma-exposed populations, offering tailored interventions aimed at mitigating the risk of substance misuse.

Dissertation Aims

My dissertation's primary goal was to investigate the affective and cognitive mechanisms that might contribute to high rates of cannabis use and CUD among those with PTSD. Further, I explored how trauma cue exposure might activate those mechanisms, particularly among those with PTSD/higher PTSD symptoms. Specifically, I experimentally tested the effects of trauma exposure and PTSD symptomatology/PTSD group on affect and on both deliberate (i.e., cannabis craving) and automatic (i.e., cannabis approach bias, memory accessibility of cannabis information) cognitive processes relevant to cannabis use across methodological variations of the traditional CRP. I began by scoping the literature on cue reactivity experiments in a population of substance users with trauma histories, followed by four experimental studies aimed to test if methodological variations in trauma CRPs activate both automatic and deliberate

theoretically relevant conditioned cognitive and affective processes among trauma-exposed cannabis users.

Study 1

Entitled "*A scoping review of the literature on trauma cue-induced substance craving in substance users with trauma histories or PTSD*", Study 1 (DeGrace et al., 2022) reviewed the use of CRPs in trauma-exposed, substance using populations across the extant literature. Study 1 filled a gap in that no work existed which had scoped and identified patterns in cue reactivity research among substance users with trauma histories or PTSD. The review identified 28 studies that assessed relevant outcomes (e.g., cognitive, physiological) following exposure to a trauma CRP. Study 1 aimed to identify patterns of responses to various cue types (e.g., neutral, substance, stress cues). Moreover, I sought to scope variations in CRP methodologies and identify any work that included cannabis users as the primary substance of interest.

Study 2

Entitled "*Do we really need two sessions? The use of a structured interview as a trauma cue reactivity paradigm*", the aims of Study 2 (DeGrace et al., 2023a) were two-fold. First, following my scoping review, I wanted to methodologically address the common issue of attrition in trauma cue reactivity studies, particularly among those with PTSD. Indeed, researchers using the gold-standard two-session method (Coffey et al., 2006) in PTSD-SUD populations have encountered high dropout rates due to the need to return for a second session. Second, I wanted to replicate common patterns of reactivity identified in my scoping review using this variation in cue reactivity methodology. Thus, I utilized a single-session semi-structured interview as a trauma CRP and hypothesized it

would elicit greater cannabis craving and negative affect, and lesser positive affect, compared to a neutral semi-structured interview. I also included PTSD symptoms (continuous) and a PTSD x trauma cue interaction as predictors of the three outcomes. I expected these results to function as a preliminary proof-of-concept for the single-session trauma CRP, with the trauma cue and PTSD symptomatology interacting to elicit the greatest degree of reactivity.

Study 3

Entitled "*Do trauma cue exposure and/or PTSD symptom severity intensify selective approach bias toward cannabis cues in regular cannabis users with trauma histories?*", the aims of Study 3 (DeGrace et al., 2023b) were also two-fold. As in Study 2, Study 3 tested the use of the single-session trauma CRP, though on a different outcome. Importantly, while Study 2 provided evidence for the use of our single-session CRP for deliberate cannabis-related processes (e.g., craving), I wanted to test if the preliminary efficacy of this CRP functioned for automatic processes as well. Specifically, I tested how one variation of automatic cannabis cognitions (specifically, cannabis approach bias) is influenced by trauma cue exposure, PTSD, and their interaction. Indeed, theoretically, a pattern of changes in automatic cognitions among trauma-exposed populations should occur following trauma (vs. neutral) cue exposure and amongst those with greater PTSD symptom severity (see Study 1). However, this had never been tested in a trauma-exposed, cannabis-using population prior to Study 3. I hypothesized that trauma (vs. neutral) cues, would elicit greater cannabis (vs. neutral) approach bias, particularly among those with greater PTSD symptom severity (continuous).

Study 4

Entitled "*Effects of trauma cue exposure and PTSD on affect and craving in cannabis users with trauma histories: Use of expressive writing as an online cue reactivity paradigm.*", Study 4 had a different methodological aim than that of Studies 2 and 3. Specifically, in Study 4 we sought to test the use of an online, fully remote expressive writing task as a trauma CRP. As in Study 2, we similarly began initial validation of this online CRP as a proof-of-concept, in that the expressive writing task should elicit the same kinds of affective and cognitive reactivity as the gold-standard, two-session CRP (e.g., Coffey et al., 2010) and the single-session CRP from Study 2. Thus, we hypothesized the trauma expressive writing task would elicit greater cannabis craving and negative affect, and lesser positive affect, compared to those assigned to complete a neutral expressive writing task. Moreover, as hypothesized in Studies 2 and 3, we expected this effect to be greatest among those with (vs. without) PTSD. Finally, while we cited high attrition for the reasoning behind our initial validation of the single-session CRP in Study 2, the online CRP had an additional benefit. As shown in Study 2 and Study 3, adequate power is needed to detect interactions between trauma cue exposure and PTSD symptoms, as they are typically small in magnitude. I reasoned a larger sample size recruited online would give us the best opportunity to detect such interactions. Further, I chose to dichotomize PTSD into a categorical predictor to maintain clinical relevance and in line with prior work indicating PTSD is best conceptualized as a categorical (vs. continuous) variable (e.g., Ayer et al., 2011; Steenkamp et al., 2012). Specifically, I hypothesized that assignment to the trauma (vs. neutral) expressive writing task, probable PTSD (vs. no PTSD), and their interaction

effect would be associated with increased cannabis craving, increased negative affect, and decreased positive affect.

Study 5

Entitled "*Expressive writing about one's trauma increases accessibility of cannabis information in memory among trauma-exposed cannabis users.",* Study 5 investigated the use of the remote, online trauma expressive writing task as used in Study 4, on automatic cannabis-related cognitions – specifically, the accessibility of cannabis-related information in memory. As in Study 2 to Study 3, I wanted to ensure I tested the expressive writing task's influence on not only controlled cognitive processes (i.e., craving), but more automatic processes as well. I hypothesized that the trauma (vs. neutral) expressive writing task would lead to greater accessibility of cannabis information in memory, and that cannabis information would be more accessible in memory among those with (vs. without) PTSD. Moreover, I hypothesized the cue exposure effect (trauma > neutral) to be greater among those with (vs. without) probable PTSD (i.e., interaction effect). Further, Study 5 allowed me to add to the literature by testing the use of the expressive writing task as not only effective in eliciting trauma cue-induced cannabis craving and negative affect, but more reflexive cognitions as well. Importantly, no studies to date have tested the main or interactive effects of trauma cue exposure and PTSD on cannabis accessibility in memory prior to Study 5.

Dissertation Outline

Each of the above-mentioned five studies are presented in turn in the upcoming chapters. Study 1 can be found in Chapter 2, Study 2 in Chapter 4, Study 3 in Chapter 6, Study 4 in Chapter 8, and Study 5 in Chapter 10. Transitions between studies can be

found in Chapters 3, 5, 7, and 9, respectively. An integrative discussion of my dissertation's findings can be found in Chapter 11.

CHAPTER 2. STUDY 1 – A SCOPING REVIEW OF THE LITERATURE ON TRAUMA CUE-INDUCED DRUG CRAVING IN SUBSTANCE USERS WITH TRAUMA HISTORIES

The manuscript prepared for this study is presented below. Readers are advised that Sarah DeGrace, under the supervision of Dr. Sherry Stewart, was responsible for data extraction with the help of a second coder, Catherine Standage. Sarah interpreted the findings of the scoping review, wrote the initial draft of the manuscript, and received and incorporated feedback from her co-authors. The manuscript then underwent peer-review. Sarah responded to reviewers and led each round of revisions. The manuscript was accepted to be published as a chapter in the edited book *Stress Related Disorders* on February 21st, 2022 and was published on April 5th, 2022. See Appendix A for copyright permission from the publisher to include this paper in the thesis. The full reference is as follows:

DeGrace, S., Romero-Sanchiz, P., Standage, C., & Stewart, S. H. (2022). A scoping review of the literature on trauma cue-induced substance craving in substance users with trauma histories or PTSD. In Ovuga, E. [Ed.], *Stress Related Disorders*. InTechOpen. https://doi.org/10.5772/intechopen.103816

Abstract

Among trauma-exposed individuals, substances may initially be used as a means of obtaining symptom relief following exposure to trauma reminders. Repeated pairing of trauma cues with substance use may lead to the development of classically conditioned craving to trauma cues – a process which may contribute to substance use maintenance. Conditioned craving following cue exposure can be studied in-lab through the use of the cue-reactivity paradigm (CRP). To map cue-reactivity research conducted with trauma-exposed substance users, we aimed to synthesize research which studied our population of interest, employed the use of a cue-reactivity paradigm, and measured craving as an outcome. Three databases (PubMed, PTSDPubs, and PsycInfo) were searched using keywords. Twenty-eight studies met our inclusion criteria. Four key themes are discussed in relation to our review of these scoped studies: 1) craving as an outcome; 2) methodological subtypes across paradigms; 3) affect as an additional outcome or as a mediator of craving; and 4) CRPs as an intervention outcome assessment tool. Overall, there is strong evidence for CRPs as useful means of eliciting craving in the lab, in response to trauma cues. Such paradigms may also be useful as an additional measure of intervention efficacy beyond symptom reduction. Our scoping review points to the need for a meta-analysis to determine the magnitude of the trauma cue-induced craving effect in substance users with trauma histories, and to determine significant moderators (e.g., PTSD symptom severity) and mediators of this effect (e.g., negative affect).

Keywords: cue-reactivity, substance use, post traumatic stress disorder, trauma, craving

Introduction

Posttraumatic stress disorder (PTSD) is an often-debilitating mental disorder which may occur following trauma exposure (American Psychological Association [APA], 2013). PTSD is characterized by four diagnostic clusters: 1) re-experiencing the traumatic event (e.g., recurrent memories, dreams, or flashbacks); 2) symptoms of avoidance (e.g., efforts to evade trauma reminders); 3) arousal (e.g., hypervigilance, sleep disruptions); and 4) negative cognitions and mood (e.g., self-blame) (APA, 2013). Substance Use Disorder (SUD) is another psychiatric disorder characterized by eleven possible symptoms which involve negative consequences arising from one's substance use and inability to control one's substance use (APA, 2013). In the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (the DSM-5; APA, 2013), craving, the often-intrusive desire to use the substance, was added as one of the 11 symptoms characterizing an SUD (APA, 2013).

PTSD often co-occurs with SUD. Research has documented high rates of comorbidity between PTSD and alcohol use disorder (AUD; Smith & Cottler, 2018), cannabis use disorder (CUD; Bonn-Miller et al., 2022; Walsh et al., 2014), and other SUDs (Khoury et al., 2010). The prognosis of comorbid PTSD-SUD is worse than either disorder alone (Berenz & Coffey, 2012) with comorbid PTSD-SUD leading to greater functional impairment in comparison to those with only PTSD or an SUD (McCauley et al., 2012).

It has been suggested that PTSD and SUD are likely functionally related to one another (e.g., Jacobsen et al., 2001) in comorbid individuals. While the precise underlying mechanisms are not well understood, there are several learning theories that

may help explain the high rates of substance misuse in people with trauma histories and help us understand the high comorbidity of PTSD with SUD. The first is two-factor learning theory which was originally developed by Mowrer to explain the acquisition and maintenance of phobias (Mowrer, 1947) and which has more recently been applied by Stasiewicz and Maisto (1993) to the acquisition and maintenance of SUDs. Two-factor learning theory applies a combination of classical conditioning and operant conditioning mechanisms to the development and maintenance phases of these disorders, respectively. Applying this theory to the co-occurrence of PTSD and SUDs in traumatized individuals, trauma-relevant cues that were paired with the original traumatic experience (e.g., loud noises of gunfire paired with witnessing a comrade fatally injured in wartime) are thought to come to elicit negative affect through the process of classical conditioning (Stasiewicz & Maisto, 1993). Future exposures to the trauma cue alone (e.g., loud noises alone) motivate avoidance/escape behavior, including substance misuse, to reduce the associated negative affect and thereby experience relief (Stasiewicz & Maisto, 1993). Avoidance/escape behaviors like substance misuse are thus negatively reinforced in individuals with trauma histories/PTSD as they remove the aversive experience of negative affect. Therefore, substance misuse is maintained as a self-medication type of coping response through operant conditioning processes where a behavior is repeated when it is followed by desirable consequences, in this case relief from negative affect.

Another theory that is relevant to understanding the links of trauma/PTSD with SUD involves the role of classical conditioning in the development of conditioned craving – a strong urge to use the substance in response to exposure to the conditioned cues. It has long been known that drug-related stimuli that are frequently paired with drug

taking can come to elicit a conditioned craving response through the process of classical conditioning (Drobes & Tiffany, 1997). For example, a needle and other drug use paraphernalia that are frequently paired with heroin use can come to elicit craving when presented alone, for an injection drug user. Similarly, for a substance user with a trauma history/PTSD, the frequent pairing of trauma cues (e.g., intrusive memories of the trauma, exposure to external trauma reminders) with substance use, as explained by the two-factor learning theory above (Stasiewicz & Maisto, 1993), can come to create strong associations between trauma cues and substance use (Blume, 2001). The result is that such trauma cues can become conditioned stimuli that elicit a conditioned craving response when presented on their own (Romero-Sanchiz et al., 2022). For example, if a young woman with sexual-assault-related PTSD drinks alcohol each time she has an intrusive memory about her sexual assault, such trauma cues can come to elicit a strong craving for a drink, which may motivate her alcohol seeking and maintain her alcohol use. The study of the above putative mechanisms under controlled, laboratory conditions is crucial for better understanding of the intertwined relationships between trauma/PTSD and substance misuse. Specifically, the use of cue-reactivity paradigms allows researchers to examine how substance-related and trauma cues may come to elicit craving and/or negative affective responses through the conditioning processes described above.

The CRP is broadly defined as a lab-based method in which participants are exposed to a set of stimuli meant to elicit a 'reactivity' response – i.e., a change from baseline in response to the stimulus (Reynolds & Monti, 2013). In the context of addictions research, stimuli may be substance-related cues, such as a syringe or other drug-related paraphernalia for an injection drug user (Carter & Tiffany, 1999); these

stimuli serve as analogues for real life stimuli which may evoke a craving response outside of the lab. Indeed, research in this area has shown that relevant drug-related cues presented in the lab can elicit a heightened craving response among substance users (Drobes, 2002; Witteman et al., 2015). More recently, cue-reactivity paradigms have been used to study conditioned craving as a possible mechanism underlying the relationship between trauma/PTSD and SUD (Coffey et al., 2010; Tull et al., 2013). Indeed, extant research has shown that in-lab exposure to cues representing trauma reminders (e.g., a video of a violent crime) activate both substance-related craving responses as well as increased negative affect (Romero-Sanchiz et al., 2022).

Craving has been measured in a number of ways in substance- and trauma-related cue-reactivity research, including with subjective self-report measures, such as the Desire for Drug Questionnaire (Franken et al., 2002), and measures specific to the substances used, such as the Alcohol Urge Questionnaire (Bohn et al., 1995) and the Marijuana Craving Questionnaire (Heishman et al., 2009). Craving has also been measured more objectively in cue-reactivity studies, albeit less commonly than via self-report. Specifically, physiological measures, such as salivary flow and heart rate monitoring, are often used as a more objective proxy measure of craving (Sayette et al., 2000). Craving has also been further differentiated into reward-related craving (i.e., a desire for reward or stimulation from a substance) and relief-related craving (i.e., a desire for reduction in tension or negative affect from using a substance) using certain self-report measures (e.g., Heishman et al., 2009).

While cue exposure paradigms are homogenous in their goal to elicit some form of reactivity (e.g., change from baseline in craving or emotional state in response to the

stimulus), the types of cues and paradigms used in this area of research have varied widely. For example, cues may be standardized across participants in the study or may be personalized to the individual's own trauma history details; cues may be presented through the use of script-driven imagery (i.e., audio recordings, such as a retelling of a traumatic event) or in-vivo (i.e., physical objects, such as drug paraphernalia); and cues may be photo or video stimuli (i.e., a video of an assault).

Indeed, it is evident that cue-reactivity paradigms vary widely in design, are used in an expansive variety of contexts and with a wide range of populations, with many different outcomes used to capture cue-reactivity effects. Thus, in this chapter, we intend to scope the extant cue-reactivity literature in the context of PTSD-SUD comorbidity research to identify patterns and variations in methodology, measures, and outcomes used in this growing field.

Aims and Objectives

Our first aim was to examine how cue-reactivity paradigms have been used in samples of substance users with trauma histories. Specifically, we were interested in how these studies lead to a further understanding of the mechanisms underlying comorbid PTSD-SUD. Second, we intended to examine the different types of cues used within the cue-reactivity paradigm as well as the specific effects, strengths, and weaknesses of variations in paradigm design. Specifically, we compared the merit of personalized vs. non-personalized cues, as well as other cue variations, in PTSD-SUD cue reactivity research (e.g., *in-vivo*, imagery-based). Third, we sought to assess the use of several measures of reactivity that have been examined using the cue-reactivity paradigm (i.e., craving [subjective, objective], negative affect) used in PTSD-SUD research. Lastly, we

examined the types of participants who have been studied using cue-reactivity methodology (e.g., trauma-exposed vs suffering from PTSD).

Method

The present scoping review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines appropriate for a scoping review. Specifically, we used the PRISMA Scoping Review checklist (Tricco et al., 2018).

Inclusion and Exclusion Criteria

Studies were included if they used an experimental design, if they utilized a cue-reactivity paradigm, and if self-reported craving was assessed following the cue-reactivity paradigm[2]. Furthermore, the population of interest had to include individuals who had experienced a traumatic event consistent with Criterion A of a DSM-5 PTSD diagnosis (APA, 2013). Alternatively, PTSD symptoms must have been assessed for each participant. Additionally, it was required that participants report on their substance use[3].

We excluded studies that were not written in English, or if humans were not the research participants. We did not exclude grey literature. Specifically, we included theses and dissertations to gather the full scope of research in this area and to reduce publication bias.

Literature Search

The databases PsycInfo, PubMed, and PTSDPubs were searched to identify studies of interest. Each search was conducted using a Boolean search logic and relevant

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[2] Post-cue substance craving was a requirement for inclusion in the scoping review to ensure differences in craving responses could be conceptualized as a function of cue reactivity methodology, cue type, etc. Post-cue negative affect was not a requirement for inclusion in the interest of capturing as many cue-elicited craving studies as possible.

[3] Substance use, but not the presence of a Substance Use Disorder, was required for inclusion in the scoping review to include as many studies as possible and to examine variations in substance use and substance use problems in this body of literature.

keywords: (“PTSD” OR “post traumatic stress disorder” OR “posttraumatic stress disorder” OR “post-traumatic stress disorder” OR “trauma”) AND (“cue” OR “cue exposure” OR “cue-reactivity” OR “conditioned response” OR “stimuli”) AND (“substance” OR “substances” OR “alcohol” OR “drug” OR “drugs” OR “cocaine” OR “cannabis” OR “marijuana” OR “opioids” OR “opiates” OR “tobacco” OR “nicotine”) AND (“craving” OR “urge”). There were no search restrictions based on year of publication or language.[4]

Results

Screening of Search Results

One-hundred-and-fifty-eight studies were initially imported into Covidence, a literature screening software. After duplicates were removed by Covidence, 128 studies remained. Abstracts of all studies were screened by two independent raters (SDG and CS) who removed all irrelevant studies; a moderate rate of agreement of 74% was achieved (McHugh, 2012). A third screener (PRS) aided in resolving any conflicts between the two raters. A total of 28 studies met our final inclusion criteria (see Figure 1).

Data Extraction

The data were extracted into a spreadsheet including information on the study sample, sample characteristics, outcome measures, cue-reactivity methodology, hypotheses/aims, outcomes of interest, and general findings[5,6]. A quality assessment and risk of bias assessment were not conducted, as these are not typical in scoping reviews

[4] Non-English language studies were captured in our search and were excluded if an English translation could not be found.
[5] Generally, most studies included did not have participants report on level of substance use involvement. Thus, we could not readily examine its impact. Future studies should assess level of substance use involvement and examine/control for its potential influence on cue-induced craving.
[6] Effect sizes were also typically not reported and thus these data were not extracted. Future work should calculate the magnitude of these effects and examine their clinical relevance (i.e., via a meta-analysis).

(Peters et al., 2015). The extracted data were then synthesized into common categories by the first author to further examine themes in the scoped research.

Summary of Included Studies

Cue-reactivity Paradigm. Script-driven imagery cues were the most common cue paradigm used in the present sample of studies (n = 20). These were often paired with a substance-related in-vivo cue (n = 9), with substance-related in-vivo cues used independently only two studies (n = 2). One study used a semi-structured interview as a cue (n = 1) where participants described their most traumatic experience verbally. Standardized video cues were employed in n = 2 studies. Photographic cues were used in n = 1 study which took place in an fMRI environment. Three (n = 3) studies utilized photographic cues as part of what we are calling "task-based" cue-reactivity paradigms, i.e., cognitive tasks that included substance or trauma-related stimuli. Specifically, Garland and colleagues (2019) used an Emotional Regulation Task as a cue exposure paradigm where participants sorted and viewed negative images. Kaag et al. (2018) also utilized a sorting task as a cue exposure where participants sorted cocaine and neutral photos. Finally, Beckham and colleagues (Beckham et al., 1996) used the Stroop colour-naming task (Scarpina & Tagini, 2017) with combat-related words as a cue exposure. Overall, 22 studies employed only personalized cues, 5 studies employed only standardized cues, and one study (Kwako et al., 2015) employed both personalized cues and standardized cues.

Craving and Other Reactivity Measures. All studies used subjective self-report measures of craving as a measure of reactivity (n = 28); this was an inclusion criterion for this scoping review. However, many did include objective craving measures in addition

to subjective measures (i.e., salivation, heart rate; n = 9). Other reactivity measures assessed included affect (n = 14), subjective stress (n = 6), objective stress (i.e., cortisol; n = 3), attentional/memory tasks (n = 3), and neural activation (n = 3).

Substances. Types of substances used/misused by participants in the study were alcohol (n = 17), cocaine (n = 6), nicotine (n = 3), heroin (n = 1), opioids (n = 1), and any substance (n = 4). It is important to note that some studies (n = 4) allowed for combinations of specific drugs (e.g., individuals who use alcohol and/or cocaine were recruited for one study).

Cue Type. Studies identified in the present scoping review employed the use of several types of cues. Specifically, neutral cues (n = 24; e.g., brushing your teeth), trauma cues (n = 23; e.g., a physical assault), substance cues (n = 14; i.e., cannabis paraphernalia), stress cues (n = 5; a presentation at work), and social cues (n = 1; speaking with a friend; i.e., Dutton, 2017) were used. The average number of cue types used per study were 2.36 (SD = .73).

Comparator. The majority of studies utilized pre-cue baseline as a comparator for their measures of reactivity (n = 22); a minority only compared reactivity data across cue types (i.e., comparing neutral vs. trauma responses; n = 6). However, several studies used a combination of comparators by comparing to baseline data and across cue types as well (n = 12).

While we have summarized the key components of included studies here, a full summary of each study across the coded variables of interest is available in Appendix A.

Population Considerations

Populations of interest were largely adults who were assessed for PTSD symptoms/diagnoses (n=15) and/or trauma history (n=13), and substance use (n=28). Participants across studies were more often male (*M* = 61.5%, SD = 24.6), with n=5 studies recruiting only males (Beckham et al., 1996; Elton et al., 2015; Kaag et al., 2018; McGuire et al., 2018; Stauffer et al., 2019) and one study recruiting only females (Garland et al., 2019). Four studies included only veterans (Badour et al., 2017; Beckham et al., 1996; McGuire et al., 2018; Ralevski et al., 2016), and 12 included only patients in treatment for SUD (e.g., Coffey et al., 2006; n = 10), PTSD (n = 1), or both (n = 1). Four studies examined emerging adult college students specifically 0and one study recruited low-income, inner-city adults (Vujanovic et al., 2018a).

All studies included participants with either PTSD (n = 14) or those who had been exposed to a lifetime trauma (n = 10), or both with PTSD and/or trauma histories assessed continuously (n = 4). PTSD was assessed but not required for some studies, with others requiring trauma exposure but not a PTSD diagnosis (see McHugh et al., 2017; Saladin et al., 2003). To assess for PTSD, most studies used some form of validated structured interview (n = 25), such as the The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), the Structured Clinical Interview for DSM-5-Revised (SCID-5-RV; First et al., 2015), and the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). Those studies examining trauma-exposed individuals typically administered a questionnaire to assess trauma history (n = 3), such as the Trauma History Questionnaire (Hooper et al., 2011) or the Life Events Checklist (LEC;

Gray et al., 2004), as well as continuous measures of PTSD symptoms, such as the PTSD Checklist for DSM-5 (PCL-5; Blevins et al., 2015).

Substance use among the study populations was similarly measured. Specifically, the majority of studies (n = 18) required an SUD as inclusion criteria (e.g., Coffey et al., 2010; Tull et al., 2013), with some using inpatients receiving treatment for PTSD, SUD, or both (n = 12; e.g., Kwako et al., 2015; Nosen et al., 2014). Fewer studies required less extreme forms of substance use, such as occasional drinking (n = 6) (see Read et al., 2017; Trautmann et al., 2018) and other cut-off points for use of various substances (n = 3; e.g., Beckham et al., 2007). To assess for the presence of an SUD, most studies (n =18) used structured interviews such as the Diagnostic Interview Schedule for Children (C-DIS IV; Segal, 2010) or the SCID-5-RV (First et al., 2015), but others used shorter self-report measures, such as the Alcohol Use Disorders Identification Test (AUDIT; n = 10) (Saunders et al., 1993).

The Cue Reactivity Paradigm

Personalized vs. Standardized Cues. Many of the studies employed personalized cues within their cue-reactivity paradigms, either through interviews where they obtained information about a participant's worst traumatic experience and transcribed the interview into an imagery-based cue (Coffey et al., 2002) or utilized the participants' preferred substance as part of an in-vivo cue (Nosen et al., 2012). The vast majority of these studies found significant reactivity results in their research, specifically noting that trauma, substance, and/or stress-related cues elicited greater craving responses e.g., greater change from baseline) compared to neutral cues (n = 24 of 28). Even interviews in which the participant described their worst traumatic experience functioned well as a

personalized cue for eliciting reactivity on craving measures (McGuire et al., 2018). Photo, video, or task-based cues were standardized rather than personalized (e.g., Garland et al., 2019; Trautmann et al., 2018). Studies utilizing standardized cues did find cue-reactivity effects on their outcomes, with some caveats. For example, Trautmann and colleagues (2018) found craving increased in response to their trauma film cues only among females. Other studies using standardized, non-personalized cues that used control groups found cue-reactivity effects (craving and neural activation, respectively) only in substance-using (Kaag et al., 2018) and trauma-exposed (Winokur, 2011) experimental groups vs non-using/non-exposed controls.

Task-Based Cues. Studies that utilized photographic cues as part of task-based cue paradigms found support that their paradigms functioned as effective CRPs, even though craving was not the primary outcome of interest. For example, Garland and colleagues (2019) showed participants trauma-related images and asked them to either simply view the photos or reappraise the photos by reinterpreting the photo's meaning to regulate their emotions in reaction to the photo. Following this task, relief craving increased for those in the view (but not reappraise) condition; this increase was associated with the number of adverse childhood experiences to which participants reported having been exposed. Similarly, Beckham et al. (1996) utilized a Stroop colour naming attentional task (Scarpina & Tagini, 2017) with trauma-related words with a veteran sample of cigarette smokers. Results demonstrated trauma words, relative to neutral words, led to greater cigarette craving as well as more withdrawal symptoms.

Subjective and Physiological Craving

One of our inclusion criteria was the measurement of craving following a cue-reactivity paradigm. Accordingly, all studies included a measure of craving, with all studies including a measure of subjective craving. Many studies measured craving using a Visual Analog Scale (VAS) or various Likert-type rating scales. Among those which examined craving changes from baseline by cue type, subjective craving responses were highest following trauma-related cues compared to substance, stress, and/or neutral cues (n = 9). Studies which did not use trauma cues found substance-related cues elicited greater craving compared to neutral cues (n = 3). In those studies that used trauma cues, substance cues, and neutral cues (n = 9), typically trauma cues elicited the greatest craving, followed by substance cues, and then neutral cues. Interestingly, studies where trauma imagery cues were paired with in-vivo substance cues (n = 5) found craving was higher for these combined cues compared to trauma imagery cues alone, as well as compared to neutral imagery and in-vivo substance cue combinations (e.g., Coffey et al., 2010; Coffey et al., 2002).

While our inclusion criteria did not specifically require objective assessment of craving, the frequent use of salivation, heart rate, and other measures of physiological reactivity suggests a brief summary of this work is warranted. Most studies which included physiological/objective craving measures did so by measuring salivary flow (n = 5). Coffey et al. (2010) found a significant increase in salivation following trauma and alcohol cues relative to neutral cues. Nosen et al. (2012) found an increase in salivation following alcohol in-vivo cues as well, and this increase was greatest when paired with trauma imagery cues. Two intervention studies examined craving pre- and post-treatment

and found a significant decrease in salivation during trauma cue exposure at post-treatment compared to pre-treatment (Nosen et al., 2014; Zambrano-Vazquez et al., 2017). Interestingly, one study did not find any significant effect of trauma cue imagery and in-vivo alcohol cue exposure on salivary flow among depressed individuals but did among those with PTSD (Bing-Canar et al., 2021). Finally, one study which used heart rate as an objective measure of craving found in-vivo alcohol cues significantly increased heart rate relative to neutral water cues among males with comorbid PTSD-AUD (Stauffer et al., 2019).

Treatment Outcome Studies

Seven studies examined outcomes of pharmacological or psychotherapeutic treatment in clinical populations, utilizing cue-reactivity as a secondary outcome measure or adjunct to symptom measures. Two studies examined the effectiveness of pharmaceuticals as treatment for comorbid PTSD-SUD. Specifically, in a pre-clinical lab-based study, Stauffer et al. (2019) examined the use of intranasal oxytocin (20 IU and 40 IU) vs. placebo in males with comorbid PTSD-AUD. Each participant took part in each condition across three counterbalanced sessions. Following drug or placebo administration, participants were exposed to in-vivo cues of their preferred alcoholic beverage and water. Both heart rate and subjective craving response increased following alcohol in-vivo cue exposure relative to neutral in-vivo (water) cues, but neither dose of oxytocin reduced cue-induced heart rate or subjective craving responses relative to placebo. Similarly, Kwako et al. (2015) combined the Trier Social Stress Test (Kirschbaum et al., 1993) with personalized in-vivo alcohol cues, and conducted separate sessions involving guided imagery scripts of stress, alcohol, and neutral cues. All

experimental cues increased subjective craving responses and blood cortisol when compared to the neutral cues. However, they found no effect of the neurokinin-1 receptor antagonist aprepitant (125mg/day) vs. placebo on subjective craving in response to stress or alcohol vs. neutral cues; however, participants who received the aprepitant had reduced cortisol levels during the presentation of the stress cue.

Five studies examined the effects of several psychotherapeutic interventions on cue-elicited craving as well as distress, PTSD symptoms, and resilience. Coffey and colleagues (2010) examined the effects of trauma-based imaginal exposure vs. relaxation using a cue-reactivity paradigm to assess trauma cue-reactivity (i.e., craving); they showed a decrease in craving to the trauma-alcohol cue combination only among those enrolled in prolonged exposure (PE) therapy but not among those in the relaxation condition. However, craving following the trauma only cue decreased relative to baseline among both intervention groups. Similarly, two studies (Nosen et al., 2014; Zambrano-Vazquez et al., 2017) assessed the merits of PE therapy in comparison to a health/lifestyle therapy using craving to a cue-reactivity paradigm as an outcome measure. One study (Nosen et al., 2014) found both healthy lifestyle (control) and trauma cue-exposure treatments led to a decrease in craving responses to trauma imagery and in-vivo substance cues compared to pre-treatment baseline responses. While the other study (Zambrano-Vazquez et al., 2017) only included those enrolled in the trauma cue-exposure therapy group in analyses, they too found a decrease in cue induced craving when exposed to trauma and substance cues from pre- to post-treatment. Additionally, a study (McGuire et al., 2018) that examined trauma cue exposure during cognitive processing therapy, a form of cognitive behavior therapy, in veterans with comorbid

PTSD-SUD, also found a decrease in trauma cue-induced craving from pre- to post-treatment, the magnitude of which was associated with degree of increase in resilience and degree of decrease in PTSD symptoms. Finally, one study (Badour et al., 2017) used in-vivo cues as part of the COPE (Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure) therapeutic intervention. Specifically, Badour et al. (2017) combined PE therapy to trauma cues with CBT for substance disorders and in-vivo substance cue presentations. They examined cue-induced craving at each in-vivo substance cue exposure session. Craving significantly decreased across sessions, and this decrease was associated with a concurrent decrease in PTSD symptom severity and distress.

Neural Activation

Three studies combined fMRI and a cue-reactivity paradigm. One study (Elton et al., 2015) examined neural activation during the presentation of stress, neutral, and substance-related cues among cocaine-dependent individuals with and without childhood maltreatment histories. Degree of craving to the stress cues predicted activation of the rostral anterior cingulate cortex to a lesser extent in the participants with maltreatment histories. The authors interpreted this to suggest that childhood maltreatment interferes with a key mechanism for resolving conflict and responding adaptively to stress (Elton et al., 2015). Conversely, degree of craving to the substance-related cues was associated with activation of the supplemental motor area and the visual cortex to a greater extent in those with maltreatment histories. The authors interpreted this latter finding to suggest that childhood maltreatment enhances the anticipatory reward response to substance cue exposure (Elton et al., 2015). Further, during substance cue presentation, another study

(Stauffer et al., 2019) found childhood trauma histories among substance users was significantly associated with increased activation of the frontal striatal circuit and the amygdala. However, a third study (Kwako et al., 2015) did not find any psychological correlates of neural activation during the presentation of substance-related vs. neutral stimuli in a sample of adults with comorbid PTSD-AUD. It is difficult to know if this failure to observe an effect of cue exposure on neural activation was due to an ineffective manipulation since craving responses were not measured.

Affect

Fourteen studies included a measure of affect as part of their evaluation of cue-reactivity. Eleven of these studies examined both positive and negative affect, and three examined negative affect only. The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was overwhelmingly used as the standardized measure of this variable (n = 10), although other measures were used as well, such as the Affect Grid (Russell et al., 1989) (n = 2). Among the majority of studies (n = 9), negative affect increased following stress and trauma-related cues (e.g., Ralevski et al., 2016). In those studies which also examined positive affect, positive affect tended to decrease following stress and trauma-related cues (e.g., Dutton, 2017; Zaso & Read, 2020) but this was not always consistent. For example, Coffey et al. (2006) did not find any statistically significant differences in positive affect across cue types. Interestingly, one study reported that substance-related cue exposure increased both positive and negative affect, and this ambivalent response was associated with the strongest substance cravings (Beckham et al., 2007).

Discussion

The primary aim of this scoping review was to map the use of CRPs in PTSD-SUD research among substance users with trauma histories and/or PTSD. Specifically, we sought to summarize the characteristics of the samples, examine outcomes measured following the CRP (e.g., subjective/objective craving, negative affect), and map how such paradigms vary across the literature on several dimensions (e.g., cue type, personalization/standardization, cue presentation). Furthermore, we aimed to assess the consequences of methodological differences in cue-reactivity research. While prior literature has summarized cue-reactivity methodology in substance use research (e.g., Betts et al., 2021) and one group has briefly summarized cue-reactivity research in a comorbid PTSD-AUD population as part of a broader review of mechanisms involved in this form of comorbidity (Vujanovic et al., 2019), we aimed to map the use of CRPs in a way which could lead to further understanding of conditioned craving as a mechanism in the maintenance of comorbid PTSD-SUD. Specifically, our systematic scoping of the literature identified 28 studies that assessed craving following a CRP in a population of substance users with trauma histories and/or PTSD.

Our scoping review revealed wide variations in methodologies used to examine cue-induced craving. Specifically, characteristics of study samples, the methodological details of the CRP, and the types of outcomes assessed, all varied broadly. We have identified four themes in the studies through our scoping of the literature that may help elucidate commonalities and important distinctions across the identified studies: 1) increases in craving following trauma cue presentation; 2) the use of methodological subtypes of cue-reactivity paradigms; 3) affect as a outcome and possible mediator of

craving in cue-reactivity research; and 4) the CRP as an adjunct outcome measure in intervention research.

From the above literature review, it is evident that craving has been repeatedly shown to increase following exposure to certain cues in substance users with trauma histories and/or PTSD. In particular, trauma cues tend to elicit the greatest increase from baseline in craving responses when compared to substance-related and neutral cues. This was true across studies using both personalized (e.g., Vujanovic et al., 2018a) and standardized cues (e.g., Trautmann et al., 2018). However, this effect was typically magnified when a combination of trauma-related imagery and in-vivo substances cues were paired together (e.g., Nosen et al., 2014; Saladin et al., 2003). The latter finding supports the notion that 'cue chains' may be an effective means of bolstering cue-reactivity responses (Drummond, 2000). Indeed, while direct comparison across all studies is made difficult due to variable methodologies across studies, it appears that trauma cues, and in particular, trauma and substance cue combinations elicit strong craving responses among individuals with trauma histories who use substances. This effect was evident across different substances used by the populations of interest (e.g., alcohol, cocaine, nicotine). Several studies found such effects were strongest among those with higher PTSD symptom severity (e.g., Saladin et al., 2003; Tull et al., 2013) or those with the greatest cumulative trauma exposure (e.g., Garland et al., 2019). Moreover, studies with control groups, such as healthy non-drug using controls (Kaag et al., 2018) and those without trauma histories (Elton et al., 2015) were unable to find any significant change in craving with cue exposure among control groups, suggesting a lack of a conditioned cue-induced craving response among controls and specificity of these

cue-reactivity effects to “experimental” groups (e.g., cocaine users with childhood trauma histories; Elton et al., 2015). These findings are consistent with predictions that would be made on the bases of the conditioning theories presented at the outset of this chapter. Specifically, it is only those with trauma histories/PTSD who would have opportunities to learn to use substances to reduce the negative affect conditioned to trauma cues (two factor learning theory; Stasiewicz & Maisto, 1993) and to develop conditioned craving responses to trauma cues (via classical conditioning; Blume, 2001). Theoretically, such cue-induced craving effects could lead to substance seeking and consumption in response to exposure to real world trauma reminders – both via intrusive traumatic memories and exposure to external reminders of the trauma – thereby contributing to SUD development, maintenance, or exacerbation in those with trauma histories and/or PTSD.

Second, the cue-reactivity methodologies used in the studies identified through our scoping review tended to vary widely. While the majority of studies utilized imagery-based audio cues to elicit cue-reactivity craving responses, some used combinations of imagery-based trauma and substance-related in-vivo cues to understand how cue combinations may further bolster craving responses (e.g., Coffey et al., 2006; Rodriguez & Read, 2020). These combined cues serve as an in-lab analogue of real-world exposure to a trauma reminder simultaneous with exposure to substance-related cues, such as when an individual with PTSD experiences an intrusive memory about their trauma within proximity of substance-related cues like a bottle of alcohol. Less commonly, standardized cues (e.g., standardized trauma-related videos) were used to elicit cue reactivity craving responses (e.g., Trautmann et al., 2018). While such standardized cues often did elicit an increase in craving responses relative to the pre-exposure baseline, there were typically

caveats to such effects which may indicate a less robust elicitation of craving given the use of non-personalized cues. For example, one study (Trautmann et al., 2018) found an increase in craving following a standardized trauma film only in females, which could perhaps be attributed to the fact that the film subject was also female. Generally, a more consistent craving response was found in studies that utilized personalized cues. Additionally, several studies used cue-reactivity paradigms involving tasks that were being used for other purposes (e.g., Stroop colour naming task (Scarpina & Tagini, 2017) to assess attentional bias) but that contained relevant trauma or substance cues, allowing for a secondary test of cue-induced craving (Beckham et al., 1996; Garland et al., 2019; Kaag et al., 2018). Indeed, combining a craving assessment with a cognitive task containing relevant cue exposures may be useful in simultaneously assessing outcomes directly related to the cognitive task and assessing cue-induced craving. For example, this was accomplished by Garland and colleagues (2019) who aimed to assessed participants' ability to regulate emotions related to trauma-related images on their emotional regulation task which simultaneously served as a cue reactivity craving assessment.

Third, while we did not systematically aim to include affect as an outcome in the present scoping review, we decided to cover this outcome as many of the studies included in the review (50%) did include a measure of affect as an additional outcome alongside craving. Our findings elucidated the potential importance of affect in helping explain the relationship between trauma cue-reactivity and craving. To elaborate, negative affect has quite consistently been shown to increase following trauma cue exposure (e.g., McHugh et al., 2017; Nosen et al., 2014). This is consistent with suggestions that conditioned

relief craving may be an important motivator of continued substance use in those with trauma histories who use substances. Relief craving involves the urge to use substances to reduce negative affective states – the very mood states that are triggered when those with trauma histories are faced with trauma reminders. This is consistent with Stasiewicz and Maisto's (1993) application of two-factor avoidance theory to substance use. They suggested that trauma reminders can be classically conditioned to elicit fear themselves, which motivates avoidance responses such as substance abuse to escape/avoid the aversive emotional state. Through this two-factor learning process, an individual may become motivated to reduce the negative affect triggered through trauma cue exposure, and to crave the relief that can be achieved through substance use. This theory is partially supported by the results of the present scoping review. Specifically, one study (Zambrano-Vazquez et al., 2017) found trauma cue-induced craving decreased following prolonged exposure treatment, and this decrease was associated with a concurrent decrease in negative emotional responses to trauma stimuli. While causality cannot be determined from these data, perhaps a decrease in trauma cue-induced negative affective responses may be responsible for the decreases in trauma cue-induced substance cravings following prolonged exposure treatment. The present scoping review found no studies which tested the links of cue-induced craving with cue-induced emotional responses; further, only one study (Garland et al., 2019) alluded to the distinction between reward and relief craving. We suggest that the roles of both cue-induced negative and positive affect in eliciting reward and relief craving should be explored further in future research.

Finally, it is important to note that seven studies utilized CRPs as an additional outcome in trauma and/or substance-related therapeutic interventions. Notably, neither of

the two pharmacological studies found an effect of the respective medications (oxytocin and neurokinin-1 receptor antagonist aprepitant) relative to placebo as a means of reducing either PTSD symptoms, or stress cue- or substance cue-induced craving (see Kwako et al., 2015; Stauffer et al., 2019). Conversely, all studies examining the efficacy of PE therapy for PTSD or PTSD-SUD found that trauma cue-induced craving, as well as other forms of cue-reactivity (e.g., salivation, distress), decreased over time in those who received PE when compared to patients who received a control intervention (Badour et al., 2017; Coffey et al., 2006; McGuire et al., 2018; Nosen et al., 2014; Zambrano-Vazquez et al., 2017). Indeed, behavioural interventions seem to be more efficacious than pharmacological interventions in reducing reactivity to both trauma and substance-related cues among trauma-exposed substance users, at least for the few pharmacotherapies that have been investigated with this paradigm thus far, and at least in comparison to PE therapy. Furthermore, the use of CRP as a secondary outcome in randomized controlled trials of therapeutic interventions speaks to the multifaceted functionality of the CRP in the PTSD/trauma-exposed population, offering a mechanism-based outcome that informs beyond the decrease of symptoms.

Limitations and Future Directions

First, it is important to note that no formal examination of study quality of the included literature was completed, as this step is not typical for scoping reviews (Peters et al., 2015). It should also be noted that our choice to include unpublished theses and dissertations in the present review may have led to the inclusion of some studies with poor methodological quality, although it does help ensure that our conclusions are not hampered by publication bias.

To further assess the studies included in the present scoping review, we recommend a formal analysis of methodological quality be completed in future to better understand how methodological variations in cue-reactivity research may influence relevant outcomes. Additionally, the use of CRPs as secondary outcomes in the context of behavioural and pharmacological intervention trials is an interesting research direction which should be studied further, as this may lead to important implications for understanding the breadth of response to the use of psychotherapeutic or pharmacological interventions in this population, and may point to potential mechanisms of action. We also recommend that a formal systematic review and meta-analysis be conducted to quantify the magnitude of trauma cue-induced craving responses in this population, and to identify significant moderators of this response in terms of sample characteristics (e.g., percentage of the sample with PTSD), and methodological variables (e.g., personalized vs. standardized cues). Providing that relevant data could be obtained from published papers or authors, novel techniques like two-step meta-analytic structural equation modelling (TS-MASEM; Cheung & Chan, 2005) could also be employed to examine theorized mediational pathways (e.g., that trauma cue exposure leads to activation of negative affect which in turn activates craving). Finally, meta-analyses could also quantify the degree of reduction in trauma cue-induced craving that is achieved with various forms of treatment for PTSD, SUD, and their comorbidity, and its relations to treatment efficacy (i.e., symptom reduction).

Conclusion

Our scoping review maps the use of CRPs across the trauma-exposed, substance-using population with and without PTSD, and summarizes methodological variations in

cue-reactivity paradigms across this body of literature, as well as the results of identified studies. Cue-reactivity paradigms have proven efficacious in eliciting cue-induced craving responses in populations of trauma-exposed individuals who use substances. Cue-reactivity research may help increase understanding of the learning processes that are involved in the development, maintenance, or exacerbation of an SUD among trauma-exposed individuals with and without PTSD who use substances. Furthermore, cue-reactivity paradigms may be used as an important means of assessing whether behavioural and/or pharmacological treatments for PTSD and/or SUD have had an impact on the ability of trauma cues to elicit a conditioned craving response in this population.

Table 1.1. Description of studies included in the present scoping review.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Elton et al. (2015)	38 cocaine-dependent males with (n = 20) and without (n = 18) childhood maltreatment histories.	Script-driven imagery. All participants listened to a personalized neutral, stress, and cocaine-related audio cue whilst in an fMRI scanner.	Brain region activation, anxiety, and subjective craving response.	Cue-induced cocaine craving was measured using visual analogue scale (VAS) from 0 – 10.	Stress-Neutral: The interaction between maltreatment severity and craving responses was associated with activation of the left premotor cortex and right cerebellum. Substance-Neutral: The interaction between maltreatment severity and craving responses was associated with activation of the bilateral occipital cortex, caudal pre-supplementary motor area [SMA], and cuneus. Findings suggest that childhood maltreatment alters neural correlates of cue-induced substance craving.
Dutton. (2017)	46 hazardous drinkers who met DSM-5 criterion A (trauma exposure) of a PTSD diagnosis	Script-driven imagery. Participants listened to a personalized neutral cue followed by either a neutral-social (n = 24) or a social conflict cue (n = 22). Each cue was 1 minute long followed by a 30 second visualization period.	State PTSD symptoms, subjective craving response, affect, and alcohol approach bias.	Cue-induced alcohol craving was measured using a VAS from 0 – 100.	Following the social conflict cue but not the neutral social cue, state PTSD symptoms increased. There were no differences in alcohol approach bias, affect, or craving between cues.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Trautmann et al. (2018)	95 healthy occasional drinkers who had experienced childhood trauma.	Standardized video. Participants watched either a 15-minute trauma film (n = 47) or a 15-minute neutral film (n = 48).	Subjective craving response, anxiety, and physiological reactivity (i.e., skin conductance, heart rate, and saliva cortisol levels)	Cue-induced alcohol craving was measured using the Alcohol Craving Questionnaire-Short Form 0.	In females, the trauma film elicited greater craving responses compared to the neutral film. In males, the number of childhood traumas positively moderated the relationship between film condition and craving responses. In males, childhood trauma was associated with increases in skin conductance, heart rate, and cortisol levels; only skin conductance was related to craving responses.
Stauffer et al. (2019)*	47 males with comorbid PTSD-AUD and 37 healthy control males.	In-vivo substance cues. Following either oxytocin or placebo administration, participants were presented with their preferred alcoholic beverage and a neutral water cue.	Effects of oxytocin as a treatment for comorbid PTSD-AUD, subjective craving responses, and heart rate variability.	Cue-induced alcohol craving was measured using a VAS from 0 – 100.	Craving responses and heart rate were higher following the alcohol cues compared to neutral cues. No effects of oxytocin compared to placebo on cue-induced craving or heart rate.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Ralevski et al. (2016)*	25 veterans with comorbid PTSD-AUD.	Script-driven imagery. All participants listened to personalized trauma, stress, and neutral audio cues.	Subjective craving responses, blood pressure, heart rate, negative affect, and salivary cortisol.	Cue-induced alcohol craving was measured using the Alcohol Craving Questionnaire-Short Form 0 and a VAS.	Craving responses, cardiovascular reactivity, and negative affect were highest following the trauma cue, but were also high following the stress cue, both compared to the neutral cue.
Winokur. (2014)	95 individuals with (n = 31) and without (n = 39) trauma histories who were heroin (n = 25) or nicotine (n = 70) dependent.	Standardized video. Participants watched standardized video cues related to either heroin or nicotine use, and a neutral video cue.	Subjective craving responses.	Cue-induced heroin or nicotine craving was measured using a Within Sessions Rating Scale (0 – 9).	Post substance-cue craving responses increased among both the opiate and nicotine-dependent groups, but was highest in the opiate-dependent group, and only among those with trauma histories.
Coffey et al. (2006)*	43 SUD inpatients with comorbid PTSD-AUD. 75% of participants who completed at least one clinical session were randomly assigned to receive six sessions of either imaginal exposure therapy (n = 12) or relaxation (control) condition (n = 12). However, only 17 participants completed the study.	Script-driven imagery and in-vivo substance cues. Participants completed the following experimental cue reactivity trials: Trial 1: All participants listened to personalized neutral and trauma cues. Trial 2: All participants listened to a personalized trauma cue followed by the presentation of either alcohol or water.	Subjective craving responses, affect, and emotional distress.	Cue-induced alcohol craving was measured using a VAS from 0 – 10.	Craving responses decreased from pre- to post- treatment among those in the imaginal exposure condition following the trauma-alcohol cue (trial 2) and did not change in the relaxation condition. Craving responses also decreased in both groups following the trauma cue (trial 1). Negative affect was highest in trial 2.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Read et al. (2017)	232 undergraduate students with PTSD (n = 28), with trauma exposure but no PTSD (n = 113), or no trauma history (n = 91) taking part in a clinical trial.	Script-driven imagery. Participants listened to either a personalized trauma (n = 111) or neutral cue (n = 121). Participants wrote about the event while continuing to imagine the scene.	Subjective craving, affect, and performance on a Stroop attentional task with trauma and alcohol-specific stimuli.	Cue-induced alcohol craving was measured using a 10-point likert scale rating urge to drink.	Participants with PTSD in the trauma cue condition showed a slowed response in the Stroop task. This effect was associated with urge to drink only among those with PTSD in the trauma cue condition.
Kaag et al. (2018)	117 adults, half cocaine users (n = 59) and half healthy controls (n = 58)	Event-related cue reactivity paradigm. All participants viewed substance-related photos, neutral photos, and photos of animals. They were instructed to press a button when photos of animals were presented.	Subjective craving and neural activation.	Cue-induced cocaine craving was measured using the Desire for Drug Questionnaire 0 at baseline and following the cue-reactivity paradigm.	Only among substance users, the presentation of cocaine cues led to neural activation in the frontal striatal circuit and the amygdala. Amygdala-striatal connectivity was associated with childhood trauma among substance users.
Coffey et al. (2002)	75 individuals receiving SUD treatment with PTSD who were cocaine (n = 30) or alcohol-dependent (n = 45)	Script-driven imagery and in-vivo substance cues. All participants took part in four cue trials, which were counterbalanced. Participants listened to a personalized cue (trauma or neutral). Immediately after, either a substance or neutral (i.e., alcohol or wood chips) in-vivo cue was placed in front of them.	Subjective craving.	Cue-induced craving was measured using the Cocaine Craving Questionnaire-Now (CCQ-Now) 0and Alcohol Craving Questionnaire-Now (ACQ-Now) 0	Both alcohol-dependent and cocaine-dependent participants evidenced greater craving following the trauma- and substance-related cues compared to the neutral cues.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
McHugh et al. (2017)	194 individuals with PTSD receiving treatment for a comorbid SUD.	Script-driven imagery. All participants listened to a personalized trauma and neutral cue, counterbalanced across two sessions, followed by a 1-minute visualization period.	Subjective craving and affect.	Cue-induced substance craving was measured on an 11-point scale. Ratings ranged from 0 (no cravings) to 11 (very strong cravings).	Craving and negative emotional reactivity were greater following the trauma cue compared to the neutral cue. Anxiety sensitivity was associated with greater emotional reactivity following the trauma cue, but there was no association between anxiety sensitivity and craving response.
McGuire et al. (2018)	29 veterans receiving treatment for comorbid PTSD-SUD.	Interview. All participants provided a detailed verbal description of their most traumatic lifetime event.	Subjective craving, resilience, and PTSD symptoms.	Cue-induced craving for alcohol and/or other substances was measured using the Alcohol Craving Questionnaire Short Form-Revised 0	Post-treatment, participants evidenced a decrease in cue-induced craving and fewer PTSD symptoms, as well as increased resiliency, relative to pre-treatment baseline.
Saladin et al. (2003)	124 individuals with trauma histories receiving SUD treatment who were alcohol- (n = 70) or cocaine-dependent (n = 54).	Script-driven imagery and in-vivo substance cues. All participants took part in four cue trials, which were counterbalanced. Participants listened to a personalized cue (trauma or neutral). Immediately after, either a substance (e.g., Jack Daniels over ice) or neutral in-vivo cue was placed in front of them.	Subjective craving.	Cue-induced substance craving was measured using a 21-point VAS.	Craving was greater following the trauma- and substance-related cues in comparison to the neutral cues. PTSD symptom severity predicted greater craving responses, but only following the trauma + substance cue pairing.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Coffey et al. (2010)	40 individuals with comorbid PTSD-AUD receiving inpatient SUD treatment.	Script-driven imagery and in-vivo. All participants listened to a personalized trauma or neutral imagery cue paired with an in-vivo substance or neutral (water) cues.	Subjective and objective craving responses; emotional distress.	Cue-induced craving was measured using a VAS from 0 – 10 and salivary flow.	Subjective craving responses, distress, and salivary flow were greater following substance and trauma cues compared to the neutral cue.
Vujanovic et al. (2018)	58 low income inner city adults.	Script-driven imagery. All participants listened to personalized trauma, substance, and neutral audio cues.	Subjective craving responses.	Cue-induced craving was measured using a VAS from 0 – 100.	Lower distress tolerance was a significant predictor of higher craving responses following the trauma cue.
Rodriguez et al. (2020)	305 undergraduate students with no trauma (n = 127), trauma exposure (n = 106), and PTSD (n = 72).	Script-driven imagery. Participants were instructed to close their eyes and imagine their most traumatic event as if it was happening to them. Participants then wrote about the scene while continuing to imagine the scene.	Subjective craving responses and affect.	Cue-induced craving was measured using the Urge to Drink Questionnaire 0, on a scale from 1 – 10.	Emotional responses to the trauma cue mediated the relationship between trauma exposure and urge to drink.
Bing-Canar et al. (2021)	184 young adults with trauma histories	Script-driven imagery and in-vivo substance cues. All participants listened to a personalized trauma or neutral imagery cue paired with an in-vivo substance or neutral (water) cues	Subjective and objective craving responses.	Cue-induced craving was measured using a three-item Alcohol Craving Scale 0 and salivation levels.	Depressive symptoms did not have any effect or interaction with the cue-reactivity paradigm to predict increased craving or salivation.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Zambrano-Vazquez et al. (2017)	85 individuals with comorbid PTSD-SUD and current alcohol dependence receiving SUD treatment. Only 66 participants who completed 8 or more prolonged exposure treatment sessions were included in analyses.	Script-driven imagery and in-vivo substance cues. Pre- and post-treatment, all participants listened to a personalized trauma or neutral imagery cue paired with an in-vivo substance or neutral (water) cues.	Subjective and objective (salivation) craving, subjective distress, and domains of functioning.	Cue-induced craving was measured using the Alcohol Craving Questionnaire-Now 0and salivation levels.	Severity in all domains of functionial impairment (Negative Valence, Arousal, and Cognitive) decreased from pre to post treatment, and this change was associated with a decrease from pre-treatment baseline in self-reported craving and salivation post-treatment following alcohol and trauma cue exposure.
Garland et al. (2019)*	36 opioid-treated chronic pain patients at risk for opioid use disorder, with adverse childhood experiences (ACEs).	Emotional Regulation Task. Participants were shown trauma-related images and were asked to both view or reappraise the images (dependent on the trial block) to regulate the emotions elicited by the image.	Subjective craving, heart rate variability, and negative affect.	Cue-induced opioid craving was measured using a 5-point scale, with 1 indicating no craving and 5 indicating very strong cravings.	Following the emotional regulation task, craving increased from pre-task baseline. This change was related to the number of ACE exposures. ACEs and duration of opioid use also predicted a blunted heart rate variability when regulating negative emotions.
Zaso et al. (2020)	611 college students with PTSD (n = 50), with trauma exposure but no PTSD (n = 325), and no trauma (n = 236) who drink alcohol	Script-driven imagery. Participants were randomized to listen to either a personalized trauma or neutral cue followed by a 2-minute writing period relating to the cues.	Subjective craving response and affect.	Cue-induced craving was measured using a 10-point scale, with 1 indicating no urge to drink and 10 indicating a very strong urge to drink.	Following the trauma cue, but not the neutral cue, participants reported greater cravings and negative affect relative to baseline, which was associated with coping drinking motives.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant F.indings
Kwako et al. (2015a)*	53 individuals with comorbid PTSD-AUD receiving inpatient SUD treatment. Participants received either aprepitant (n = 26) or a placebo (n = 27) prior to cue exposure.	Script-driven imagery, in-vivo alcohol cues, standardized photos of alcohol and neutral cues. Following the Trier Social Stress test, participants handled in-vivo cues of their preferred substance. In another session, participants listened to either a personalized stress, alcohol, or neutral cue. In an fMRI session, participants viewed photos of substance-related and neutral stimuli.	Subjective craving, blood cortisol, , and neural activation.	Cue-induced alcohol craving was measured using the Alcohol Urge Questionnaire 0	Alcohol and stress cues induced more craving compared to the neutral cue. There was no significant neural activation following the substance-related relative to the neutral stimuli.
Nosen et al. (2012)	108 adults with comorbid PTSD-AUD who were receiving residential treatment for SUD.	Script-driven imagery and in-vivo substance cues. All participants listened to a personalized trauma or neutral imagery cue paired with an in-vivo substance or neutral (water) cues. (TN; TS; NS; NN).	Subjective and objective (salivation) craving and affect.	Cue-induced alcohol craving was measured using a three-item alcohol craving scale 0and salivation levels.	Trauma and substance cue pairings elicited the greatest subjective craving responses, negative affect, and salivation vs. all other cue combinations. Ambivalent affective responses predicted strongest craving.
Tull et al. (2013)	60 cocaine-dependent individuals with (n = 30) and without PTSD (n = 30) in treatment for a SUD	Script-driven imagery. Across two sessions, all participants listened to a personalized cue (trauma or neutral; 1 min) followed by a visualization period (1 min).	Subjective craving response and affect.	Cue-induced cocaine craving was measured using an 11-point scale, with 0 indicating no cravings and 10 indicating very strong cravings.	PTSD was associated with greater craving and negative affect following the trauma cue, but not the neutral cue. Among men, this relationship was mediated by self-conscious emotions.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Nosen et al. (2014)	120 individuals with comorbid PTSD-AUD in treatment for a SUD. Participants were assigned to receive exposure therapy (n = 52) or health and lifestyle treatment (n = 35); only those who completed treatment (n = 87) were included in analyses.	Script-driven imagery and in-vivo substance cue exposure. All participants were presented four counterbalanced cue combinations: They first listened to a personalized cue (trauma or neutral). Immediately after, either a substance or neutral in-vivo cue was placed in front of them.	Subjective and objective (salivation) craving response, distress, and affect.	Cue-induced craving was measured using a three-item alcohol craving scale 0and salivation levels.	Pre-treatment, the trauma + substance cue elicited the strongest craving responses, negative affect, and distress. Post-treatment, trauma cues no longer elicited greater craving compared to substance cues alone. Both treatments led to a decrease in salivation and subjective craving following cue exposure.
Badour et al. (2017)*	54 veterans with comorbid PTSD-SUD taking part in a COPE RCT.	Participants were presented with personalized in-vivo substance cues across nine sessions.	Subjective craving and distress.	Cue-induced craving for participants' preferred substance was measured using a VAS (0 – 100).	Between-session reduction of substance cue-induced craving and distress responses were associated with a decrease in PTSD symptom severity.
Tull et al. (2018)	133 individuals with trauma histories in treatment for an SUD.	Script-driven imagery. Participants listened to a personalized trauma cue (1min) followed by a visualization period (1min).	Subjective craving, emotional regulation, negative affect, and salivary cortisol.	Cue-induced craving for participants' preferred substance was measured using an 11-point scale, with 0 indicating no cravings and 11 indicating very strong cravings.	Following the trauma cue, craving increased relative to pre-cue baseline. This change was associated with greater PTSD symptom severity. PTSD symptom severity was related to both adaptive and maladaptive emotional regulation strategies.

First Author (Year)	Sample Characteristics and Context	Cue Reactivity Paradigm & Method	Outcome(s) of Interest	Craving Measure	Relevant Findings
Beckham et al. (2007)	129 smokers with (n = 82) and without PTSD (n = 47) randomly assigned to either a nicotine or a non-nicotine smoking condition.	Script-driven imagery. Participants listened to either a personalized trauma, neutral, or stress cue (30 sec) followed by a visualization period (30 sec) both before and after smoking a nicotine or denicotinized cigarette.	Subjective craving and affect.	Cue-induced craving to smoke was measured using the Questionnaire on Smoking Urges 0.	Trauma-related cues produced greater cravings and negative affect compared to stress scripts and neutral scripts. This effect was most pronounced among those with PTSD. Smoking either the nicotine or non-nicotine cigarettes reduced craving, negative affect, and PTSD symptoms following the trauma and stress script relative to the neutral script.
Beckham et al. (1996)	25 veterans receiving PTSD treatment who smoke cigarettes.	Stroop task with combat/trauma related words. Participants named the ink color of three blocks of trauma related and three blocks of neutral words.	Subjective craving, affect, somatic symptoms, and alertness.	Cue-induced craving to smoke was measured using a modified Smoking Withdrawal Questionnaire Short Form-Revised 0	Craving, negative affect, somatic symptoms, and lack of alertness were all greater following the presentation of trauma-related words compared to neutral words.

Note: * = randomized controlled trial.

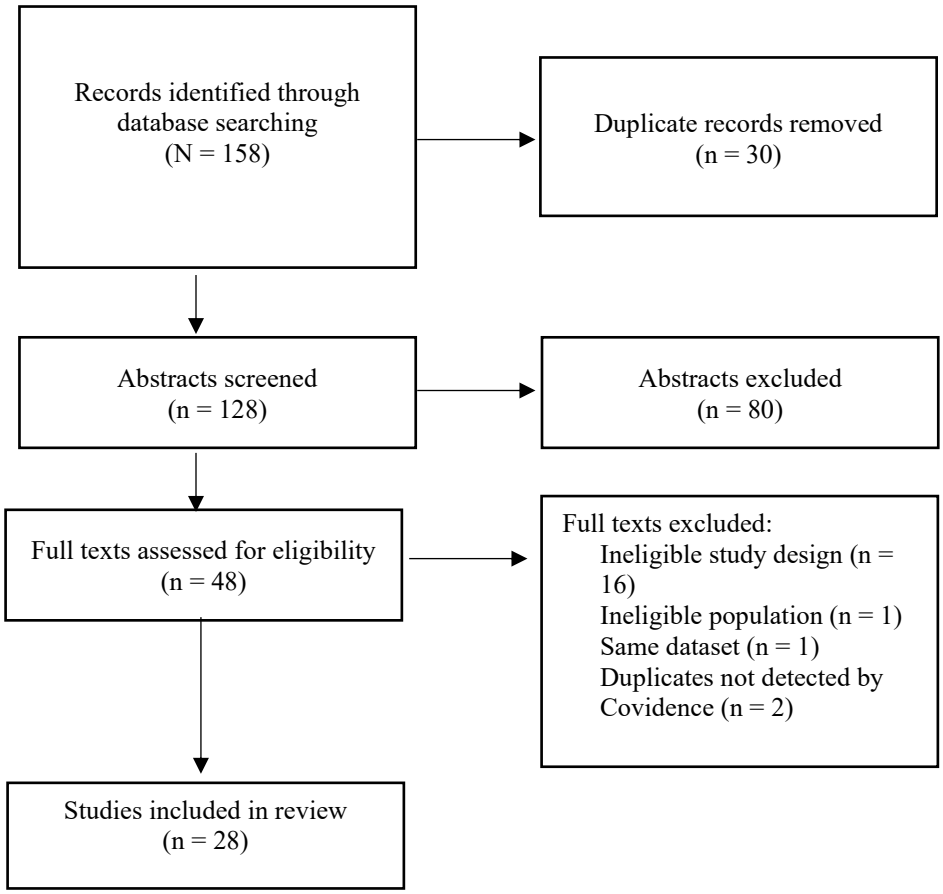


Figure 1.1. PRISMA flowchart of literature search and screening.

CHAPTER 3: TRANSITION FROM STUDY 1 TO STUDIES 2 – 5.

The CRP is commonly used in the PTSD-SUD comorbidity field to experimentally investigate affective and cognitive mechanisms underlying this form of comorbidity. Study 1 – a scoping review – allowed me to examine the cue reactivity literature in a population of trauma-exposed substance users from a bird's eye view. Specifically, I identified methodological subtypes (e.g., use of in-vivo, audio, and visual cues) and common outcomes (i.e., affect, craving, automatic cognitions) in cue reactivity research conducted in trauma exposed, substance using populations. Further, my scoping review established trauma cues as elicitors of greater cravings compared to cravings at baseline, as well as following neutral and, often, following substance-related cue exposure. The review also revealed several gaps in the literature. Two of the most important identified gaps were as follows. First, the methodology typically used for CRP studies was associated with attrition issues. This is perhaps not surprising given the population of interest is trauma-exposed individuals who are susceptible to PTSD and thus, by definition, avoidant of trauma reminders. Second, while this body of literature has primarily focused on alcohol, cocaine, and nicotine users, very little work has applied CRPs to trauma-exposed *cannabis* users specifically. As discussed in Chapter 1, existing theory and PTSD-SUD comorbidity research suggests the same patterns of trauma cue induced craving and negative affect should also be found for cannabis as the substance of interest. Indeed, there are important practical and clinical implications of understanding the mechanisms underlying PTSD-CUD, given cannabis is often recommended as a therapeutic means of managing PTSD symptoms (Berardi et al., 2016). Individually, these gaps in the literature aligned to inform Studies 2 – 5. Specifically, only two cue

reactivity studies on trauma-exposed cannabis users (Tull et al., 2015; Romero-Sanchiz et al., 2022) existed in the literature, with only Romero-Sanchiz and colleagues (2022) included in Study 1, Chapter 2 due to the inclusion criteria of measuring cannabis craving; thus, I sought to make cannabis users with trauma histories the population of interest across my subsequent four empirical studies.

For Study 2, I formally tested prior findings obtained with the traditional two-session CRP using a single-session CRP to minimize attrition. Specifically, I aimed to replicate common patterns of increased cravings and negative affect, and lesser positive affect, as they were common outcomes identified in Study 1, Chapter 2, and in prior work using two-session CRPs among trauma-exposed substance users (e.g., Romero-Sanchiz et al., 2022; Tull et al., 2013). Indeed, only one prior study had utilized a single-session interview format as a trauma CRP (see Study 1, Chapter 2), but this interview was unstandardized, creating difficulties for future replication. Thus, I tested a manualized, semi-structured interview (Sinha & Tuit, 2012) which acts as a first step (i.e., session one) in the gold standard CRP protocol (e.g., Coffey et al., 2010), as a standalone CRP.

CHAPTER 4. DO WE REALLY NEED TWO SESSIONS? THE USE OF A STRUCTURED INTERVIEW AS A TRAUMA CUE REACTIVITY PARADIGM

The manuscript prepared for this study is presented below. Readers are advised that Sarah DeGrace, under the supervision of Dr. Sherry Stewart, was responsible for designing the study, developing the research hypotheses, gaining ethical approval, collecting the data, training research assistants to collect data, preparing the dataset for analyses, conducting the analyses, and interpreting the study results. Sarah wrote the initial draft of the manuscript and incorporated suggestions and edits by her coauthors. Sarah then prepared the manuscript for submission and led the response to the journal's requests for revisions. The manuscript was published online in the *International Journal of Methods in Psychiatric Research* on July 5th, 2023. See Appendix B for copyright permission from the publisher to include this paper in the thesis. The reference is as follows: DeGrace, S., Romero-Sanchiz, P., Barrett, S. P., Tibbo, P. G., Cosman, T., Atasoy, P., & Stewart, S. H. (2023). Do we really need two sessions? The use of a structured interview as a trauma cue reactivity paradigm. *International Journal of Methods in Psychiatric Research*, e1979. https://doi.org/10.1002/mpr.1979

Abstract

Objectives: Derived from classical conditioning theory and rooted in motivational mechanisms, cue reactivity paradigms (CRPs) are used in addictions research to measure participants' propensities for substance-relevant responses (e.g., craving) during exposure to substance-relevant cues (e.g., drug paraphernalia). CRPs are also useful in PTSD-addiction research, allowing the study of affective and substance-relevant responses to trauma cues. However, studies using traditional CRPs are time-consuming with high attrition rates due to repeat testing. Thus, we sought to test whether a single session semi-structured trauma interview could serve as a CRP in terms of eliciting theorized cue exposure effects on craving and affect measures.

Method: Fifty regular cannabis users with trauma histories provided detailed descriptions of their most traumatic lifetime experience, and a neutral experience, according to an established interview protocol (Sinha & Tuit, 2012). Linear mixed models examined the effect of cue type (trauma vs. neutral) on affective and craving responses.

Results: As hypothesized, the trauma interview elicited significantly greater cannabis craving (and alcohol craving among the drinkers), and greater negative affect particularly among those with more severe PTSD symptoms, compared to the neutral interview.

Conclusion: Results suggest Sinha and Tuit's (2012) semi-structured interview may function effectively as a CRP for use in trauma and addictions research.

Keywords: cue reactivity paradigm, addiction, PTSD, craving, trauma interview.

Introduction

Individuals with substance use disorder tend to experience both physiological (e.g., increased heart rate; Starcke et al., 2018) and psychological (e.g., increased substance craving; Romero-Sanchiz et al., 2022) reactions when exposed to substance-related cues. Cue-reactivity paradigms (CRPs) allow researchers to examine whether exposure to a particular cue or reminder elicits *reactivity* or a change in state (e.g., craving, affect, heart rate). Traditionally, CRPs have utilized drug-related stimuli to understand how relapse might occur when individuals are exposed to situational antecedents of drug use (i.e., *cues*). CRPs are derived from classical conditioning theory (e.g., to study involuntary craving elicited by exposure to a substance use cue established through classical conditioning; Sayette et al., 2000) and operant conditioning theories (e.g., learning to associate substance use with reward or relief; Verheul et al., 1999). Both learning theories suggest that, over time, repeated exposure to substance use-related cues can lead to the development of conditioned craving (Carter & Tiffany, 1999). Indeed, research has shown that exposure to substance use cues is associated with both increased craving (Coffey et al., 2006) and substance use behavior (Drobes, 2002) in substance-using samples.

In laboratory-based CRPs, participants are exposed to an audio and/or visual cue (e.g., an audio clip describing substance use imagery and/or a visual reminder such as drug paraphernalia), and their subjective (e.g., self-reported craving, self-reported negative affect [NA] and/or positive affect [PA]) and/or physiological responses (e.g., salivation, heart rate) are measured during or immediately following the cue exposure

and compared to levels of the same variable during/following a neutral cue (e.g., toothbrush) and/or to their baseline (pre-cue exposure) levels.

CRPs have also been used to help understand why certain addictive disorder-mental health disorder comorbidities occur. For example, post-traumatic stress disorder (PTSD) shows high rates of comorbidity with substance use disorder (SUD; Walsh et al., 2014). Individuals with trauma histories generally, and PTSD particularly, may use substances as a means of coping with NA responses to trauma reminders (e.g., encounters with external trauma reminders or experiences of intrusive traumatic memories; Jacobsen et al., 2001). Theoretically, strong memory associations are likely to form between the trauma cue, substance use behavior, and relief consequences that may elicit conditioned craving and reinforce substance use when the individual reencounters trauma cues (Romero-Sanchiz et al., 2022). For example, an individual with PTSD might use cannabis when reminded of a past traumatic event to feel relief from the NA elicited by that reminder. Repeated cannabis use in such situations may lead to the development of conditioned cannabis craving (Sayette et al., 2000) during exposure to trauma cues, as the user has been conditioned to associate trauma cues with aversive NA (Stacewicz & Maisto, 1993) and cannabis use with relief of the NA (Romero-Sanchiz et al., 2022).

Consistent with this theory, lab-based research has demonstrated a general pattern of greater self-reported NA and substance craving during exposure to trauma cues (compared to neutral cues or pre-exposure levels) across populations of trauma-exposed substance users (Study 1, Chapter 2). Moreover, research has shown that drinkers with PTSD (vs. no PTSD) experience greater conditioned alcohol craving following trauma cue exposure (Read et al., 2017). Similarly, Romero-Sanchiz and colleagues (2022)

found that PTSD symptom severity was positively associated with relief cannabis craving and NA responses to trauma vs. control cues in cannabis users with trauma histories. However, as described by Nosen and colleagues (2012), cue reactivity research has yet to firmly establish if an increase in/greater NA during trauma cue exposure (compared to pre-exposure levels or neutral cue exposure) is accompanied by a decrease in/lesser PA, or more ambivalent (e.g., high NA and PA) responses. Taken together, these findings using traditional CRP methods suggest that NA responses and conditioned substance craving to trauma cues may be greater among those trauma exposed individuals with greater PTSD symptomatology; this provides a possible mechanism to help explain high rates of PTSD-SUD comorbidity (Walsh et al., 2014).

Trauma CRP cues are often chosen to be specific to the participant's own trauma history (e.g., Romero-Sanchiz et al., 2022) as such personalized cues have been shown to elicit greater cue reactivity compared to standardized, non-personalized cues (Conklin et al., 2011). While protocols have varied somewhat across studies (Vujanovic et al., 2018a; Witteman et al., 2015), a two-session format is typically used. In a first lab-based session, a semi-structured interview developed by Sinha and Tuit (2012) to study the role of stress in addiction is used to obtain personalized details about a traumatic and a neutral event; these interviews are used to develop standardized imagery cues for the script-driven imagery used in the second CRP session. The protocol for eliciting vivid imagery in the first session's interviews is based on Lang's (1979) theory of emotional imagery and is considered the gold standard in cue reactivity research (Coffey et al., 2002). These interviews are audio-recorded and later summarized into short and detailed standardized retellings of the events (also guided by the Sinha & Tuit [2012] protocol), which are then

recorded and played for the participant in a second CRP session where cue reactivity effects are studied.

While this two-session CRP protocol is valid and well-established in the trauma and addictions field (Study 1, Chapter 2), high attrition rates (i.e., participants failing to return for the cue exposure session after the initial interview) are difficult to avoid (e.g., Coffey et al., 2006). This is especially important to consider in the context of trauma-exposed substance users with PTSD, as one symptom of PTSD is avoidance of trauma reminders (American Psychiatric Association [APA], 2013). Results may be less generalizable if our studies only reflect the experiences of those who are more likely to return to the second (CRP testing) session (e.g., less avoidant individuals). Additionally, obtaining results in a single session would minimize the overall distress to the participant. Moreover, the time and resources needed to run CRP studies in this traditional manner are demanding of both participant and researcher. Thus, a less demanding protocol would be a welcome methodological addition to the field, particularly when working with trauma-exposed individuals and those with PTSD.

Thus, this study served as a proof-of-concept to determine whether semi-structured interviews (Sinha & Tuit, 2012) alone could serve as an effective CRP. Specifically, we conducted an initial test of the construct validity of the semi-structured interviews as a form of CRP in terms of their ability to elicit theorized reactivity responses. Behavioral theory predicts that CRPs should elicit certain conditioned responses acquired through learning (Drummond, 2000; Reynolds & Monti, 2013). Thus, we reasoned that if the semi-structured interviews were valid as a CRP, they would elicit similar reactivity on response indices (i.e., substance craving, NA, PA) elicited by

traditional CRP methodologies (Study 1, Chapter 2). Such findings could provide researchers with a feasible means of conducting CRP studies with avoidant individuals without compromising their validity. Moreover, the use of the standardized Sinha and Tuit (2012) protocol, which is published and readily accessible to researchers around the world, for undertaking the interviews would allow for cue exposure replicability across future studies. Indeed, while interviews have been used as cues in some CRP studies (e.g., McGuire et al., 2018), the protocols for such interviews are often not described, which can create difficulties with replicability. We hypothesized that a semi-structured trauma interview, administered according to the protocol developed by Sinha and Tuit (2012), would elicit greater cannabis craving (*H1*), greater NA (*H2*), and lesser PA (*H3*) than a semi-structured neutral interview administered using the same protocol in a sample of individuals with trauma histories who use cannabis, and that the above effects would be stronger among participants with more severe PTSD symptoms (*H4*). Additionally, for the subset of participants who were drinkers, we expected that the trauma interview would elicit greater alcohol craving than the neutral interview (*H5*) demonstrating generalizability of the utility of the interview-based CRP across substances.

Method[7]

Participants.

Fifty[8] participants (34% male; *M* [*SD*] age=*37.8* [10.02] years) living in the Halifax Regional Municipality in the Canadian province of Nova Scotia were recruited to participate in an in-person study investigating the relationship between past trauma

[7] All methods and measures described were approved by the Nova Scotia Health Research Ethics Board (ref #: 1026315).
[8] Sample size for a CCC design was determined a priori with power analyses utilizing the protocol by Judd, Westfall, and Kenny (2016).

exposure and cannabis use. Participants were recruited via posters, Veterans associations, clinics including an Operational Stress Injury (OSI) clinic, and on social media (e.g., Facebook). Participants were required to meet the following protocol and inclusion/exclusion criteria to be eligible: aged between 19 and 65 years; and no current diagnosis of a serious and persistent mental illness (i.e., bipolar disorder, schizophrenia, or other psychotic disorder). Participants were also required to report having been exposed to at least one lifetime traumatic event on the Life Events Checklist (LEC; Gray et al., 2004) and to report current regular cannabis use (at least one gram per week for the last month; as in Gabyrs & Porath, 2019). Sample characteristics, including substance use, can be found in Table 2.1.

Measures: Eligibility.

Trauma Exposure. The LEC (Gray et al., 2004) was administered during a telephone eligibility screening. The LEC is a 17-item measure used to assess criterion A of a PTSD diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5; APA, 2013). If participants indicated they had been exposed to more than one lifetime trauma, they were instructed to focus on their most distressing lifetime trauma when answering questionnaires about the trauma, and in the semi-structured trauma interview.

Measures: Predictor.

Semi-Structured Interviews. Both the neutral and trauma interviews were conducted following the protocol by Sinha and Tuit (2012) for creating detailed imagery-based scripts for use in stress and addiction research. Based on Lang's (1979) theory of emotional imagery, this protocol involves the "re-living" of the event through guided

recall and imagery. To help elicit this imagery, the experimenter followed an interview guide (Sinha & Tuit, 2012) which provided sample probes to ensure that each participant was exposed to specific types of details about the event. However, as compared to a fully structured interview, the respondent was allowed to tell their story without substantial interruption and was only probed for details that they had not provided spontaneously during their event retelling. This semi-structured interview format allowed participants to become more immersed in details and tell their story naturally, with the prompts ensuring that all participants are exposed to similar details during the interview. Participants were asked to retell the event from their perspective and were probed for details throughout the interview to retrieve significant sensory aspects of the experience (e.g., the smell of smoke) as well as the participant's feelings and thoughts that occurred during the event (e.g., "I'm going to die"). These probed details focused on what the participant saw, heard, smelled, how they felt, which details stuck with them, and thoughts they were having at the time. Neutral events included those without substance or stressful subject matter; researchers suggested describing an event that takes place during their daily routine (e.g., morning routine, grocery shopping). These trauma and neutral interviews served as the CRP cues in the present study (i.e., the first within-subjects independent variable).

PTSD. PTSD symptom severity and the presence of current (past month) PTSD were assessed using the 20-item *Clinician-Administered PTSD Scale for DSM-5* (CAPS-5; Weathers et al., 2018). We used continuous CAPS-5 scores (i.e., PTSD symptom count; possible range=0-20) as a predictor of each cue reactivity outcome (i.e., the second within-subjects independent variable). Established CAPS-5 scoring rules (i.e., presence

of at least one symptom for each of criteria B and C, and at least two symptoms for each of criteria D and E) were also used to determine the proportion of the sample meeting DSM-5 (APA, 2013) criteria for PTSD for sample description purposes. The CAPS-5 possesses excellent interrater reliability, test-retest reliability, and high internal consistency (Weathers et al., 2018; current study $\alpha = .88$).

Measures: Outcomes.

Cannabis Craving. The *Marijuana Craving Questionnaire-Short Form* (MCQ-SF; Heishman et al., 2009) is a 12-item (e.g., *Smoking marijuana would be pleasant right now*) measure of cannabis craving scaled from 1 (strongly disagree) to 7 (strongly agree) which assess the degree to which a participant is currently craving cannabis. The MCQ-SF has good convergent validity when compared to the original 47-item Marijuana Craving Questionnaire (Heishman et al., 2001). The MCQ-SF total score was used to assess cannabis craving – one of the main dependent variables in the current study (current study $\alpha = .93$ and $\alpha = .94$ for the neutral and trauma cues, respectively).

Alcohol Craving. A 0 – 100 Visual Analog Scale (VAS) was used as a single-item measure of alcohol craving, as in Coffey et al. (2006) and Vujanovic et al. (2018a).

Affect. The *Positive and Negative Affect Schedule-Short Form* (PANAS-SF; Serafini et al., 2016) is a 20-item (10 NA items, 10 PA items) measure on which participants indicate the extent to which they are currently feeling NA-related (e.g., *nervous, distressed*) and PA-related (e.g., *enthusiastic, proud*) affective states on a scale from 1 (very slightly or not at all) to 5 (extremely). The PANAS-SF has good psychometric properties (i.e., excellent reliability [Crawford & Henry, 2004] and good convergent and discriminant validity [Serafini et al., 2016]). The PANAS-SF was used to

assess NA (current study α = .90 and α = .81) and PA (current study α = .88 and α = .87) for the neutral and trauma cues, respectively.

Procedure.

Screening. Individuals who expressed interest were contacted via telephone to assess their eligibility to participate. Respondents answered questions regarding demographic characteristics, the quantity and frequency of their cannabis use, and past trauma exposure (LEC; Gray et al., 2004) to ensure study eligibility. If eligible, they were booked for an in-person session. Participants were then sent a link to a virtual consent form and a battery of descriptive questionnaires.

Lab Session. A licensed psychiatrist and/or clinical psychologist was available on call during each lab session. Researchers interacting with participants were carefully trained and supervised. Participants were asked to abstain from cannabis, alcohol, and illicit drug use for 12 hours, and caffeine for 2 hours, prior to testing. At the beginning of the testing session, participants were screened verbally to ensure they had abstained from cannabis for 12 hours prior to testing. Abstinence from all other substances was verified using a urine test and a breathalyzer. Participants were clinically assessed for PTSD symptoms with the CAPS-5 (Weathers et al., 2018). Then, their baseline affect, alcohol craving, and cannabis craving were assessed using the PANAS-SF (Serafini et al., 2016) and the MCQ-SF (Heishman et al., 2009), respectively. Participants were then randomized to begin with either the neutral or trauma semi-structured interview, before completing the other interview (Sinha & Tuit, 2012). Immediately following each interview, participants completed the same measures of NA, PA, alcohol craving, and

cannabis craving as at baseline, with instructions to respond according to how they were feeling *during* the interview.

Statistical Approach. A set of three linear mixed-effects models (R v. 4.2.1; lme4 package) was used to examine the effects of cue type (fixed effect; neutral vs. trauma) on cannabis craving (H1), NA (H2), and PA (H3) with the interactive effects of PTSD (H4) and on alcohol craving among drinkers (H5), respectively. Participants were inputted as a random effect to control for individual mean responses. We used the Nakagawa formula (Nakagawa & Schielzeth, 2013) and the Johnson (2014) expansion to calculate conditional and marginal R^2 values (which served as a measure of effect size). Finally, a set of sensitivity analyses was conducted to ensure the effects persisted when covariates were controlled and when interactions were considered.

Results

Sample Characteristics. See Table 2.1 for a summary of demographic, clinical, and substance use characteristics of our sample.

Hypothesis Tests: Main Analyses. See Table 2.2 for omnibus results of the main linear mixed-effects models.

Cannabis Craving. As hypothesized in H1, cannabis craving was significantly higher during the trauma than the neutral interview ($t[99] = 4.01$, $p<.001$, 95% CI [0.48 – 1.40]; see Figure 2.1). However, contrary to H4, there was no significant interaction between cue condition and PTSD symptom severity ($t[99] = -0.60$, 95% CI [-0.04 – 0.04]). Our model accounted for 12.3% of the variance (marginal R^2) in cannabis craving scores (see Table 2.2).

Negative Affect. As hypothesized in H2, NA scores were significantly higher during the trauma than the neutral interview (t[99] = 3.23, p=.002, 95% CI [2.24 – 9.18]; see Figure 2.2). Moreover, this main effect was qualified by the interactive effect of cue type and PTSD symptoms predicted in H4 (t[99] = 2.28, p=.027, 95% CI [0.05 – 0.65]) with the cue type effect stronger among those with higher PTSD symptom severity (see Figure 2.2). Our model accounted for 46.0% of the variance (marginal R^2) in NA scores (see Table 2.2).

Positive Affect. Contrary to H3 and H4, there was no main effect of cue type on PA (t[99] = -1.61, p=0.11, 95% CI [-5.41 – 0.54]) and no interactive effect of cue type x PTSD symptoms ((t[99] = 0.30, p=0.76, 95% CI [-0.22 – 0.30); however, a main effect of PTSD symptoms emerged (t[99] = -2.56, p = .013, 95% CI [-1.12 - -0.15] with greater PTSD symptoms associated with lower PA (see Figure 2.3). Our model accounted for 17.5% of the variance (marginal R^2) in PA scores (see Table 2.2)

Sensitivity Analyses. First, we ran t-tests (and chi-square tests for categorical variables) to determine if sample characteristics, or baseline craving, NA, or PA differed by groups randomized to each order of cue presentation (trauma cue first (n = 29) vs. neutral cue first (n = 21)). All tests were non-significant, suggesting there were no systematic differences in those randomized to the two cue presentation orders.

Second, we ran a supplementary linear mixed model (H5) examining the effect of cue type on alcohol craving to test if our results generalized beyond cannabis. We conducted this analysis only among those who reported being drinkers (n = 34) to avoid zero inflation and for conceptual reasons (as alcohol craving to trauma cues is only relevant among those participants who drink alcohol). The sample size of drinkers was

too small to allow for a test of the interactive effects of cue type by PTSD symptoms, so we restricted this analysis to focus on cue type main effects. As hypothesized in H5, alcohol craving was significantly greater (*M*=19.53) following the trauma cue (t[67] = 3.53, p=.001, 95% CI [4.32 – 15.62]) compared to the neutral cue (*M*=9.56). The effect of our cue manipulation accounted for 4% of the variance (marginal R^2) in our single-item index of alcohol craving.

Next, we re-ran our linear mixed models examining the effect of cue type on craving (H1) and affect (H2 & H3), with participants' baseline (pre-interview) levels of each respective outcome and the order of cue presentation controlled for. Cue order did not significantly predict NA or PA, nor alcohol or cannabis craving. Moreover, in the case of all four outcome variables, baseline levels showed significant effects on the CRP outcome for cannabis craving (F[1, 47] = 166.47, p<.001), NA (F[1, 45] = 38.74, p<.001), PA (F[1, 44.3[1]] = 67.08, p<.001), and alcohol craving (F[1, 47] = 6.08, p<.001) with higher baseline levels predicting higher levels during the interview in each case. Nonetheless, a similar pattern of results emerged for our hypothesis tests as with our main analyses, even when these covariate effects were controlled. Specifically, cannabis craving (H1; t[99] = 3.95, p<.001, 95% CI [0.48 – 1.40]; Marginal R^2 = 0.76) and NA (H2; t[99] = 3.07, p=.004, 95% CI [2.05 – 9.18]; Marginal R^2 = 0.65) were significantly higher during the trauma (vs. neutral) interview. Additionally, our interaction between cue condition and PTSD symptoms for NA was retained t[99] = 2.21, p<.001, 95% CI [0.04 – 0.67] despite the inclusion of these covariates. However, the main effect of PTSD symptoms for PA observed in the main analyses was no longer significant following inclusion of these covariates.

The results of our various sensitivity analyses generally showed the stability of our findings across analytic methods.

Discussion

To begin to examine the construct validity of semi-structured interviews alone as a CRP among trauma-exposed current cannabis users, we conducted a proof-of-concept study measuring indices of *cue reactivity* commonly used in both the trauma and addictions literatures in response to both a trauma and neutral interview. Specifically, we measured self-reported cannabis craving, NA, and PA (and alcohol craving among the drinkers) using a semi-structured interview to elicit vivid imagery of the events of interest (Sinha & Tuit, 2012). Consistent with H1, H2, and H5, the trauma interview elicited significantly greater cannabis craving, alcohol craving (for the drinkers), and NA compared to the neutral interview. However, for NA, this main effect was qualified by the interactive effects of cue type and PTSD; consistent with H4, the cue condition effects on NA were stronger among those participants with more severe PTSD symptoms. Inconsistent with H3, there was no significant main effect of cue type on PA, and inconsistent with H4, no interaction of cue condition with PTSD symptoms was seen. Instead, a main effect of PTSD symptoms on PA emerged with those with more severe PTSD symptoms experiencing less positive affect than those with less severe PTSD symptoms regardless of interview type. Overall, the present results provide evidence of the construct validity for the use of the Sinha and Tuit (2012) interview protocol alone as a CRP (Reynolds & Monti, 2013) in that the trauma interview elicited greater substance craving and NA than the neutral interview.

These findings are consistent with prior research that utilized brief script-driven imagery audio cues (e.g., Rodriguez & Read, 2020), and a combination of audio and in-vivo cues (e.g., Nosen et al., 2012) as CRP cues in populations of trauma-exposed substance users. Specifically, like studies that have utilized standardized script-driven audio and/or visual cues tested during a two-session protocol (Study 1, Chapter 2), the single-session trauma interview used in the present study (Sinha & Tuit, 2012) provoked higher levels of cannabis craving and NA compared to the neutral interview. Moreover, the magnitude of effects was very similar in our study on our various outcomes to those obtained using a two-session protocol. For example, in a recent study, Berenz and colleagues (2021) measured craving during a combination of narrative imagery (neutral vs. trauma) and in-vivo (water vs. alcohol) cue. The variance explained by their within-subjects narrative imagery cue type manipulation (Marginal $R^2 = 0.122$) is comparable to the within-subjects interview cue type manipulation in the present study (Marginal $R^2 = 0.105$) without the addition of PTSD to our model. Similarly, Nosen and colleagues (2012) reported the effects of a within-subjects narrative imagery cue (trauma vs. neutral) on PA and NA in combination with a neutral in-vivo cue (i.e., water). Converted to R^2, the proportions of variance in NA ($R^2 = 0.460$) explained by their traditional CRP cue manipulation are similar to the proportions of variance explained by the interview cue manipulation alone in our study (i.e., Marginal $R^2 = 0.391$). Such results support the use of semi-structured interviews originally developed to elicit details for the later development of script-driven imagery as an appropriate cue to use themselves as a CRP.

To the authors' knowledge, this is the first proof-of-concept of a standardized interview method for cue exposure in trauma CRP studies. Indeed, while some prior work

has utilized interviews (i.e., a detailed verbal description) as CRP cues (e.g., McGuire et al., 2018), standardization processes were not described. The present study provides evidence supporting a more feasible personalized CRP than the two sessions required for developing and administering personalized script-driven imagery, which would aid in reducing CRP study attrition (e.g., Coffey et al., 2006), particularly when studying avoidant populations like those with PTSD. Indeed, it is important to have a feasible protocol and representative samples in CRP research since this research has potentially important clinical implications. Specifically, CRPs can be used to study the antecedents of substance use and relapse, which may then inform the development and refinement of cue exposure treatments (Drummond, 2000).

There were some additional findings of note. Importantly, primary findings did not change in direction, significance, or magnitude when we controlled for order of cue presentation in sensitivity analyses, with the exception of losing significance of the main effect of PTSD symptoms on PA. Additionally, the effects of the interview cue manipulation were much stronger for NA than for PA, with respect to there being no main effect of cue type for PA and more variance accounted for in our NA model. A similar pattern of ambivalence in PA responses has been obtained in prior research using the gold standard brief personalized trauma vs. neutral cues (e.g., Nosen et al., 2012) and suggests that the Sinha and Tuit (2012) trauma interview is primarily a NA induction.

While the findings of the present study are an important first step in validating the use of semi-structured standardized interviews following the protocol by Sinha and Tuit (2012) in a single session, several methodological considerations should be noted. First, our sample was only comprised of individuals with trauma histories who use cannabis.

While we did run a supplementary analysis on alcohol craving, these analyses were restricted to the subsample of drinkers and thus were underpowered for testing interactions with PTSD symptoms. Moreover, the sample was selected to be regular cannabis users, perhaps explaining the weaker effects of cue exposure for alcohol (vs. cannabis). Additionally, the single item nature of the alcohol craving measure compared to the multi-item cannabis craving measure may have introduced measurement error. Thus, we recommend further validation of our methodology across other substance-using populations (e.g., alcohol, cocaine users) with multi-item craving measures, as traditional CRPs have been useful in studying this comorbidity in a variety of substance-using populations (Vujanovic et al., 2018a). Second, our study assessed cannabis craving and affect. Future work should test the validity of this CRP method for other cue reactivity measures, such as cognitive reactions (e.g., attentional tasks) and physiological reactions (e.g., salivation). Third, the present findings are simply the first step in evaluating the validity of this CRP methodology. For example, reactivity elicited by the interviews was not directly compared to that elicited by gold standard methods (e.g., Coffey et al., 2006) within the same sample. Thus, convergent validity of the interviews has yet to be demonstrated; however, direct comparisons will always be confounded by potential order effects since the gold standard requires the interview to precede the briefer CRP session. Finally, while the proportion of variance in our outcomes explained by our manipulation was similar to that obtained in similar studies using traditional CRP methods (e.g., audio cues), we cannot assert full confidence that the interview achieves similar effects to other types of cue manipulations from these indirect comparisons alone. Future research should

aim to quantify the magnitude of trauma cue-induced craving and affective responses across the literature to date to provide a more robust comparator for new CRP paradigms.

It is also important to note that our semi-structured interviews were not completely standardized. For example, because the interview protocol by Sinha and Tuit (2012) calls for the participant to tell their story in an uninterrupted fashion, interviews may vary in length and the degree of detail elicited. Furthermore, prompts from the researcher do not necessarily occur in a standardized order and not all prompts are required in every interview. Future research should compare the semi-structured interview to a more standardized version of the interview. Strict standardization might increase the magnitude of reactivity effects by ensuring imaginal exposure to all important sensory details. Alternatively, strict standardization might instead disrupt the flow of the interview, thus interrupting the participants' experience of reliving the event, possibly enough to dampen affective and/or craving responses to the cue. Moreover, future researchers may wish to establish the inter-rater reliability of this interview (i.e., across interviewers). Despite its limitations, the present study suggests that a single-session interview cue manipulation can elicit significant effects on cannabis craving, NA, alcohol craving, the same effects that are obtained by procedures requiring at least two sessions (Berenz et al., 2021; Nosen et al., 2012).

Table 2.1. Descriptive and clinical characteristics.

Demographic and clinical characteristics		N (%)/Mean (SD)
Age (in years)		37.8 (10.02)
Sex	Male	17 (34%)
	Female	33 (66%)
Military status	Previous or current military	10 (20%)
	Civilian	40 (80%)
Cannabis Use Disorder status	None	15 (30%)
	Mild	12 (24%)
	Moderate	6 (12%)
	Severe	17 (34%)
Cannabis Use Disorder symptom severity		3.72(2.84)
Past month PTSD	Present	29 (58%)
	Absent	21 (42%)
PTSD symptom severity		10.52 (4.88)
Primary trauma type	Interpersonal	41 (82%)
	Intrapersonal	9 (18%)
Past month substance use	Alcohol	37 (74%)
	Nicotine/Tobacco	20 (40%)
	Hallucinogens	2 (4%)
	Prescription Stimulants	5 (10%)
	Opiates	1 (2%)
	Sedatives	8 (16%)
Prescribed psychiatric medication	Yes	35 (70%)
	No	15 (30%)

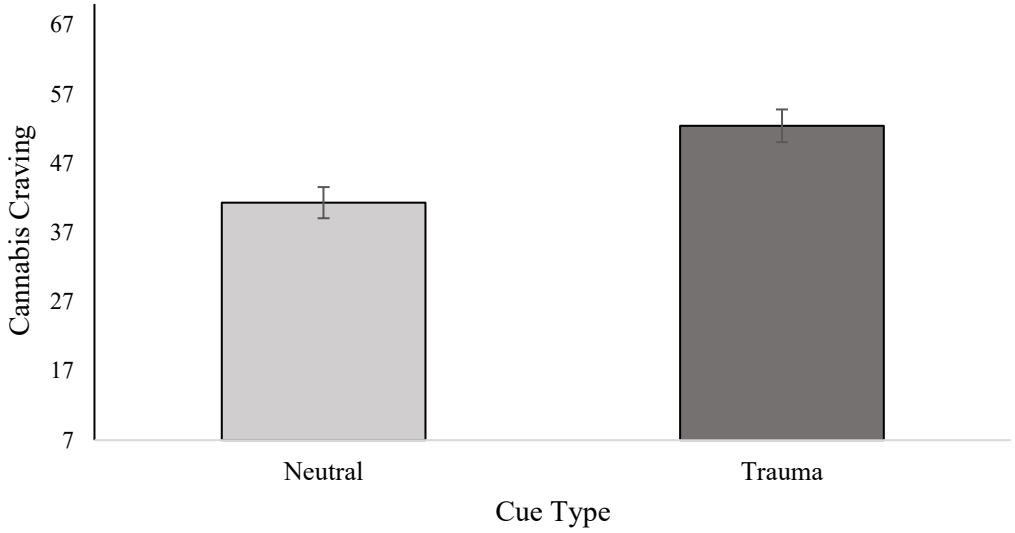
Note. Cannabis use disorder status and symptom count: Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015); Past month PTSD and PTSD symptom severity: Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2018); Trauma type: Life Events Checklist (LEC; Gray et al., 2004). Gender corresponded with sex in 98% of cases; thus, only sex is reported.

Table 2.2. Linear mixed models' omnibus results.

	Estimate (*b*)	CI (95%)	*p*
Outcome: Cannabis Craving		Marginal R^2 = 0.123 / Conditional R^2 = 0.936	
Condition (Neutral = 0)	0.94	0.48 – 1.40	0.001**
PTSD Symptoms	0.04	-0.04 – 0.11	0.342
Condition*PTSD Symptoms	-0.00	-0.04 – 0.04	0.952
Outcome: Negative Affect		Marginal R^2 = 0.460 / Conditional R^2 = 0.922	
Condition (Neutral = 0)	5.71	2.24 – 9.19	0.002**
PTSD Symptoms	0.18	-0.15 -0.50	0.289
Condition*PTSD Symptoms	0.35	0.05 – 0.65	0.026*
Outcome: Positive Affect		Marginal R^2 = 0.175 / Conditional R^2 = 0.917	
Condition (Neutral = 0)	-2.44	-5.14 – 0.54	0.113
PTSD Symptoms	-0.59	-0.95 - -0.23	0.002**
Condition*PTSD Symptoms	0.04	-0.22 – 0.30	0.762

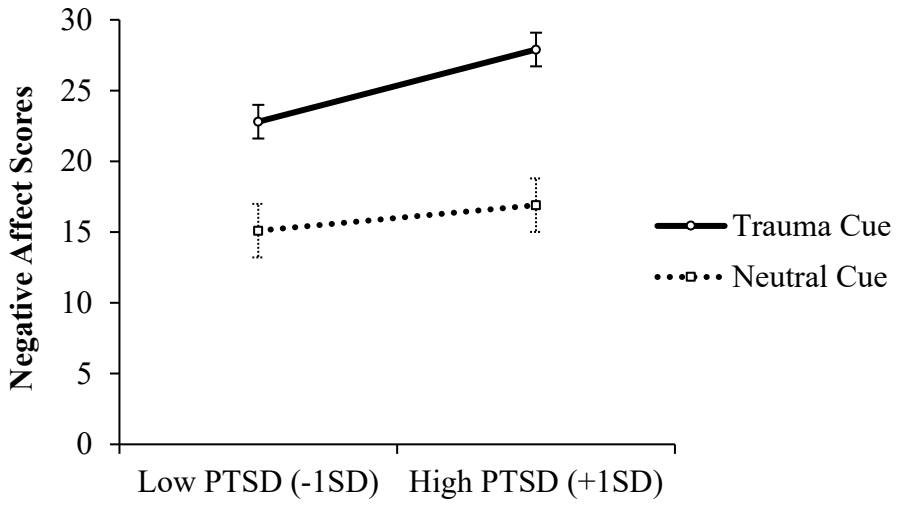
Note. * $p < .05$, ** $p < .01$.

Figure 2.1. Average cannabis craving scores on the MCQ-SF across trauma vs. neutral interview conditions.



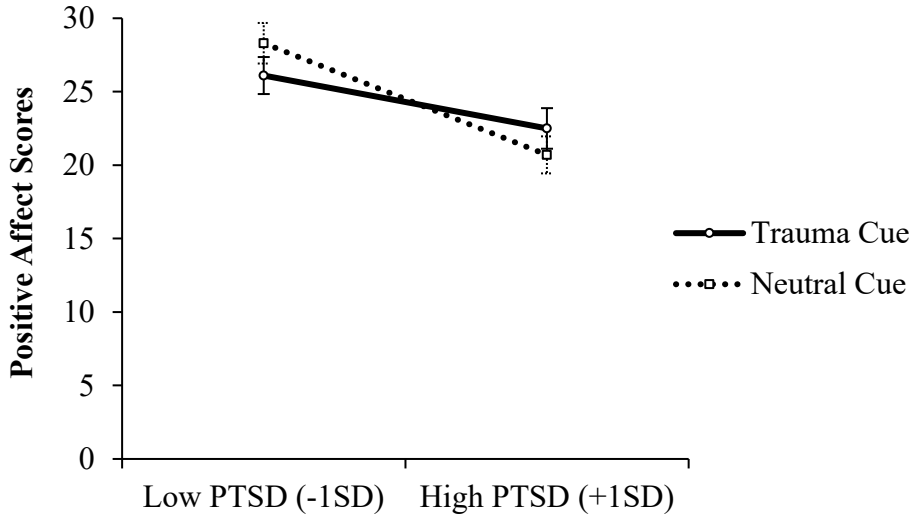
Notes: Error bars represent the standard error. MCQ-SF = Marijuana Craving Questionnaire – Short Form (Heishman et al., 2009).

Figure 2.2. Interactive effect between PTSD and cue condition (trauma vs. neutral) on negative affect.



Notes: Error bars represent the standard error. PTSD symptom severity assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2018); Negative affect assessed with the negative affect scale of the PANAS-SF = Positive and Negative Affect Schedule – Short Form (Serafini et al., 2016).

Figure 2.3. Effect of PTSD symptom severity on positive affect in each cue condition (trauma vs. neutral)



Notes: Only the main effect of PTSD was significant; no interaction was detected. Error bars represent the standard error. PTSD symptom severity assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2018); PANAS-SF = Positive and Negative Affect Schedule – Short Form (Serafini et al., 2016).

CHAPTER 5: TRANSITION FROM STUDY 2 TO STUDY 3

There are high rates of attrition from the first to the second session in CRP research relevant to PTSD-SUD comorbidity when the gold-standard two-session CRP is used (Coffey et al., 2006). Study 2 provided some evidence to support the use of a single-session CRP, consisting of a semi-structured interview (Sinha & Tuit, 2012) in trauma-exposed cannabis users. Specifically, I found the expected effects of trauma-cue induced cannabis craving and negative affective responses. The main effect of the trauma cue on negative affect was qualified by an interaction effect with PTSD symptoms (greater effect of trauma cues in those with greater PTSD symptoms); however, the predicted interaction did not emerge for cannabis craving. Positive affect was not predicted by trauma cue exposure but was lower among those with PTSD regardless of interview type (trauma vs. neutral). Importantly, the results of Study 2 have added to the cue reactivity literature by replicating these commonly detected patterns of effects in a population of trauma-exposed *cannabis* users. Moreover, I elicited effects similar in magnitude to those elicited by a two-session trauma CRP, suggesting the additional session may not be necessary. A valid single session trauma CRP provides a means of reducing the attrition common to the gold-standard two session trauma CRP which may bias results towards those with less extensive trauma-related avoidance (a symptom of PTSD).

As discussed in the General Introduction in Chapter 1, in dual process models of addiction (Wiers et al., 2013), cannabis craving is considered a controlled cognitive process. While Study 1 shows effects of trauma cue exposure on an addiction relevant controlled cognitive process (i.e., craving), it remains to be established whether trauma cue exposure might also activate more automatic cognitive processes that might also

impact cannabis use, particularly in those with greater PTSD symptoms. Now that I have shown that previously-established findings with a traditional two session trauma CRP in activating increased craving and negative affect among cannabis users with trauma histories (Romer-Sanchiz et al., 2022) can be observed in this population with only a single-session CRP (semi-structured interview), I wanted to test if this semi-structured interview about one's trauma would also activate cannabis-relevant automatic cognitions that may contribute to PTSD-CUD comorbidity. Specifically, I hypothesized main effects of trauma cue exposure, cannabis stimuli, and PTSD on approach biases, as well as a three-way interaction. In plain language, I expected those with more severe PTSD symptoms (on the PCL-5; Bovin et al., 2016) would demonstrate greater approach bias towards cannabis (vs. neutral) stimuli, particularly following trauma (vs. neutral) cue exposure.

My primary justification for Study 3 was based on Study 1, Chapter 2, as only two peer-reviewed manuscripts (Beckham et al., 1996; Read et al., 2017) and one dissertation (Dutton, 2017) used a trauma CRP to examine the effects of trauma cue exposure on automatic cognitive processes relevant to addictive behaviors. Additionally, none of these three prior automatic cognitions studies had examined cannabis users with trauma histories, and none had specifically examined automatic approach bias. Thus, the aims of Study 3 were two-fold. First, to my knowledge Study 3 was the first published experimental test of trauma cue-induced cannabis approach bias in cannabis users with trauma histories. Second, as I provided a proof-of-concept for a single-session trauma CRP in Study 2, Study 3 aimed to use the same CRP to test predictions emerging from learning theories of addiction described in Chapter 1 (Baker et al., 2004; Stascewicz &

Maisto, 1993) on automatic cannabis approach bias. Indeed, such theories posit robust memory connections are made between trauma cues, cannabis, and approach behaviors, leading to the activation of an automatic approach bias toward cannabis upon exposure to trauma cues. This effect is expected to be heightened in individuals with greater PTSD symptoms, as they are especially inclined to seek escape or avoidance from the negative affect conditioned to trauma cues via substance use (Baker et al., 2004). Automatic approach bias was chosen as the cognition to tap in this case as they simulate real-world scenarios involving cannabis and other environmental stimuli by requiring participants to actively engage with stimuli and make approach or avoidance movements. This task provides a nuanced understanding of cognitive biases by directly assessing automatic behavioral action tendencies rather than relying solely on self-report measures or reaction times alone (Solzbacher et al., 2022).

In transitioning from Study 2 to Study 3, the shift from utilizing the CAPS to the PCL-5 was motivated by the nature of the severity scores in Study 2, which were based on symptom counts. The absence of any observed interaction between cue condition and PTSD on craving contradicted the hypothesis derived from both theoretical considerations and the findings of Romero-Sanchiz et al. (2022). It is plausible that the measure of PTSD symptoms lacked the necessary sensitivity to detect the interaction. Therefore, the decision was made to adopt the PCL-5, where participants rate the severity of each symptom individually, allowing for a more nuanced analysis compared to the symptom count approach of the CAPS. This adjustment aimed to enhance the likelihood of detecting an interaction between cue condition and PTSD on the cognitive measure, specifically cannabis approach bias.

CHAPTER 6. DO TRAUMA CUE EXPOSURE AND/OR PTSD SYMPTOM SEVERITY INTENSIFY SELECTIVE APPROACH BIAS TOWARD CANNABIS CUES IN REGULAR CANNABIS USERS WITH TRAUMA HISTORIES?

The manuscript prepared for this study is presented below. Readers are advised that Sarah DeGrace, under the supervision of Dr. Sherry Stewart, was responsible for designing the study, developing the research hypotheses, gaining ethical approval, collecting the data, training research assistants, preparing the dataset for analyses, conducting the analyses, and interpreting the study results. Sarah wrote the initial draft of the manuscript and received and incorporated feedback from her co-authors. Sarah submitted the manuscript to *Behaviour Research and Therapy* for peer review on May 5th, 2023, led the response to reviews and the revisions process, and the paper was published on October 25th, 2023. See Appendix C for permission from the publisher to include the manuscript in this thesis. The reference is as follows: DeGrace, S., Romero-Sanchiz, P., Tibbo, P., Barrett, S., Arenella, P., Cosman, T., Atasoy, P., Cousijn, J., Wiers, R., Keough, M. T., Yakovenko, I., O'Connor, R., Wardell, J., Rudnick, A., Carleton, R. N., Heber, A., & Stewart, S. H. (2023). Do trauma cue exposure and/or PTSD symptom severity intensify selective approach bias toward cannabis cues in regular cannabis users with trauma histories? *Behaviour Research and Therapy*, *169*, 104387. https://doi.org/10.1016/j.brat.2023.104387

Abstract

Trauma cue-elicited activation of automatic cannabis-related cognitive biases are theorized to contribute to comorbid posttraumatic stress disorder (PTSD) and cannabis use disorder (CUD). This phenomenon can be studied experimentally by combining the trauma cue reactivity paradigm (CRP) with cannabis-related cognitive processing tasks. In this study, we used a computerized cannabis approach-avoidance task (AAT) to assess automatic cannabis (vs. neutral) approach bias following personalized trauma (vs. neutral) CRP exposure. We hypothesized that selective cannabis (vs. neutral) approach biases on the AAT would be larger among participants with higher PTSD symptom severity, particularly following trauma (vs. neutral) cue exposure. We used a within-subjects experimental design with a continuous between-subjects moderator (PTSD symptom severity). Participants were exposed to both a trauma and neutral CRP in random order, completing a cannabis AAT (cannabis vs. neutral stimuli) following each cue exposure. Current cannabis users with histories of psychological trauma (n=50; 34% male; mean age=37.8 years) described their most traumatic lifetime event, and a similarly detailed neutral event, according to an established interview protocol that served as the CRP. As hypothesized, an AAT stimulus type x PTSD symptom severity interaction emerged (p=.042) with approach bias greater to cannabis than neutral stimuli for participants with higher (p=.006), but not lower (p=0.36), PTSD symptom severity. Contrasting expectations, the stimulus type x PTSD symptoms effect was not intensified by trauma cue exposure (p=0.19). Selective cannabis approach bias may be chronically activated in cannabis users with higher PTSD symptom severity and may serve as an automatic cognitive mechanism to help explain PTSD-CUD co-morbidity.

Keywords: cue reactivity paradigm, CUD, PTSD, approach bias, trauma.

Introduction

Posttraumatic stress disorder (PTSD) is characterized by intrusive memories, physiological reactivity to and avoidance of trauma reminders, and negative mood following trauma exposure (American Psychiatric Association [APA], 2013). Of trauma-exposed individuals, 5.9-19.5% will meet diagnostic criteria for PTSD (Atwoli et al., 2015) while others may experience subthreshold PTSD symptoms; though not meeting criteria for a full PTSD diagnosis, subthreshold PTSD symptoms may nonetheless be distressing. Cannabis is commonly prescribed or self-administered to help with PTSD symptom management, with some experts suggesting cannabis as beneficial (Walsh et al., 2017). Emerging research provides preliminary support for this (Jetly et al., 2015); however, a recent review suggests the evidence-base supporting using cannabinoids for treating PTSD is currently slim and of low quality (McKee et al., 2021).

Emerging research suggests that cannabis use may be particularly risky for persons with PTSD. For example, cannabis use has been associated with worse PTSD outcomes longitudinally (Wilkinson et al., 2015) and a relationship has also been documented between medicinal cannabis use and cannabis dependence (Yarnell, 2015). High comorbidity rates have been reported between PTSD and cannabis use disorder (CUD; Walsh et al., 2014), leading some to caution against cannabis for PTSD treatment (APA, 2013). Cannabis as a medicant for PTSD remains controversial; nevertheless, experts agree that more research is needed to test potential mechanisms underlying PTSD-CUD co-occurrence.

One set of mechanisms potentially contributing to PTSD-CUD comorbidity involves cannabis-related cognitive processes thought to arise though classical and

operant conditioning. Individuals with PTSD who uses cannabis to cope with adverse reactions to trauma reminders form strong memory associations between the trauma cue, cannabis use, and desired relief outcomes (Romero-Sanchiz et al., 2022). On subsequent exposure to trauma cues (e.g., intrusive thoughts or nightmares about the trauma, external trauma reminders), memory associations with substance use and relief are activated, giving rise to trauma cue-elicited cannabis craving, which in turn promotes cannabis use (Romero-Sanchiz et al., 2022). This use of cannabis provides subjective relief from PTSD symptoms, thereby negatively reinforcing future cannabis use (Hawn et al., 2020) and strengthening memory associations. Consistent with this theory, among cannabis users with a history of trauma, exposure to personalized trauma cues led to greater self-reported cannabis craving than did exposure to personalized cannabis cues, particularly among those with higher PTSD symptom severity (Romero-Sanchiz et al., 2022).

Trauma cue-elicited cannabis craving represents only one motivational process arising through learning that might contribute to PTSD-CUD comorbidity. Specifically, automatic cognitive processes are thought to drive a phenomenon reported by many individuals with addictions that they sometimes find themselves engaged in their addictive behaviour without having made a conscious decision to do so and without having experienced a conscious craving to use (Wiers et al., 2016). Exposure to trauma cues in a cannabis user with PTSD could automatically activate strong memory associations between cannabis use and approach behaviour (Wiers et al., 2016). Cannabis approach bias is an automatically activated action tendency to approach cannabis, making cannabis use much more likely following cannabis cue exposure (Cousijn et al., 2011; Walsh et al., 2017). Approach biases can be studied in the lab with the approach-

avoidance task (AAT; Cousijn et al., 2011), a computerized reaction time (RT) task that uses substance-related (vs. neutral) visual stimuli to measure individual biases to approach or avoid the substance of interest. Approach bias towards cannabis stimuli appears stronger in heavier cannabis users than current non-users with limited cannabis use history and predicts escalations in cannabis use over time (Cousijn et al., 2011). Heavy cannabis users with deficient control over cannabis action tendencies are also more likely to show increases in cannabis-related problems over time (Cousijn et al., 2012).

The effects of trauma cue exposure on various substance-related cognitive biases can be experimentally examined using the cue-reactivity paradigm (CRP). CRPs involve exposing participants to validated audio and/or visual cues, often personalized to the individual's lived experience, pertaining to both a psychologically traumatic event (e.g., a past car accident) and a similarly detailed neutral control event (e.g., brushing one's teeth; DeGrace et al., 2022). This lab-based cue exposure serves as an experimental analogue for the real-world scenario of being faced with a trauma reminder. CRPs allow for examination of whether exposure to trauma (vs. neutral) cues elicit greater 'reactivity' on addiction-relevant outcomes, including substance-related cognitive biases (e.g., attentional bias towards alcohol cues on a computerized Stroop task; Read et al., 2017).

Recent evidence from a sample of individuals with trauma histories who regularly use cannabis suggests a structured interview protocol (Sinha & Tuit, 2012) focused on an individual's worst lifetime trauma can serve as a valid lab-based CRP (Study 2, Chapter 4). The interview-based CRP elicited greater self-reported cannabis craving and, particularly among those with greater PTSD symptoms, greater negative affect, than the

interview-based neutral CRP (Study 2, Chapter 4); however, it remains to be determined whether trauma cue exposure via the interview-based trauma CRP would have similar effects in activating automatic cannabis-related cognitive biases, particularly among participants with greater PTSD symptoms. The present study used the interview-based CRP (Study 2, Chapter 4; Sinha & Tuit, 2012) to examine the impact of personalized trauma versus neutral cue exposure on participants' degree of automatic approach bias towards cannabis stimuli on the cannabis AAT (Cousijn et al., 2011), in the same sample used in our CRP validation study (Study 2, Chapter 4). We also assessed participants' PTSD symptom severity[9] (Blevins et al., 2015) to examine trauma cue-elicited activation of the cannabis approach bias among those with higher vs. lower PTSD symptom severity. We hypothesized: [H1] a greater approach bias towards cannabis than neutral stimuli on the AAT in those with higher versus lower PTSD symptom severity; and [H2] that the stimulus type effect on approach bias (cannabis > neutral) in those with higher PTSD symptom severity would be stronger in the trauma versus neutral cue condition.

Method[10]

Participants.

Participants (n = 50; 34%M; M age=*37.8* years, *SD=10.02*) were recruited via social media platforms, Veterans' associations, local mental health clinical services, and community posters (e.g., supermarkets) to take part in an in-person study examining associations between trauma exposure and cannabis use. Eligible respondents had to meet the following inclusion/exclusion criteria: aged 19-65 years; no diagnosis of serious

[9] PTSD symptom severity was assessed using a validated self-report measure as in Romero-Sanchiz et al. (2022) rather than the CAPS-5 symptom count (Weathers et al., 2018) used in Study 2 for the reasons outlined in Chapter 3 (bridging chapter).

[10] All methods and measures described were approved by the Nova Scotia Health Research Ethics Board (ref #: 1026315).

mental illness (i.e., bipolar, schizophrenia, or other psychotic disorder); at least one lifetime exposure to a potentially traumatic event on the Life Events Checklist (LEC; Gray et al., 2004); and current regular cannabis use (Gabrys & Porath, 2019; ≥1 g/week in the last month on the Cannabis Timeline Followback [C-TLFB]; Sobell & Sobell, 1992).

Measures.

Trauma Exposure. The Life Events Checklist (LEC; Gray et al., 2004) is a 17-item self-report measure used to assess criterion A of PTSD (APA, 2013). In the present study, the LEC was used to assess participant exposures to qualifying potentially psychologically traumatic events. Participants who indicated exposure to multiple potentially psychologically traumatic events during their lifetimes were instructed to focus on the most distressing event for the PTSD measures and the trauma CRP described below.

Post Traumatic Stress Disorder. The 20-item self-report PTSD Checklist for DSM-5 (PCL-5) was used as a psychometrically-sound continuous measure of DSM-5 (APA, 2013) PTSD symptom severity (Blevins et al., 2015; Bovin et al., 2016). Each item is rated on a 0-4 severity scale and item scores are summed for a total score and four subscales corresponding to each PTSD symptom cluster. PCL-5 scores for our sample showed good internal consistency for the total score ($\alpha = .88$) and acceptable-to-good internal consistency for the four subscales ($\alpha \geq .6$ for clusters B [re-experiencing], C [avoidance], and E [hyperarousal]; $\alpha > .8$ for cluster D [negative cognitions]).[11] The sample was further characterized by quantifying what proportion met DSM-5 (APA,

[11] While $\alpha \geq .7$ is usually considered an acceptable level of internal consistency, $\alpha \geq .6$ is considered acceptable for short scales (Loewenthal & Lewis, 2001).

2013) criteria for past-month PTSD based on the 20-item Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) interview (Weathers et al., 2018).

Cannabis Use and CUD. The sample was also characterized by quantifying what proportion met DSM-5 criteria for past-year CUD based on the 11-item Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV; First, 2015; Osório et al., 2019) SUD module. The Cannabis Timeline Follow Back (C-TLFB; Norberg et al., 2012; Robinson et al., 2014) was used to assess the frequency (number of use days) and dose (in grams) of cannabis used in the past 30 days. Participants were guided by an interviewer to estimate on a calendar how many days in the past month they had used cannabis and how much cannabis (in grams) was used each of those days. The C-TLFB responses were used to verify eligibility (≥1 g/week in the last month).

Anxiety. The Generalized Anxiety Disorder-7 (GAD-7; Spitzer et al., 2006) is a seven-item measure of anxiety disorder symptoms with good reliability and validity (Spitzer et al., 2006). Participants were asked to rate how often they had experienced each anxiety symptom over the past two weeks on a scale from 0 (not at all) to 3 (nearly every day). Scores were summed (possible range: 0 – 21), with higher scores indicating greater endorsement of anxiety symptoms. The GAD-7 has excellent internal consistency, good test re-test reliability, and procedural validity (Spitzer et al., 2006). This measure was used as a covariate to establish specificity of findings to PTSD symptoms in sensitivity analyses.

Depression. The Beck Depression Inventory (BDI-II; Beck et al., 1996) is a 21-item measure of endorsement of depressive symptoms. Specifically, participants indicated on a 0 (e.g., I do not feel sad) to 3 (e.g., I am so sad that I can't stand it) scale

their intensity of each depressive symptom over the past two weeks. Scores were summed (possible range: 0 – 63), with higher scores indicating greater endorsement of depressive symptoms. The BDI-II has good reliability and discriminant validity (Wang & Gorenstein, 2013). This measure was used as a covariate to establish specificity of findings to PTSD symptoms in sensitivity analyses.

Approach Avoidance Task. The cannabis AAT was adapted from an existing validated alcohol AAT (Wiers et al., 2009) available through Inquisit (Inquisit 5, 2016), a psychological task software. Our within-subjects design used two versions of the AATs with distinct stimuli developed to reduce practice effects across cue conditions. Each AAT included a total of 80 stimuli: 20 cannabis-related (e.g., *bong*) and 20 neutral (e.g., *pencil*), as well as 20 positive (e.g., *diver*) and 20 negative (e.g., *snake*) stimuli. Positive and negative stimuli were used as fillers (Wiers et al., 2009). Cannabis and neutral stimuli were drawn from an existing, validated stimulus set, with both types of stimuli visually matched for physical attributes (Macatee et al., 2021). Participants were shown 40 cannabis-related stimuli and 40 neutral stimuli across the two AAT versions. Each stimulus appeared in one of two orientations (i.e., portrait or landscape). Participants were instructed to either "pull" the stimulus towards them (by pulling the mouse towards themselves) or to "push" the stimulus away from them (by pushing the mouse away from themselves) as quickly as possible based on the orientation of the stimulus. A pull response resulted in the picture becoming bigger on the screen to give the appearance of movement towards the participant; a push response resulted in the picture becoming smaller on the screen to give the appearance of movement away from the participant. Assignment of push and pull responses to each picture orientation (portrait or landscape)

was randomized. Reaction times for each push and pull response were computer recorded (in milliseconds) as were errors in orientation identification. A cannabis approach bias is said to occur when the pull response is completed significantly more quickly than the push response, only for the cannabis stimuli (Cousijn et al., 2011). Stimuli were presented in a pseudo-random order with no more than three of the same orientation or stimulus type in a row (Wiers et al., 2009).

Procedure.

Telephone Screening. In a telephone-administered screening, participants answered questions about their demographics, cannabis use, and history of trauma exposure (LEC) to ensure eligibility. If eligible, they then completed the PCL-5 and were booked for an in-person lab session. They were sent a virtual consent form to complete prior to the lab session.

Lab Session. To avoid potential confounding effects on our experimental manipulation, participants were required to remain abstinent from cannabis, nicotine (smoked or vaped), alcohol, and illicit drugs for 12 hours, and from caffeine for 2 hours, prior to testing. Abstinence from substances (except cannabis) was verified using a urine test and breathalyzer; abstinence from cannabis was verified verbally. Participants first completed the C-TLFB and then were assessed for past-month PTSD and CUD using the CAPS and SCID, respectively. Participants were then asked to describe the most psychologically traumatic event in their lifetime and an emotionally neutral event (e.g., a morning routine); participants were asked to share sensory details of the event such as associated sights, smells, and sounds. These semi-structured interviews were administered in randomized order, audio-recorded, personalized to each participant

following an established protocol (Sinha & Tuit, 2012), and validated for use as CRPs (Study 2, Chapter 4). Following both the trauma and neutral interview (hereafter referred to as 'cue'), participants completed a different version of the computerized cannabis AAT.

Data Preparation and Analysis.

Power Analysis. We calculated the number of participants needed for our study design using published guidelines (Judd et al., 2017). We specified a CNC design indicating the following: participants crossed within condition; targets nested within condition; and two random factors (i.e., target and participants) crossed within condition. With power set at .90 and 80 total targets (i.e., cannabis and neutral stimuli), we determined that we would need n=50 participants to detect a medium effect. We reasoned that a medium effect size could be clinically meaningful (i.e., have potential clinical practice implications).

AAT scoring. AAT scores were corrected for outliers by removing all reaction times $^{+/-}$ 3 standard deviations from the participants' mean reaction time, as well as any scores less than 200ms or more than 2000ms to account for inattention or anticipatory response errors (Cousijn et al., 2011). Error trials (i.e., incorrectly identified orientation) were also removed, and error rates were calculated. If a participant's error rate exceeded 60% on either of the two versions of the AAT, data for that AAT version was treated as missing (Cousijn et al., 2014). One participant had >60% errors on both versions of the AAT and another two had >60% errors on only one version of the AAT (i.e., in only one cue condition).[12] Next, each participant had eight median AAT reaction time scores

[12] Our sample had an overall mean error rate of 17.5%.

calculated in the context of each cue type (neutral vs. trauma), stimulus type (neutral vs. cannabis), and response type (pull vs. push). As with prior AAT research (Cousijn et al., 2011), approach bias scores were calculated by subtracting participants' median approach (i.e., pull) from their median avoidance (i.e., push) reaction times, with more positive scores indicating stronger approach bias to the given stimuli (i.e., quicker approach [pull] than avoidance [push] responses; Cousijn et al., 2011). A Monte Carlo split-half reliability estimate for the AAT was calculated using an established protocol (Pronk et al., 2022) wherein we calculated an RT difference score (push-pull) for each stimulus and stratified on study design characteristics (AAT stimulus type x cue condition). We obtained evidence of acceptable reliability (Spearman Brown coefficient = 0.83).

Results

Sample characteristics. The mean PCL-5 score for the sample was 38.5 (*SD*=13.4; range=6-68), which was lower than that of a Canadian psychiatric outpatient sample with diagnosed PTSD (i.e., *M*=56.6, *SD*=19.5; Boyd et al., 2022), higher than a trauma-exposed Canadian psychiatric outpatient sample without PTSD (i.e., *M*=33.56, *SD*=13.7; Boyd et al., 2022), and above a validated cut-off for probable PTSD (i.e., $\geq$33; Bovin et al., 2016). More than half of our sample (62%) scored at or above this PCL-5 clinical cut-off. Approximately half of our sample (58%) met criteria for past-month PTSD based on the CAPS-5 interview (Weathers et al., 2018). The mean scores on the GAD-7 (Spitzer et al., 2006) and BDI-II (Beck et al., 1996) indicated that the average participant was experiencing both anxiety and depressive symptoms of moderate severity. Many (70%) met criteria for past-year CUD on the SCID (First et al., 2015) with mild (2-3 symptoms; 24%), moderate (4-5 symptoms; 12%), or severe CUD (6+ symptoms; 34%;

APA, 2013). Demographic and clinical characteristics of the sample are provided in Supplemental Table 3.1.

Linear mixed models (R v. 4.2.1; package lme4) were used to examine the main and interactive effects of cue type (fixed effect; neutral vs. trauma), AAT stimulus type (fixed effect; neutral vs. cannabis), and continuous PTSD symptom severity on approach bias scores, allowing us to examine both hypotheses in a single analysis. Participants were inputted as a random effect and a restricted maximum likelihood model was used. The omnibus model (see Table 3.1) evidenced a statistically significant two-way interaction between AAT stimulus type (cannabis vs. neutral) and PTSD symptoms (t[137]=2.05, p=.042, b=2.20, 95% CI [0.12 – 4.28]; see Figure 3.1). We probed this two-way interaction by examining the simple main effects of AAT stimulus type at high (+1SD) and low (-1SD) PTSD symptom severity levels, collapsed across cue type (see Figure 3.1). Consistent with H1: a statistically significant simple main effect of stimulus type was observed at high PTSD symptom severity (t[137]=-2.81, b=-45.2, p=0.006) with greater approach bias towards cannabis than neutral stimuli; and no statistically significant simple main effect of stimulus type was observed at low PTSD symptom severity (t[137]=-0.94, b=-15.4, p=0.36; see Figure 3.1). Contrary to H2, the three-way interaction between AAT stimulus type, PTSD symptoms, and cue type was not statistically significant (see Table 3.1).

Significance of the two-way interaction between AAT stimulus type and PTSD symptoms persisted when order of cue presentation (trauma or neutral first), frequency and quantity of past month cannabis use (on the C-TLFB; Sobell & Sobell, 1992), and past year CUD symptom count on the SCID (First et al., 2018), were controlled for in a

single model (t[137]=2.02, p=0.045, *b*=2.20, 95% CI [0.10 – 4.09]. This interaction also persisted when all three participants with AAT error rates greater than 60% overall were removed entirely (t[135]=2.48, p=0.014, *b*=2.58, 95% CI [0.57 – 4.60].[13] This interaction further persisted when controlling for depression, measured using the BDI-II (Beck et al., 1996; t[137] = 2.04, p = .043, *b*=2.20, 95% CI [0.12 – 4.28]) but became marginally significant when controlling for anxiety, measured using the GAD-7 (Spitzer et al., 2006; t[137] = 1.85, p = .065, b=2.29, 95% CI [-0.09 – 4.67]). Nonetheless, probing of the latter marginal two-way interaction revealed that the simple main effect of stimulus type remained significant at high levels of PTSD (t[119]=2.59, p=0.011) and non-significant at low levels of PTSD (t[119]=0.97, p = .333) when controlling anxiety scores.

As an additional set of exploratory analyses, we re-ran our original model replacing total PTSD symptoms (PCL-5 total scores) with each PCL-5 subscale score in turn (representing severity of each PTSD symptom cluster). Only one symptom cluster, cluster E (hyperarousal), produced a significant two-way interaction between AAT stimulus type and PTSD symptoms (t[137]=2.49, p=.014, *b*=8.20, 95% CI [1.84 – 14.56]) suggesting that the original interaction effect is driven by selective approach toward cannabis stimuli among those with high PTSD hyperarousal symptoms, in particular. See Supplementary Tables 3.2-3.9 for a full presentation of these sensitivity and additional exploratory analyses.

[13] In this analyses, a main effect of stimulus type also emerged (t[135]=-2.00, b=-126.47, p=0.047, 95% CI [-248.48 - -4.46] with approach bias to cannabis stimuli (M=58.0, SE=11.4) being significantly greater (t[135] = -2.46, p=.017) than to neutral stimuli (M=30.2, SE=11.0).

Discussion

The current study was designed to quantify automatic approach bias towards cannabis (vs. neutral) stimuli among trauma-exposed cannabis users with varying PTSD symptom severities following exposure to a personalized trauma (vs. neutral) cue. Consistent with H1, approach bias was stronger towards cannabis than neutral stimuli at higher PTSD symptom severity. Contrary to H2, the selective approach bias towards cannabis in participants with higher PTSD symptoms was not intensified by trauma cue exposure.

The finding that participants with higher PTSD symptoms (particularly PTSD hyperarousal symptoms) showed greater approach bias towards cannabis (vs. neutral) stimuli extends prior work demonstrating that automatic approach towards cannabis stimuli is greater among heavy cannabis users compared to controls (Cousijn et al., 2011). The fact that this AAT stimulus type x PTSD symptoms interaction persisted in sensitivity analyses even after controlling cannabis use levels, CUD, depressive, and anxiety symptoms suggests this approach bias towards cannabis in those with higher PTSD symptoms was not simply due to greater cannabis use/problems or to greater depression or anxiety. The result suggests that selective cannabis approach bias may be a cognitive mechanism contributing to PTSD-CUD comorbidity (Walsh et al., 2014). Moreover, this effect was unexpectedly not intensified by trauma cue exposure, suggesting the tendency to selectively approach cannabis may be chronically activated in those with higher PTSD symptoms. Given research linking cannabis approach bias on the AAT to longitudinal increases in cannabis use (Cousijn et al., 2011), our results suggest

that cannabis users with higher PTSD symptoms may be at risk of escalations in their cannabis use over time.

There are several possible explanations for our not observing evidence of the hypothesized three-way interaction between AAT stimulus type (cannabis vs. neutral), PTSD symptom severity, and cue type (trauma vs. neutral) on approach bias scores. The cue manipulation was effective given the trauma verses neutral interview elicited the expected changes in affect and conscious cannabis craving (Study 2, Chapter 4); nevertheless, an interview-based CRP might have been so long as to allow for habituation to the trauma cue and consequent dissipation of the hypothesized trauma cue-elicited enhancement of cannabis approach bias in higher PTSD participants. Alternatively, placement of the AAT immediately following cue exposure may have been too soon to observe our predicted trauma cue effects in intensifying automatic cannabis approach bias at higher PTSD symptom levels. The trauma interview may elicit distractingly high levels of negative affect (Study 2, Chapter 4) and/or rumination among participants with higher PTSD symptoms, interfering with the emergence of a strengthened cannabis approach bias. Alternatively, trauma cue exposure may only intensify selective cannabis approach bias in higher PTSD participants if cannabis is simultaneously available. Trauma cue exposure studies in the PTSD-SUD field often pair trauma cue exposure with in vivo substance cue exposure (see Study 1, Chapter 2). Two studies using RT-based cognitive tasks show that trauma cue exposure causes a general slowing of cognitive processing in those with higher PTSD symptoms (Read et al., 2017; Zinchenko et al., 2017). The cannabis AAT is also an RT task, which suggests a reduction in cognitive resources caused by preoccupation with the trauma reminder (Read et al., 2017;

Zinchenko et al., 2017) could have adversely impacted our cannabis AAT validity following trauma cue exposure in participants with higher PTSD symptoms. Future studies could explore these possibilities using a more standard short audio-visual cue as the CRP (Study 1, Chapter 2), placing the cannabis AAT further out from the interview-based CRP, simultaneously presenting in vivo cannabis cues when conducting the trauma CRP (Study 1, Chapter 2), or using non-RT based automatic cannabis-related cognitive bias measures such as word association tasks (Ames et al., 2007; see also Study 5, Chapter 10).

The current study had several potential limitations. First, a variety of cannabis-related stimuli were used in the AAT (e.g., flower, dabs, vapes), but other common stimuli were not (e.g., edibles, oral concentrates like CBD oil). Some participants (e.g., those endorsing edibles but not smoked cannabis) may not have identified with the specific cannabis stimuli presented, perhaps reducing their inclination to automatically approach those stimuli. We observed expected effects of stimulus type on the AAT at higher PTSD symptom severity as hypothesized in H1, but the effect magnitude might have been minimized by lower-than-optimal applicability of the AAT cannabis stimuli for some participants. Second, a power analysis was used to determine that we were adequately powered to detect medium effects, but we were likely underpowered to detect small effects. The insufficient power may have obfuscated evidence supporting the hypothesized three-way interaction in H2, as higher-order interactions do require additional power, particularly for small effect sizes. However, if our study was underpowered to detect the hypothesized three-way interaction due to inadequate sample size, the moderating effect of trauma cue exposure on the selective cannabis approach

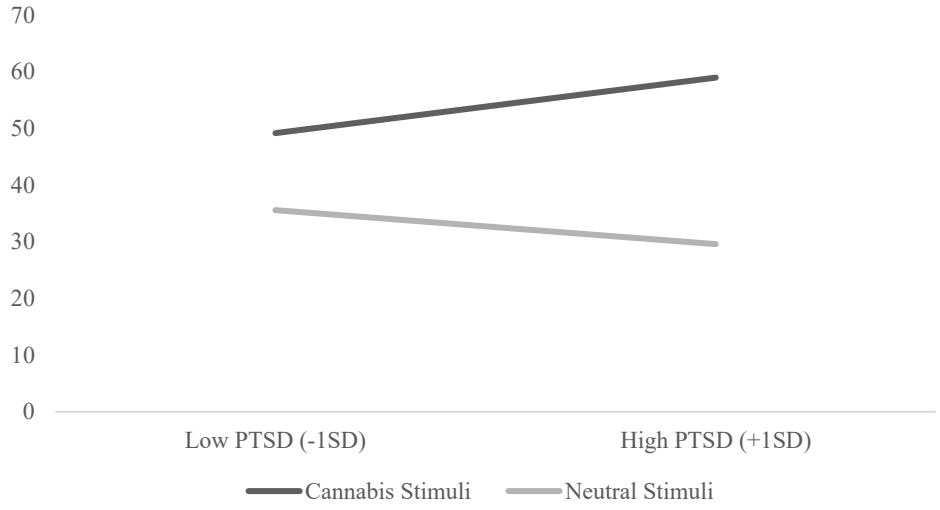
bias among those with higher PTSD symptom severity may be too small to be practically clinically meaningful. Third, while we saw a significant interaction between AAT stimulus type and continuous PTSD symptom severity, we were underpowered to conduct a sub-analysis among only those participants who met full diagnostic criteria for clinical PTSD on the CAPS (n = 29). In future, researchers may wish to replicate our analyses with a larger sample meeting the diagnostic threshold for PTSD to determine whether the current results stay the same regardless of PTSD diagnostic status or are different in this clinically relevant subgroup. Fourth, PTSD is not only comorbid with CUD but with other SUDs (e.g., Read et al., 2017) which also tend to co-occur with CUD (Budney et al., 2019); however, we did not assess for or exclude other forms of SUD. Thus, while we ruled out CUD symptoms as accounting for our cannabis approach bias findings in those with higher PTSD severity, we cannot rule out the impact of other forms of SUD. Finally, our planned analyses were not pre-registered on a publicly available platform prior to data collection[14].

Despite limitations, the current study was the first to combine a trauma CRP with a cognitive task used to measure automatic cannabis approach bias. The results were the first to demonstrate that selective cannabis (vs. neutral) approach bias is more pronounced at higher PTSD symptom severity – particularly higher severity of PTSD hyperarousal symptoms. Not finding evidence that trauma cues intensify the selective cannabis approach bias at higher levels of PTSD symptom severity may indicate that selective cannabis approach bias is chronically activated in cannabis users with higher PTSD symptoms. But the absent three-way interaction also raised important

[14] While our analyses were not pre-registered on a public platform, they were described in a Mental Health Commission of Canada – Cannabis Catalyst Grant which funded the project.

considerations for future research methods to determine conditions under which trauma cue exposure might activate or intensify automatic substance-related cognitive biases in those with higher PTSD symptoms. The current study has added to a small literature examining trauma cue exposure effects on automatic substance-related cognitions in substance users with varying PTSD symptom severity levels (Study 1, Chapter 2). Our results show that automatic approach bias towards cannabis stimuli is more pronounced in those cannabis users with higher PTSD symptom severity. This finding points to the role of automatic memory associations in explaining the greater potential of those with PTSD to develop problems with cannabis (Walsh et al., 2014), particularly given research showing that cannabis users with poor control over cannabis-related action tendencies on the AAT are more likely to develop cannabis-related problems over time (Cousijn et al., 2012). Given preliminary results that a cannabis approach bias modification intervention can reduce both conscious cannabis craving to a CRP and cannabis use (Sherman et al., 2018), our results may represent the first step towards opening new avenues for preventing and treating comorbid PTSD-CUD in cannabis users with trauma histories.

Figure 3.1. Two-way interaction between Approach-Avoidance Task (AAT) stimulus type (cannabis vs. neutral) and PTSD symptom severity (continuous PCL-5 scores; Blevins et al., 2015) on AAT approach bias scores (in msec) collapsed across trauma vs. neutral cue condition.



Note: Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Table 3.1. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT).

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	-10.14	84.26	-173.26 – 152.97	1.17	.904
PTSD Symptoms	-0.61	0.86	-2.31 – 1.09	-0.71	.482
Stimuli (Cannabis = 1; Neutral = 0)	-98.85	64.84	-224.36 – 26.66	-1.52	.130
Cue*PTSD Symptoms	0.34	1.39	-2.36 – 3.04	0.245	.806
Cue*Stimuli	128.36	100.59	-66.36 – 323.09	1.28	.204
PTSD Symptoms*Stimuli	2.20	2.20	0.12 – 4.28	2.05	.042*
Cue*Stimuli*PTSD Symptoms	-2.18	1.67	-5.42 – 1.05	-1.31	.193

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Blevins et al., 2018). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Study 3 Supplementary Materials

Supplementary Table 3.1. Demographic and clinical characteristics of the sample.

Demographic and clinical characteristics		N (%)/Mean (SD)
Age (in years)		37.8 (10.02)
Sex	Male	17 (34%)
	Female	33 (66%)
Anxiety symptoms		11.16 (5.35)
Depressive symptoms		22.10 (9.22)
Current cannabis use	Grams used in past month	54.40 (45.55)
	Days used in past month	26.42 (6.68)
Cannabis Use Disorder status	None	15 (30%)
	Mild	12 (24%)
	Moderate	6 (12%)
	Severe	17 (34%)
Cannabis Use Disorder symptom severity		3.72(2.84)
Cannabis consumption method	Smoke	38 (76%)
	Vaporize	12 (24%)
	Edibles	21 (42%)
Past month PTSD	Present	29 (58%)
	Absent	21 (42%)
Psychiatric medication	Yes	35 (70%)
	No	15 (30%)

Notes: Current cannabis use was assessed using the C-TLFB (Sobell & Sobell, 1992); Cannabis use disorder (CUD) status and severity were measured using the SCID-5 (First, 2015). Past month PTSD was determined using the CAPS-5 interview (Weathers et al., 2018) corresponded with sex in 98% of cases; thus, only sex is reported. Anxiety symptoms were assessed using the GAD-7 (Spitzer et al., 2006). Depressive symptoms were measured using the BDI-II (Beck et al., 1996).

Supplementary Table 3.2. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with participants exceeding error rate cut-off of 60% removed (N=47).

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	-24.11	84.95	-188.47 – 140.34	-0.28	.777
PTSD Symptoms	-0.73	0.86	-2.43 – 0.96	-0.85	.398
Stimuli (Cannabis = 1; Neutral = 0)	-126.47	63.05	-248.48 – -4.46	-2.00	.047*
Cue*PTSD Symptoms	0.54	1.40	-2.17 – 3.25	0.38	.702
Cue*Stimuli	148.60	100.99	-46. 84 – 344.03	1.47	.143
PTSD Symptoms*Stimuli	2.58	1.04	0.57 – 4.60	2.48	.014*
Cue*Stimuli*PTSD Symptoms	-2.46	1.66	-5.69 – 0.76	-1.47	.141

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2015) Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Supplementary Table 3.3. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with cannabis-related and order covariates included.

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	-9.22	84.43	-170.88 – 152.44	-0.11	.913
PTSD Symptoms	-0.49	0.87	-2.20 – 1.22	-0.56	.579
Stimuli (Cannabis = 1; Neutral = 0)	-98.62	65.55	-224.14 – 26.90	-1.50	.135
Cue Order (Trauma 1st = 1; Neutral 1st = 0)	17.42	17.62	-17.00 – 51.83	0.99	.329
Past Month Cannabis Use Frequency	0.08	1.38	-2.63 – 2.78	0.06	.955
Past Month Cannabis Use Quantity	-0.02	0.21	-0.44 – 0.40	-0.10	.935
CUD Symptoms	-3.90	3.12	-9.99 – 2.20	-1.25	.219
Cue*PTSD Symptoms	0.33	1.40	-2.35 – 3.01	0.24	.814
Cue*Stimuli	129.38	100.30	-62.67 – 321.43	1.29	.199
PTSD Symptoms*Stimuli	2.20	1.11	0.12 – 4.28	2.02	.045*
Cue*Stimuli*PTSD Symptoms	-2.19	1.66	-5.38 – 0.99	-1.32	.189

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. All other variables were inputted as covariates. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2016). CUD Symptoms assessed continuously as a symptom count from the SCID-5 (First, 2015). Past month cannabis use frequency and quantity assessed continuously with the Cannabis Timeline Follow Back (C-TLFB; (Sobell & Sobell, 1992). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Supplementary Table 3.4. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with depressive symptoms included as covariate.

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	-3.14	56.72	-112.66 – 106.38	-0.05	.956
PTSD Symptoms	-0.22	0.92	-2.02 – 1.59	-0.23	.816
Stimuli (Cannabis = 1; Neutral = 0)	-54.84	44.27	-140.32 – 30.64	-1.23	.218
Depressive Symptoms	-1.20	1.04	-3.26 – 0.85	-1.15	.254
Cue*PTSD Symptoms	0.34	1.37	-2.32 – 3.00	0.24	.805
Cue*Stimuli	85.37	68.25	-46.39 – 217.13	1.25	.213
PTSD Symptoms*Stimuli	2.20	1.07	0.12 – 4.28	2.04	.043*
Cue*Stimuli*PTSD Symptoms	-2.19	1.66	-5.40 – 1.02	-1.31	.189

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. All other variables were inputted as covariates. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2016). Depressive Symptoms assessed using Beck Depression Inventory (BDI-II; Beck et al., 1996). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Supplementary Table 3.5. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with anxiety symptoms included as a covariate.

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	21.08	51.47	-78.08 – 120.23	0.41	.683
PTSD Symptoms	-1.13	1.13	-3.35 – 1.09	-0.99	.324
Stimuli (Cannabis = 1; Neutral = 0)	-52.76	48.13	-145.48 – 39.96	-1.09	.275
Anxiety Symptoms	3.58	2.25	-0.85 – 8.01	1.58	.120
Cue*PTSD Symptoms	-0.69	1.32	-3.23 – 1.84	-0.52	.599
Cue*Stimuli	73.33	74.28	-69.77 – 216.42	0.98	.326
PTSD Symptoms*Stimuli	2.29	1.23	-0.09 – 4.67	1.85	.065†
Cue*Stimuli*PTSD Symptoms	-2.19	1.66	-5.40 – 1.02	-1.31	.189

Notes: †p < .07. *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. All other variables were inputted as covariates. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2016). Anxiety Symptoms assessed using GAD-7 (Spitzer et al., 2006). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Supplementary Table 3.6. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with total PCL-5 scores replaced with the Cluster B [Re-experiencing] Symptoms PCL-5 subscale.

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	-33.11	78.29	184.68 – 118.44	-0.42	.673
Cluster B Symptoms	-1.58	3.26	-8.02 – 4.86	-0.48	.631
Stimuli (Cannabis = 1; Neutral = 0)	-29.22	63.08	-151.33 -92.90	-0.46	.644
Cue*Cluster B Symptoms	2.90	5.14	-7.05 – 12.84	0.56	.574
Cue*Stimuli	67.84	95.55	-117.14 – 252.82	0.71	.479
Cluster B Symptoms*Stimuli	4.04	4.14	-3.97 – 12.06	0.97	.330
Cue*Stimuli*Cluster B Symptoms	-4.58	6.27	-16.74 – 7.58	-0.72	.467

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. All other variables were inputted as covariates. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2016) Cluster B subscale (items 1-5). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Supplementary Table 3.7. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with total PCL-5 scores replaced with the Cluster C [Avoidance] Symptoms PCL-5 subscale.

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	-1.28	68.22	-133.36 – 130.78	-0.01	.984
Cluster C Symptoms	-1.71	5.52	-12.59 – 9.17	-0.31	.759
Stimuli (Cannabis = 1; Neutral = 0)	-62.56	53.57	-166.28 – 41.16	-1.16	.245
Cue*Cluster C Symptoms	1.49	8.84	-15.64 – 18.61	0.16	.867
Cue*Stimuli	99.79	82.43	-59.80 – 259.37	1.21	.228
Cluster C Symptoms*Stimuli	12.56	6.94	-0.89 – 26.01	1.80	.073
Cue*Stimuli*Cluster C Symptoms	-13.43	10.68	-34.13 – 7.26	-1.23	.211

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. All other variables were inputted as covariates. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2016) Cluster C subscale (items 6-7). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Supplementary Table 3.8. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with total PCL-5 scores replaced with the Cluster D [Negative Cognitions] Symptoms PCL-5 subscale.

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	0.63	63.14	-121.60 – 122.85	0.01	.992
Cluster D Symptoms	-0.66	1.76	-4.14 – 2.83	-0.37	.711
Stimuli (Cannabis = 1; Neutral = 0)	-42.19	48.83	-136.72 – 52.35	-0.86	.389
Cue*Cluster D Symptoms	0.45	2.86	-5.10 – 6.00	0.15	.876
Cue*Stimuli	90.80	75.55	-55.46 – 237.06	1.20	.232
Cluster D Symptoms*Stimuli	3.49	2.23	-0.83 – 7.80	1.56	.120
Cue*Stimuli*Cluster D Symptoms	-4.33	3.43	-10.97 – 2.31	-1.26	.209

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. All other variables were inputted as covariates. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2016) Cluster D subscale (items 8-14). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

Supplementary Table 3.9. Linear mixed model omnibus test results predicting approach bias on the Cannabis Approach Avoidance Task (AAT) with total PCL-5 scores replaced with the Cluster E [Hyperarousal] Symptoms PCL-5 subscale.

Predictors	Estimate (b)	Std. Error	95% CI	t	p
Cue (Trauma = 1; Neutral = 0)	-15.01	79.18	-168.30 – 138.28	-0.19	.850
Cluster E Symptoms	-3.26	2.66	-8.51 – 2.00	-1.22	.228
Stimuli (Cannabis = 1; Neutral = 0)	-120.05	61.92	-239.93 - -0.17	-1.93	.055
Cue*Cluster E Symptoms	1.34	4.21	-6.81 – 9.50	0.32	.751
Cue*Stimuli	110.34	93.53	-70.73 – 291.41	1.18	.240
Cluster E Symptoms*Stimuli	8.20	3.28	1.84 – 14.56	2.49	.014*
Cue*Stimuli*Cluster E Symptoms	-5.98	4.98	-15.64 – 3.68	-1.20	.233

Notes: *p < .05. **p < .01. ***p < .001. Cue and Stimuli were inputted as fixed effects. All other variables were inputted as covariates. PTSD Symptoms assessed continuously with the PTSD Checklist (PCL-5; Bovin et al., 2016) Cluster E subscale (items 15-20). Approach bias scores calculated as median push minus median pull reaction time (in msec); higher scores indicate greater approach bias (Cousijn et al., 2014).

CHAPTER 7. TRANSITION FROM STUDY 3 TO STUDY 4

The results of Study 3 provided evidence to support cannabis approach bias as particularly activated among those with more severe PTSD symptoms. Specifically, regardless of trauma cue exposure, individuals with greater PTSD experienced greater biases towards cannabis (vs. neutral) stimuli on the AAT. The lack of trauma cue effect on cannabis cognitions was contrary to our expectations. Indeed, in both Studies 2 and 3, the anticipated interaction between cue type and PTSD on cognitive measures, whether controlled or automatic, failed to materialize as expected. This absence prompts speculation: either such interactions do not exist, or their magnitude is too subtle to be detected within our modest sample size of n=50. Consequently, the imperative arises to expand our participant pool and bolster statistical power for detecting smaller interactions than we had been powered to detect in Studies 2 and 3. Yet, recruiting ample numbers for lab-based studies, particularly individuals with avoidant tendencies like those with PTSD, has proven difficult (e.g. Coffey et al., 2006). Thus, in Study 4, we aimed to test the use of a self-administered, online expressive writing trauma CRP, adapted based on the gold standard cue reactivity paradigm (e.g., Read et al., 2017) and guidelines for writing to provoke emotional imagery (Lang, 1979). Specifically, we reasoned that if the expressive writing task is valid as a CRP, similar effects to those observed in the prior CRP literature with the gold-standard two session CRP (e.g., Coffey et al., 2006) should be detected, specifically on affective and controlled cognitive processes (i.e., craving).

By transitioning to a self-administered online CRP in Study 4, I aimed to not only broaden the reach to a larger sample, allowing for the detection of interactions relatively small in magnitude, but also circumventing the necessity for in-lab visits, thus reducing barriers to participation. Indeed, if the general lack of observed cue x PTSD interactions in the previous

studies stemmed from insufficient statistical power to detect smaller interactions, the online and self-administered nature of the expressive writing task positioned me favorably to detect such interactions, should they indeed exist. In Study 4, I also chose to conceptualize PTSD in my analyses as categorical rather than as a continuous symptom count or continuous symptom severity score, as done in Studies 2 and 3, respectively. This change in methodology came about when trying to make sense of my lack of interactive effect in Studies 2 and 3, as literature came to my attention which suggested the categorization of PTSD (i.e., latent classes) vs. no PTSD may be more appropriate (Ayer et al., 2011; Breslau et al., 2005; Steenkamp et al., 2012), perhaps aiding in the detection of the trauma cue x PTSD interaction in my subsequent studies. Further, categorical approaches are more similar to the diagnostic approach used in clinical practice. Thus, I reasoned this change might make my analyses more sensitive to detecting PTSD effects on my outcomes.

CHAPTER 8: EFFECTS OF TRAUMA CUE EXPOSURE AND PTSD ON AFFECT AND CANNABIS CRAVING IN CANNABIS USERS WITH TRAUMA HISTORIES: USE OF EXPRESSIVE WRITING AS AN ONLINE CUE REACTIVITY PARADIGM

The manuscript prepared for this study is presented below. Readers are advised that Sarah DeGrace, under the supervision of Dr. Sherry Stewart, was responsible for designing the study, developing the research hypotheses, successfully applying for funding for the project through a Nova Scotia Health grant as first author and as coauthor on a Mental Health Commission of Canada grant, gaining ethical approval, preparing the dataset for analyses, conducting the analyses, and interpreting the study results. Sarah wrote the initial draft of the manuscript and received and incorporated feedback from her co-authors. Sarah submitted the manuscript to a special issue of the *Canadian Journal of Psychiatry* on concurrent mental health and addictive disorders on January 15th, 2024, and led the team in the revision process; the paper was accepted for publication on April 18th, 2024. The reference is: DeGrace, S., Barrett, S., Yakovenko, I., Tibbo, P.G., Romero-Sanchiz, P., Carleton, R. N., Snooks, T., Rudnick, A., & Stewart, S. H. (in press). Effects of trauma cue exposure and PTSD on affect and cannabis craving in cannabis users with trauma histories: Use of expressive writing as an online cue reactivity paradigm. *Canadian Journal of Psychiatry*.

Abstract

Objectives: Posttraumatic stress disorder (PTSD) and cannabis use disorder (CUD) commonly co-occur. Conditioned associations between psychological trauma cues, distress, cannabis use, and desired relief outcomes may contribute to the comorbidity. These conditioned associations can be studied experimentally by manipulating trauma cue exposure in a cue-reactivity paradigm (CRP) and examining effects on affective and cognitive outcomes in participants with and without PTSD. However, traditional CRPs take place in-lab limiting recruitment/power. We aimed to examine effects of CRP condition (trauma, neutral) and PTSD group (likely PTSD+, PTSD-) on affective and craving outcomes using a stand-alone online expressive writing CRP. Methods: Participants (*n*=202; 43.6% male; *M* age=42.94 years, *SD*=14.71) with psychological trauma histories and past-month cannabis use completed a measure of PTSD symptoms (PTSD Checklist-5 [PCL-5]) and were randomized to complete either a trauma or neutral expressive writing task. Then they completed validated measures of affect (Positive and Negative Affect Schedule-Short Form [PANAS-SF]) and cannabis craving (Marijuana Craving Questionnaire-Short Form [MCQ-SF]). Results: Linear mixed models tested the hypothesized main and interactive effects of CRP condition (trauma, neutral) and PTSD group (likely PTSD+, PTSD-) on negative and positive affect (PANAS-SF) and cannabis craving dimensions (MCQ-SF). The hypothesized main effects of trauma vs. neutral expressive writing were found for negative affect and the expectancy dimension of cannabis craving and of PTSD group for negative affect and all cannabis craving dimensions; no interactions were observed. Conclusions: Expressive writing appears a useful online CRP. Interventions focused on reducing negative affect and expectancy craving to trauma cues may prevent/treat CUD among cannabis users with PTSD.

Keywords: PTSD, cue-reactivity paradigm, cannabis, craving, affect, trauma.

Introduction

Posttraumatic stress disorder (PTSD) involves distressing symptoms (e.g., physiological reactivity to and avoidance of trauma reminders) following exposure to a traumatic event (APA, 2013). There is a high comorbidity between PTSD and substance use disorder (SUD; Berenz & Coffey, 2012). PTSD-SUD is clinically significant given its more severe symptoms, poorer treatment response, and higher relapse rates compared to either disorder alone (Blakey et al., 2022; Leza et al., 2021; Vujanovic et al., 2016). This comorbidity extends to cannabis use disorder (CUD; Kevorkian et al., 2015; Walsh et al., 2014): individuals with CUD are four times more likely to have PTSD than those without CUD (Hasin et al., 2016). Moreover, longitudinal research suggests continued cannabis use is associated with worse PTSD outcomes (Wilkinson et al., 2015). With few randomized controlled trials conducted (McKee et al., 2021), some caution against the use of cannabis as a means of addressing PTSD symptoms (Bedard-Gilligan et al., 2022). Mechanistic studies to understand PTSD-cannabis use/CUD links are vital to identify intervention targets.

One mechanism proposed to underlie comorbid PTSD-CUD is trauma cue-elicited substance craving arising through conditioning. Two-factor learning theory (Stasiewicz & Maisto, 1993) posits stimuli paired with a traumatic experience can become conditioned cues, inducing negative affect (NA) upon future exposure. This conditioned NA may drive substance use for relief, negatively reinforcing the behavior. Given frequent pairing of trauma cues/reminders with substance use to cope, trauma cues come to elicit conditioned substance craving. Research shows that substance users with trauma histories exhibit higher NA, lower positive affect (PA), and increased substance craving when exposed to trauma cues compared to neutral cues (Chapter 2, Study 1). These responses are theoretically stronger in individuals with

PTSD diagnoses or more severe PTSD symptoms (Chapter 4, Study 2) and research supports this (McHugh et al., 2017; Read et al., 2017; Romero-Sanchiz et al., 2022).

In the context of PTSD-SUD research, cue reactivity paradigms (CRPs) can be used in a laboratory setting to experimentally examine the effects of trauma (vs. neutral) cue exposure on substance-relevant responses, like affective reactions and substance craving. The gold-standard protocol for CRP research in the PTSD-SUD comorbidity field (Coffey et al., 2002) draws from a prominent theory of emotional imagery (Lang, 1979) using a two-session protocol (Chapter 6, Study 3). The first session uses a semi-structured interview (Sinha & Tuit, 2012) to have participants recall details of their most traumatic experience, which are later distilled into a brief personalized audiovisual cue used as the CRP in the second session (Romero-Sanchiz et al., 2022). An identical procedure is used for the neutral/control cue.

As avoidance of trauma reminders is a symptom of PTSD, (APA, 2013) CRP research is fraught with high attrition between the interview and CRP session (Coffey et al., 2002). Our recent work suggests that the semi-structured interview alone, requiring only a single lab visit, can serve as a valid CRP in eliciting relevant cannabis craving and NA responses (Chapter 4, Study 2). A remaining issue is obtaining in-lab sample sizes large enough to detect theorized, smaller magnitude, interactions (Berenz et al., 2021). Online data collection can achieve a broader reach for recruitment, thereby permitting the necessary larger samples.

In this study, we used an online expressive writing task (trauma vs. neutral) based on Pennebaker's (1997) work as a novel stand-alone CRP, allowing single-session administration and increased sample size. Previous studies have only used brief expressive writing in combination with audio CRPs to study co-occurring PTSD-SUD (Read et al., 2017; Rodriguez & Read, 2020), but this necessitates lab-based administration. Our study is the first to use

expressive writing alone as a CRP in eliciting theorized conditioned affective and craving responses to trauma cues that are potentially mechanistically involved in PTSD-CUD comorbidity (Chapter 2, Study 1). We hypothesized those randomized to a trauma expressive writing task would display greater reactivity across cannabis craving dimensions (H1), greater NA (H2), and lesser PA (H3), relative to those assigned to a neutral writing task. We also hypothesized that participants with likely PTSD[15] would display greater reactivity across cannabis craving dimensions (H4), greater NA (H5), and lesser PA (H6), relative to those without PTSD. Finally, we hypothesized cue condition x PTSD interactions for cannabis craving (H7), NA (H8), and PA (H9), with writing task effects stronger for those with (vs. without) likely PTSD.

Method[16]

Participants.

Participants were recruited via Qualtrics Panels, an online survey company which uses researcher-specified recruitment criteria. We advertised for cannabis users with a past traumatic experience(s). Eligibility criteria were: residing in Canada; 19[17]-65 years old; lifetime exposure to ≥1 DSM-5 (APA, 2013) PTSD Criterion A potentially traumatic event(s) (Gray et al., 2004); and past month cannabis use (≥1 g). *N*=6917 potential participants responded to our survey. *N*=5973 of these did not meet one or more eligibility criteria; 520 did not follow the writing task

[15] While we have used a continuous approach to PTSD assessment in our past research (i.e., PTSD symptom severity; see Chapter 4, Study 2 and Chapter 6, Study 3), we reasoned a categorical assessment of PTSD would be more clinically relevant to understanding PTSD-CUD comorbidity.

[16] All methods and measures described were approved by the Nova Scotia Health Research Ethics Board (ref #: 1028354).

[17] Our age inclusion criteria began at age 19 as it is the legal age to purchase and use cannabis in Nova Scotia, the province where the study received ethics approval. This legal age varies across provinces in Canada and 19 was the lowest age limit that would ensure all participants were adults of legal age, regardless of province of domicile.

instructions (e.g., one word written repeatedly; wrote about a stressful event that was not a Criterion A trauma); 98 were from duplicate IP address; 77 did not respond appropriately to cannabis regimen measures to be used in another study; and 47 failed an attention check (e.g., "Select '4' for this item"). After this stringent quality assurance check, there was a final sample of 202 participants (43.6% male; M age=42.94 years, SD=14.71). Participants were compensated by Qualtrics at a rate based on factors like survey length, panelist profile, and target acquisition difficulty.

Tasks and Measures.

Demographics. Participants reported demographic information (i.e., sex, age).

Trauma Exposure. The Life Events Checklist (LEC; Gray et al., 2004) assessed lifetime trauma[18] (DSM-5 PTSD criterion A; APA, 2013). If respondents had >1 lifetime trauma exposure, they were instructed to answer all further trauma-related questions/tasks with respect to their most traumatic event[19].

PTSD. The 20-item PTSD Checklist for DSM-5 (PCL-5; Bovin et al., 2016) was used to categorize participants into two groups. Participants self-reported how bothered (0=*not at all* to 4=*extremely*) they were by each PTSD symptom (e.g., repeated, disturbing memories of the event) over the past month. The PCL-5 has good psychometric properties (Blevins et al., 2015);

[18] For the purposes of the present study, trauma was defined as exposure to a potentially psychologically traumatic event (Bovin et al., 2016).
[19] Researchers vetted all writing task data to ensure criterion A was met and that participants only wrote about their most traumatic Criterion A event as identified on the LEC (Gray et al., 2004).

in our sample, α=.95. Those scoring ≥38 were placed in the likely PTSD group (Cohen et al., 2014) and the rest in the no PTSD group.[20,21]

Cannabis Use. The Cannabis Timeline Followback (C-TLFB; Sobell & Sobell, 1992) a method with excellent inter-rater reliability (Norberg et al., 2012) assessed past-month cannabis use to confirm study eligibility. Participants indicated on a past-month calendar the days they had used cannabis, and the amount used (in grams) on each day. Conversion rates were provided for concentrates and edibles (i.e., 1g concentrate=4g flower; 1000mg edible=1g flower; Government of Canada, 2023b).

CUD Symptom Severity. The 8-item Cannabis Use Disorder Identification Test-Revised (CUDIT-R; Adamson et al., 2010) measured CUD symptom severity. Participants indicated on a 0-4 scale (*never* to *daily or almost daily*) how often in the past six months they experienced various cannabis-related problems. Scores were summed. The CUDIT-R has good psychometric properties (Adamson et al., 2010); internal consistency was adequate in our sample, α=.75.

Distress. The 9-item Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) and 7-item Generalized Anxiety Disorder scale (GAD-7; Spitzer et al., 2006) are validated (Kroenke et al., 2001; Spitzer et al., 2006) measures of depressive and general anxiety symptom frequency, respectively. Items are rated on 0-3 scales (*not at all* to *nearly every day*). We used these measures to create a 'distress' composite (i.e., the validated PHQ-ADS; Kroenke et al., 2016) to use as a covariate in supplementary analyses to determine specificity of findings to PTSD given

[20] While a number of cut-offs on the PCL-5 have been suggested for identifying likely PTSD (Bovin et al., 2016) we chose a relatively high categorical cut-off for likely PTSD as our predictor to minimize false positives which are more likely when using a self-report questionnaire vs. clinical interview for case identification. Additionally, this cut-off has undergone validation in evaluating likely PTSD in civilian samples, distinguishing it from other commonly used thresholds which have been validated in military, clinical, and mostly male populations (Cohen et al., 2014).

[21] The cutoff of 38 was established based on a total score across all PCL-5 items and, unlike the DSM-5, did not require endorsement of a specified number of symptoms from each of the four dimensions of PTSD symptomatology.

the high co-occurrence of PTSD with depression and anxiety (Rytwinski et al., 2013; Spinhoven et al., 2014). The reliability of the PHQ-ADS in our sample was excellent (α=.95).

Expressive Writing. Participants were randomized to one of two expressive writing tasks (Pennebaker, 1997): trauma-related (i.e., worst lifetime trauma) or neutral (i.e., morning routine). First, the writing task instructed participants to describe what happened and to detail the bodily sensations, thoughts, and feelings that occurred during the event (Sinha & Tuit, 2012). After reading these instructions, participants wrote for two minutes minimum with the instructions remaining for reference throughout the task. Participants were encouraged to take their time, and only allowed to proceed to the second screen after at least two minutes; there they were instructed to continue visualizing the event (Read et al., 2017) just described for another two minutes. Task programming ensured these minima.

Craving. The reliable and valid 12-item Marijuana Craving Questionnaire-Short Form (MCQ-SF; Heishman et al., 2009) assessed four 3-item cannabis craving dimensions: Compulsivity (inability to control cannabis use; α=.76), emotionality (cannabis use in anticipation of relief from negative mood; α=.84), expectancy (anticipation of positive outcomes from cannabis use; α=.77), and purposefulness (intention to use cannabis; α=.89).

Affect. The psychometrically-sound (Serafini et al., 2016) 20-item Positive and Negative Affect Schedule- Short Form (PANAS-SF; Watson et al., 1988) assessed state PA (α=.86) and NA (α=.91). Participants indicated how much (1=*very slightly or not at all* to 5=*extremely*) they were feeling each of 10 positive (e.g., *active, inspired*) and 10 negative (e.g., *distressed, nervous*) affective states. Items for each type of affect were summed.

Procedure.

Potential participants first provided informed consent and responded to questionnaires assessing eligibility (demographics; C-TLFB [Sobell & Sobell, 1992]; LEC [Gray et al., 2004]). For eligible respondents, the survey began with the PCL-5 (Bovin et al., 2016), CUDIT-R (Adamson et al., 2010) and baseline MCQ-SF (Heishman et al., 2009) and PANAS-SF (Watson et al., 1988). Next, participants were randomized to complete the assigned expressive writing task CRP (trauma [*n*=96]; neutral [*n*=106]). Prior to data cleaning, randomization was 1:1 across the two writing conditions; randomization was not stratified on any variables. Participants again completed the MCQ-SF (Heishman et al., 2009) and the PANAS-SF (Watson et al., 1988), this time for how they were feeling during the writing task.

Analyses.

For our main analyses, we ran linear mixed models (Rv.4.2.1; lme4 package) with cue condition, PTSD group, and their interaction[22] predicting each cannabis craving dimension, NA, and PA. To determine which variables should be covaried in sensitivity analyses, we ran 2x2 linear mixed models with cue condition, PTSD group, and their interaction predicting theoretically-relevant covariates (age, PHQ-ADS, CUDIT-R, writing task word count, and baseline craving and affect).[23] A 4 x 2 (group x sex) chi square tested group differences in sex distribution. Sensitivity analyses involved re-running our primary models with necessary covariates (each in a separate analysis).

[22] All predictors were inputted as fixed effects. Participants were inputted as a random effect and a restricted maximum likelihood model was used.

[23] Potential covariates were identified based on theory and prior research. However, the choice to enter them in sensitivity analyses was determined empirically: only those where PTSD group and/or cue condition effects were observed in our data were controlled as potential confounders. While randomization should have taken care of confounders in the case of cue condition, there are known differences in each of the selected covariates between those with and without clinical PTSD, and theoretically people may write more details about an emotionally relevant than neutral personal experience.

Results

Sample characteristics: Table 4.1 presents sample demographic and clinical characteristics by cue condition and PTSD group. The mean PCL-5 score was 31.51 (*SD*=18.71) with 36% (n=73) scoring ≥38 indicating likely PTSD (Cohen et al., 2014). The mean CUDIT-R (Adamson et al., 2010) score of 11.37 (*SD*=6.25; *range*=0-32) was above the cutoff for hazardous use (≥8) and just below the cut-off for likely CUD (≥12; Adamson et al., 2010). In the past month, the average total grams of cannabis used by our sample was 37.33 (*SD*=90.90) and mean number of cannabis-using days was 14.03 (*SD*=10.40).

Craving. Partially consistent with H1, expectancy craving was higher in the trauma (*M*=4.67, *SD*=1.80) than neutral (*M*=4.30, *SD*=1.79) cue condition (*t*[198]=2.13, 95%CI [0.05-1.24], *p*=.035). However, cue condition failed to predict the other three craving dimensions (Table 4.2). Consistent with H4, the expectancy (*t*[198]=4.47, 95%CI [0.87-2.24], *p*<.001), emotionality (*t*[198]=4.31, 95%CI [0.87-2.34], *p*<.001), compulsivity (*t*[198]=4.19, 95%CI [0.78-2.16], *p*<.001), and purposefulness craving dimensions (*t*[198]=2.81, 95%CI [0.34-1.96], *p*<.001), were higher in the likely PTSD vs. no PTSD group (Figure 4.1, Table 4.2). Contrary to H7, there were no cue condition x PTSD group interactions for any craving dimension (Table 4.2).

Affect. Consistent with H2 and H5, NA was greater in the trauma vs. neutral cue condition (*t*[198]=2.05, 95%CI [0.11-5.73], *p*=.042) and among those with vs. without likely PTSD (*t*[198]=7.97, 95%CI [9.86-16.34], *p*<.001), but contrary to H8, no cue condition x PTSD Group interaction emerged (Figure 4.2, Table 4.3). Contrary to H3, H6, and H9, PA did not differ between the trauma and neutral cue conditions, or between those with and without likely PTSD, and no interaction emerged (Figure 4.2, Table 4.3).

Analyses of Potential Covariates: Our analyses of potential covariates revealed a statistically significant effect of PTSD group on age (t[198]=-9.36, 95%CI [-15.00—3.72], p<.001), CUDIT-R (t[198]=10.59, 95%CI [8.40-12.78], p=.002), PHQ-ADS (t[198]=18.28, 95%CI [14.61-21.95], p<.001), baseline NA ((t[198]=12.27, 95%CI [8.93-15.62], p<.001), and baseline emotionality (t[198]=1.29, 95%CI [0.60-1.98], p<.001), expectancy (t[198]=1.23, 95%CI [0.57 – 1.88], p=<.001), and compulsivity craving (t[198]=1.24, 95%CI [0.60-1.88], p=<.001), a significant effect of cue condition on writing task word count (t[198]=30.16, 95%CI [3.77-56.55], p=.025), and a significant interaction between PTSD and cue condition on number of lifetime traumas (t[198]=2.57, 95%CI [-0.02-5.17], p=.05). These covariates were controlled in a series of sensitivity analyses to test whether effects in the primary analyses persisted.

Sensitivity Analyses: All PTSD group effects remained when controlling PTSD group differences in the identified covariates except: compulsivity craving when controlling baseline levels; expectancy, emotionality, and purposefulness craving when controlling PHQ-ADS; and purposefulness craving when controlling CUDIT-R. Both cue condition effects remained when controlling cue condition differences in writing task word count and number of lifetime traumatic experiences (Supplementary Tables 4.2-4.4).

Discussion

The primary aims of our study were to eliminate the attrition common to two-session trauma CRP studies and recruit a sufficiently large sample to allow detection of both main and interactive cue condition and PTSD group effects on outcomes relevant to understanding PTSD-CUD comorbidity. Our online trauma cue exposure—an expressive writing task—significantly increased expectancy cannabis craving and NA relative to neutral writing task. Likely PTSD was a significant predictor of all craving dimensions and NA. No interactions emerged for any

outcome, though for NA and expectancy craving, the greatest reactivity was observed in those with likely PTSD who completed the trauma expressive writing task.

Partially consistent with expectations (H1), writing about a personal traumatic (vs. neutral) event did enhance expectancy craving. Theory suggests trauma cue exposure might enhance state expectancies regarding the perceived relieving effects of cannabis (Glöckner-Rist et al., 2013). While the MCQ-SF expectancy scale lacks relief-reward differentiation (Birch et al., 2004) two of its three items conceptually tap cannabis relief expectancies (i.e., decreased nervousness, sleeping better); this suggests the expectancy of relief from cannabis following trauma cue exposure may drive the increased cannabis craving tapped on this scale. Importantly, other CRP studies (Romero-Sanchiz et al., 2022; Tull et al., 2013) have shown effects of trauma CRPs eliciting cannabis craving across all four dimensions of the MCQ-SF. This difference may be due to the nature of our trauma CRP, an online writing task, whereas prior CRP studies (Romero-Sanchiz et al., 2022; Tull et al., 2013) used an in-person CRP. Perhaps the potential to stop writing (Read et al., 2017) combined with the lack of experimenter presence, reduced the efficacy of our CRP in eliciting some cannabis craving dimensions (e.g., feeling more in control might reduce compulsivity craving).

As expected (H4), likely (vs. no) PTSD significantly predicted heightened cannabis craving across MCQ-SF subscales. This is partially consistent with prior findings of main effects of PTSD symptom severity on the compulsivity, purposefulness, and emotionality (but not expectancy) dimensions of cannabis craving (Romero-Sanchiz et al., 2022). Perhaps our use of a categorical predictor (i.e., likely PTSD vs. no PTSD) was more sensitive to PTSD effects on expectancy craving than the continuous PTSD symptom severity measure used previously (Romero-Sanchiz et al., 2022) given the results of latent class analyses that emphasize

categorical variations rather than continuous gradients in PTSD symptoms within trauma-exposed samples (Ayer et al., 2011; Breslau et al., 2005; Steenkamp et al., 2012).

As expected (H2) and consistent with prior work, (Coffey et al., 2002; Tull et al., 2013) NA was greater following the trauma than neutral expressive writing CRP. This finding replicates our prior research showing trauma CRPs to be predictors of increased NA compared to neutral cues or baseline (Chapter 2, Study 1; Chapter 4, Study 2). Further, likely PTSD predicted greater post-cue NA overall, a result consistent with H5 and with prior findings (Romero-Sanchiz et al., 2022). Contrary to H3 and H6, neither cue condition nor PTSD predicted lesser PA. This pattern of results, along with the greatest effect sizes in our study being detected for NA (Table 4.3), provides evidence that trauma CRPs are primarily NA inductions (Romero-Sanchiz et al., 2022; Study 2, Chapter 4) and is consistent with reports that greater PTSD symptoms predict greater NA but not lesser PA to trauma cue exposure (Romero-Sanchiz et al., 2022).

Interestingly, NA and expectancy craving were influenced by both the expressive writing condition and PTSD Group. Although no interactions were detected, individuals with likely PTSD in the trauma condition showing the highest levels of NA and expectancy craving post-writing, indicating activation of negative affect and relief craving by trauma cue exposure, as possible mechanisms of PTSD-CUD comorbidity. Indeed, this finding supports Baker et al.'s (2004) theoretical framework, suggesting the act of writing about a personal trauma may heighten not only distress but also substance cravings among users as substance use is anticipated to relieve the distress provoked by trauma memories.

Several potential limitations should be considered when interpreting our results. First, while our data were stringently vetted for quality, the online method precluded determining

whether participants precisely followed expressive writing instructions. Specifically, while we asked participants to write for a minimum of two minutes and prevented them from moving on until this minimum had elapsed, many responses were short. Verbal descriptions from in-lab interviews may offer more vivid imagery than written ones without an experimenter present, possibly explaining the lack of interactions on all outcomes. In fact, some prior research using the traditional CRP in the two-session protocol showed positive interactions between cue condition and PTSD in predicting cue-elicited craving for cocaine and cannabis (Romero-Sanchiz et al., 2022; Tull et al., 2013). Perhaps those with PTSD were more avoidant during the trauma writing task (e.g., stopping writing when feeling anxious), working against the hypothesized interactions.

To maintain participant focus without the necessity of a laboratory setting, in future, participants might be asked to report on the quality of their visualization experience, including the option to indicate if they did not attempt to visualize the event. This additional step could screen out participants who did not fully engage with the task. While consistent with some prior research (Read et al., 2017) the 2-minute minimum was substantially shorter than the 20-minute writing sessions recommended by Pennebaker (1997). Future research should establish the optimal length of trauma expressive writing in eliciting various forms of cue reactivity. A further limitation is that participants' prior experience with prolonged exposure-based therapies was not measured or controlled. Finally, PTSD group was established via a single-score cutoff on a self-report questionnaire rather than a clinical interview (the latter was not practical in a larger *N*, online study), which may have led to mis-categorization.

Supplementary analyses suggested PTSD group effects on some outcomes may have been secondary to pre-existing baseline differences in the case of compulsivity craving; PTSD

group differences in general distress in the cases of expectancy, emotionality, and purposefulness craving; and PTSD group differences in CUD symptoms in the case of purposefulness craving. Thus, studies of PTSD group effects on cue-induced craving should assess and control for these potentially important confounds. Finally, we only focused on a controlled cognitive process (i.e., craving; Romero-Sanchiz et al., 2022). Automatic cognitive processes (i.e., requiring less awareness, assessed indirectly through reaction time or association tasks; Wiers & Stacy, 2006) may also be relevant to understanding PTSD-CUD comorbidity (see Chapter 6, Study 3; Read et al., 2017) and should be probed using the stand-alone expressive writing CRP in future.

Our findings have several clinical implications. NA and expectancy craving were highest in participants with likely PTSD who wrote about trauma, suggesting these affective and cognitive outcomes elicited by trauma cue exposure should be specific targets of intervention for treating/preventing comorbid CUD in cannabis users with PTSD. It would be informative to test whether exposure-based intervention for PTSD-CUD not only reduces NA to trauma cue exposure but also trauma cue elicited cannabis relief expectancies or whether specific interventions to target these expectancies need to be added, such as via expectancy challenge techniques (Darkes & Goldman, 1993). Indeed, existing safe and efficacious integrated therapies for concurrent PTSD-SUD (including CUD), such as the COPE treatment (Back et al., 2019) address both disorders concurrently and target underlying mechanisms that contribute to their maintenance and exacerbation (Back et al., 2019). Such integrated treatments involve verbal recounting of the trauma with one's provider rather than written expressions of trauma as the exposure component. Given lower attendance, but higher efficacy, was seen for cannabis users receiving in person exposure-based (vs. non-exposure-based) treatment for comorbid PTSD-

SUD in a recent meta-analysis (Hill et al., 2024) remote exposure-based interventions may be helpful for increasing treatment attendance in this population.

Future trials could aim to validate the use of remote expressive writing about one's trauma as the exposure component in such integrated treatments for comorbid PTSD-SUD (Peirce et al., 2020) given our findings that the expressive writing CRP successfully elicited the NA necessary for corrective emotional processing (Foa & Kozak et al., 1986). Indeed, extending work showing expressive writing about trauma to be an effective exposure therapy for PTSD (Darkes & Goldman, 1993; Back et al., 2013) a randomized controlled trial of 149 women with an SUD assigned to either a four-session trauma or neutral expressive writing intervention showed those randomized to the trauma condition reported decreased PTSD symptoms at follow-up (Meshberg-Cohen & McMahon, 2014). Moreover, the anxiety elicited by the trauma writing task habituated by the fourth session (Meshberg-Cohen & McMahon, 2014). These results suggest promise for expressive writing as a form of exposure therapy for comorbid PTSD-SUD, but results require extension to substance-relevant outcomes (Dawson et al., 2021). Overall, it is important to conduct feasible, adequately powered CRP research, as this work can inform refinements to integrated trauma exposure-based treatments for comorbid PTSD-SUD (Sloan et al., 2023).

Table 4.1. Descriptive and clinical characteristics.

N (%)/Mean (SD)

PTSD status		PTSD+		PTSD-		
		n=73		n=129		
Cue condition		Trauma	Neutral	Trauma	Neutral	Overall Sample
		n=36	n=37	n=60	n=69	N=202
Age (in years)*		36.86 (12.68)	36.57 (11.62)	47.08 (14.89)	45.93 (15.07)	42.94 (14.71)
Sex	Male	11 (30.6%)	13 (35.1%)	32 (53.3%)	32 (46.4%)	106 (52.5%)
	Female	25 (69.4%)	24 (64.9%)	28 (46.7%)	37 (53.6%)	96 (47.5%)
CUDIT-R score*		13.36 (6.81)	13.49 (6.39)	10.87 (6.37)	9.62 (5.16)	11.37(6.25)
PHQ-ADS Score*		29.27 (9.40)	30.70 (10.34)	13.60 (8.77)	12.42 (8.60)	19.12 (12.24)
PCL-5 score*		51.70 (9.79)	52.36 (10.32)	20.21 (10.61)	19.62 (11.10)	31.51 (18.71)
Writing Task Word Count**		97.55 (65.19)	51.67 (36.31)	91.65 (110.84)	61.49 (56.47)	75.08 (77.44)

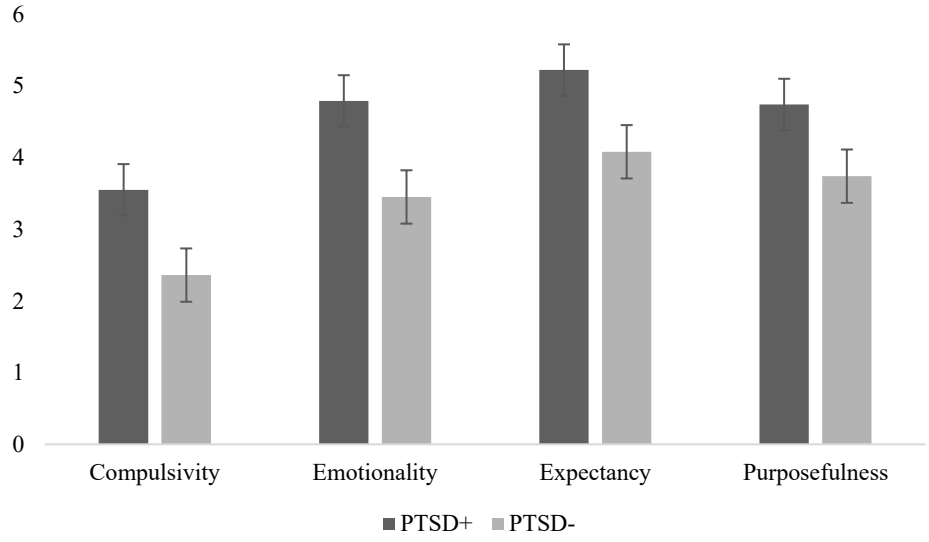
Notes: CUDIT-R score: Cannabis Use Disorder Identification Test-Revised (Adamson et al., 2010); PTSD Status and PCL-5 Score: PTSD Checklist for DSM-IV (Blevins et al., 2015). Sex was tested in a 4 x 2 (group x sex) chi square which was not significant (X^2 (3) = 6.098, p = .107.
*variable with a PTSD Group main effect ($p < .05$)
**variable with a Cue Condition main effect ($p < .05$)

Table 4.2. Linear mixed models' omnibus results for craving responses.

Subscales	*Compulsivity*	*Emotionality*	*Expectancy*	*Purposefulness*
Condition (Neutral = 0)	*b*=0.42, *p*=0.170	*b*=0.52, *p*=0.107	*b*=0.64, *p*=0.035*	*b*=0.33, *p*=0.360
PTSD Status (PTSD- = 0)	*b*=1.47, *p*<0.001***	*b*=1.47, *p*<0.001***	*b*=1.56, *p*<0.001***	*b*=1.15, *p*=0.006**
Condition*PTSD Status	*b*= -0.56, *p*=0.270	*b*= -0.55, *p*=0.309	*b*= -0.84, *p*=0.096	*b*= -0.30, *p*=0.616
Marginal R^2 / Conditional R^2	0.112 / 0.098	0.124 / 0.111	0.117 / 0.104	0.060 / 0.046

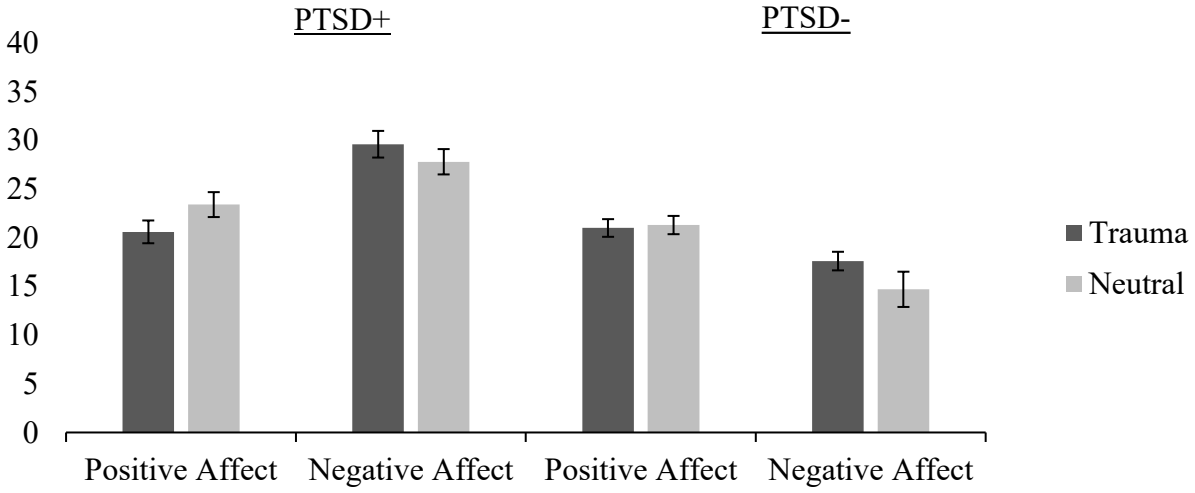
Notes: * $p < .05$, ** $p < .01$, *** $p < .001$. Marginal and conditional R^2 values represent effect sizes.

Figure 4.1. Mean cannabis craving subscale scores by PTSD Group.



Note: Error bars represent the standard error.

Figure 4.2. Mean negative and positive affect scores by PTSD and cue condition.



Note: Error bars represent the standard error.

Supplementary Table 4.1. Descriptives of baseline craving subscales and baseline affect.

PTSD status	PTSD- n=129	PTSD+ n=73	Overall Sample N=202
Expectancy*	4.18 (1.68)	5.02 (1.51)	4.48 (1.67)
Compulsivity*	2.41 (1.50)	3.45 (1.75)	2.79 (1.66)
Emotionality*	3.67 (1.77)	4.64 (1.60)	4.03 (1.77)
Purposefulness	4.08 (1.96)	4.70 (1.88)	4.31 (1.95)
Negative Affect*	15.99 (7.49)	27.60 (9.56)	20.19 (9.98)
Positive Affect	27.57 (8.63)	24.25 (8.77)	26.37 (8.81)

*Note: *significant PTSD Group main effect ($p < .05$)*

Supplementary Table 4.2. Descriptives of baseline craving subscales and baseline affect compared to post-cue craving subscales and affect.

Condition	Pre-Trauma Cue Exposure	Post-Trauma Cue Exposure	Pre-Neutral Cue Exposure	Post-Neutral Cue Exposure
	n=96		n=106	
Expectancy*	4.59 (1.56)	4.67 (1.80)	4.41 (1.77)	4.30 (1.79)
Compulsivity	2.67 (1.61)	2.91 (1.85)	2.90 (1.71)	2.66 (1.77)
Emotionality	3.67 (1.77)	4.11 (2.03)	4.01 (1.76)	3.75 (1.85)
Purposefulness	4.04 (1.78)	4.22 (2.14)	4.39 (1.94)	3.98 (1.98)
Negative Affect*	20.15 (9.86)	22.08 (10.02)	20.23 (10.14)	19.25 (10.08)
Positive Affect	26.10 (8.48)	22.85 (7.00)	26.60 (9.12)	22.04 (7.82)

*Note: *significant Condition Group main effect ($p < .05$)*

Supplementary Table 4.3. Linear mixed models' omnibus results for craving responses with cannabis-related, distress, word count, and demographic covariates.

Subscales	*Compulsivity*	*Emotionality*	*Expectancy*	*Purposefulness*
Condition (Neutral = 0)	*b*=0.44, *p*=0.146	*b*=0.55, *p*=0.091	*b*=0.65, *p*=0.031*	*b*=0.35, *p*=0.329
PTSD Status (PTSD- = 0)	*b*=1.30, *p*<0.001***	*b*=1.43, *p*<0.001***	*b*=1.45, *p*<0.001***	*b*=0.99, *p*=0.020*
Age	*b*= -0.02, *p*=0.035*	*b*= -0.02, *p*=0.039*	*B*= -0.85, *p*=0.092	*b*= -0.00, *p*=0.084
Condition*PTSD Status	*b*= -0.57, *p*=0.252	*b*= -0.56, *p*=0.291	*b*=0.65, *p*=0.031*	*b*= -0.31, *p*=0.596
Subscales	*Compulsivity*	*Emotionality*	*Expectancy*	*Purposefulness*
Condition (Neutral = 0)	*b*= 0.26, *p*=0.342	*b*= 0.35, *p*=0.224	*b*= 0.48, *p*=0.076	*b*= 0.13, *p*=0.685
PTSD Status (PTSD- = 0)	*b*= 0.98, *p*=0.003**	*b*= 1.08, *p*=0.002*	*b*= 1.05, *p*<0.001***	*b*= 0.53, *p*=0.150
CUDIT-R Score	*b*= 0.13, *p*<0.001***	*b*= 0.14, *p*<0.001***	*b*= 0.13, *p*<0.001***	*b*= 0.16, *p*<0.001***
Condition*PTSD Status	*b*= -0.38, *p*=0.397	*b*= -0.36, *p*=0.454	*b*= -0.66, *p*=0.141	*b*= -0.08, *p*=0.881
Subscales	*Compulsivity*	*Emotionality*	*Expectancy*	*Purposefulness*
Condition (Neutral = 0)	*b*= 0.39, *p*=0.201	*b*= 0.44, *p*=0.148	*b*= 0.56, *p*=0.048*	*b*= 0.26, *p*=0.457
PTSD Status (PTSD- = 0)	*b*= 1.00, *p*=0.019*	*b*= 0.37, *p*=0.433	*b*= 0.31, *p*=0.637	*b*= 0.06, *p*=0.902
PHQ-ADS Score	*b*= 0.03, *p*=0.057	*b*= 0.03, *p*=0.057	*b*= 0.07, *p*<0.001***	*b*= 0.06, *p*<0.001***
Condition*PTSD Status	*b*= -0.49, *p*=0.329	*b*= -0.37, *p*=0.466	*b*= -0.66, *p*=0.161	*b*= -0.14, *p*=0.805
Subscales	*Compulsivity*	*Emotionality*	*Expectancy*	*Purposefulness*

Condition (Neutral = 0)	-----	-----	*b*= 0.56, *p*=0.048*	-----
PTSD Status (PTSD- = 0)	-----	-----	*b*= 0.31, *p*=0.637	-----
Writing Task Word Count	-----	-----	*b*= 0.07, *p*<0.001***	-----
Condition*PTSD Status	-----	-----	*b*= -0.66, *p*=0.161	-----
Subscales	*Compulsivity*	*Emotionality*	*Expectancy*	*Purposefulness*
Condition (Neutral = 0)	*b*= 0.43, *p*=0.160	*b*= 0.58, *p*=0.076	*b*= 0.68, *p*=0.028*	*b*= 0.36, *p*=0.312
PTSD Status (PTSD- = 0)	*b*= 1.46, *p*<0.001***	*b*= 1.57, *p*<0.001***	*b*= 1.53, *p*<0.001***	*b*= 1.12, *p*=0.007*
Lifetime Traumatic Experiences	*b*= 0.01, *p*=0.646	*b*= 0.05, *p*=0.079	*b*= 0.04, *p*=0.179	*b*= 0.03, *p*=0.284
Condition*PTSD Status	*b*= -0.59, *p*=0.249	*b*= -0.68, *p*=0.210	*b*= -0.93, *p*=0.067	*b*= -0.31, *p*=0.519

Notes: * $p < .05$, ** $p < .01$, *** $p < .001$. Sensitivity analyses involving the writing task word count as a covariate were only performed for the expectancy craving subscale as it was the only craving subscale with a condition main effect in the primary analyses

Supplementary Table 4.4. Linear mixed models' omnibus results for negative affective responses with cannabis-related, distress, and demographic covariates included.

	Estimate (*b*)	CI (95%)	*p*
Negative Affect		Marginal R^2 = 0.404 / Conditional R^2 = 0.392	
Condition (Neutral = 0)	3.06	0.31 – 5.81	0.030*
PTSD Status (PTSD- = 0)	11.96	8.60 – 15.22	<.001***
Age	-0.12	-0.20 – -0.04	<.001***
Condition*PTSD Status	-1.25	-5.82 – 3.32	0.590
Negative Affect		Marginal R^2 = 0.439 / Conditional R^2 = 0.428	
Condition (Neutral = 0)	2.39	-0.28 – 5.07	0.079
PTSD Status (PTSD- = 0)	11.47	8.32 – 14.63	<.001***
CUDIT-R Score	0.42	0.25 – 0.60	<.001***
Condition*PTSD Status	-0.57	-5.01 – 3.87	0.801
Negative Affect		Marginal R^2 = 0.465 / Conditional R^2 = 0.454	
Condition (Neutral = 0)	2.53	-0.08 – 5.14	0.058
PTSD Status (PTSD- = 0)	7.00	3.33 – 10.67	<.001***
Distress	0.33	0.22 – 0.45	<.001***
Condition*PTSD Status	-0.28	-4.62 – 4.06	0.900
Negative Affect		Marginal R^2 = 0.376 / Conditional R^2 = 0.363	
Condition (Neutral = 0)	2.89	0.03 – 5.74	0.047*
PTSD Status (PTSD- = 0)	13.11	9.86 – 16.37	<.001***
Writing Task Word Count	0.00	-0.01 – 0.02	0.883
Condition*PTSD Status	-1.16	-5.85 – 3.52	0.624
Negative Affect		Marginal R^2 = 0.377 / Conditional R^2 = 0.366	
Condition (Neutral = 0)	3.01	0.18 – 5.83	0.037*
PTSD Status (PTSD- = 0)	13.03	9.78 – 16.29	<.001***
Lifetime Traumatic Experiences	0.08	-0.17 – 0.34	0.507
Condition*PTSD Status	-1.37	-6.08 – 3.35	0.569

Notes: * $p < .05$, ** $p < .01$, *** $p < .001$. Sensitivity analyses were only performed for the negative affect scale as it was the only PANAS-SF (Watson et al., 1988; Serafini et al., 2016) subscale with a PTSD status or condition main effect in the primary analyses. Lifetime traumatic experiences were defined as the number of categories participants selected on the LEC (Gray et al., 2004) that were relevant to them.

Supplementary Table 4.5. Linear mixed models' omnibus results predicting craving subscales and negative affective responses while controlling for baseline levels of relevant outcomes.

	Estimate (*b*)	CI (95%)	*p*
Compulsivity		Marginal R^2 = 0.616 / Conditional R^2 = 0.609	
Condition (Neutral = 0)	0.50	0.11 – 0.90	0.012*
PTSD Status (PTSD- = 0)	0.46	-0.01 – 0.93	0.057
Baseline Compulsivity	0.81	0.71 – 0.91	<.001***
Condition*PTSD Status	-0.22	-0.87 – 0.44	0.514
Emotionality		Marginal R^2 = 0.705 / Conditional R^2 = 0.699	
Condition (Neutral = 0)	0.30	-0.30 – 0.50	0.112
PTSD Status (PTSD- = 0)	0.48	0.04 – 0.93	0.032*
Baseline Emotionality	0.97	0.78 – 0.96	<.001***
Condition*PTSD Status	0.03	-0.59 – 0.64	0.936
Expectancy		Marginal R^2 = 0.774 / Conditional R^2 = 0.769	
Condition (Neutral = 0)	0.27	-0.23 – 0.50	0.081
PTSD Status (PTSD- = 0)	0.44	0.08 – 0.80	0.016*
Baseline Expectancy	0.91	0.83 – 0.98	<.001***
Condition*PTSD Status	-0.11	-0.61 – 0.40	0.672
Negative Affect		Marginal R^2 = 0.715 / Conditional R^2 = 0.709	
Condition (Neutral = 0)	2.84	0.94 – 4.74	0.004**
PTSD Status (PTSD- = 0)	4.34	1.87 – 6.81	0.001**
Baseline Negative Affect	0.71	0.62 – 0.81	<.001***
Condition*PTSD Status	-0.18	-3.34 – 2.98	0.910

Notes: * $p < .05$, ** $p < .01$, *** $p < .001$. Sensitivity analyses controlling baseline levels of the given outcome were only performed for the compulsivity, emotionality, and expectancy craving dimensions and for the negative affect scale as they were the only MCQ-SF (Heishman et al., 2009) and PANAS-SF (Watson et al., 1988) subscales with a PTSD main effect in the primary analyses.

CHAPTER 9. TRANSITION FROM STUDY 4 TO STUDY 5

The findings from Study 4 offered insight supporting the efficacy of another single-session CRP. Specifically, participants engaging in the remote trauma expressive writing task (vs. the neutral writing task) exhibited heightened negative emotions and increased cannabis expectancy craving. Moreover, individuals with probable PTSD[24] (vs. no PTSD) displayed elevated negative emotions and heightened craving across all four dimensions of cannabis craving. This preliminary evidence underscores the utility of expressive writing as a CRP. Building upon these findings, Study 5 employed the expressive writing task to explore the impact of trauma cue exposure and likely PTSD on automatic cognitive processes. I hypothesized that participants assigned to the trauma writing task (vs. neutral writing task), particularly those with probable PTSD, would demonstrate increased accessibility of cannabis-related information in memory. To assess this, the Cannabis Word Association Task (CWAT; Pilin et al., 2022) was utilized, chosen for its practicality for online administration compared to more complex cognitive reaction time tasks that need to be programmed, like the AAT or Stroop test. Indeed, with remote administration, technical errors could not be monitored, and assurances of compatibility with the platform used by each participant could not be assured. Additionally, considering previous research by Read and colleagues (2017) indicating a general slowing of reaction times following trauma cue exposure, and the lack of trauma cue reactivity on approach bias observed in Study 3, Chapter 6, the decision was made to switch from a reaction time to a word association automatic cognition task. Finally, given the challenges of participant attrition discussed in

[24] Probable PTSD is defined as an individual who likely meets diagnostic criteria from PTSD, given we did not use a clinical diagnostic interview, based on our cut point identified in Studies 4 and 5.

Chapter 7, the present study was conducted online to both enhance recruitment (via increased accessibility) and mitigate dropout rates.

CHAPTER 10: EXPRESSIVE WRITING ABOUT ONE'S TRAUMA INCREASES ACCESSIBILITY OF CANNABIS INFORMATION IN MEMORY AMONG TRAUMA-EXPOSED CANNABIS USERS

The manuscript prepared for this study is presented below. Readers are advised that Sarah DeGrace, under the supervision of Dr. Sherry Stewart, was responsible for designing the study, developing the research hypotheses, gaining ethical approval, working closely with Qualtrics Panels to ensure data quality, scoring the data, training and supervising a second coder (SJT), preparing the dataset for analyses, conducting the analyses, and interpreting the study results. Sarah was also part of the team that secured funding from the Mental Health Commission of Canada for this work. Sarah wrote the initial draft of the manuscript and received and incorporated feedback from her co-authors. Sarah submitted the manuscript to a special issue of *Cannabis* focusing on cannabis in the Canadian context since legalization on January 31st, 2024 and the manuscript is under review. The reference is: DeGrace, S., Tibbo, P., Pilin, M. A., Krank, M. D., O'Connor, R., Wardell, J., Keough, M. T., Snooks, T., Trottier., S. J., & Stewart, S. H. (under review). Expressive writing about one's trauma increases accessibility of cannabis information in memory among trauma-exposed cannabis users. Submitted to *Cannabis*.

Abstract

Trauma survivors are more likely than others to use cannabis, and post-traumatic stress disorder (PTSD) commonly co-occurs with cannabis use disorder (CUD). Automatic memory associations between trauma reminders and cannabis use have been suggested as contributing mechanisms. These associations can be studied experimentally by manipulating trauma cue exposure in a cue-reactivity paradigm (CRP) and examining effects on the accessibility of cannabis information in memory in trauma survivors with and without PTSD. Cannabis users with trauma histories (N=202) completed a PTSD measure (PTSD Checklist-5) and were randomized to a trauma or neutral expressive writing task as an online CRP. Next, participants completed a cue-behavior word association task, which involved presentation of a series of ambiguous cue words to which participants provided the first word that came to mind. Some of these ambiguous cues pertained to cannabis (e.g., *weed, pot*) and some to other substances (e.g., *blow, shot*). This task was scored by two independent raters. Linear regression models tested the hypothesized main and interactive effects of CRP condition (trauma, neutral) and PTSD group (probable PTSD, no PTSD) on the number of cannabis and other substance responses generated. Main effects of CRP condition were found for cannabis responses (trauma > neutral) but not other substance responses. Unexpectedly, no main effects or interactions of PTSD group were observed for either outcome. In cannabis users with trauma histories, writing about one's trauma specifically activates greater accessibility of cannabis-related information in memory, regardless of PTSD.

Keywords: PTSD, cue-reactivity paradigm, cannabis, automatic cognitions, word association

Introduction

Since cannabis was legalized for recreational use in 2018, Canada has seen an increase in the use of cannabis: past three-month use rose from 22% to 27% of those aged 16 and older from 2017 to 2022 (Government of Canada, 2023b). Currently, 25% of Canadian cannabis users aged 16 years and older engage in daily or near daily use (Government of Canada, 2021). One risk factor for cannabis use is exposure to a traumatic event: those with trauma histories have a significantly increased odds of cannabis use (Kevorkian et al., 2016) and of regular cannabis use (Bassir Nai et al., 2023). Use of cannabis is in turn linked with increased risk of several physical and mental health conditions in the shorter- and longer-term such as high blood pressure, risks to lung health, cognitive impairments, CUD, psychosis, and anxiety (Connor et al., 2021; Cougle et al., 2016; Hasin et al., 2016) and expensive emergency department visits (Crocker et al., 2023).

One potential reason that those with trauma histories have an increased cannabis use risk is that they may use cannabis to cope with the negative affect resulting from exposure to reminders of their traumatic experience (Study 1, Chapter 2). Some of this cannabis use may be deliberate, other use may be reflexive. Indeed, while specific, fully conscious, and deliberate coping motives may initially drive cannabis use in traumatized populations, automatic memory associations may form over time between the context in which substance use occurs (e.g., trauma-related contextual cues) and substance use behavior (van der Vorst et al., 2013). Thus, a person with a sexual assault history, for example, who uses cannabis to manage negative affect in response to trauma reminders (e.g., hearing about a sexual assault in the media) is thought to form strong memory associations over time between trauma cues, negative affect, cannabis use, and relief outcomes (Edalati & Krank, 2015; Romero-Sanchiz

et al., 2022). These automatic cognitive associations are quick, spontaneous, and require little conscious awareness or reflection (Cousijn et al., 2011; Krank & Robinson, 2017; Stacy & Wiers, 2010). They can be tapped using tasks that capture automatic processes measured in various ways, including but not limited to reaction time (Study 3, Chapter 6; Read et al., 2017) or word association tasks (Ames et al., 2007; Pilin et al., 2022). Performance on such automatic cognition measures have been positively associated with substance use behavior (e.g., Ames et al., 2007).

Theoretically, among cannabis users with trauma histories, exposure to trauma reminders should activate the previously formed memory associations between trauma cues and cannabis-related information (e.g., stimuli associated with cannabis use in the past like rolling papers). Because of this activation, trauma cue exposure should increase accessibility in memory of cannabis-related information which should, in turn, give rise to reflexive cannabis use behavior. This would be consistent with substance users' accounts of often finding themselves using their substance without deliberation (Stacy & Wiers, 2010). Researchers can study the effect of trauma (vs. neutral) cue exposure on these automatic cognitions experimentally using cue reactivity paradigms (CRPs): lab-based exposure to relevant stimuli to elicit *reactivity*, or a relevant change in state (e.g., emotional [affect], physiological [salivation], cognitive [craving]). In-lab exposure to a personalized trauma cue is intended to simulate the context of encountering a trauma reminder in everyday life.

A well-established CRP entails a two-session approach (Coffey et al., 2002). During the initial session, a semi-structured interview (Sinha & Tuit, 2012), developed to elicit emotional imagery (Lang et al., 1979), guides participants through describing their most traumatic experience. This material is later condensed into a brief, personalized audiovisual

cue used in the second CRP session (Romero-Sanchiz et al., 2022). An equivalent procedure is followed in developing and presenting the neutral control cue. Attrition rates are high between the initial semi-structured interview session and the second CRP exposure session within this two-session protocol (e.g., Coffey et al., 2006). We addressed this issue in a prior study, where we used the semi-structured interview alone, expecting it would itself elicit similar emotional and cognitive responses seen with the two-session protocol. However, while some controlled processes (e.g., cannabis craving) were successfully elicited by the single-session CRP (Study 2, Chapter 4), the semi-structured interview alone did not evoke increased automatic cannabis-related cognitions using a reaction time task (Study 3, Chapter 6). This points to a need to explore alternative CRPs that not only mitigate study attrition, but also demonstrate sensitivity to the effects of trauma cue exposure on cannabis-relevant automatic cognitive processes.

Thus, the present study utilized a novel stand-alone expressive writing task (trauma vs. neutral) as a single-session method of administering a CRP remotely. Prior work in our lab has found this task to be efficacious in eliciting negative affect and positive cannabis outcome expectancies (including relief expectancies) in a sample of recent cannabis users with trauma histories (Study 4, Chapter 8). The expressive writing task was developed in accordance with two-session CRPs that incorporate brief expressive writing tasks into the protocol (Read et al., 2017; Rodrigeuz & Read, 2020) and in accordance with the work of Pennebaker (1997) on the therapeutic benefits of expressive writing about one's trauma. However, our prior work (Study 4, Chapter 8) and the present study are novel in using the expressive writing task as a stand-alone CRP in eliciting cognitions relevant to understanding cannabis use among cannabis users with trauma histories. We studied trauma cue-elicited

controlled cognitive processes (i.e., self-reported craving) in our prior expressive writing study (Study 4, Chapter 8) and trauma cue-elicited automatic cognitive processes (i.e., cue-behavior memory associations) in the present expressive writing study.

Theoretically, for those with PTSD, the effects of trauma cue exposure in activating automatic accessibility of cannabis-related information in memory should be particularly strong. This is because those with PTSD show greater coping motivated cannabis use (Atasoy et al., 2023) providing greater opportunity for strong memory associations to develop between trauma cues and cannabis use. Indeed, PTSD co-occurs at high rates with cannabis use and CUD (Cougle et al., 2011; Kevorkian et al., 2016; Metrik et al., 2022; Walsh et al., 2014). For example, in a study of cannabis users with trauma histories, lifetime PTSD was associated with increased odds of lifetime CUD even after controlling potential confounds (e.g., depression, anxiety, alcohol dependence; Kevorkian et al., 2016). Importantly, longitudinal work shows that continued cannabis use is associated with worse PTSD outcomes (Wilkinson et al., 2015).

Trauma cue-elicited increases in automatic accessibility of cannabis information in memory might be an underlying mechanism to help explain this high co-occurrence of PTSD with cannabis use and CUD. Specifically, cue condition (trauma vs. neutral) effects on relevant automatic association measures should be strongest among those with PTSD (i.e., an interaction). We tested this possibility in a recent study using a reaction time task – specifically, a cannabis approach-avoidance task (Study 3, Chapter 6). However, we showed only that those with greater PTSD symptoms displayed a greater cannabis approach bias than those with lesser PTSD symptoms; we failed to show that this automatic cognitive bias was enhanced among those exposed to a trauma (vs. neutral) CRP in an N=50 lab study. This

suggested that automatic cannabis approach bias may be chronically activated among those with higher PTSD symptom severity. However, cue condition x PTSD symptoms interactions have been detected in other studies of deliberative, controlled cognitive processes, such as self-reported craving (e.g., Romero-Sanchiz et al., 2022). This suggests that such interactions may be observable for automatic cognition measures as well, provided a study is adequately powered to detect an (often smaller magnitude) interaction effect. Thus, we utilized our expressive writing task remotely in an online study to acquire a sufficiently large sample to detect such theorized cue condition x PTSD interactions in a single session.[25]

We hypothesized those cannabis users with trauma histories randomly assigned to the trauma (vs. neutral) expressive writing task would display greater accessibility of cannabis-related information in memory (H1). We also expected that individuals with (vs. without) probable PTSD would show increased accessibility of cannabis-related information in memory (H2). Further, we hypothesized a cue condition by PTSD group interaction, with the trauma (vs. neutral) cue-elicited accessibility of cannabis-related information in memory being greater among those with (vs. without) probable PTSD (H3). Finally, we hypothesized specificity of the above expected effects to the ambiguous cannabis items on the Cannabis Word Association Task (CWAT; Pilin et al., 2022) that would not generalize to the other substance items on the CWAT (H4).

[25] Using R (R v. 4.2.1; pwr package), we calculated the number of participants needed to detect a small to medium (d=.3) effect for a 2x2 design, with power set at .80 and 12 total targets (i.e., cannabis and substance-primed CWAT items). This analysis determined that we would need n=44 participants per cell to detect this effect size (i.e., a minimum of N=176). Thus, we aimed to recruit ~200 participants to allow for some potential incomplete responding.

Method[26]

Participants.

Qualtrics Survey Panels were used to recruit cannabis users with trauma histories. To participate, participants must have been residing in Canada; aged 19-65 years old; exposed to 1 or more lifetime traumatic event(s) (Gray et al., 2004); and have used at least one gram of cannabis in the past month.[27] Our final sample, after data scrubbing,[28] was N=202 participants (43.6% male; *M* age=42.94 years, *SD*=14.71). This is the same sample used in our prior expressive writing study (Study 4, Chapter 8).

Tasks and Measures.

Demographics. Participants reported their sex and age.

Trauma Exposure. The Life Events Checklist (LEC; Gray et al., 2004) was used to assess exposure to one or more DSM-5 (APA, 2013) PTSD Criterion A traumatic event(s) (e.g., sexual assault, environmental disaster) to ensure study eligibility. If respondents indicated more than one lifetime traumatic event exposure, they answered all further questions about trauma (e.g., PTSD assessment; expressive writing task) in relation to their worst lifetime trauma.

Cannabis Use. Past month cannabis use (frequency and quantity) was assessed with an online version of the Cannabis Timeline Followback (C-TLFB; Sobell & Sobell, 1992). Scores were used to ensure eligibility and were analyzed as potential covariates for use in

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[26] All methods and measures described were approved by the Nova Scotia Health Research Ethics Board (ref #: 1028354).

[27] This minimum cannabis use threshold was set lower than that used in DeGrace et al. (2023, 2024) (i.e., at least 1 gram per week over last month; see Gabrys & Porath, 2019) in order to feasibly recruit a sufficiently large sample to detect PTSD group x cue condition interactions if they were present.

[28] In order to ensure data quality, 597 respondents were excluded for failure to follow writing task instructions (e.g., did not write about the assigned topic; wrote the same word repeatedly), 98 respondents were removed for duplicate IP addresses, and 47 respondents were excluded due to failed speeder checks (performed by Qualtrics) and/or failed attention checks (e.g., “Select ‘3’ for this item”).

sensitivity analyses. The C-TLFB has excellent inter-rater reliability and test-retest reliability (Norberg et al., 2012) and self-reported online versions of the TLFB have been shown to be psychometrically sound (Rueger et al., 2012).

CUD Symptom Severity. To assess CUD symptom severity, we used the 8-item Cannabis Use Disorder Identification Test-Revised (CUDIT-R; Adamson et al., 2010). Participants rated the frequency of experiencing various cannabis-related problems over the past six months on a scale from 0 to 4 (ranging from "never" to "daily or almost daily"). The scores were then totaled. Our sample demonstrated satisfactory internal consistency with an alpha coefficient of .75, indicating the CUDIT-R's robust psychometric properties.

PTSD Group. The PTSD Checklist for DSM-5 (PCL-5; Bovin et al., 2016) was used to describe sample PTSD symptom severity and to categorize[29] participants into two PTSD groups: probable PTSD (≥38;[30] Cohen et al., 2015) or probable no PTSD (<38). The PCL-5 has good reliability and validity and good sensitivity and specificity in detecting clinically diagnosed PTSD (Blevins et al., 2015). In our sample, internal consistency was excellent (α=.95).

Expressive Writing Task. Participants were randomly assigned to complete a trauma-related (i.e., describing their worst lifetime trauma) or a neutral expressive writing task (i.e., describing their morning routine). Programmed prompts queried for details on what happened, and bodily sensations, thoughts, and feelings that occurred during the event (Sinha & Tuit, 2012). Participants were required to write for two minutes minimum and then to continue imagining the event as if it were happening now (Read et al., 2017; Rodriguez &

[29] We chose a categorical (vs. dimensional) measure of PTSD in order to best establish clinical relevance, as in Study 4.
[30] We reasoned a relatively high cut-off point should be used to classify probable PTSD to minimize false positives, given we used a self-report (vs. clinician-administered) measure.

Read, 2020) for another two minutes. These minima were enforced through task-programming. Length of the written passage was recorded (total word count) and later analyzed.

Cannabis-related automatic cognitions. The Cannabis Word Association Task (CWAT; Pilin et al., 2022), a cue-behavior association test (Ames et al., 2007), assessed degree of accessibility of cannabis-related information in memory. This was estimated by the likelihood of generating a cannabis-related word associate to an ambiguous cannabis word. Participants were shown a list of 35 ambiguous words, five of which could be associated with cannabis use (e.g*., pipe, joint*). To examine specificity to cannabis associations in memory, an additional seven items on the CWAT were ambiguous words which could be associated with other substance use (e.g., *blow, shot*). Participants filled in a blank next to each word in the list with the first word that came to mind. Two Independent raters, both blind to PTSD group and cue condition, coded each response as cannabis-related, other substance-related, or neither.[31] Summed totals to each category were calculated (e.g., if a participant responded with 4 cannabis-related responses to the 5 ambiguous cannabis words, their CWAT cannabis score was a 4). These coded responses to the CWAT's ambiguous cannabis (possible range=0-5; κ=0.84) and other substance-related words (possible range=0-7; κ=0.86) were used as CWAT outcomes in analyses.

Procedure.

If trauma exposure (LEC; Gray et al., 2004), and cannabis use (C-TLFB; Sobell & Sobell, 1992) eligibility requirements were met, participants were redirected to complete other measures (Study 4, Chapter 8) including assessment of PTSD symptoms (PCL-5;

[31] The coding of the first rater (SJT), who was naïve to study hypotheses and objectives, was used in analyses, as we reasoned this rater would be less prone to biases.

Boivin et al., 2016). Participants were then automatically randomized to complete either the trauma (n=96) or neutral (n=106) expressive writing task, which served as our remote CRP. Following expressive writing, participants completed the CWAT (Pilin et al., 2022).

Analysis Strategy. We ran two separate linear regression models (R v. 4.2.1; lme4 package) with cue condition, PTSD group, and the condition by PTSD interaction term, predicting accessibility of cannabis and other substance-related information in memory (i.e., count of cannabis-related and other substance-related words generated to the appropriate ambiguous prompts on the CWAT, respectively). We also tested for potential covariates (i.e., age, sex, cannabis use quantity and frequency, self-reported cannabis use problems, expressive writing word count) that were theoretically and empirically related to both the predictors and CWAT outcomes that might need to be controlled in our main analyses.

Results

Sample Characteristics. Demographic and clinical characteristics are reported in Table 5.1 for the overall sample and by cue condition. Over one-third of the sample (36%; n=73) scored 38 or higher on the PCL-5 indicating probable PTSD (Cohen et al., 2015). The sample average CUDIT-R score was just below the cutoff of 12 for probable CUD and above the cutoff of 8 for hazardous use (Adamson et al., 2010). Sample demographic and clinical characteristics are reported elsewhere further broken down by cue condition x PTSD group (Study 4, Chapter 8; see Table 4.1).

Cannabis Accessibility. Consistent with H1, a significant main effect of cue condition emerged for CWAT cannabis responses (t[198]=1.99, 95%CI [0.00-0.81], p=.048), with more cannabis responses generated to the ambiguous cannabis-related words in the trauma than the neutral condition (see Figure 5.1, Table 5.2). Contrary to H2 and H3, there was no

PTSD group main effect or interaction with cue condition for CWAT cannabis responses (see Table 5.2). Consistent with H4, the significant main effect of cue condition seen for CWAT cannabis responses (see H1 above) did not extend to a significant main effect of cue condition for other substance-related responses (t[198]=0.17, 95%CI [-0.25-0.59], p=.424) on the CWAT, and neither PTSD group nor its interaction with cue condition predicted other substance-related responses on the CWAT.

Tests for Potential Covariates. To identify potential covariates possibly needing to be controlled for in sensitivity analyses, we used a set of 2 (PTSD group) x 2 (writing condition) linear mixed models to examine if any writing condition effects emerged that might need to be controlled as covariates in the hypothesis tests. A separate analysis was run for each potential covariate: age, sex, cannabis use quantity and frequency, self-reported cannabis use problems, and writing task word count. Results indicated a statistically significant effect of cue condition only on writing task word count (t[198]=30.16, 95%CI [3.77-56.55], p=.025) with more words written by those randomized to the trauma expressive writing than those randomized to the neutral expressive writing condition. We then assessed if writing task word count was related to our outcome (cannabis-related responses on the CWAT) by running a correlational analysis. Writing task word count and cannabis related CWAT responses were not significantly correlated (r = .10, p = .149). Thus, with no potential covariates differing by cue condition influencing our outcome, we did not conduct sensitivity analyses including covariates.

Discussion

The present study served two primary purposes. First, our single session online trauma expressive writing CRP had a methodological purpose, as it could help mitigate the

attrition common to CRP studies conducted in person across two sessions (Coffey et al., 2006) and permitted acquisition of a larger sample to increase power to detect potential interactions. Second, our trauma expressive writing task allowed us to examine trauma cue-elicited activation of relevant automatic cognitions that might help us understand why individuals with trauma histories are more likely than others to use cannabis (Kevorkian et al., 2016; Bassir Nia et al., 2023). Specifically, this study provided preliminary evidence for the stand-alone trauma expressive writing CRP to successfully elicit greater accessibility to cannabis-related information in memory relative to the neutral expressive writing CRP, consistent with H1. This finding is partially consistent with prior work: a study on automatic attention allocation found a slowing of automatic responses among drinkers with PTSD assigned to the trauma relative to the neutral CRP condition, with the CRP including (but not specific to) an expressive writing task (Read et al., 2017).

While cue condition was a significant predictor of the accessibility of cannabis related information in memory, the CRP manipulation had no impact on responses to other substance-related ambiguous cues on the CWAT, consistent with our cannabis-specificity hypothesis (H4). At first glance, this pattern of findings suggests that among a broad sample of recent cannabis users with trauma histories, the activation of substance-related information in memory in response to personalized trauma cue exposure (via expressive writing) may be specific to cannabis rather than generalizable to a variety of other substances (i.e., substance-related responses on the CWAT to other substance-related ambiguous prompts [e.g., *blow, shot*]). In a previous study using a semi-structured interview (Sinha & Tuit, 2012) as the CRP, in a sample of regular cannabis users with trauma histories, trauma (vs. neutral) cue exposure elicited not only increased cannabis craving but also increased craving for alcohol

(Study 2, Chapter 4). This difference may indicate cannabis specificity for automatic cognitive processes and generalizability to other substances for more controlled, deliberative cognitive processes like craving (Tiffany, 1999). Alternatively, the discrepancy may be due to methodological differences: in Study 2 (Chapter 4), we only examined alcohol craving in the subset of cannabis users who were drinkers while we did not obtain information on other substance use in the present study. Thus, it remains possible that expressive writing about a personal traumatic experience may indeed activate increased accessibility to other substance-related information in memory for those cannabis users who also use other substances.

Contrary to expectations and prior work, probable PTSD status did not predict greater cannabis-related cognitions (H2; cf., Study 3, Chapter 6), nor did probable PTSD status interact with the trauma cue to predict such cognitions (H3; cf., Romero-Sanchiz et al., 2022). While we had a larger sample than our previous study using the single session CRP interview (Study 2, Chapter 4), like that previous study, we were unable to detect an interaction between PTSD and randomly assigned cue condition (trauma vs neutral) on cannabis cue-behavior associations. This absence of a PTSD by cue condition interaction is also consistent with our recent study using the same expressive writing task in this same sample (see Study 4, Chapter 8) showing a main effect of cue condition on negative affect and expectancy craving (a controlled cognitive process; Tiffany, 1999) but no interaction with PTSD. Other work from our group has, however, shown a significant interaction between PTSD and CRP cue condition for compulsivity cannabis craving – a controlled cognitive process (Romero-Sanchiz et al., 2022). Since these prior studies have not systematically varied CRP (single- vs. two-session; audiovisual cue vs. structured interview vs. expressive writing), cognitive outcome (automatic vs. controlled process; word

association vs. reaction time task), or PTSD conceptualization (categorical vs. continuous; self-reported vs. clinical interview), more work is needed in identifying the conditions under which cue condition and PTSD interact in predicting cognitive outcomes relevant to understanding PTSD-CUD comorbidity (e.g., Cougle et al., 2011; Kevorkian et al., 2016).

Another possible explanation for the lack of PTSD effects in the present study could be that the automatic substance-related cognitions tapped by the CWAT may be relevant for all cannabis users with trauma histories rather than being particularly relevant to those with PTSD. Indeed, the type of automatic cognitions assessed may be worth noting in interpreting the results of this study. For example, we found an effect of PTSD status, but no cue condition effects, on cannabis approach bias in Study 3 Chapter 6, whereas we found an effect of trauma cue assignment, but no effect of PTSD, on the accessibility of cannabis information in memory in the present study. This suggests we cannot assume results with one automatic cannabis-related cognitive bias will extend to another measure tapping another type of cognitive bias. Future work may aim to directly compare, in a single study, trauma CRP and PTSD main and interactive effects on different automatic cognition outcomes using word association (e.g., cue-behavior; behavior-outcome; Ames et al., 2007) and reaction time tasks (e.g., selective attention to cannabis; automatic cannabis approach bias; e.g., Read et al., 2017; Study 3 Chapter 6) in this population.

Our study presents limitations which should be considered when interpreting our results. Firstly, while steps were taken to ensure data quality in this online study (e.g., attention and speeder checks; replacement of participants who clearly did not follow expressive writing instructions), the lack of experimenter presence in the online environment may have enabled participants to escape from the CRP (e.g., stopping writing about trauma if

anxiety became too intense), potentially minimizing the magnitude of cue condition effects. Given that avoidance of trauma reminders is a symptom of PTSD (APA, 2013), escape from the writing task specifically among those with probable PTSD may have worked against the PTSD group x cue condition interaction hypothesized in H3. Second, while we coded PTSD categorically for greater clinical relevance to understanding PTSD-CUD comorbidity, and for consistency with the results of latent class analysis studies suggesting PTSD is better conceptualized as categorical than as dimensional (Ayer et al., 2011; Breslau et al., 2005; Steenkamp et al., 2012), this choice may have reduced power to detect PTSD main or interactive effects relative to studies that have examined PTSD symptoms continuously (e.g., Romero-Sanchiz et al., 2022). Third, our categorizing participants into probable PTSD and probable no PTSD groups based on a cutoff on a self-report measure (although a high cutpoint relative to other suggested cutoffs; e.g., Bovin et al., 2016) likely resulted in some misclassification relative to if we had used a diagnostic interview like the Clinician Administered PTSD Scale (CAPS-5; Weathers et al., 2018); misclassification could potentially explain the absence of the hypothesized main and interactive PTSD group effects.

Despite limitations, the present study provided preliminary evidence for the use of a remote, self-administered expressive writing task as a CRP, in eliciting specific automatic cannabis-related cognitions – namely increased accessibility of cannabis-related information in memory. However, the presence of likely PTSD did not intensify this trauma vs. neutral CRP effect on cannabis accessibility in memory. Thus, in-person CRP administration (with an in-person experimenter to monitor participant engagement) may be needed to successfully intensify these automatic cannabis-related cognitions in individuals with PTSD, given their tendency to avoid trauma reminders (APA, 2013). While the absence of PTSD group effects

or an interaction of PTSD group with cue condition suggests cue-behavior associations are an unlikely candidate for an automatic cognitive process to explain the high comorbidity of PTSD and CUD (Cougle et al., 2011), the main effects of cue condition may well be useful in understanding why those with trauma histories are at increased risk of cannabis use (Bassir Nia et al., 2023; Kevorkian et al., 2015). Indeed, the tendency of trauma cue exposure to increase accessibility of cannabis information in memory among cannabis users with trauma histories may promote increased cannabis use, even without the individual's conscious awareness or reflection (Ames et al., 2007). This trauma cue-elicited reflexive cannabis use among those with trauma histories may be particularly likely in an environment where cannabis is readily accessible, such as in Canada's legalized context.

Table 5.1. Descriptive characteristics.

				N (%)/ Mean (SD)
Cue Condition		Trauma n=96	Neutral n=106	Overall Sample N=202
Age (in years)		43.25 (14.89)	42.55 (14.61)	42.94 (14.71)
Sex	Male	43 (44.8%)	45 (42.5%)	88 (43.6%)
	Female	53 (55.2%)	61 (57.5%)	114 (56.4%)
CUDIT-R score		11.80 (6.62)	10.97 (5.89)	11.37 (6.25)
TLFB past month cannabis use (days used)		14.24 (10.68)	13.84 (10.18)	14.03 (10.40)
PCL-5 score		32.02 (18.44)	31.05 (19.03)	31.51 (18.71)
% with probable PTSD		36 (37.5%)	37 (34.9%)	73 (36.1%)
Expressive writing task word count		93.86 (95.94)	58.06 (50.39)	75.08 (77.45)

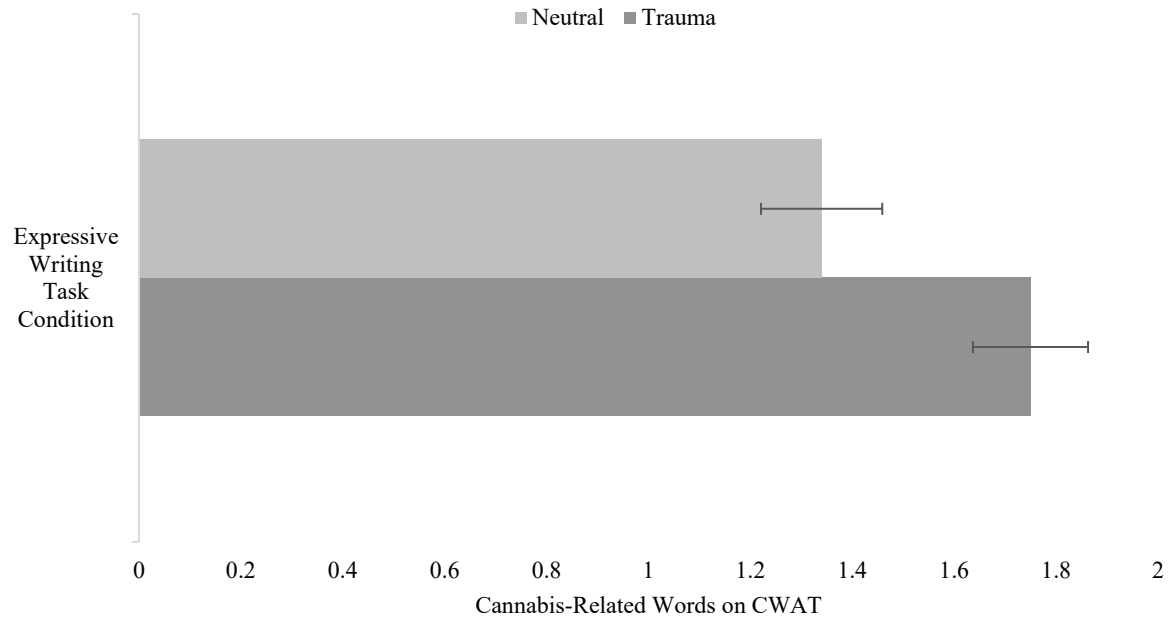
CUDIT-R score: Cannabis Use Disorder Identification Test-Revised (Adamson et al., 2010). TLFB = Timeline Follow-back (Sobell & Sobell, 1992). PCL-5 = PTSD Checklist for DSM-5 (Bovin et al., 2016).

Table 5.2. Linear mixed models' omnibus results for cannabis and substance-related automatic cognitions.

	Estimate (*b*)	CI (95%)	*p*
Cannabis Words Generated		Marginal R^2 = 0.034 / Conditional R^2 = 0.019	
Condition (Neutral = 0)	0.41	0.00 – 0.81	0.048*
PTSD Status (PTSD- = 0)	-0.15	-0.62 – 0.32	0.534
Condition*PTSD Status	0.01	-0.66 – 0.69	0.966
	Estimate (*b*)	CI (95%)	*p*
Substance Words Generated		Marginal R^2 = 0.018 / Conditional R^2 = 0.003	
Condition (Neutral = 0)	0.17	-0.25 – 0.59	0.424
PTSD Status (PTSD- = 0)	-0.28	-0.77 – 0.20	0.251
Condition*PTSD Status	0.25	-0.44 – 0.95	0.472

Note. * $p < .05$, ** $p < .01$, *** $p < .001$.

Figure 5.1. Mean number of cannabis-related responses on the Cannabis Word Association Task (CWAT) by cue type (trauma vs. neutral expressive writing task).



Note: Bars represent the standard error.

CHAPTER 11. GENERAL DISCUSSION

The aim of my dissertation was to improve our understanding of the mechanisms contributing to PTSD-CUD comorbidity by testing the trauma cue-elicited affective and cognitive responses predicted by learning theory that theoretically might promote cannabis use in those with PTSD. Specifically, I sought to experimentally test two methodological variations of trauma CRPs on relevant outcomes that should theoretically contribute to this comorbidity. To achieve this, I conducted five studies – one a scoping review and the other four empirical studies employing various trauma CRPs. In the upcoming sections of this general discussion, I provide a summary and synthesis of the results obtained from my dissertation research, integrating them both with the extant literature and with each other. Following that, I delve into the methodological, theoretical, and clinical implications arising from my dissertation. The conclusion assesses the strengths and limitations of my work, along with recommendations for potential future research.

Summary and Integration of Findings

Summary

Study 1 scoped the existing experimental literature using CRPs among those who have experienced lifetime trauma or PTSD and who engage in substance use. Specifically, Study 1 categorized methodological subtypes (e.g., cue types [stress, trauma, substance]; CRP types [interview, in-vivo, script-driven]) and common vs. rarer outcomes (such as affect, craving, and automatic cognitions) in CRP research. Further, Study 1 established that trauma cues trigger greater cravings compared to baseline, as well as compared to exposure to neutral and often substance-related cues. Additionally, the review revealed gaps in the literature in several key areas. Firstly, there are notable attrition issues associated with the

typical two-session methodology used in CRPs, especially considering the trauma-exposed nature of the population (many suffering from PTSD which includes avoidance symptoms), leading to avoidance of trauma reminders. Secondly, although the existing literature predominantly concentrates on traumatized alcohol, cocaine, and nicotine users, there remains a notable gap in research utilizing CRPs among cannabis users with trauma histories. Third, there is a relative paucity of research examining the effects of trauma reminders on substance-relevant automatic cognitions. Fourth, most such studies were comprised of small to medium-sized (average n=112) samples collected in-lab, limiting power to detect theorized cue condition x PTSD interactions. Finally, some of the included studies did not assess for affect (n=14), and those that did showed variability in whether negative affect alone or both positive and negative affect are involved.

Emerging from the results of my scoping review (Study 1), I identified the population of interest, the experimental manipulation, the main moderator variable, and the outcome variables that would inform the subsequent four empirical studies included in my dissertation. First, I chose a trauma-exposed, cannabis using population, as cannabis was the clearly understudied in this body of literature. Second, regarding the experimental manipulation, my scoping review (Study 1) revealed promise for trauma CRPs to reveal mechanisms contributing to the high rates of PTSD-SUD comorbidity. However, given the attrition common to the gold-standard two-session trauma CRP (Coffey et al., 2006), I aimed to validate two alternative single session trauma CRPs to address this glaring methodological barrier in the field (see Studies 2 and 4). Third, given that my dissertation was intended to inform on mechanisms contributing to high rates of cannabis use and CUD in those with PTSD, and given theoretical contention that the learning mechanisms under study should be

most applicable to those with PTSD diagnoses or high levels of PTSD symptoms, I consistently examined PTSD as a moderator of trauma CRP effects across my four studies; I paid particular attention to ensuring adequate power to detect such interactions in my second data collection (Studies 3 and 4). Finally, my scoping review helped inform my chosen outcome variables across my four empirical studies. Given the findings of my scoping review that trauma cue-elicited substance craving and negative affect were commonly observed outcomes across studies, I chose these as the main outcomes in my two trauma CRP methodological validation studies (Studies 2 and 4). And given that my scoping review (Study 1) revealed variable results for trauma cue-induced reductions in positive affect, I measured not only negative affect but also positive affect in Studies 2 and 4 to contribute additional findings to that debate. Finally, given the paucity of studies that included substance-relevant automatic cognition measures as outcomes in trauma CRP studies (Study 1), I focused on two different cannabis-relevant automatic cognition measures as outcomes in Studies 3 and 5 – namely cannabis approach bias (an RT task) and memory accessibility of cannabis information (a word association task), respectively.

I began by testing an in-person variation of a trauma CRP in Studies 2 and 3. Specifically, I utilized only the first of two in-laboratory sessions of the gold-standard CRP (Coffey et al., 2002). This was designed to address the issue of high drop out rates between sessions. In Study 2, we first examined the use of a methodological variation of the gold standard CRP – specifically, we tested the effect of the single-session trauma CRP (and PTSD symptoms) on cannabis craving, as well as negative and positive affect. The cannabis craving outcome represented a more controlled, deliberate cognitive process that can be triggered by trauma cue exposure and may underly comorbid PTSD-CUD. The results of

Study 2 provided data consistent with learning theory predictions. Specifically, I found that the trauma cue exposure and PTSD interacted to predict increased negative affect. Only a main effect of the trauma CRP predicted increased craving, and positive affect remained unaffected by the CRP but was lower overall among those with a higher PTSD symptom count. This study represented the second published empirical work examining these outcomes among trauma-exposed cannabis users (Romero-Sanchiz et al., 2022), and the first to use a single-session, semi-structured interview (Sinha & Tuit, 2012) as a trauma CRP.

Using our validated single-session trauma CRP from Study 2, Study 3 examined the effects of trauma cue exposure and PTSD symptoms on automatic cannabis-related cognitions – specifically, cannabis approach bias (Cousijn et al., 2011). This change in outcome allowed me to study the main and interactive influences of exposure to trauma reminders and of PTSD symptom severity on one form of automatic cannabis cognition that may mechanistically influence PTSD-CUD comorbidity. Results demonstrated a greater automatic cannabis approach bias among those with more (vs. less) severe PTSD symptoms; however, this effect was unexpectedly not intensified by the trauma CRP suggesting this approach bias toward cannabis may be chronically activated among cannabis users with trauma histories who have more severe PTSD symptoms. Notably, Study 3 is the first study to examine either trauma cue exposure or PTSD as predictors of cannabis approach bias.

Given the trauma cue x PTSD interactions I hypothesized in Studies 2 and 3 did not emerge for positive affect or cannabis cognitions, respectively (only seen for negative affect), Studies 4 and 5 had the primary aim of testing a single session, online, self-administered trauma CRP in order to achieve sample sizes that could provide the needed power to detect these potentially small interaction effects. In Study 4, I tested the effects of the online-

administered CRP on cannabis craving, negative affect, and positive affect, as in Study 2, to validate use of expressive writing about trauma as an online, self-administered CRP. I found the expected main effects of the trauma (vs. neutral) online CRP on negative affect and the expectancy dimension of craving, and main effects of probable PTSD on negative affect and all four dimensions of cannabis craving. Contrary to our expectations, no cue condition x PTSD interactions were detected even with a sample size that was quadruple that used in Studies 2 and 3. Further, we had switched our conceptualization of PTSD from continuous (as in Studies 2 and 3) to categorical, as some latent class analysis research suggests this categorical conceptualization may be a more appropriate conceptualization of PTSD than a dimensional one (Ayer et al., 2011; Breslau et al., 2005; Steenkamp et al., 2012). Overall, the results of Study 4 suggested the self-administered trauma CRP can elicit increased negative affect and craving involving positive expectancies about cannabis use. Moreover, main effects of probable PTSD suggested cannabis craving and negative affect may be more chronically activated among those with vs without PTSD. However, despite the lack of PTSD x cue exposure interaction, the two main effects meant that the highest levels of both negative affect and expectancy cannabis craving were observed in those with probable PTSD following writing about their trauma; this points to trauma cue elicited negative affect and expectancy craving as mechanisms that may drive increased cannabis use in those cannabis users with PTSD.

Finally, Study 5 used the same online, self-administered trauma CRP used in Study 4 (i.e., expressive writing about one's trauma) to induce increased automatic cannabis-related cognitions. Specifically, I used a cannabis word association task – the CWAT (Pilin et al., 2-2022) – in Study 5, which differed from the cannabis AAT used in Study 3 (which measured

automatic approach biases toward cannabis stimuli) in that it measured accessibility of cannabis-related information in memory. Results demonstrated those assigned to the trauma CRP had cannabis-related information more accessible in memory (i.e., generated more cannabis-related words on the CWAT) relative to those in the neutral expressive writing condition. However, unexpectedly, no main effects of probable PTSD nor interactions between the CRP condition and PTSD group were found. Study 5 advanced the literature by demonstrating that writing about one's own trauma specifically activates increased accessibility of cannabis-related information in memory in comparison to the writing about a neutral personal event, regardless of probable PTSD status.

Integration of Study Findings

The findings of the current dissertation have provided evidence for the role that exposure to trauma cues has in activating affective and cognitive processes that are theorized to predict increased cannabis use, ultimately increasing risk for CUD, particularly for those with PTSD. Indeed, while Study 1 identified a paucity of cannabis-specific CRP research in a trauma-exposed population, informing my four subsequent studies, Studies 2 – 4 contributed experimentally to the literature. Specifically, Study 2 and Study 4 add to the literature suggesting that trauma reminders elicit cannabis craving and negative affect among cannabis users with trauma histories. Such results replicate experimental literature on PTSD-CUD (Romero-Sanchiz et al., 2022), PTSD-AUD (Coffey et al., 2010), and PTSD-Cocaine use disorder (Tull et al., 2013). These results also showcase methodological advancements – specifically, my work provides proof-of-concept validation for a single-session, lab-based CRP interview (Study 2) and a single session, online, self-administered written CRP (Study 4), respectively. Importantly, my results demonstrating that both cannabis craving and

negative affect are elicited in response to trauma reminders (Studies 2 and 4) provides empirical evidence for deliberative cognitive processes (i.e., craving) and affective processes being important in the mechanistic relationship underlying trauma exposure and cannabis use Indeed, these increases in craving support the involvement of deliberative cognitive processes triggered by trauma cues. Similarly, the increase in negative affect is consistent with theories positing a role for heightened negative emotions in influencing substance craving (Baker et al., 2004; Khantzian, 1997). This is particularly evident in the breakdown of craving outcomes into distinct dimensions in Study 4, suggesting that trauma cue-elicited negative affect might prompt contemplation of cannabis's potential for relieving such feelings (expectancy craving). While not directly examined in this thesis, this sequence (Drummond, 2000) could theoretically enhance the inclination to use cannabis as a coping mechanism in such situations. Indeed, this falls in line with Drummond's (2000) theory on cue chains. Each cue (i.e., external trauma reminder followed by internal negative affect) within the chain acts as a conditioned stimulus that becomes associated with the relieving effects of substance use, serving to elicit craving and substance-seeking behaviors. As discussed in the introduction, negative affect alone may act as a discriminative stimulus that signals relief consequences will be experienced if the individual engages in substance use now. The sequential occurrence of cues in a cue chain sets off a cascade of learned associations, wherein the presence of one cue increases the salience and expectancy of subsequent cues, ultimately leading to substance use initiation (Drummond, 2000). For example, an individual is reminded of their traumatic motor vehicle accident when the same model and color of vehicle passes them when they are out on a walk. They begin to experience hypervigilance and to feel anxious (i.e., experiencing negative affect, a

discriminative stimulus). As they walk further, they pass a group of teenagers smoking a joint. The smell of the cannabis, in addition to the reminder of their past traumatic event, triggers a strong craving as this individual has come to associate cannabis use with relief from trauma cue-elicited negative emotions. The individual changes their route to stop by the cannabis store on their way home and buy a pre-rolled joint and a lighter. In this hypothetical example, each cue within the chain serves to activate associative memory networks linked to previous experiences of relief following cannabis use, thereby heightening the individual's craving and positive expectancies of substance use. The sequential occurrence of cues in the chain sets off a cascade of learned associations. The prior exposure to the trauma reminder heightened the salience of the cannabis cues (teenagers passing around a joint) the latter of which are not normally enough to activate craving for this individual when they occur alone. Additionally, the repetition of this cue chain over time strengthens the associative connections between cues and substance use, making it increasingly difficult for the individual to engage in thoughtful decision-making prior to engaging in substance use behaviors (Drummond, 2000). Indeed, while such theories and work examining co-occurring PTSD and AUD have long posited the role of conditioning processes in the development and maintenance of this comorbidity (e.g., Stewart, 1996; Bailey et al., 2013), as identified in Study 1, little empirical work has been done to examine these mechanisms for CUD, in particular.

Further, the present dissertation’s findings extend to examining the effects of exposure to trauma reminders and PTSD group on automatic cognitive processes. Specifically, Study 3 utilized a single-session trauma CRP to elicit cannabis approach bias, hypothesized to be greatest among those with greater PTSD symptom severity. Partially

consistent with those expectations, greater PTSD symptoms (though not the trauma CRP or the PTSD x CRP interaction) predicted increased cannabis approach bias. Alternatively, Study 5 utilized a remote, online trauma expressive writing task to activate increased cannabis-related information in memory, and this effect was also expected to be most pronounced among those with PTSD. Partially consistent with this hypothesis, Study 5 showed that the trauma CRP (and not probable PTSD or the PTSD x cue type interaction) predicted increased accessibility of cannabis information in memory. Both approach bias (Study 3) and memory associations/accessibility (Study 5) are theorized to contribute to comorbid PTSD-CUD through associative memory processes which become automatized with repetition (Baker et al., 2004). Notably, Studies 3 and 5 represent the first studies to combine trauma CRP methods with automatic cognition tasks to test predictions emerging from this theory among cannabis users with trauma histories. This work is somewhat aligned with prior cue reactivity studies. Specifically, work by Read and colleagues (2017) had participants exposed to a trauma or neutral cue, followed by a Stroop colour naming task containing trauma, alcohol, and neutral stimuli (i.e., words). They expected PTSD+ participants to show attentional bias toward the trauma and alcohol stimuli following trauma cue exposure; however, results demonstrated individuals with PTSD exposed to the trauma cue had slowed reaction times on the Stroop task, regardless of stimulus type (Read et al., 2017). The authors reasoned this general slowing may represent a preoccupation with the trauma reminder and/or a depletion of cognitive resources following the trauma CRP among those with PTSD (Read et al., 2017). This is a finding that is somewhat consistent with theory, as Baker and colleagues (2004) emphasized that a depletion of cognitive resources following trauma cue exposure may lead to lesser use of more deliberative decision-making

processes, thus the individual is more likely to impulsively defer to the learned automatic behavior of substance use (Baker et al., 2004).

Both studies I employed to examine trauma cue-elicited deliberative cognitive processes (i.e., craving) and affective processes underlying comorbid PTSD-CUD demonstrated main effects of trauma cue exposure on negative affect and some aspect of cannabis craving (overall craving in Study 2; expectancy craving in Study 4). However, in line with results of Study 2, Study 4 did not detect an interaction effect between trauma cue and PTSD on cannabis craving. This lack of interaction effect between trauma (vs. neutral) cue and PTSD is inconsistent with cue reactivity experiments in trauma exposed alcohol users (e.g., Read et al., 2017 found slowed responses on the STROOP task only for alcohol users with PTSD in the trauma condition). The results of Studies 2 and 4 are interesting to examine in the context of prior findings from my lab – specifically, Romero-Sanchiz and colleagues (2022) detected a significant CRP condition x PTSD interaction on compulsivity craving only when a cannabis CRP, not a neutral CRP, was used as the comparator for the trauma CRP. Indeed, this differed from our hypothesized interaction with a neutral cue used as a comparator. Perhaps compulsivity (i.e., relief) craving is strongly associated with trauma cues among those with PTSD, whereas cannabis cues alone are not typically associated with eliciting relief craving. Thus, perhaps the interaction with this comparator (i.e., cannabis cue as opposed to a neutral cue) produced a more robust result.

In addition to the lack of interaction effect, in Study 4 the trauma cue exposure failed to elicit increases in three of four cannabis craving dimensions, contrary to our expectations. Nonetheless, main effects of both CRP condition and PTSD were observed for expectancy craving, with expectancy craving scores highest for those with probable PTSD who had been

exposed to the trauma interview. Thus, the findings of Study 4 imply that expectancy craving, activated by trauma cue exposure, may play a role in driving the elevated rates of cannabis use and CUD among individuals with PTSD. However, these results were not replicated in Study 2, where only a main effect of trauma CRP (and no main effect of PTSD symptom count) was observed for craving. Importantly though, Study 2 only examined a total cannabis craving score (vs. the examination of specific craving dimensions in Study 4), precluding us from making as detailed conclusions on the type of cannabis craving that was activated by trauma cue exposure in Study 2.

Another potential explanation for the discrepancy of trauma cue effects between Studies 2 and 4 could lie in the nature of the trauma expressive writing task employed in Study 4. Indeed, given Study 2 demonstrated trauma cue effects on overall craving and Study 4 broke down craving into its constituent dimensions, it follows logically that trauma cue effects should manifest in at least half of those dimensions (or exhibit a notably substantial effect on a single dimension). However, this was not the case, given the variance explained by trauma cue exposure alone on overall craving in Study 2 was 12%, whereas the trauma expressive writing task alone accounted for only about 1% of the variance in each dimension of craving in Study 4. It is conceivable that the expressive writing task used in Study 4 did not sufficiently activate traumatic memories to elicit a broad craving response beyond increasing positive cannabis outcome expectancy. Similarly, the in-person trauma interview used in Study 2 explained 40% of the variance in elicited negative affect, whereas the expressive writing task in Study 4 accounted for only 2% of the variance in the participants' negative affect. Unlike traditional trauma CRP methods that aim to evoke vivid recollections of traumatic events, the expressive writing task may not have provided participants with

adequate immersion in memories of their trauma-related experiences. Indeed, consistent with Read and colleagues' (2017) protocol, participants engaged with the writing task for at least two minutes, which is much shorter than expressive writing tasks used in other studies (see Pennebaker, 1997). Consequently, the level of activation of trauma schema elicited by the writing task may have been insufficient to trigger robust negative affect and cannabis craving responses, leading to the unexpected findings observed in Study 4 (i.e., only one of four cannabis craving dimensions showing trauma cue reactivity; generally small effect sizes). This interpretation aligns with the notion that the intensity of trauma cues may play a crucial role in eliciting craving responses among substance users with comorbid PTSD (Carter & Tiffany, 1999; Study 1, Chapter 2).

Comparatively, the results of Studies 3 and 5 examining the automatic processes underlying co-occurring PTSD-CUD also demonstrated differing effects from that of the literature (e.g. Read et al., 2017) and from each other. Importantly, only two prior studies (as identified in Study 1, Chapter 2) had examined automatic cognitions in trauma-exposed substance users; both studies did not detect trauma cue exposure effects. In line with these identified studies (Read et al., 2017), I did not find trauma exposure to be a predictor of cannabis approach bias or to interact with PTSD symptoms as had been hypothesized in Study 3. Instead, results suggested that cannabis approach bias was chronically activated among those with more PTSD symptoms, regardless of trauma cue exposure. Conversely, I *did* find trauma exposure to be a predictor of accessibility of cannabis-related information in memory in Study 5, yet PTSD was not significant for this outcome either as a main or as an interactive effect with cue exposure. Such differences could be primarily due to a lack of power to detect the traditionally small effects of trauma cue exposure in empirical literature

(Berenz et al., 2021), as Study 3 had significantly fewer participants than that of Study 5, where a trauma cue effect *was* detected. This, however, does not explain the unexpected lack of effects of PTSD on the accessibility of cannabis-related information in memory in Study 5. One possible methodological explanation for this difference could be the tasks used to measure automatic cannabis-relevant cognitions across the two studies. Specifically, while Study 3 employed a reaction time task to measure immediate cognitive associations between trauma cues and approach toward cannabis-related stimuli, Study 5 employed a memory accessibility task with cannabis-related word associates, focusing on the accessibility (i.e., ease/immediacy of retrieval) of cannabis-related information from memory rather than the automatic action tendency to approach cannabis stimuli in the environment. Theoretically, these tasks tap different aspects of automatic cognition, and thus it is possible they are influenced by different predictors. Alternatively, perhaps the cannabis words used in Study 5 were not relevant for individuals with higher PTSD. For example, one study found those using cannabis medicinally were 3.16 times more likely to have PTSD compared to those using cannabis recreationally (Metrik et al., 2018). Given medicinal cannabis is often ingested (e.g., sprays, edibles, oils) rather than smoked (Arnold et al., 2020), perhaps prompts on the CWAT failed to increase cannabis salience in memory for these individuals. Alternatively, perhaps the use of photos (visual cues) in the AAT served as more powerful stimuli than words on the CWAT to individuals with PTSD. Some research supports this, as either words or photos are used in common measures of automatic associations (Ames et al., 2007), and some argue these two formats tap different modes of cognition (Dell'Acqua et al., 2007). Then again, this difference may also be due to the types of CRPs used in Study 3 vs. Study 5. Specifically, Study 5 used an online, self-administered trauma writing task as a CRP

whereas Study 3 used a lab-based interview about the trauma with a trained experimenter. Given individuals with greater PTSD symptoms tend to be avoidant of trauma reminders (APA, 2013), researchers using the self-administered expressive writing CRP in the future should be aware of these potential methodological barriers of using a CRP that is easily controlled (i.e., participants can readily stop writing if fear becomes overwhelming) and not having an experimenter present to encourage participants to continue writing, for populations of highly avoidant trauma-exposed individuals. For example, as noted earlier, it is possible those with more severe PTSD stopped writing or engaging with the task (Study 5), given there was no experimenter present (compared to Study 3 which did have an experimenter present). This might have wiped out interactive effects of PTSD by trauma cue on the CWAT that might have been seen with another less controllable trauma CRP. A third explanation for this difference may lie in the dichotomous approach to PTSD classification used in Study 5 rather than the continuous approach used in Study 3. For example, the dimensional, continuous approach in Study 3 might have been more sensitive to individual differences in PTSD severity, while the categorical approach used in Study 5 would emphasize group-level, diagnostic distinctions. Notably, the dimensional approach in Study 3 appeared more sensitive to nuances in PTSD severity, potentially elucidating the relationship between PTSD and automatic cannabis-related cognitions more effectively than the categorical approach employed in Study 5. Whatever their explanation(s), the differences in results of Study 3 and Study 5 point to the importance of not generalizing findings from one automatic cognitive bias related to cannabis to another measure that assesses a different type of automatic cognitive process.

As briefly mentioned above, notably, some of these variations in results may be due differences in the operationalization of PTSD symptomology and craving outcomes across Studies 2-5. Specifically, in Studies 2 and 3, PTSD symptoms were operationalized as a continuous measure that was administered by the experimenter (CAPS-5 symptom count in Study 2) or self-administered by the participant (PCL-5 continuous scores in Study 3). Conversely, Studies 4 and 5 conceptualized PTSD in a categorical manner, and these measures were self-administered by the participant via an online survey (PCL-5) and established civilian cutoffs were used to classify participants as having probable PTSD or no PTSD. The primary reasoning underlying this methodological choice to use a categorical method in the latter two studies was based on my uncovering evidence that latent subgroups (as described by Ayer et al. [2011], Breslau et al. [2005] and Kline et al. [2024]) may better describe PTSD (vs. continuous measures). Moreover, this categorical conceptualization enables our findings to inform clinical interventions more effectively given that categorical diagnoses are used in clinical practice. For instance, the observation that individuals with probable PTSD exhibited heightened negative affect and expectancy craving in response to expressive writing about their trauma highlights these factors as crucial targets for intervention in cannabis users with PTSD within clinical settings. This is particularly important to consider given clinicians often rely on diagnostic categories (Frances, 2013) rather than interpreting varying degrees of symptom severity in their daily practice.

In terms of cannabis craving, Study 2 conceptualized craving as an overall, continuous score on the MCQ-SF (Heishman et al., 2009), whereas Study 4 utilized the MCQ-SF in a dimensional manner by examining its four subscales as distinct outcomes. In this context, the absence of significant PTSD effects on craving in Study 2 may suggest that

PTSD symptoms did not exert a discernible influence on the overall craving experience, as measured by the MCQ-SF. However, the emergence of PTSD effects on approach bias in Study 3 suggests that while PTSD symptoms may not directly impact the overall intensity of cravings (a controlled cognitive process), they could still influence automatic cognitive processes related to cannabis use, such as automatic approach tendencies in the same participants. Conversely, Study 4 used the MCQ-SF in a dimensional manner, allowing me to examine craving across different domains – specifically, compulsivity, emotionality, expectancy, and purposefulness. This dimensional approach provided insights into the specific facets of craving affected by probable PTSD, rather than treating craving as a singular construct. The finding of PTSD group effects on all four facets of craving in Study 4 but not on accessibility of cannabis information in memory in Study 5 may reflect the differential impact of PTSD on specific aspects of cannabis relevant cognitions. For instance, probable PTSD might heighten self-reported cannabis craving (an aspect of cannabis cognition of which participants are aware), as captured by the MCQ-SF subscales in Study 4, while not exerting a significant influence on accessibility of cannabis-related information in memory (a more automatic aspect of cannabis cognition) as captured by the CWAT in Study 5.

It is important to note that the evolution of measurement approaches used across Studies 2-5 introduces a layer of complexity to the interpretation of results and making direct comparisons between studies challenging. For PTSD assessment, for example, the shift from an experimenter-administered continuous measure (Study 2) to a self-administered dimensional measure (Study 3) to a self-administered measure that was dichotomized using clinical cut-points (Study 4 and 5) reflects one example of a methodological adaptation that

may have impacted the comparability of findings across studies. Other differences across Studies 2-3 vs. Studies 4-5 include the utilization of a lab-based vs. expressive writing CRP; the measurement of overall craving vs. dimensional craving (subscales); and the use of an AAT (reaction time) vs. word association (memory bias) task, respectively.

Theoretical Implications

As described in-depth in Chapter 2, the self-medication hypothesis (Khantzian et al., 1993), two-factor learning theory (Stascewicz & Maisto, 1993), negative reinforcement theory (Baker et al., 2004), classically conditioned trauma cue-elicited craving (Romero-Sanchiz et al., 2022), and associative learning (Wiers & Stacy, 2006) are all theoretically based upon classical and operant conditioning principles. Such conditioning processes play a role in the development and maintenance of comorbid PTSD-SUD. Specifically, during a traumatic event, fear and distress become associated with initially neutral stimuli associated with the trauma. For example, a Veteran is injured in an explosion while deployed; when he hears loud noises from then on, he experiences an increase in negative affect due to the association of the noises with the initial trauma, despite there being no actual danger associated with the noises in the present non-military context. Then, when the Veteran chooses to use a substance as a means of escaping the negative affect elicited by the trauma reminder (Khantzian et al., 1993), he develops a learned association between the substance use and subsequent relief from negative affect (Stascewicz & Maisto, 1993). Thus, over time, trauma-exposed individuals may consume cannabis in response to the distress caused by a trauma reminder. The removal of the aversive stimuli (i.e., negative affect provoked by trauma cue exposure) provided by substance use serves as a negative reinforcement (Baker et al., 2004), strengthening the likelihood of the individual engaging in similar substance use to

cope when encountering trauma reminders in the future. For instance, a person experiencing intrusive memories or flashbacks related to a traumatic event may use cannabis to dampen this negative affect provoked by the trauma reminder, with the relief experienced following cannabis use functioning as a form of negative reinforcement (Anderson et al., 2015; Baker et al., 2004). This reinforcement strengthens the likelihood of future engagement in substance use in similar contexts in the future. Over time, this operant conditioning process perpetuates the cycle of substance use as a maladaptive coping mechanism for managing trauma cue-elicited distress, particularly in those with greater PTSD symptoms who should be more susceptible to trauma cue-elicited distress. This is supported by the interactive effect of the trauma cue and PTSD symptoms on negative affect in Study 2.

From the classical conditioning perspective, the repeated pairing of trauma cues with substance use results in a conditioned craving for the substance, in that exposure to the conditioned stimulus (i.e., trauma cue) elicits a conditioned response (i.e., craving). Indeed, a person with PTSD-CUD may then experience heightened craving when they are repeatedly exposed to cues associated with past trauma, such the red car or loud noises. Conversely, Baker and colleagues (2004) suggest that trauma cue-induced negative affect can become linked with craving through conditioning processes by acting as an interoceptive, discriminant cues. Specifically, over time, the internal signals indicate to the user that if they were to engage in substance use at that moment, desired relief from the negative affect would be attained, thereby eliciting conditioned craving responses.

Indeed, Studies 2 and 4 are consistent with expectations of conditioned craving, as they demonstrate that both single-session and self-administered trauma cue reactivity paradigms elicited elevated cannabis craving (overall craving in Study 2; expectancy craving

in Study 4) compared to neutral cues. Study 2 highlighted trauma cue exposure led to an increase in cannabis craving that was not necessarily linked to PTSD, as evidenced by the absence of main or interactive effects of PTSD symptom count. Similarly, Study 4 indicated a main effect of trauma cue condition on expectancy craving; however, in contrast to Study 2 findings, main effects of likely PTSD were observed across all four cannabis craving dimensions, including compulsivity, purposefulness, expectancy, and emotionality. The increase in sample size from Study 2 (N=50) to Study 4 (N=202) may have better allowed us to detect PTSD main effects. Alternatively, the methods used to assess PTSD symptoms may account for this discrepancy. Specifically, the symptom count on the CAPS-5 (Weathers et al., 2018) used in Study 2 may have been less sensitive or comprehensive compared to the PCL-5 (Bovin et al., 2016) used in Study 4. Indeed, while the CAPS-5 interview is considered the gold standard of PTSD assessment, I used a symptom count based on this interview, not the diagnostic method. Conversely, the PCL-5 allowed participants to rate the severity of each PTSD symptom themselves (vs. the judgement of the interviewer), perhaps accounting for the robust PTSD effects found in Study 4. Alternatively, the lack of PTSD effect in Study 2 may have been due to measurement error. Additionally, in Studies 4 and 5, PTSD was dichotomized, making it a coarser indicator compared to the dimensional measures used in Studies 2 and 3. It is plausible that surpassing the clinical threshold for PTSD is more relevant to cannabis craving than the number of distinct symptoms experienced. However, it is also worth considering the principle of 'patient knows best', highlighting the importance of individual self-assessment in understanding the relationship between PTSD and cannabis craving. Regardless, the findings across both studies that cued trauma reminders elicit increased negative affect is consistent with two-factor learning theory

(Stasewicz & Maisto, 1993), as they replicate experimentally demonstrated and theoretically significant processes of negative affective states in response to trauma cues in this population. Moreover, as overall cannabis craving (Study 2) and cannabis expectancy craving (Study 4) were also activated by the trauma CRP (theoretically, a conditioned response), it is consistent with predictions emerging from the perspective of classically conditioned craving among individuals with PTSD.

As identified as a common outcome in Study 1, I measured negative affect as an outcome in Studies 2 and 4; however, I did not explore its role as a mediator in the relationship between trauma cue exposure and cannabis craving. This is noteworthy because negative affect is a multifaceted construct with complex interactions with both PTSD and substance use. It serves as a critical component in the self-medication hypothesis (Khantzian, 1997) and operant conditioning theory (Baker et al., 2004), which posits that individuals learn to use substances to alleviate negative emotions (Khantzian, 1997) and this behavior becomes negatively reinforced over time (Baker et al., 2004). Importantly, across Studies 2 and 4, a main effect of trauma cue exposure on negative affect was always present when there was also a main effect of trauma cue exposure on cannabis craving. Indeed, it is possible that negative affect must be present for the trauma cue-elicited conditioned craving to occur (mediation). Perhaps the use of Baker et al.'s (2004) 'cue chains' can be applied here, with the discriminative stimulus of negative affect (an interoceptive cue) needed for conditioned craving to trauma cues to be activated. Alternatively, the degree of negative affect experienced by the participant may also influence this magnitude of the trauma cue to craving relationship (moderation). I will explore this further in the Future Directions section.

Posttraumatic Stress Disorder

The samples of trauma-exposed cannabis users involved in the experiments described in Studies 2 – 5 further bolster the prevailing narrative suggesting a heightened propensity for CUD among individuals experiencing distress following trauma reminders or those with PTSD. This aligns with prior research, such as Kevorkian et al. (2015), which has consistently indicated that individuals with PTSD are more inclined to turn to cannabis compared to their counterparts without PTSD or with subclinical levels of PTSD symptoms. While cannabis use itself was not a dependent variable in the present dissertation, craving is a symptom of CUD (APA, 2022), suggesting my findings corroborate the established link between PTSD and cannabis use. Indeed, Study 4 found those with (vs. without) probable PTSD were experiencing greater cannabis craving across all four craving dimensions. Importantly, this result remained consistent even when accounting for extant variables that differed by the presence of probable PTSD, including cannabis-related problems (as measured by the CUDIT-R; Adamson et al., 2010), age, and number of lifetime traumatic events (see Supplementary Table 4.3). However, I did not include measures of cannabis use quantity and frequency in these analyses; thus, I cannot speak to the degree of cannabis use as a function of PTSD. Additionally, the PTSD group effect on expectancy, emotionality, and purposefulness craving did not remain when controlling for anxiety and depression symptoms (as measured by the PHQ-ADS; Kroenke et al., 2016). Given PTSD and anxiety-depression are highly comorbid (Qassem et al., 2021; Rytwinski et al., 2013) it follows that the PTSD effect was driven by these related variables rather than PTSD.

In contrast to Study 4, PTSD did not significantly predict negative affect or cannabis craving in Study 2. Notably though, Study 2 detected a significant negative association between PTSD and positive affect, meaning those higher in PTSD symptoms reported

significantly lesser positive affect overall. This observation underscores the importance of considering both positive and negative affective states independently, rather than viewing them as opposite ends of a single continuum (Warr et al., 1983). While negative affect is often the focus in studies related to PTSD and substance craving, the significant association between PTSD and reduced positive affect highlights the need for a more nuanced understanding of emotional experiences in individuals affected by trauma. While this suppression of positive affect was not evident among those with PTSD in Study 4, nor was it influenced by the trauma CRP in either study, it is evidently important to consider positive affect as a separate construct from negative affect.

Automatic Cognitions

The current dissertation also falls in line with prior work using trauma CRPs to investigate the role of trauma cue-induced cognitive reactivity among trauma-exposed substance users. Indeed, prior CRP literature has explored the role of trauma cue-induced automatic cognitions in relation to comorbid PTSD-SUD with alcohol (Dutton, 2017; Read et al., 2017) and nicotine (Beckham, 1996) being most widely explored (Study 1, Chapter 2). Importantly, it has expanded a small body of research exploring the role of cognitions in co-occurring PTSD-CUD. Notably, prior to my dissertation Studies 2 and 4, only one prior study had examined the relationship between trauma cue exposure, PTSD, and deliberative cognitions that are thought to drive addictive behaviors (i.e., cannabis craving; Romero-Sanchiz et al., 2022). Further, Studies 3 and 5 represented the first to experimentally test the impact of trauma reminders and PTSD on automatic cannabis-related cognitions, and one of only a handful in the PTSD-SUD field that examined trauma cue elicitation of such addiction-relevant automatic cognitions. Study 3 found significant effects of PTSD on

automatic cannabis cognitions, in that regardless of cue exposure, people with more severe PTSD symptoms were more inclined to automatically approach cannabis (vs. neutral) stimuli on the AAT. Conversely, Study 5 found significant effects of trauma cue condition on the degree of accessibility of cannabis information in memory, but no PTSD effects on this automatic cognition outcome. Interestingly, this is also reverse of the effects in Study 2 and 3 – specifically, in Study 2 trauma cue exposure influenced craving, whereas in Study 3, with the same sample, cue exposure had no impact on cannabis approach bias. Similarly, in Study 4, PTSD affected all craving dimensions, yet in Study 5, with the same sample, PTSD showed no influence on the accessibility of cannabis-related information in memory. Indeed, while these findings are contrary to my hypothesized interaction between the trauma cue and PTSD in predicting cannabis-related words on the CWAT (Pilin et al., 2022), they align with dual process models (Wiers et al., 2013). Specifically, these models propose that these cognitive processes operate independently and respond to distinct triggers. The divergent outcomes observed across studies suggest that different cognitive mechanisms (i.e., deliberate vs. automatic processes) might be at play in response to trauma cues and PTSD symptoms, as well as in the processing of cannabis-related stimuli. These studies offer novel insights into the cognitive and affective processes underlying the relationship between PTSD and cannabis use, shedding light on the mechanisms through which trauma exposure and PTSD symptoms may impact both relatively more controlled and more automatic cognitive processes that in turn may promote cannabis use. By expanding the scope of inquiry to include automatic cognitive processes, my dissertation adds a nuanced understanding of the complexities inherent in the comorbidity of PTSD and CUD, thus contributing to the broader literature on trauma's relationship to substance use and SUDs.

Clinical Implications

My research on the cognitive and affective mechanisms underlying the co-occurrence of PTSD and CUD highlights the importance of considering both automatic and deliberative cognitions and both negative and positive affect in understanding these complex conditions. Automatic cognitions, such as cannabis approach bias and accessibility of cannabis-related information in memory, are deeply ingrained and often operate outside one's awareness, driving individuals to reflexively seek out and use cannabis (Wiers et al., 2013). Indeed, the finding of chronically activated cannabis approach bias in Study 3 among those with greater PTSD symptoms underscores the reflexive inclination towards cannabis use, consistent with work by Kevorkian and colleagues (2015) demonstrating increased cannabis use among those with (vs. without) PTSD. Moreover, Study 5 demonstrated an effect of trauma cue exposure on the salience of cannabis words espousing the role of trauma reminders as potential catalysts for cannabis use, given they increase the accessibility of cannabis-related information in memory as in Study 5. Providing research linking PTSD and trauma exposure to these automatic processes, if further replicated and clinically tested, could enable clinicians to intervene at a fundamental level, disrupting the cycle of substance use and helping clinicians tailor interventions to target these specific cognitive vulnerabilities (Verdejo-Garcia et al., 2022).

For example, cognitive bias modification (CBM) interventions typically involve computer-based tasks designed to modify automatic cognitive biases. One form of CBM intervention modifies attentional biases by repeatedly directing attention away from disorder-relevant stimuli and toward neutral or positive stimuli. CBM tasks might involve presenting ambiguous scenarios and training participants to interpret them in a less threatening or

negative manner. In the context of trauma-exposed substance use populations, CBM could be used to target cognitive biases related to both trauma and substance use. For example, CBM tasks could aim to modify automatic cognitive biases toward trauma-related cues, as well as memory biases associated with cannabis-related stimuli. Importantly, one study found individuals with PTSD (vs. matched healthy controls) exhibited negative affect-related attentional biases and, following a 4-session eye movement desensitization and reprocessing therapy, the PTSD patients responded similarly to controls in the attentional bias tasks (El Khoury et al., 2011).

Indeed, the other studies have gleaned potential in cognitive bias modification in SUD treatment (Houben et al., 2010; Wiers et al., 2015) and interventions targeting cannabis approach bias have been used to retrain individuals' automatic responses to cannabis cues when they arise. For example, Sherman and colleagues (2018) conducted a double-blind randomized controlled experiment where cannabis users were assigned to complete a cannabis approach bias modification (ApBM) task or a sham version of the task. The cannabis ApBM involves altering automatic responses to cannabis-related stimuli to guide participants in avoiding, rather than approaching, cannabis stimuli. Individuals assigned to the experimental ApBM (compared to the sham ApBM) demonstrated a reduction in cannabis cue-induced craving. Importantly, in the present dissertation, Study 2 showed greater cannabis approach bias in cannabis users with more PTSD symptoms, suggesting that ApBM training may be efficacious in reducing cannabis craving in trauma-exposed cannabis users with higher PTSD symptoms. Indeed, by pairing typically approached stimuli (i.e., cannabis) with an avoidance task, one can strengthen inhibitory control over substance-related impulses. These interventions can weaken the automatic associations between

cannabis stimuli and approach, reducing the likelihood of relapse and promoting long-term recovery (Beerten-Duijkers et al., 2022). Importantly, ApBM has proven efficacious for those with AUD (Manning et al., 2022) although its effects did not persist beyond a 3-month follow-up period in this study, and it was ineffective when delivered remotely in another (Jones et al., 2018). Evidently, consistent and in-person delivery of substance ApBM training may be necessary to sustain its benefits, and more research is needed. Indeed, Wiers and colleagues (2018) emphasized the effects of interventions to reduce cognitive biases are typically short-lived, particularly when not paired with clinical treatment. Such results in combination with a meta-analysis of meta-analyses which gleaned the effects of ApBM and CBM (Jones & Sharpe, 2017) suggest potential in CBM for SUD treatment and my dissertation results point to the potential utility of ApBM for cannabis users with PTSD.

Similarly, interventions targeting conditioned craving focus on extinguishing the learned associations between trauma reminders and negative affect, as well as trauma reminders and substance craving, as both are thought to promote substance use (Najavits et al., 2020). Exposure therapies, like prolonged exposure (PE), aims to facilitate habituation to trauma cues, reducing the emotional arousal (negative affect) and substance craving typically elicited by these reminders (Morrison et al., 2014). By repeatedly exposing individuals to their trauma triggers in a safe and supportive setting, exposure therapy allows individuals to confront and process the associated distress more effectively over time. In relation to the content of the present dissertation, this is theoretically explained through habituation/ extinction theory (Badour et al., 2017). Rooted in behavioral principles, habituation posits that repeated exposure to trauma triggers leads to a reduction in the emotional response elicited by these cues. Through systematic and prolonged exposure, individuals learn that the

feared outcomes associated with the trauma cues fail to materialize, leading to a process of habituation (Badour et al., 2017). With repeated exposure to trauma reminders without danger or escape from the trauma reminder, the conditioned fear response weakens, and the distress associated with the trauma triggers diminishes through extinction processes. Indeed, as the conditioned response to trauma cues weakens through repeated exposure without substance use, the intensity of craving diminishes, and the risk of substance use relapse decreases (Baschnagel et al., 2006; Lortye et al., 2021; Morrison et al., 2014). This therapeutic approach capitalizes on the principles of learning (i.e., classical conditioning) and memory to rewire maladaptive associations, ultimately empowering individuals to better manage their PTSD symptoms (e.g., trauma cue induced distress) and reduce their reliance on cannabis as a maladaptive coping strategy. However, existing studies on PE therapy have overlooked its application in treating comorbid PTSD and problematic cannabis use.

Nonetheless, those studies (Hoeboer et al., 2024) and the results described in the present dissertation suggest potential shared mechanisms of cannabis use with PTSD and other substance use. Indeed, Study 4 identified both negative affect and expectancy craving as significantly activated by the trauma writing task, and significantly related to PTSD symptoms, lending to the importance to consider interventions which target these aspects when considering avenues for PTSD-CUD treatment. The existing cognitive-behavioral therapy for PTSD (Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure; COPE) treatment (Back et al., 2019) combines skill-based training, such as stress management and emotion regulation training, with PE to equip individuals with healthier coping strategies to manage distressing emotions without resorting to substance use (Vujanovic et al., 2018b). However, this intervention has not been tested in a

trauma-exposed, *cannabis* using population, pointing to a need for clinical trials to aid in understanding PTSD-CUD comorbidity. Indeed, if successfully applied to PTSD-CUD, this integrated approach could not only facilitate the processing of traumatic memories but also cultivate adaptive coping mechanisms to mitigate the risk of engaging in substance use as a maladaptive coping strategy. In the context of my results, COPE could be modified to include expectancy challenge (Darkes & Goldman, 1993), as Study 4 identified a significant role of expectancy craving. Indeed, my results, if replicated, suggest it could also be important for patients with PTSD to practice challenging those positive cannabis expectancies following trauma cue exposure.

A final avenue for clinical work as related to the current dissertation is based on the results of Study 4 and 5. Indeed, the trauma expressive writing task may also be a useful clinical tool for addressing comorbid PTSD-CUD. This suggestion extends from previous research demonstrating the effectiveness of expressive writing in trauma-focused exposure therapy for PTSD in women (Meshberg-Cohen & McMahon, 2014). As related to the discussion of habituation above, participants who completed the trauma expressive writing task experienced no increases in negative affect (compared to sharp increases in negative affect in response to the expressive writing task pre-intervention; Meshberg-Cohen & McMahon, 2014). Similarly, a trial of Veterans with PTSD had participants write about their traumatic event at five sessions with a clinician; results indicated over 70% of participants no longer met criteria for a PTSD diagnosis at three-month follow-up after treatment (Sloan et al., 2013). Indeed, future clinically oriented research should consider a pilot of the expressive writing task in treating both PTSD and substance use issues. However, as the length of the expressive writing task employed in Studies 4 and 5 was considerably shorter than the tested

writing tasks described above, it is important to determine the optimal length of expressive writing to achieve benefits for both PTSD and CUD symptoms.

Strengths and Limitations

While I have addressed the strengths and limitations of each study within their respective manuscripts, there are overarching strengths and limitations to my research that merit mention in this general discussion section. These broader aspects are outlined below.

Sample

The samples included in this dissertation consisted of predominantly of White female adults. Despite this work being limited to this group, results provide valuable insights into the interplay between trauma exposure, PTSD, and cannabis-relevant affective and cognitive outcomes. Indeed, while males are traditionally more likely to experience certain traumatic events (e.g., war, accidents), females are much more likely to experience sexual assault in childhood and adulthood (Tolin & Foa, 2006). Importantly, research has also shown females are 2-3 times more likely to develop PTSD (Olff, 2017) and tend to experience more severe PTSD symptoms (Tolin & Foa, 2006) compared to males, suggesting that while our sample is limited in generalizability, it is applicable to a group (i.e., females) that do experience more severe PTSD symptoms compared to their male counterparts. Conversely, research has shown that males are diagnosed with CUD more frequently than females (Khan et al., 2013), thus the underrepresentation of males in our samples might be a concern in generalizing to a group at higher relative risk for CUD. Indeed, there was a sex bias across Studies 2 and 3 (i.e., 66% females) but became relatively balanced in Studies 4 and 5 (47.5% females), suggesting in-lab experiments may be biased to female participants. Importantly, it is essential to recognize that these findings may not be universally applicable to all sexes (e.g.,

female, male, intersex) or genders (e.g., women, men, gender non-conforming) nor across other demographic groups. For instance, adolescents or individuals from diverse gender and ethnic backgrounds might exhibit distinct patterns of response to trauma-related cues or of cannabis use. While some research, such as that conducted by Read and colleagues (2017), has explored similar themes among college-aged students, and studies involving participants experiencing homelessness have utilized trauma cue reactivity paradigms (Vujanovic et al., 2019), there remains a notable gap in understanding how problematic cannabis use manifests in more diverse populations of cannabis users with trauma histories. Further investigation (e.g., moderation by important demographics) into these characteristics is crucial for developing a comprehensive understanding of the complex relationship between trauma, PTSD, and affective and cognitive outcomes across varied populations.

Limitations regarding sample characteristics are also evident. For instance, Studies 2 and 3 encompassed individuals who reported using alcohol and other substances alongside cannabis within the past month, and those who consumed substances other than cannabis were not prevented from taking part in Studies 4 and 5, although their other forms of substance use were unfortunately not quantified. Consequently, my findings may not be applicable to samples exclusively using cannabis. However, in not excluding those who use other substances we allowed for a more generalizable sample, as finding individuals with trauma histories who exclusively use cannabis would be difficult and would not capture the full scope of this population, given many cannabis users are polysubstance users (Crummy et al., 2020). A similar limitation of the sample in my studies is the omission of an examination into the role of co-use (use of multiple substances, not necessarily together) or simultaneous use (ingesting multiple substances at once) of other substances in trauma cue reactivity and

cannabis use. The co-use of substances has been shown to be especially relevant among trauma-exposed individuals (DiGuiseppi et al., 2020), meaning important results related to substance co-use were not elucidated by my work. Additionally, more information is needed on factors that distinguish when craving for one substance over another is triggered by trauma and substance cues in co-users. There may be other salient cues, such as social context, that influence this distinction. For example, trauma cue exposure might trigger alcohol craving in a social context and cannabis craving in a solitary context, depending on the usual social context of use for a given co-user. While in Study 2, I observed trauma cue effects on alcohol craving among cannabis users who also used alcohol, I did not examine the specificity to cannabis craving in Study 4. However, the inclusion of alcohol craving alone as a secondary outcome is not sufficient to capture the broader picture of substance co-use in our sample.

An additional limitation of the included samples lies in a difference in cannabis use eligibility criteria across studies. Specifically, Studies 2 and 3 required cannabis use at least 1gram/week for the past month. Alternatively, for Studies 4 and 5, participants were only required to have consumed 1 gram of cannabis in the past month (vs. a minimum of 4 grams in the past month in Studies 2 and 3). This was a limitation placed by Qualtrics Panel Surveys as they were concerned about the feasibility of recruiting more frequent cannabis users from amongst their panelists. While the lower cut-point for cannabis use in Studies 4 and 5 makes results less directly comparable to Studies 2 and 3, it does make the results of Studies 4 and 5 potentially applicable to a broader range of cannabis users with trauma histories. Participants in Studies 2 and 3, with their higher cannabis consumption threshold, may represent a subgroup of more frequent and potentially heavier cannabis users compared

to those in Studies 4 and 5. Consequently, the observed effects in Studies 2 and 3 may be influenced by factors related to chronic and heavier cannabis use, such as tolerance, dependence, and cumulative neurobiological changes, which may not be as pronounced in participants from Studies 4 and 5. The use of in-person experimental methodology in Studies 2 and 3 also differed from the remote, panel samples recruited in Studies 4 and 5, perhaps contributing to differences in outcomes across studies. Finally, sampling variability may also account for the above-described discrepancies across studies.

THC/CBD Concentration

A significant limitation of the current research is that we did not account for information regarding the concentration of THC (tetrahydrocannabinol) in the cannabis used by participants. THC is the primary psychoactive compound in cannabis and plays a crucial role in its effects on cognition, emotion, and behavior (Colizzi et al., 2020). Without knowing the THC concentration, it is challenging to discern the potency of the cannabis consumed by participants, which could have profound implications for their responses in the study. Research suggests that higher THC concentrations are associated with increased intoxicating effects, cognitive impairment, and the exacerbation of psychiatric symptoms, including anxiety and paranoia, especially in vulnerable populations such as individuals with PTSD (Rehman et al., 2021). Moreover, variations in THC levels can impact the therapeutic efficacy of cannabis for managing PTSD symptoms, with the results of one meta-analysis suggesting that lower THC-to-CBD ratios may be more beneficial for symptom relief (McKee et al., 2021). Indeed, higher potency THC products have more addiction potential and greater anxiogenic effect compared to low dose THC (Sharpe et al., 2020) though regular

cannabis users do not typically use less cannabis than normal even when using higher potency products (Leung et al., 2021).

On the other hand, perhaps accounting for CBD potency may have elucidated the trauma cue x PTSD interaction I did not detect in Studies 2 and 4. Indeed, individuals tend to associate CBD (vs. THC) with anxiolytic effects (Spinella et al., 2023), and research has shown that the expectation of the stress relief associated with CBD use actually may be what is contributing to the anxiolytic effects, rather than (or in addition to) the effects of the substance itself (Spinella et al., 2021). Importantly, cannabis products like CBD are thought to be relatively safe compared to high THC products, but some recent work has outlined potential health consequences associated with CBD, such as liver toxicity (Lo et al., 2023). Indeed, as cannabis expectancy craving was activated by both the trauma cue condition and PTSD symptoms in Study 4, further exploration into the nuances of cannabis components (THC, CBD) and their impact on expectancy dynamics is warranted.

The Endocannabinoid System

The endocannabinoid system is a complex network consisting of endocannabinoids, which are lipid-based neurotransmitters; cannabinoid receptors (primarily CB1 and CB2); and enzymes responsible for synthesizing and degrading endocannabinoids. The CB1 receptors are predominantly found in the central nervous system, particularly in brain regions involved in emotional regulation (Hill et al., 2009), memory (Ranganathan & D'Souza, 2006), and fear extinction (Marsicano et al., 2002), while CB2 receptors are mainly located in the peripheral nervous system and immune cells (Bie et al., 2018). Endocannabinoids bind to these receptors, modulating various physiological processes. Evidence demonstrates that long-lasting changes can be made to the endocannabinoid system following trauma exposure

(Hillard, 2014). Indeed, individuals with trauma histories or PTSD experience downregulation of signalling in the endocannabinoid system (Hill et al., 2005) perhaps reducing their ability to regulate distress and negative affect (Bassir Nia et al., 2019).

THC primarily targets CB1 receptors, triggering a dopaminergic response that mediates the substance's rewarding effects (Connor et al., 2021). However, as CB1 receptors become less sensitive or decrease in number due to prolonged cannabis use, users often need to consume higher doses of cannabis to achieve the same effects they once experienced with lower doses. Indeed, repeated regular cannabis use is associated with downregulation of the CB1 receptor as well as enzymes in the endocannabinoid system (Haney, 2022), contributing to cannabis tolerance, a factor associated with the development of CUD (Freeman & Winstock, 2015; van der Pol et al., 2014). Indeed, these disruptions to the endocannabinoid and reward systems may contribute to cannabis-seeking behaviors and a decreased ability to regulate one's mood (Volkow et al., 2017).

While my work did not delve into the role of the endocannabinoid system in relation to trauma exposure, PTSD symptoms, and their effects on cannabis and mood-related outcomes, future research can build on this foundation by examining how trauma-related changes in the endocannabinoid system impact cannabis use patterns and craving. Specifically, researchers could investigate how altered endocannabinoid signaling in individuals with PTSD influences their response to trauma cues and subsequent cannabis craving. Additionally, understanding how cannabis use modifies endocannabinoid system function in the context of trauma exposure could reveal potential targets for therapeutic interventions (Martin & McRae-Clark, 2020). By integrating findings from my research with studies on endocannabinoid system function, future research can contribute to a more

comprehensive understanding of how trauma and substance use interact at a neurobiological level, ultimately informing strategies for improving treatment outcomes and managing co-occurring conditions.

Types of Automatic Cognitive Task

I chose to use two different types of tasks assessing automatic cannabis-related cognitions, and this choice comes with both strengths and weaknesses. The cannabis approach avoidance task (AAT) used in Study 2 is effective in assessing automatic or "implicit" biases by measuring reaction times to approach and avoid cannabis-related (vs. neutral) stimuli (Cousijn et al., 2011). This task provides real-time data on participants' automatic action tendency to approach cannabis stimuli, which may not be fully captured by self-report measures. However, the AAT also presents certain limitations. For example, the task's reliance on reaction time measurements may be influenced by factors such as individual differences in motor skills and processing speed, potentially influencing the results (Fricke & Vogel, 2020). Moreover, the task simulates approach and avoidance behaviors in a controlled laboratory setting, which may not fully reflect the complexities of real-world situations where individuals encounter cannabis-related stimuli in their daily lives. Nonetheless, the cannabis AAT has been validated in showing a longitudinal relationship between cannabis approach bias and increased cannabis use (Cousijn et al., 2011) and cannabis use problems (Cousijn et al., 2012).

In contrast, the cannabis word association task (CWAT; Pilin et al., 2022) employed in Study 4 offers a different set of strengths. By tapping into participants' memory associations with ambiguous cannabis-related word associates, this task provides insights into the cognitive processes involved in memory retrieval related to the accessibility of

cannabis information. It allows researchers to explore the semantic networks associated with cannabis use and identify salient cognitive associations (Field & Wiers, 2012). However, the CWAT also has its limitations. Unlike the AAT, which measures automatic biases, this task relies on participants' explicit memory associations, which may be influenced by conscious processing and cognitive strategies as well as more automatic semantic associations (Wiers et al., 2013; Wiers et al., 2015). In other words, the CWAT may be a less “pure” measure of automatic cognitive processes relative to the cannabis AAT. Additionally, the CWAT's reliance on language and vocabulary may introduce variability based on individual differences in linguistic abilities. Furthermore, the task may lack the temporal precision of reaction time measurements, making it more challenging to capture the rapid nature of automatic cognitive processes (Wong et al., 2017).

It should be acknowledged that my employment of two distinct automatic cognitions tasks facilitated an in-depth exploration of the impacts of trauma cue exposure and PTSD on cognitive processes within the scope of my thesis, offering a certain degree of breadth in our investigation. However, the decision to alter the cognitive task between Studies 3 and 5 posed a challenge in directly comparing the outcomes across the two different cognitive tasks since other changes were made between Studies 3 and 5 (e.g., CRP employed; continuous vs. categorical PTSD). Indeed, it could be argued that scientific progress functions best through incremental advancements, with each study contributing to a broader understanding of complex phenomena. It is possible that, in my enthusiasm to examine various pertinent processes, I inadvertently modified too many variables simultaneously, potentially reducing our ability to pinpoint which design changes might underly differing results across studies.

Thus, future research endeavors may benefit from a more gradual and systematic modification of variables to ensure more ready comparison across studies.

Assessment of PTSD

My using a continuous measure of PTSD in Studies 2 and 3 offered advantages. Continuous assessment allows for the examination of PTSD symptoms along a gradient, capturing variations in symptom severity and providing a more nuanced understanding of individual differences. This approach maximizes the information gleaned from participants and enhances statistical power by preserving the full range of variability in symptom expression.

Using PTSD as a categorical predictor in Studies 4 and 5 offers several strengths. Indeed, several studies have supported the conceptualization of PTSD as categorical, rather than as a dimensional construct (Ayer et al., 2011; Breslau et al., 2005). Specifically, latent class analyses have been used to examine which conceptualization of PTSD best fits, and some research shows that symptom severity (e.g., continuous symptom count) as the operationalization of PTSD did not fit the data as well as when approached categorically (Burton et al., 2021; Kline et al., 2024). One advantage to categorical classification is the simplicity and ease of interpretation it affords. Categorizing individuals as either meeting or not meeting diagnostic criteria for PTSD facilitates comparisons between groups, enhancing the interpretability of study findings. Additionally, categorical classification aligns with diagnostic conventions used in clinical practice, enabling researchers to draw direct connections between their research outcomes and established diagnostic criteria (Clark et al., 2017; Frances, 2013). This choice may have enhanced the clinical relevance of the results of Studies 4 and 5, thus potentially aiding the translation of research into practice. However,

employing PTSD as a categorical predictor also entails certain limitations. One drawback is the potential loss of information inherent in dichotomizing a continuous construct. By categorizing individuals into distinct diagnostic groups in Studies 4 and 5, I may have overlooked important variability in PTSD symptom severity within each group. This may have resulted in a loss of statistical power and reduced sensitivity to detect subtle differences between individuals with varying levels of symptom severity. Furthermore, categorical classification may obscure nuances in symptom presentation and fail to capture the full spectrum of PTSD-related phenomena (Clark et al., 2017).

Study 2 assessed PTSD using a clinical interview, whereas Studies 3 – 5 utilized a self report measure of PTSD, which presents challenges. Most importantly, it does not allow for a direct comparison of Study 2's PTSD effects to those of Studies 3 – 5. Another limitation of this choice is the potential for measurement error and subjectivity inherent in self-report measures of symptom severity. Participants may have varied in their interpretation and reporting of PTSD symptoms, leading to inconsistencies in measurement across individuals relative to the clinical judgement allowed by the interview used in Study 2. Despite these limitations, the self-reported assessment of PTSD in Studies 3 – 5 offered valuable insights into the nature of PTSD – for example in Study 3, self-reported PTSD symptom severity increased in conjunction with cannabis approach bias, even after controlling for relevant covariates. In Study 4, probable PTSD established through cut-points on the self-report PCL-5 were associated with greater scores on all dimensions of cannabis craving and with higher scores on a measure of negative affect.

Finally, Studies 4 and 5 used a civilian cut-off of <38 for probable PTSD on the PCL-5 (Cohen et al., 2014), which is not as well known as the typical cut-off of <33 on the PCL-5

(Bovin et al., 2016) established with Veterans. While this choice was important in to avoid false positives, given the use of the self-report PCL-5 (Blevins et al., 2015), it did preclude me from making direct comparisons between my studies and those that use the more common, lower cut-off point for probable PTSD. Moreover, given this validated PCL-5 cut-off score method does not require a specific number of symptoms be present across each of the four PTSD symptom clusters, it is not comparable to studies that used the DSM-5-TR to categorize participants with present (vs. absent) PTSD (APA, 2022).

Use of Self-Report Measures

The research conducted in this dissertation heavily relied on self-reported data, a commonly employed methodological approach in psychological studies due to its efficiency and practicality. However, it is important to recognize and address the limitations inherent in self-report measures, particularly within the context of substance use research.

One significant limitation of self-report data is the susceptibility to various biases and inaccuracies, which may compromise the reliability and validity of the findings. For instance, individuals may provide socially desirable responses (Latkin et al., 2017; Patterson et al., 2019), leading to an overestimation or underestimation of their behaviors or experiences. Additionally, memory recall bias can influence the accuracy of self-reported information when participants are required to recall past substance use behaviors or experiences (Merrill et al., 2020). Indeed, the reliability of self-report measures hinges on participants' willingness and ability to accurately report their thoughts, feelings, and behaviors. However, factors such as social desirability, stigma, and cognitive biases can influence participants' responses, potentially distorting the data. Furthermore, individuals may encounter difficulties in accurately assessing and articulating their experiences, particularly when addressing complex

phenomena like substance use and trauma. Nevertheless, for all self-report measures employed in the present dissertation, meticulous attention was devoted to the selection of psychometrically validated instruments and their administration was conducted in a manner aimed at augmenting precision (e.g., providing confidentiality assurances). Studies 4 and 5 were conducted online to safeguard privacy and mitigate potential self-presentation biases.

Ethical Considerations

Administering trauma cue reactivity paradigm requires careful consideration of several ethical implications to ensure the safety and well-being of participants. One of the primary concerns is the potential for distress or re-traumatization that participants might experience when exposed to trauma-related cues. Researchers must carefully balance the scientific benefits of the study with the emotional well-being of participants. In the context of the current dissertation, the ethical approach used in relation to trauma cue reactivity paradigms is a strength. In Studies 2 and 3, participants were given the option to speak with a clinical psychologist or psychiatrist on the research team following the study if they experienced continued distress. This provided immediate access to professional support that would have helped to address any adverse emotional reactions participants might have experienced. However, no adverse events were observed by the researchers or reported by participants during lab-based Studies 2 and 3. Moreover, based on a qualitative study with participants drawn from the sample tested in the lab by Romero-Sanchiz and colleagues (2022), participants generally reported extremely low rates of continued distress following the completion of the study and felt that their participation was worthwhile and an important contribution to scientific advancement (Ethier-Gagnon et al., 2024b). In Studies 4 and 5, participants were redirected to a mental health resource page, including live chat options,

after completing the survey, providing them with immediate access to mental health support. This proactive approach ensured that participants had the necessary resources to seek help if needed. To further mitigate potential risks in future, in the case of remote trauma cue reactivity paradigm administration, either regular feedback collection from participants to identify potential concerns and/or thorough walk-through debriefing scripts could be implemented. Further study of the ethics of the online written cue exposure using the Ethier-Gagnon et al. (2024b) methodology which probes the personal experiences of participants who have undergone the procedure, would be useful as a next stage in this research. Such future investigation would help determine whether this is a viable method for conducting cue-exposure research in a safe and ethical manner with larger and more generalizable samples.

Future Directions

As I contemplate the future trajectory of my research, it becomes evident that there are numerous promising directions to pursue, building upon the insights gleaned from the findings presented in my dissertation. Firstly, there is a compelling need to integrate objective measures alongside traditional self-report data. Exploring both subjective and objective craving in future research offers a promising direction for understanding substance use in individuals with trauma histories. Subjective craving refers to the individual's personal experience of desire or urge to use a substance, often measured through self-report questionnaires or interviews. Objective craving, on the other hand, refers to measurable physiological responses associated with the desire to use a substance, such as skin conductance and salivation. Physiological arousal is associated with subjective cue-induced substance craving (Wang et al., 2020). While few studies in our specific field (N=5; as

identified in Study 1) have measured objective (physiological) craving specifically (as opposed to salivary cortisol; heart rate variability; other physiological measurements not typically operationalized as craving) following trauma cue exposure, theoretically, subjective and objective craving responses may be differentially affected in individuals with trauma histories in PTSD (Danielson et al., 2021). Thus, future work should aim to include an objective measure of craving in conjunction with a subjective self-report measure. By incorporating established physiological indices of craving, we can gain a more comprehensive understanding of the intricate relationship between PTSD and trauma cue-induced cannabis craving. By establishing trauma cue-induced craving as indexed by these physiological measures, researchers can then examine the underlying neural basis of these craving responses. Indeed, eligible participants in Studies 2 and 3 were offered the opportunity to participate in a second fMRI session which is trying to do just that – study the underlying neural mechanisms that explain elevated cannabis craving to trauma cues in this population (Cosman et al., 2022; Ethier-Gagnon et al., 2024a). Another future direction related to physiological indices of cue reactivity is the study of salivary flow in cannabis using samples. Salivary flow is an established measure of alcohol craving because alcohol consumption is a consummatory behavior, and salivation serves as a preparatory response to this consumption. However, smoking cannabis is not a consummatory behavior in the same way, so salivary flow may not be as relevant for measuring cannabis craving (Habib et al., 2021). This potential difference should be examined empirically in future studies.

Secondly, exploring mediating and moderating factors holds significant potential for unraveling the complex pathways through which trauma cue exposure influences substance-relevant outcomes (see Tull et al., 2013). Although negative affect was measured as an

outcome variable in my dissertation, I did not delve into exploring its potential role as a mediator in the relationship between trauma cue exposure and cannabis craving. The possibility of negative affect as a mediator is supported by prior cue reactivity work in other trauma-exposed, substance using populations (Tull et al., 2013). Specifically, Tull et al. (2013) investigated the impact of trauma cue exposure on cocaine cravings among inpatients with cocaine dependence, comparing those with and without posttraumatic stress disorder (PTSD). They explored the potential mediating role of overall negative affect and discrete negative emotional states in this relationship. The findings revealed that trauma cue exposure increased cocaine cravings, and this effect was partially mediated by both overall negative affect and specific negative emotional states – specifically, shame and guilt. Such findings are supported by the theorizing of Baker and colleagues (2004), who extended the self-medication hypothesis. Their affective processing model of negative reinforcement posits that individuals engage in substance use as a means of alleviating or escaping from negative emotional states. Plainly, negative affect serves as a powerful motivator driving addictive behaviors. According to their model, substance use provides temporary relief or distraction from these aversive emotional states, reinforcing the behavior and perpetuating the cycle of addiction (Baker et al., 2004). Indeed, considering the relationship between PTSD symptoms and negative affect (Tull et al., 2013), understanding the mediating role of negative affect could shed light on how negative affect can activate conditioned cannabis craving, leading to maladaptive coping strategies such as increased cannabis use. The observation that negative affect frequently fluctuated in tandem with cannabis craving in response to our experimental manipulations' hints at the potential role of conditioned negative affect to trauma cues as a precursor to conditioned craving to trauma cues. This possibility prompts consideration of

separate processes underlying reward and relief craving (Glockner-Rist et al., 2013), with trauma cue-induced negative affect potentially preceding the onset of relief craving. However, current cannabis craving measurement tools fail to tap this conceptual distinction. The cannabis craving measure (MCQ-SF; Heishman et al., 2009) utilized in our studies was not tailored to differentiate between reward and relief craving. In fact, only a limited number of craving measures in the field distinguish between these two facets, and none do for cannabis craving, in particular (see review in Romero-Sanchiz et al., 2022). Even the cannabis expectancy craving dimension found to be activated by trauma cue exposure in Study 4 appears to encompass a blend of both reward and relief expectancies. Consequently, there is a pressing need for the development of more refined measurement approaches that can disentangle these theoretically distinct components of craving in future research endeavors.

Third, in my studies, reactivity to trauma cues was measured in the lab using proxy measures of cannabis use outcomes. However, lab-based cue reactivity does not always strongly correlate with cue reactivity in real-world scenarios (Shiffman et al., 2015). To address this, future research could utilize ecological momentary assessment (EMA) to study cue-induced craving outside the lab in participants' day-to-day lives, providing a more accurate picture of how trauma cues influence craving in natural environments (Serre et al., 2015). Additionally, there's the issue of focusing on cognitive processes like craving, which do not always correlate strongly with actual substance use behavior (Sayette, 2016). To address this, future studies should extend my dissertation work by examining the effects of trauma cue exposure on actual cannabis use in the lab, thereby exploring whether lab-based trauma cue-elicited craving translates into lab-based trauma cue-elicited cannabis use.

Ultimately, once we understand whether current findings on craving in the lab extend to real-world craving and whether trauma cue-elicited craving leads to actual cannabis use in the lab, future research could combine these approaches. This would provide a comprehensive view of how trauma cues influence both craving and substance use across different contexts.

Finally, longitudinal studies tracking the trajectories of PTSD symptoms, trauma cue-induced cannabis craving, and cannabis use patterns over time offer a promising avenue for elucidating the temporal dynamics of their inter-relationships. By examining changes in these variables over time, we can better understand the evolving nature of PTSD and trauma cue-induced cannabis craving interplay and inform the timing and nature of intervention strategies. Additionally, expanding the scope of sample representation to encompass a broader range of demographic groups is imperative for enhancing the generalizability of findings and understanding the nuanced manifestation of PTSD and cannabis craving across diverse populations. By including participants from various demographic backgrounds, we can better capture the heterogeneity of experiences and tailor interventions to meet the unique needs of different subpopulations. For example, perhaps groups who have experienced intergenerational trauma, such as Indigenous groups (e.g., Mi'kmaw, Navajo), cannabis craving or biases may be elicited by trauma reminders not only for traumas experienced by the individual, but those experienced by that individual's family members or nation. For example, future researchers could test the emotional and addiction-relevant outcomes elicited by exposure to intergenerational trauma reminders (Bombay et al., 2014; e.g., residential schools, forcible relocation).

Conclusions

In conclusion, the culmination of my dissertation research has provided valuable insights into the complex interplay between trauma exposure, PTSD, and cannabis-relevant outcomes that may contribute to elevated rates of cannabis use and CUD in a trauma-exposed, cannabis-using population. Specifically, through a scoping review and four experimental studies, I have examined the cognitive and affective processes underlying comorbid PTSD and CUD, shedding light on the trauma cue reactivity mechanisms driving this co-occurrence. By employing a combination of self-report measures, clinical interviews, and experimental paradigms, I have uncovered the multifaceted nature of trauma cue-elicited affect and cannabis-relevant cognition in trauma-exposed individuals, highlighting the impact on both deliberative and automatic cognitive processes alike. I have also contributed to examining the specificity of the impact of trauma cue exposure on affect by examining trauma cue exposure effects in not only in eliciting negative affect but also in (potentially) reducing positive affect. Study 1 scoped the existing experimental research using CRPs in trauma-exposed, substance-using samples. Study 2 established the use of a single-session trauma CRP (semi-structed interview) as a predictor of cannabis craving and how it interacted with PTSD to predict negative affect. This result provides researchers with a more feasible means of conducting CRP studies in trauma-exposed individuals and replicates in cannabis users, common patterns of trauma cue-elicited craving and negative affect previously seen in other types of substance users. Study 3 represents the first study to test the effects of a trauma CRP and PTSD on automatic cognitions in trauma-exposed cannabis users. This study's findings suggest an automatic approach bias toward cannabis may be chronically activated among those cannabis users with a higher PTSD symptom count, regardless of trauma cue exposure. Study 4 aimed to replicate the design of Study 2 but using

an online self-administered survey and trauma CRP in the form of expressive writing about one's trauma in data collection. Results indicated both trauma reminders and PTSD contributed to greater cannabis expectancy craving and negative affect establishing expressive writing about trauma as a method for reaching a wider range of traumatized, cannabis using participants in CRP research. Finally, Study 5 provided evidence for the self-administered, expressive writing trauma CRP as successful in increasing the accessibility of cannabis-related information in memory. Taken together, my dissertation has contributed to a body of work establishing the mechanistic underpinnings of comorbid PTSD-CUD, rooted in learning theory, and extended this work to trauma-exposed cannabis users, an understudied group. Indeed, my work indicates both deliberative and automatic cognitive processes, as well as affective mechanisms, are at play when individuals with varying degrees of PTSD are exposed to a trauma reminder – mechanisms that may promote and maintain problematic cannabis use.

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