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Chapter

A Scoping Review of the Literature on Trauma Cue-Induced Drug Craving in Substance Users with Trauma Histories or PTSD

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Abstract

Among trauma-exposed individuals, substances may 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. Conditioned craving following cue exposure can be studied in-lab using the cue-reactivity paradigm. To map cue-reactivity research conducted with trauma-exposed substance users, we aimed to synthesize research which studied our population of interest, used a cue-reactivity paradigm, and measured craving as an outcome. Three databases were searched using relevant keywords. Twenty-eight studies met our criteria. Four key 19 themes are discussed in 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 cue-induced craving; and (4) cue-reactivity paradigms as an intervention outcome assessment tool. Overall, there is strong evidence for cue-reactivity paradigms as a useful means of eliciting craving in response to trauma cues. Our scoping review suggests 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, posttraumatic stress disorder, trauma, craving

1. Introduction

Posttraumatic stress disorder (PTSD) is an often debilitating mental disorder that may occur following trauma exposure [1]. PTSD is characterized by four diagnostic clusters—(1) the 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) [1]. Substance use disorder (SUD) is another psychiatric disorder characterized by 11 possible symptoms which involve negative consequences arising from one's substance use and inability to control one's substance use [1]. In the last version of the *Diagnostic and Statistical Manual of Mental Disorders* (the DSM-5; [1]), craving, the often intrusive desire to use the substance, was added as one of the 11 symptoms characterizing a SUD [1].

PTSD often co-occurs with SUD. Research has documented high rates of comorbidity between PTSD and alcohol use disorder (AUD) [2], cannabis use disorder (CUD) [3, 4], and other SUDs [5]. The prognosis of comorbid PTSD-SUD is worse than either disorder alone [6] with comorbid PTSD-SUD leading to greater functional impairment in comparison to those with only PTSD or a SUD [7].

It has been suggested that PTSD and SUD are likely functionally related to one another [8] 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 the two-factor learning theory which was originally developed by Mowrer to explain the acquisition and maintenance of phobias [9] and which has more recently been applied by Stasiewicz [10] 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 [10]. 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 [10]. 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 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 [11]. 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 [10], can come to create strong associations between trauma cues and substance use [12]. The result is that such trauma cues can become conditioned stimuli that elicit a conditioned craving response when presented on their own [13]. 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 a 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 cue-reactivity paradigm is broadly defined as a lab-based method in which participants are exposed to a set of stimuli meant to elicit a “reactivity” response—that is, a change from baseline in response to the stimulus [14]. 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 [15]; these stimuli serve as analogs 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 [16, 17]. More recently, cue-reactivity paradigms have been used to study conditioned craving as a possible mechanism underlying the relationship between trauma/PTSD and SUD [18, 19]. Indeed, extant research has shown that in-lab exposure to cues representing trauma reminders (e.g., a video of a violent crime) activates both substance-related craving responses as well as increased negative affect [20].

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 [21], and measures specific to the substances used, such as the Alcohol Urge Questionnaire [22] and the Marijuana Craving Questionnaire [23]. 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 [24]. 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 a reduction in tension or negative affect from using a substance) using certain self-report measures [23].

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 a 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.

1.1 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 a cue-reactivity methodology (e.g., trauma-exposed vs. suffering from PTSD).

2. 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 [25].

2.1 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. 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 [1]. Alternatively, PTSD symptoms must have been assessed for each participant. Additionally, it was required that participants report on their substance use.

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

2.2 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 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.¹

3. Results

3.1 Screening of search results

One hundred 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

¹ Non-English language studies were captured in our search and were excluded if an English translation could not be found.

CS) who removed all irrelevant studies; a moderate rate of agreement of 74% was achieved [26]. A third screener (PRS) aided in resolving any conflicts between the two raters. A total of 28 studies met our final inclusion criteria (**Figure 1**).

3.2 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. A quality assessment and risk of bias assessment were not conducted, as these are not typical in scoping reviews [27]. The extracted data were then synthesized into common categories by the first author to further examine themes in the scoped research.

3.3 Summary of included studies

3.3.1 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

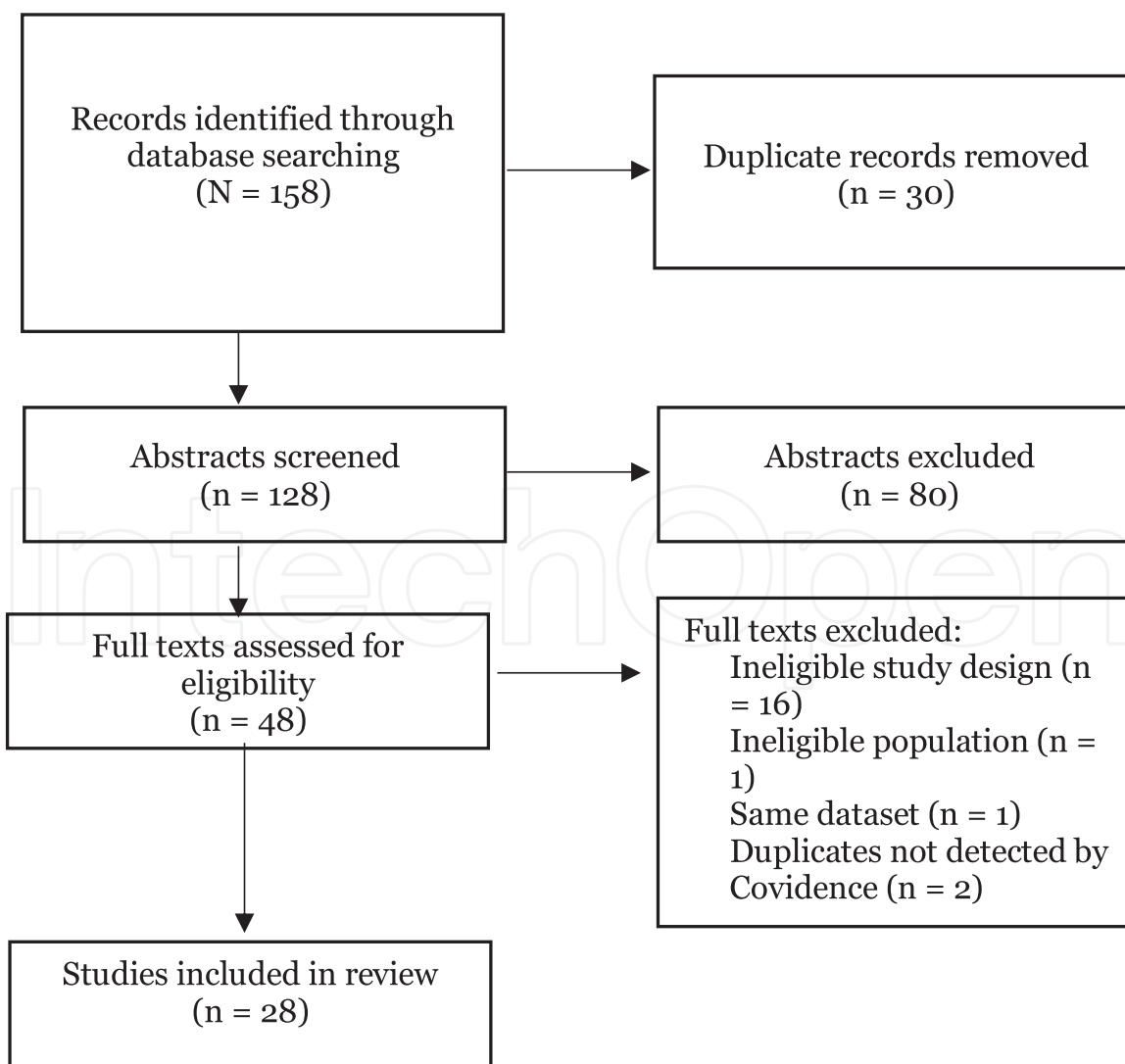


Figure 1.
PRISMA flowchart of literature search and screening.

in vivo cue (n = 9), with substance-related *in vivo* cues used independently only in 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 the 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, that is, cognitive tasks that included substance or trauma-related stimuli. Specifically, Garland and colleagues [28] used an Emotional Regulation Task as a cue exposure paradigm where participants sorted and viewed negative images. Kaag et al. [29] also utilized a sorting task as a cue exposure where participants sorted cocaine and neutral photos. Finally, Beckham and colleagues [30] used the Stroop color-naming task [31] with combat-related words as a cue exposure. Overall, 22 studies employed only personalized cues, five studies employed only standardized cues, and one study [32] employed both personalized cues and standardized cues.

3.3.2 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).

3.3.3 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 (i.e., individuals who use alcohol and/or cocaine were recruited for one study).

3.3.4 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; [33]) were used. The average number of cue types used per study was 2.36 (SD = .731).

3.3.5 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, many 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.

3.4 Population considerations

Populations of interest were largely adults who were assessed for PTSD symptoms/diagnoses and/or trauma history, and substance use. Participants across studies were more often male ($M = 61.5\%$, $SD = 24.6$), with $n = 5$ studies recruiting only males [29, 30, 34–36] and one study recruiting only females [28]. Four studies included only veterans [30, 36–38], and 12 included only patients in treatment for SUD ([39]; $n = 10$), PTSD ($n = 1$), or both ($n = 1$). Four studies examined emerging adult college students specifically [13, 40–42] and one study recruited low-income, inner-city adults [43].

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 [44, 45]). To assess for PTSD, most studies used some form of a validated structured interview ($n = 25$), such as the MINI [46], the SCID-5-RV [47], and the Clinician-Administered PTSD Scale [48]. Those studies examining trauma-exposed individuals typically administered a questionnaire to assess trauma history ($n = 3$), such as the Trauma History Questionnaire [49] or the Life Events Checklist [50], as well as continuous measures of PTSD symptoms, such as the PTSD Checklist for DSM-5 [51].

Substance use among the study populations was similarly measured. Specifically, the majority of studies ($n = 18$) required an SUD as inclusion criteria [18, 52], with some using inpatients receiving treatment for PTSD, SUD, or both ($n = 12$; [32, 53]). Fewer studies required less extreme forms of substance use, such as occasional drinking ($n = 6$) (see [13, 54]) and other cut-off points for use of various substances ($n = 3$; [55]). To assess for the presence of a SUD, most studies ($n = 18$) used structured interviews, such as the C-DIS IV [56] or the SCID-5-RV [47], but others used shorter self-report measures, such as the Alcohol Use Disorders Identification Test (AUDIT; $n = 10$) [57].

3.5 The cue-reactivity paradigm.

3.5.1 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 [58] or utilized the participants' preferred substance as part of an *in vivo* cue [59]. 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 (i.e., 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 [36]. Photo, video, or task-based cues were standardized rather than personalized [28, 54] although one study did take into account participants' preferred substances when selecting substance-related video cues [60]. Studies utilizing standardized cues did find cue-reactivity effects on their outcomes, with some caveats. For example, Trautmann and colleagues [54] 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 [29] and trauma-exposed [60] experimental groups vs. non-using/non-exposed controls.

3.5.2 Task-based cues

Studies that utilized photographic cues as part of task-based cue paradigms found to support that their paradigms functioned as effective cue-reactivity paradigms, even though craving was not the primary outcome of interest. For example, Garland and colleagues [28] 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; this increase was associated with the number of adverse childhood experiences to which participants reported having been exposed. Similarly, Beckham et al. [30] utilized a Stroop color-naming attentional [31] task 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.

3.6 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 who 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 that 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 [18, 58].

While our inclusion criteria did not specifically require an objective assessment of craving, the frequent use of salivation, heart rate, and other measures of physiological reactivity warrants a brief summary of this work. Most studies that included physiological/objective craving measures did so by measuring salivary flow (n = 5). Coffey et al. [18] found a significant increase in salivation following trauma and alcohol cues relative to neutral cues. Nosen et al. [59] 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 [53, 61]. 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 [41]. 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 [35].

3.7 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 a treatment for comorbid PTSD-SUD. Specifically, in a pre-clinical lab-based study, Stauffer et al. [35] 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 the following alcohol *in vivo* cue exposure relative to neutral *in vivo* (water) cues, but neither dose of oxytocin reduced cue-induced heart rate nor subjective craving responses relative to placebo. Similarly, Kwako et al. [32] combined the Trier Social Stress Test [62] 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 (125 mg/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 [18] examined the effects of trauma-based imaginal exposure vs. relaxation using a cue-reactivity paradigm to assess trauma cue-reactivity (i.e., craving), showing 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 ([53, 61]) assessed the merits of PE therapy in comparison to a health/lifestyle therapy using a craving to a cue-reactivity paradigm as an outcome measure; one study [53] 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 [61] only included those enrolled in the trauma cue-exposure 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 [36] 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 a degree of increase in resilience and degree of decrease in PTSD symptoms. Finally, one study [37] 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. 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.

3.8 Neural activation

Three studies combined fMRI and a cue-reactivity paradigm. One study [34] examined neural activation during the presentation of stress, neutral, and substance-related cues among cocaine-dependent individuals with and without childhood maltreatment histories. The 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 [34]. Conversely, the 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 [34]. Further, during substance cue presentation, another study [35] found childhood trauma histories among substance users were significantly associated with increased activation of the frontal striatal circuit and the amygdala. However, a third study [32] 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.

3.9 Affect

Fourteen studies included a measure of affect as part of their evaluation of cue-reactivity. Eleven of such studies examined both positive and negative affect, and three examined negative affects only. The Positive and Negative Affect Schedule or PANAS [63] was overwhelmingly used as the standardized measure of this variable ($n = 10$), although other measures were used as well, such as the Affect Grid [64] ($n = 2$). Among the majority of studies ($n = 9$), negative affect increased following stress and trauma-related cues [38]. In those studies which also examined positive affect, positive affect tended to decrease following stress and trauma-related cues [42, 33] but this was not always consistent. For example, Coffey et al. [39] 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 [55].

4. Discussion

The primary aim of this scoping review was to map the use of cue-reactivity paradigms 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 followed the cue-reactivity paradigm (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 [65] 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 [66], we aimed to map the use of cue-reactivity paradigms 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 cue-reactivity paradigm 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 cue-reactivity paradigm, 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 an outcome and possible mediator of craving in cue-reactivity research; and (4) the cue-reactivity paradigm 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 [43] and standardized cues [54]. However, this effect was typically magnified when a combination of trauma-related imagery and *in vivo* substances cues were paired together [45, 53]. The latter finding supports the notion that “cue chains” may be an effective means of bolstering cue-reactivity responses [67]. 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 that such effects were the strongest among those with higher PTSD symptom severity [45, 52] or those with the greatest cumulative trauma exposure [28]. Moreover, studies with control groups, such as healthy non-drug using controls [29] and those without trauma histories [34] 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 [34]). These findings are consistent with predictions that would be made on the basis 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; [10]) and to develop conditioned craving responses to trauma cues (via classical conditioning; [12]). 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 to cue combinations may further bolster craving responses [39, 40]. These combined cues serve as an in-lab analog 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 [54]. 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 [54] 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 color-naming task [31] to assess attentional bias) but that contained relevant trauma or substance cues, allowing for a secondary test of cue-induced craving [28–30]. 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 [28] who aimed to assess 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 effect 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 effect as an additional outcome alongside craving. Our findings elucidated the importance of effect 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 [44, 59]. 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 application of the two-factor avoidance theory to substance use [10]. They suggested that trauma reminders can be classically conditioned to elicit fear themselves, which motivates avoidance responses such as substance abuse to escape 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 [61] 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 [28] 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 cue-reactivity paradigms 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 [32, 35]). 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 [36, 37, 39, 53, 61]. Indeed, behavioral 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 cue-reactivity paradigms as a secondary outcome in randomized controlled trials of therapeutic interventions speaks to the multifaceted functionality of the cue-reactivity paradigm in the PTSD/trauma-exposed population, offering a mechanism-based outcome that informs beyond the decrease of symptoms.

5. Limitations and future directions

First, it is important to note that no formal examination of the study quality of the included literature was completed, as this step is not typical for scoping reviews [27]. 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 the future to better understand how methodological variations in cue-reactivity may influence relevant outcomes. Additionally, the use of cue-reactivity paradigms as secondary outcomes in the context of behavioral and pharmacological intervention trials is an interesting research direction that 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, such as two-step meta-analytic structural equation modeling (TS-MASEM; [68]) 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).

6. Conclusion

Our scoping review maps the use of cue-reactivity paradigms 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 a 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 behavioral 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.

Appendix A

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
Elton et al. [34]	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 the visual analog scale (VAS) from 0 to 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

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
					alters neural correlates of cue-induced substance craving.
Dutton [33]	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 to 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.
Trautmann et al. [54]	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 [69].	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.

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
Stauffer et al. [35]*	47 males with comorbid PTSD-AUD and 37 healthy control males.	<i>In vivo</i> 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 to 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.
Ralevski et al. [38]*	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 [69] 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 [60]	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 were highest in the opiate-dependent group, and only among those with trauma histories.
Coffey et al. [39]*	43 SUD inpatients with comorbid PTSD-AUD. 75% of participants who completed at least one clinical session were randomly assigned to receive six	Script-driven imagery and <i>in vivo</i> substance cues. Participants completed the following experimental cue reactivity trials: Trial 1: All participants listened to personalized	Subjective craving responses, affect, and emotional distress.	Cue-induced alcohol craving was measured using a VAS from 0 to 10.	Craving responses decreased from pre- to post-treatment among those in the imaginal exposure condition following the trauma-alcohol cue (trial 2) and

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
	sessions of either imaginal exposure therapy (n = 12) or relaxation (control) condition (n = 12). However, only 17 participants completed the study.	neutral and trauma cues. Trial 2: All participants listened to a personalized trauma cue followed by the presentation of either alcohol or water.			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.
Read et al. [13]	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 an urge to drink only among those with PTSD in the trauma cue condition.
Kaag et al. [29]	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 [21] 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. [58]	75 individuals receiving SUD treatment with PTSD who were cocaine (n = 30) or alcohol-dependent (n = 45)	Script-driven imagery and <i>in vivo</i> substance cues. All participants took part in four cue trials, which were counterbalanced. Participants listened to a	Subjective craving.	Cue-induced craving was measured using the Cocaine Craving Questionnaire-Now (CCQ-Now) [70] and Alcohol Craving Questionnaire-	Both alcohol-dependent and cocaine-dependent participants evidenced greater cravings following the trauma- and substance-

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
		personalized cue (trauma or neutral). Immediately after, either a substance or neutral (i.e., alcohol or wood chips) <i>in vivo</i> cue was placed in front of them.		Now (ACQ-Now) [71]	related cues compared to the neutral cues.
McHugh et al. [44]	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. [36]	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 [71]	Posttreatment, 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. [45]	124 individuals with trauma histories receiving SUD treatment who were alcohol- (n = 70) or cocaine-	Script-driven imagery and <i>in vivo</i> substance cues. All participants took part in four cue trials, which were counterbalanced.	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.

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
	dependent (n = 54).	Participants listened to a personalized cue (trauma or neutral). Immediately after, either a substance (e.g., Jack Daniels over ice) or neutral <i>in vivo</i> cue was placed in front of them.			PTSD symptom severity predicted greater craving responses, but only following the trauma + substance cue pairing.
Coffey et al. [18]	40 individuals with comorbid PTSD-AUD receiving inpatient SUD treatment.	Script-driven imagery and <i>in vivo</i> . All participants listened to a personalized trauma or neutral imagery cue paired with an <i>in vivo</i> substance or neutral (water) cues.	Subjective and objective craving responses; emotional distress.	Cue-induced craving was measured using a VAS from 0 to 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. [43]	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 to 100.	Lower distress tolerance was a significant predictor of higher craving responses following the trauma cue.
Rodriguez et al. [40]	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 [22], on a scale from 1 to 10.	Emotional responses to the trauma cue mediated the relationship between trauma exposure and the urge to drink.
Bing-Canar et al. [41]	184 young adults with trauma histories	Script-driven imagery and <i>in vivo</i> substance	Subjective and objective	Cue-induced craving was measured using	Depressive symptoms did not have any

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
		cues. All participants listened to a personalized trauma or neutral imagery cue paired with an <i>in vivo</i> substance or neutral (water) cues	craving responses.	a three-item Alcohol Craving Scale [72] and salivation levels.	effect or interaction with the cue-reactivity paradigm to predict increased craving or salivation.
Zambrano-Vazquez et al. [61]	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 the analyses.	Script-driven imagery and <i>in vivo</i> substance cues. Pre- and post-treatment, all participants listened to a personalized trauma or neutral imagery cue paired with an <i>in vivo</i> 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 [69] and salivation levels.	Severity in all domains of functional 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. [28]*	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 the 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. [42]	611 college students with	Script-driven imagery.	Subjective craving	Cue-induced craving was	Following the trauma cue, but

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
	PTSD (n = 50), with trauma exposure but no PTSD (n = 325), and no trauma (n = 236) who drink alcohol	Participants were randomized to listen to either a personalized trauma or neutral cue followed by a 2-minute writing period relating to the cues.	response and affect.	measured using a 10-point scale, with 1 indicating no urge to drink and 10 indicating a very strong urge to drink.	not the neutral cue, participants reported greater cravings and negative affect relative to baseline, which was associated with coping drinking motives.
Kwako et al. [32]*	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, <i>in vivo</i> alcohol cues, standardized photos of alcohol, and neutral cues. Following the Trier Social Stress test, participants handled <i>in vivo</i> 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 [22]	Alcohol and stress cues induced more cravings compared to neutral cues. There was no significant neural activation following the substance-related relative to the neutral stimuli.
Nosen et al. [59]	108 adults with comorbid PTSD-AUD who were receiving residential treatment for SUD.	Script-driven imagery and <i>in vivo</i> substance cues. All participants listened to a personalized trauma or neutral imagery cue paired with an <i>in vivo</i> 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 [72] and 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 the strongest craving.

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
Tull et al. [19]	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.
Nosen et al. [53]	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 <i>in vivo</i> substance cue exposure. All participants have presented with four counterbalanced cue combinations: They first listened to a personalized cue (trauma or neutral). Immediately after, either a substance or neutral <i>in vivo</i> 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 [72] and 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. [37]*	54 veterans with comorbid PTSD-SUD taking part in a COPE RCT.	Participants were presented with personalized <i>in vivo</i> 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. [52]	133 individuals with trauma histories in treatment for a SUD.	Script-driven imagery. Participants listened to a personalized trauma cue (1 min) followed	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	Following the trauma cue, craving increased relative to the pre-cue baseline. This change was

First author (year)	Sample characteristics and context	Cue reactivity paradigm and method	Outcome(s) of interest	Craving measure	Relevant findings
		by a visualization period (1 min).		indicating no cravings and 11 indicating very strong cravings.	associated with greater PTSD symptom severity. PTSD symptom severity was related to both adaptive and maladaptive emotional regulation strategies.
Beckham et al. [55]	129 smokers with (n = 82) and without PTSD (n = 47) were 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 [73].	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. [30]	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 [71]	Craving, negative affect, somatic symptoms, and lack of alertness were all greater following the presentation of trauma-related words compared to neutral words.

*randomized controlled trial.

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