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Trauma exposure among cannabis use disorder individuals was associated with a craving-correlated non-habituating amygdala response to aversive cues.

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ABSTRACT

The relationship of cannabis-use disorder and trauma exposure at the level of the brain is not well-understood. Cue-reactivity paradigms have largely focused on characterizing aberrant subcortical function by averaging across the entire task. However, changes across the task, including a non-habituating amygdala response (NHAR), may be a useful biomarker for relapse vulnerability and other pathology. This secondary analysis utilized existing fMRI data from a CUD population with (TR-Y, $n = 18$) or without trauma (TR-N, $n = 15$). Amygdala reactivity to novel and repeated aversive cues was examined between TR-Y vs. TR-N groups, using a repeated measures ANOVA. Analysis revealed a significant interaction between TR-Y vs. TR-N and amygdala response to novel vs. repeated cues in the amygdala (right: $F(1,31) = 5.31$, $p = 0.028$; left: $F(1,31) = 7.42$, $p = 0.011$). In the TR-Y group, a NHAR was evident, while the TR-N group exhibited amygdala habituation, resulting in a significant difference between groups of amygdala reactivity to repeated cues (right: $p = 0.002$; left: $p < 0.001$). The NHAR in the TR-Y (but not TR-N) group was significantly correlated with higher cannabis craving scores, yielding a significant group difference ($z = 2.1$, $p = 0.018$). Results suggest trauma interacts with the brain's sensitivity to aversive cues, offering a neural explanation for the relationship between trauma and CUD vulnerability. These findings suggest the importance of considering the temporal dynamics of cue reactivity and trauma history in future studies and treatment planning, as this distinction may help decrease relapse vulnerability.

1. Introduction

1.1. Cannabis use disorder and trauma

Approximately 18% (~50 million) of U.S. individuals aged 12 and older reported past-year cannabis use; of these, 28% (~14 million) met criteria for cannabis use disorder (CUD) (SAMHSA, 2021). Cannabis use is associated with several adverse consequences, including attention and memory impairments (Lundqvist, 2005), an increased likelihood of comorbid psychiatric disorders (Agrawal and Lynskey, 2014; Satre et al., 2018), and deficits in emotion regulation (Zimmermann et al., 2017). A recent review (Sehl et al., 2021) summarizing fMRI findings indicated that cannabis users, when exposed to cannabis cues, typically evidence greater brain activity in the striatum, prefrontal regions, parietal cortex, hippocampus and amygdala, with findings also lending preliminary support for correlations between amygdala and striatal activity and cannabis craving. Despite individuals carrying comparable CUD diagnoses, heterogeneity exists within this population in terms of neural signatures and treatment prognosis (Kroon et al., 2020; Sherman and McRae-Clark, 2016). While some patients struggle with CUD throughout their lives, others successfully respond to treatment (Davis et al., 2015). One factor contributing to cannabis use and relapse is a history of trauma exposure. For example, exposure to trauma has been linked to greater odds of lifetime cannabis use (Kevorkian et al., 2015; Cougle et al., 2011; Werner et al., 2016) and cannabis-related problems (Grant et al., 2017). However, the neural underpinnings of the trauma-exposure and cannabis misuse relationship are not well understood. Identifying whether trauma exposure contributes to unique brain and behavioral characteristics among those with CUD would help clarify individual differences relevant to drug-use severity and treatment response.

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1.2. Neural cue-reactivity: traditional vs. temporal dynamics

Cue-exposure paradigms have been broadly implemented into neuroimaging paradigms to characterize cue-induced brain reactivity among individuals with substance use disorder (SUD) (Carter and Tiffany, 1999; Childress et al., 1999; Pineles et al., 2013; Regier et al., 2021, 2017; Volkow, 2006; Wetherill et al., 2014). A recent review supports the utility of cue-reactivity paradigms with the observation that enhanced corticolimbic brain reactivity to drug cues measured at baseline predicts future relapse (Moeller and Paulus, 2018). Although hundreds of addiction neuroimaging publications have used fMRI cue-reactivity paradigms to assess brain activity among SUD populations (Ekhtiari et al., 2022), the conventional approach has been to average the cue-response (versus a control condition) across the entire duration of the paradigm (Hartwell et al., 2011; Schacht et al., 2013; Van Hedger et al., 2018). This approach assumes a cue-induced brain response is consistent across the duration of a task; however, data from our lab (Regier et al., 2021, 2017) and others (Ekhtiari et al., 2021) suggest that the brain exhibits temporal dynamics in response to repeated evocative stimuli.

Measuring the change in brain response to repeated stimuli within a task (e.g., habituation of the amygdala response to repeated stimuli) has been found to be more reliable than averaging over the entire task (Plitcha et al., 2014), and it may be a novel method for identifying aberrant underlying neural circuits. Indeed, research suggests that a non-habituating amygdala response (which we have labeled NHAR) may be a biomarker for certain mental health conditions, including anxiety (Avery and Blackford, 2016; Bas-Hoogendam et al., 2019; Blackford et al., 2013), autism (Kleinhans et al., 2016, 2009; Swartz et al., 2013), and schizophrenia (Holt et al., 2005; Williams et al., 2013). NHAR refers only to the deviation from the "typical" adaptive response of the amygdala (i.e., habituation); thus, NHAR could include responses that are the same or even increasing across the task. In the addiction literature, recent studies have begun to examine neural habituation to cue exposure in individuals with SUD (Ekhtiari et al., 2021; Jafakesh et al., 2022; Murphy et al., 2018; Regier et al., 2021). For example, a recent paper demonstrated habituation to drug cues in a population with methamphetamine use disorder but no relationship to lifetime drug use or craving (Ekhtiari et al., 2021). Recent data from our lab suggest that variability in neural habituation is found in individuals with active SUD and that it corresponds with prior experiences, such as trauma (Regier et al., 2017), and with future behaviors, such as drug use (Regier et al., 2021). For example, a NHAR (as well as a lack of habituation in other regions) to drug cues was associated with worse outcomes (i.e., >85% positive urine drug screens during 8 weeks of outpatient treatment), whereas habituation to drug cues characterized better outcomes (i.e., <40% positive urine drug screens during 8 weeks of outpatient treatment). One other study found that patients with opioid use disorder demonstrated NHAR compared to healthy controls, and this differential temporal response was related to increased craving (Murphy et al., 2018).

1.3. Neural correlates of trauma and cannabis-use disorder

Research indicates that exposure to trauma and childhood maltreatment has long-lasting neurobiological effects on the amygdala (Pagliaccio et al., 2015; Yamamoto et al., 2017), regardless of whether trauma exposure leads to PTSD (Hart and Rubia, 2012). A common finding in neuroimaging research examining individuals with trauma history is increased activity in the amygdala to evocative stimuli, especially 'threatening' or 'aversive' stimuli (Kim et al., 2019; Patel et al., 2012; Regier et al., 2017; Shvil et al., 2013; Stevens et al., 2017; Teicher et al., 2016). In addition, previous studies have found a lack of neural habituation (in the amygdala and other regions) among trauma-exposed (non-PTSD) populations (Kim et al., 2019; Regier et al., 2017; Stevens et al., 2017). For example, our study found a relationship between prior trauma and an increased neural response to novel drug cues and a non-habituating neural response to repeated drug cues in a population with cocaine use disorder (Regier et al., 2017). However, no studies have studied NHAR as it relates to prior trauma and behavioral correlates in a population with CUD.

1.4. Cue-Reactivity, trauma, and behavioral correlates

A heightened neural response to stimuli is thought to reflect problems characteristic of posttraumatic stress, including disrupted cognitive and emotional processing and impaired regulation of negative affective states (Shvil et al., 2013), which parallels neuroimaging findings associated with SUD (Koob and Volkow, 2016), including CUD. Similarly, NHAR is thought to stem from dysregulated inhibitory circuits that result in maladaptive responses to familiar, non-threatening stimuli (Kosaka et al., 2003; Wright et al., 2001). Impaired regulation is a risk factor for drug misuse and developing a SUD (Quinn and Fromme, 2010), and aberrant amygdala activity has been observed among cannabis users when attempting to regulate emotions in response to aversive cues (Zimmermann et al., 2017). Several research studies have shown that hyperactive subcortical circuits (including the amygdala) are related to increased drug craving (Childress et al., 1999; Hartwell et al., 2011; Murphy et al., 2018; Volkow, 2006). In addition, studies with trauma-exposed cannabis users demonstrated increased cannabis craving following personalized trauma-cue exposure (Farrelly et al., 2022), shown to correlate with PTSD symptom severity (Romero-Sanchiz et al., 2022).

1.5. Purpose of present study

As described above, the variability in temporal dynamics (e.g., NHAR) may offer a unique way of identifying nuanced heterogeneity among psychiatric populations that might otherwise be overlooked using conventional approaches (e.g., averaging brain response across an entire cue task). The present study aims to determine differential temporal patterns within a single aversive cue-exposure task among a cohort of individuals with CUD grouped by those with trauma-exposure (TR-Y) vs. those without (TR-N). This study focused on an aversive cue-reactivity paradigm to evaluate group differences. Considering prior work on amygdala reactivity to aversive cue-exposure among trauma-exposed individuals (Kim et al., 2019; Patel et al., 2012; Protopopescu et al., 2005; Regier et al., 2017; Stevens et al., 2017; Teicher et al., 2016), we hypothesized that, in a CUD population, amygdala response to aversive cues would differ between groups. Specifically, the TR-Y (vs. TR-N) group would exhibit amygdala hyperreactivity to novel aversive cues and a NHAR to repeated aversive cues. We further hypothesized that these differences would be related to self-reported emotional dysregulation and cannabis craving.

2. Materials and methods

2.1. Participants

The study sample included 33 individuals (23 men) with CUD, taking part in a larger cannabis outpatient treatment study examining neural and behavioral features predictive of treatment outcomes (Wetherill et al., 2014). The data used in the analyses is from a neuroimaging session at baseline. Participants had not set a quit date, nor had they begun treatment. All participants were medically stable, met criteria for CUD, and had no additional comorbid psychiatric disorders, including PTSD, other than tobacco use disorder (See Table 1 for demographics). Recruitment, informed consent, and eligibility criteria procedures are detailed in prior published work (Wetherill et al., 2014). All study procedures adhered to the Declaration of Helsinki and were approved by the University of Pennsylvania Institutional Review Board.

Table 1
Demographics and behavioral health variables by trauma group.

	Total sample (n = 33)	Trauma-No (n = 15)	Trauma-Yes (n = 18)	Group Differences
Age (M, SD)	29.45 (7.44)	30.73 (7.18)	28.39 (7.67)	.376
Sex (n,%)				
-Male	23 (69.7%)	9 (60%)	14 (77.8%)	.448
-Female	10 (30.3%)	6 (40%)	4 (22.8%)	
Race (n,%)				
-White	6 (18.2%)	2 (13.3%)	4 (22.2%)	.484
-Black	25 (75.8%)	12 (80%)	13 (72.2%)	
-Other	2 (6%)	1 (6.7%)	1 (5.6%)	
Ethnicity (n,%)				
-Not Hispanic/Latino	30 (90.9%)	13 (86.7%)	17 (94.4%)	.579
-Hispanic/Latino	3 (9.1%)	2 (13.3%)	1 (5.6%)	
Education (years)	12.82 (1.67)	13.00 (2.04)	12.67 (1.38)	.576
Cannabis use, past 30 days (TLFB)	24.79 (7.39)	25.00 (6.88)	24.61 (7.97)	.882
Cannabis use, years (ASI)	11.15 (7.91)	11.20 (8.51)	11.11 (7.63)	.975
Cannabis Craving	4.06 (3.03)	4.00 (3.00)	4.11 (3.142)	.918
Cigarette Smoker (n,%)	20 (60.6%)	8 (53.3%)	12 (66.7%)	.493
Cigarettes Per Day (TLFB) (M, SD)	10.24 (9.46)	9.33 (10.80)	11.00 (8.42)	.622
NicDays30 (TLFB) (M, SD) ‘	15.19 (14.30)	13.86 (14.90)	16.22 (14.24)	.651
PCL (*M*, SD)	**26.64 (9.124)**	**23.20 (6.85)**	**29.5 (9.94)**	**0.046**
DERS (M, SD)	65.24 (17.91)	61.20 (18.77)	68.61 (16.94)	.243
HAM-D (M, SD)	3.42 (3.75)	2.13 (2.97)	4.50 (4.06)	.070
HAM-A (M, SD)	3.55 (4.03)	4.47 (4.89)	2.78 (3.19)	.237

Note. Abbreviations: M (SD): mean (standard deviation); n (%): frequency (sample percentage); TLFB: Timeline Followback; ASI: Addiction Severity Index; PCL: PTSD Checklist; DERS: Difficulties with Emotion Regulation Scale; HAM-D: Hamilton Rating Scale for Depression; HAM-A: Hamilton Rating Scale for Anxiety.

2.2. Study procedures

Participants completed a battery of self-report questionnaires, diagnostic and clinical interviews, and an MRI session. Participants were instructed to abstain from alcohol and illicit substances for 24 h before the MRI session and completed a urine drug screen (UDS) and alcohol breathalyzer prior to scanning. All participants tested positive on the UDS for cannabis and negative for other substances. Tobacco using participants were permitted to smoke cigarettes on scan-day but were prohibited from smoking within the 20-minute period leading up to the scanning session to mitigate any cardiovascular effects of recent smoking on brain imaging results.

2.3. Measures

Cannabis, alcohol, and other drug use within the past 30 days was assessed with the Timeline Followback interview (TLFB; Sobell and Sobell, 1992), and the Addiction Severity Index (ASI; Denis et al., 2013) assessed lifetime alcohol and substance use and age of onset for cannabis use. The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to assess psychiatric diagnoses, and the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and Hamilton Anxiety Scale (HAM-A; (Hamilton, 1959) assessed for depression and anxiety. To characterize symptoms that can emerge in response to trauma exposure, the PTSD Checklist for Civilians (PCL; Weathers et al., 1993) measured posttraumatic stress symptom severity and as a clinical validator for the TR-Y subgroup. The Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004) assessed self-reported difficulties regulating unpleasant emotions. As previously described (Childress et al., 1999), craving was measured during the MRI sessions prior to cue presentation. Briefly, participants were instructed to give a verbal answer to the prompt: “*Using a scale of 0–9, with 0 meaning none or not at all and 9 meaning extremely, indicate to what degree you are now experiencing any craving or desire for marijuana?*” (Fig. 1 and Fig. 2).

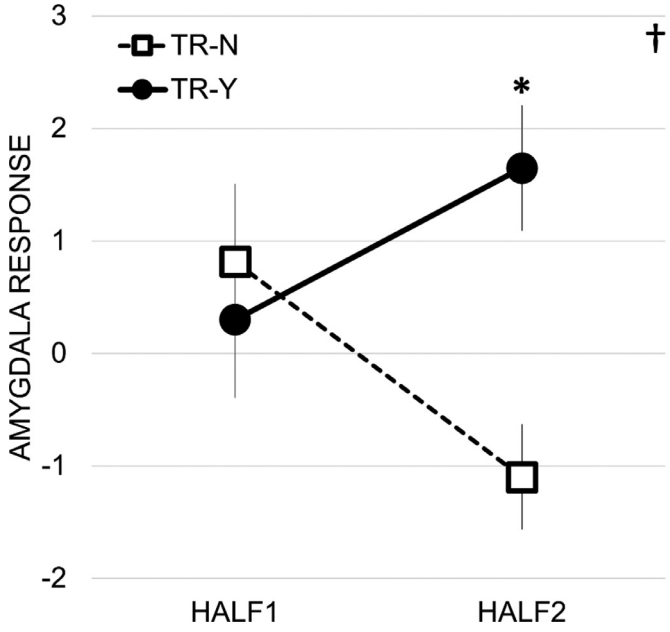

Fig. 1. Significant interaction of group (TR-Y [filled circle, solid] vs TR-N [open square, dashed]) x Half (novel cues in Half1 vs repeated cues in Half2) for the (averaged) bi-lateral amygdala response (i.e., parameter estimates, see methods). Changes across the task resulted in a significant difference to repeated cues between TR-Y and TR-N. † indicates a significant interaction; * indicates a significant difference between groups in Half2 (repeated cues).

2.4. Trauma-Yes vs. Trauma-No subgroups

In the present study, trauma status was based on participant responses to the clinician-administered MINI (i.e., *‘have you ever experienced…an extremely traumatic event…’*) and an ASI addendum question about trauma (i.e., “*In your life, have you ever had any experiences that*

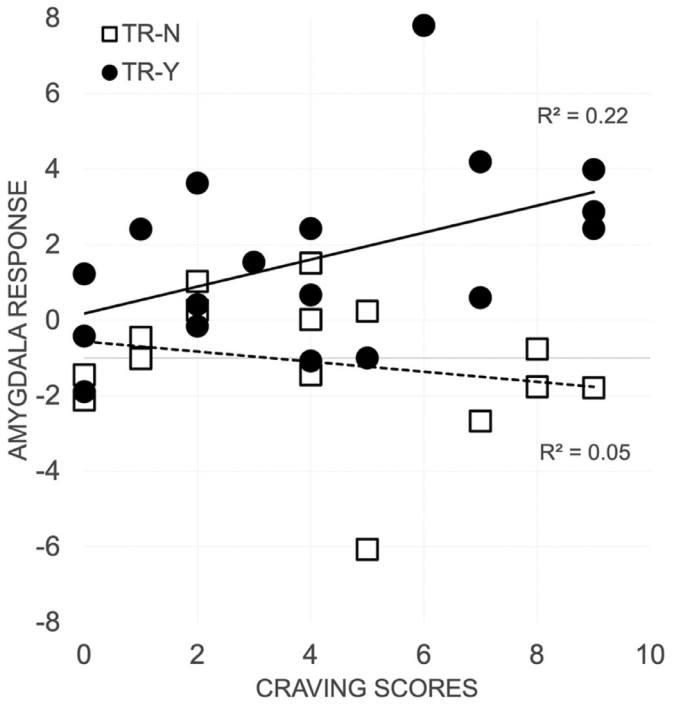

Fig. 2. Brain response to aversive cues in Half2 (repeated cues) correlated with baseline craving scores, plotted separately for TR-Y (filled circles, solid line) and TR-N (open squares, dashed lines) groups. There was no overall correlation of brain response to repeated cues and craving; however, between the correlations of TR-Y with craving ($r = 0.47$, $p < 0.05$) and TR-N with craving ($r = -0.22$, NS) there was a significant difference (z score = 2.1, $p = 0.02$).

were so frightening, horrible, or upsetting that others rarely go through?"). Participants who endorsed trauma via both the MINI and the ASI question were designated as the trauma-exposure group. Participants who did not endorse trauma via either method were designated as the no-trauma group. When discrepancies ($n = 4$) were noted (i.e., endorsing trauma on ASI but not MINI or vice versa), a licensed clinical psychologist carefully reviewed MINI and ASI responses; PCL items that referenced 'symptoms due to past events' were used as guidance to help make the final determination of trauma status. Using these methods, 18 individuals were designated as the trauma-exposure group (TR-Y) and 15 as the no-trauma group (TR-N). Of note, no participants in the present study were diagnosed with PTSD as this diagnosis was exclusionary for the parent study.

2.5. Imaging methods

Neural responses were measured during exposure to aversive stimuli, described elsewhere (Wetherill et al., 2014). The scanning session was composed of a 33 ms cue-presentation paradigm, a Go/No-Go task, and 500 ms cue-presentation task, with all tasks presented in the same order across all participants. The present study restricted focus to the 500 ms task. Briefly, target (aversive) and neutral (comparator) cues were presented for 500 ms interspersed with an interstimulus interval of random duration (i.e., jittered) of between 1000 and 2000 ms. Target stimuli consisted of 24 aversive and 24 comparator (i.e., neutral) cues, presented once (Half1) during the first half and then repeated, in pseudo-random order, during the second half (Half2) of the cue task. This resulted in 48 presentations of both aversive and neutral cues. Aversive cues were selected from the bottom quartile (most negative) of the International Affective Picture Series database (Lang et al., 1999); neutral cues that matched the aversive cues in size, luminosity and complexity consisted of buildings, signs, everyday objects, etc. Target stimuli were intermixed with other evocative cues (cannabis, sex) and presented in a pseudo-random order.

2.5.1. MRI acquisition, preprocessing, and analyses

As described in detail previously (Wetherill et al., 2014), T2*-weighted blood oxygen level-dependent (BOLD) images were acquired using a Siemens 3T scanner (Siemens AG, Erlangen, Germany). Parameters used for the single-shot gradient echo (GRE) echo planar imaging (EPI) sequence were: field of view (FOV) = 192, matrix 64×64, TR = 2 s, TE = 30 ms, flip angle = 80°. Images were slice time corrected, realigned and unwarped, co-registered to the structural MRI image, normalized to the Montreal Neurological Institute (MNI) standard space, and smoothed using an 8-mm full-width at half-maximum Gaussian kernel. Individual first-level (within-subject) analyses were conducted using a general linear model to measure relationships between event-related BOLD signals and regressors encoding experimental conditions (e.g., 500 msec aversive cues). Experimental conditions and canonical hemodynamic response functions were convolved to create regressors. Motion estimates made during motion correction were added as control factors. Two first-level contrasts were used for this analysis: aversive – neutral in Half1 (novel exposure) and aversive – neutral in Half2 (repeated exposure). Imaging data analyses were run with Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, London, UK) within a MATLAB environment (MATLAB 2019a; The Mathworks, Inc., Natick, Massachusetts, USA).

2.5.2. Primary analyses

Second-level analyses tested for associations between trauma and change in response from novel to repeated exposure in the amygdala. Left and right amygdala were defined *a priori* as anatomical regions of interest (aROIs) via the Harvard-Oxford probabilistic anatomical atlas included with the FMRIB Software Library (FSL); they were then thresholded (min=20) and binarized via FSL maths. Using these aROIs, mean parameter estimates were extracted via Marsbar (http://marsbar.sourceforge.net) from the two first-level contrasts and entered into a 2 × 2 repeated measures ANOVA: Group (TR-Y vs. TR-N) x Half (novel vs repeated exposure). Four post-hoc tests were conducted: 1) TR-Y vs. TR-N, novel; 2) TR-Y vs. TR-N, repeated; 3) TR-Y, novel vs repeated; and 4) TR-N, novel vs repeated. False Discovery Rate (FDR) was used to correct for multiple comparisons. Effect sizes for the primary analyses were calculated via Cohen's *d* (Cohen, 1992). Parameter estimates from the amygdala were subsequently used to test whether changes in the brain response to novel or repeated aversive cues were associated with baseline craving and emotional regulation scores. R values were calculated for the overall cohort and for TR-Y and TR-N separately. Putative differences in R values between the two groups were determined with a Fisher z transformation analysis.

2.5.3. Exploratory analyses

Exploratory analyses were run for additional aROIs, which were defined *a priori* (see Section 2.5.2 for method). These aROIs, including ventral medial frontal and visual cortices, ventral striatum, posterior cingulate cortex, and hippocampus, were previously identified as important for distinguishing subgroups in the literature (Avery and Blackford, 2016; Blackford et al., 2013; Kleinhans et al., 2009; Sinha et al., 2016; Stevens et al., 2017; Williams et al., 2013).

3. Results

3.1. Corroboration of trauma status

Individuals' posttraumatic stress symptom severity, assessed with PCL scores, was examined for a potential corroboration of the trauma split. Scores on the PCL range from 17 to 85, with higher scores reflecting greater posttraumatic stress symptom severity. The TR-Y group endorsed significantly higher scores on the PCL ($M = 29.50$, $SD = 9.94$)

than the TR-N group ($M = 23.20$, $SD = 6.85$; $t(31) = 2.075$, $p = 0.046$), as would be expected (see Table 1).

3.2. Demographic comparisons

There were no differences between TR-Y and TR-N groups on any demographic measures, clinician-administered measures, self-report measures, or substance use severity measures, except for PCL scores (see 3.1).

3.3. Imaging results: Primary

Analysis revealed a significant interaction of Group (TR-Y vs. TR-N) x Half (novel vs repeated exposure) in the left ($F(1,31)=7.42$, $p = 0.011$, Cohen's $d = 0.95$) and right amygdala ($F(1,31)=5.31$, $p = 0.028$, Cohen's $d = 0.95$). Posthoc tests showed significant amygdala reactivity differences between groups to repeated (but not novel) cues (left amygdala: $p < 0.001$, Cohen's $d = 1.25$; right amygdala: $p = 0.002$, Cohen's $d = 1.19$). There were no differences between the left and right amygdala; thus, parameter estimates were averaged and treated as one aROI for the remainder of the analyses.

A significant relationship was found for greater TR-Y amygdala reactivity to repeated cues and higher craving scores ($r = 0.47$, $p < 0.05$); there was a non-significant inverse correlation between TR-N amygdala response to repeated cues and craving scores ($r = -0.22$, NS). This resulted in a significant difference between the two correlations (z score = 2, $p = 0.018$). There was no significant association between amygdala response and emotion regulation scores, as measured by the DERS.

3.4. Results: Exploratory

Exploratory analyses tested whether there were interaction (or main) effects in other relevant aROIs (see methods). Uncorrected results suggest a significant interaction effect in the hippocampus (See Supplemental Figure 1).

4. Discussion

4.1. Summary and interpretations

This study tested whether prior trauma interacted with the amygdala response to novel or repeated aversive cues in individuals with CUD. Specifically, we tested whether there were differences in the initial response to novel aversive (vs. neutral) cues and whether there was a non-habituating amygdala response (NHAR) to repeated aversive (vs. neutral) cues. We found a significant interaction of TR-Y vs. TR-N and amygdala response to novel vs. repeated cues, with group differences to repeated (but not novel) cues; the TR-Y group exhibited a NHAR to repeated cues compared to the TR-N group. NHAR significantly corresponded with baseline craving scores for the TR-Y group, with greater amygdala response to repeated cues positively correlating with higher craving scores, significantly different from the (non-significant) inverse correlation in the TR-N group.

The study is in line with recent evidence showing a non-habituating response (in the amygdala and other regions) in trauma-exposure (non-PTSD) populations (Kim et al., 2019; Regier et al., 2017) and other types of pathology. Typically, the amygdala reliably habituates to repeated stimuli (Plichta et al., 2014). Thus, when it does not (i.e., NHAR), it has been linked to mental health conditions, including anxiety (Avery and Blackford, 2016; Bas-Hoogendam et al., 2019; Blackford et al., 2013), autism (Kleinhans et al., 2016; Swartz et al., 2013), and schizophrenia (Holt et al., 2005; Williams et al., 2013). Of note, prior studies found that those with trauma exposure *and* a diagnosis of PTSD did not appear to have a NHAR to negative cues. Instead, increased habituation in those with PTSD was linked to worse PTSD symptoms (Kim et al., 2019; Stevens et al., 2017); yet, it is unclear whether this is due to a heightened response to novel negative stimuli or a non-habituating response to repeated negative stimuli. Previously, we found that both the initial "heightened but rapidly habituating" response and the "non-habituating response to repeated cues" were linked to prior trauma (Regier et al., 2017), but only a non-habituating response was linked to outcomes (Regier et al., 2021).

The present study adds to this data, showing findings of an interaction between trauma exposure and NHAR associated with craving in a CUD population, and that in the TR-Y group, the NHAR corresponded with baseline craving and thus relapse vulnerability (e.g., Seo and Sinha, 2014; Serre et al., 2015; Weiss, 2005). Only one other study found a relationship between NHAR and craving in a substance-use population (Murphy et al., 2018). However, this is the first study to show a relationship in those with CUD and that prior trauma interacts with NHAR and craving. Recent findings show that trauma-exposed cannabis users report increased cannabis craving following trauma cues (Farrelly et al., 2022) and that the link between symptom severity and craving is greater following trauma cues relative to cannabis cues (Romero-Sanchiz et al., 2022). Trauma exposure is common within the CUD population (Kevorkian et al., 2015) and contributes to difficulty with cannabis cessation (Bonn-Miller et al., 2015). For example, studies have found that cannabis use is linked with greater posttraumatic stress symptom severity (Bonn-Miller et al., 2013; Lee et al., 2018; Wilkinson et al., 2015) and increased distress intolerance (Farris and Metrik, 2016).

In contrast to our hypothesis, we did not find a relationship between emotional regulation (measured with DERS) and NHAR. Prior work supports a relationship between emotion dysregulation and CUD (Bonn-Miller et al., 2015), and the relationship between symptom severity and aspects of CUD appears to be fully mediated by difficulties in emotion regulation (Bonn-Miller et al., 2011). However, the present results suggest NHAR may not be an underlying neural correlate of the relationship between emotional dysregulation and CUD.

Our results suggest a putative brain mechanism by which NHAR among TR-Y subjects may reflect a unique clinical feature requiring a transdiagnostic treatment approach. Transdiagnostic treatment approaches, which integrate evidence-based interventions to simultaneously address a range of disorders (Schaeuffele et al., 2021), may hold promise for CUD and posttraumatic stress. Prior research suggests the utility of integrating specific components of cognitive behavioral therapy (CBT) for anxiety and posttraumatic stress with CBT and motivation enhancement therapy components for drug misuse (Murray et al., 2014; Buckner et al., 2021, 2019). However, additional research is needed to determine how such approaches result in desired outcomes across CUD populations with varying posttraumatic stress. Although mental health symptoms did not differ between groups and no one had PTSD (in this pre-existing dataset), recent research showing an association between untreated traumatic stress and increased prospective cannabis use (Hicks et al., 2022; Metrik et al., 2022) warrants the implementation transdiagnostic treatment approaches to mitigate cannabis use.

4.2. Limitations and future directions

Several limitations should be considered. The sample size was small; a larger CUD sample with and without trauma is needed to replicate the current findings. The small sample size also precluded analyses of the DERS sub-factors or how specific emotion regulation difficulties may be associated with brain reactivity. The sample was also comprised of both tobacco users and non-users. While the TR-Y and TR-N groups did not statistically differ in terms of number of smokers, frequency or number of cigarettes smoked, nicotine dependence is an important comorbidity that should be accounted for statistically in future studies. Future studies might apply the current study's conceptual framework (i.e., measuring the change in amygdala response over time to aversive cues) to a larger CUD sample with greater variability in trauma exposure. Additionally,

a more thorough evaluation type of trauma exposure (i.e., Life Events Checklist for DSM-5; Weathers et al., 2013) and PTSD (i.e., Clinician-Administered PTSD Scale, CAPS; Weathers et al., 2013) would enable a more nuanced investigation into the role that specific trauma exposures and PTSD symptom clusters (i.e., avoidance, hyperarousal) might interact with CUD and associate with NHAR, in addition to helping address noted discrepancies of self-reported trauma. Additional limitations are inherent due to the study being a secondary analysis utilizing previously collected data. First, there are only two repetitions for which to measure the NHAR; multiple repetitions would allow for applying a slope analysis suggested by previous studies (Plichta et al., 2014). Second, this secondary analysis focused on aversive cue exposure using a task that included other evocative cues and was part of a battery of fMRI tasks. Therefore, it cannot be ruled out that exposure to other cues presented in the present task (i.e., drug, sex) or preceding tasks influenced the present findings. Another limitation is the lack of control or comparison groups (i.e., non-CUD trauma-exposed cohort, healthy controls), limiting the inferences that can be made.

4.3. Conclusions

This is a novel secondary analysis of data collected in individuals with CUD with or without prior trauma. We found that those with CUD and trauma exhibited a non-habituating amygdala response (NHAR) to repeated aversive cues compared to those with CUD but without trauma. NHAR aligned with craving scores in the TR-Y (but not TR-N) group, with amygdala response to repeated cues positively correlating with craving scores. These results suggest that NHAR may interact with trauma, producing a relapse-vulnerability subgroup and that interventions aimed at addressing NHAR may help prevent craving and subsequent relapse.

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Author disclosures

Role of funding source

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Conflict of Interest

Given her role as Editor-in-Chief, Teresa Franklin, PhD had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Given her role as an Editorial Board Member, Reagan Wetherill, PhD had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Associate Editor, Sherry McKee, PhD.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dadr.2022.100098.

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