The BDNF Val66Met Polymorphism Moderates the Relationship Between Posttraumatic Stress Disorder and Trauma Script-evoked Attentional Bias to Cocaine Cues Among Patients with Cocaine Dependence


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ABSTRACT

There is extensive variability in cocaine-related attentional bias (AB) following trauma script exposure among cocaine-dependent (CD) patients with posttraumatic stress disorder (PTSD). Therefore, research is needed to identify the specific PTSD-CD patients most likely to exhibit an AB to cocaine cues. A common polymorphism in brain-derived neurotrophic factor (BDNF), Val66met, is associated with risk for stimulant addiction, and thus, was examined as a moderator of the association between PTSD and cocaine-related AB following trauma script exposure in this study. Adult CD patients with (n = 17) and without (n = 28) PTSD were exposed to a personalized trauma script, followed by a visual dot-probe task assessing cocaine-related AB. Task response times were used to examine traditionally calculated AB scores, as well as trial level bias scores (TL-BS) that more accurately model the temporal dynamics of AB. PTSD-CD patients homozygous for the BDNF Val/Val genotype exhibited greater bias for attending to cocaine-related stimuli following trauma script exposure than those carrying the Met allele. The PTSD by BDNF interaction did not predict response time variability on trials for which only neutral stimuli were presented, thus increasing confidence that the observed effect is specific to cocaine-related stimuli. PTSD-CD patients homozygous for the BDNF Val/Val genotype may be at particularly high risk for negative clinical outcomes (e.g., relapse, treatment dropout) as a function of prolonged attentional engagement with cocaine cues when exposed to trauma reminders.

1. Introduction

Cocaine dependence (CD) is associated with heightened exposure to traumatic events (2003, Back et al., 2000; Najavits et al., 1998), and both lifetime (e.g., 42.9%; Back et al., 2000) and current (e.g., 20.5%; Najavits et al., 1998) prevalence rates of posttraumatic stress disorder (PTSD) exceed prevalence rates observed in the general population (8.3% lifetime and 4.7% current prevalence; Kilpatrick et al., 2013). Moreover, CD patients with PTSD (compared to those without PTSD and to other PTSD-substance use disorder [SUD] patients) are both more resistant to treatment and more likely to relapse upon completing treatment (Najavits et al., 2007). Additional research aimed at identifying specific factors associated with relapse among CD patients with PTSD may lead to the development of targeted interventions for improving SUD treatment outcomes in this at-risk group of patients.

Cocaine-related attentional bias is one mechanism that warrants consideration, as it has been theoretically and empirically linked to both the development and maintenance of drug use (Fadardi, Ziaee, & Shamloo, 2009), treatment dropout, and relapse (Carpenter, Martinez, Vadhan, Barnes-Holmes, & Nunes, 2012; Gardini, Caffarra, & Venneri, 2009). Moreover, literature on the function of substance use in PTSD suggests that this bias may be greater in CD patients with PTSD, particularly in certain contexts. CD patients with (vs. without) PTSD are more likely to use cocaine in response to negative emotions (Waldrop, Back, Verduin, & Brady, 2007) and report greater cocaine cravings following exposure to trauma-related reminders (Coffey et al., 2002; Tull, Kiel, McDermott, & Gratz, 2013). As such, CD patients with PTSD may be particularly motivated to use cocaine to escape emotional...
distress. As cocaine is increasingly used to escape emotional distress, cocaine-related cues may gain motivational significance due to their ability to predict reward (i.e., emotional relief), leading to the allocation of attention toward such cues in the context of emotional distress (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Robinson & Berridge, 1993). Specifically, in-line with both negative reinforcement (Baker et al., 2004) and incentive-sensitization (Robinson & Berridge, 1993) models of addiction, when CD patients with PTSD experience a particularly salient stressor (i.e., a trauma-related cue), they are more likely to notice and become preoccupied with cocaine-relevant stimuli in their environment. This, in turn, is expected to increase cravings for cocaine and risk for treatment dropout and relapse. In support of this model, Tull, McDermott, Gratz, Coffey, and Lejuez (2011) found greater attentional bias to cocaine-related cues in CD patients with PTSD (but not in trauma survivors without PTSD) only after exposure to a trauma script. These findings support the idea that cocaine-related attentional biases in CD patients with PTSD may be more salient in the context of trauma-related emotional distress.

However, the aforementioned study found considerable variability in attentional bias to cocaine cues following trauma script exposure among CD patients with PTSD (Tull et al., 2011). Thus, consistent with past findings that SUD patients with PTSD use a variety of emotion regulation strategies (Tull, Berghoff, Wheelless, Cohen, & Gratz, 2018), some CD patients with PTSD may have greater attentional control or a reduced desire to seek out cocaine in the context of trauma-related emotional distress. Given this variability, research is needed to identify the specific PTSD-CD patients most likely to evidence an attentional bias to cocaine cues and related risk for relapse. In particular, specific gene polymorphisms found among some patients with PTSD-CD may help identify those who are especially likely to exhibit cocaine-related attentional bias.

The brain-derived neurotrophic factor (BDNF) protein is a neurotrophin that is important for neural development and synaptic plasticity (Andreo & Ressler, 2005). BDNF has been identified as regulator of several types of neurons, including sensory neurons, retinal ganglion cells, and dopaminergic neurons (Allen, Watson, Shoemark, Barus, & Patel, 2013). A BDNF polymorphism (G196A; rs66265) has received considerable attention in the scientific literature for its potential role in a wide variety of psychological, neurodevelopmental, and neurodegenerative disorders (for a review, see Kim et al., 2011). This polymorphism results in a valine (Val) to methionine (Met) substitution at amino acid 66, which affects intracellular trafficking of BDNF. Of particular relevance to the present study, these allelic variants (i.e., Val/Val, Val/Met, and Met/Met) are associated with the modulation of dopaminergic functions related to substance use (Chen et al., 2004). Specifically, Val homozygous individuals (Val/Val vs. Met carriers) (a) appear to be at risk for synaptic modification after prolonged withdrawal periods that is indicative of enhanced responsiveness to cocaine (Grimm et al., 2003), and (b) exhibit enhanced cocaine seeking behaviors for prolonged periods following cessation of cocaine use (Lu, Dempsey, Liu, Bossert, & Shaham, 2004). As such, CD patients with PTSD carrying the Val/Val genotype may be especially vulnerable to the rewarding effects of cocaine, thereby increasing the allocation of attention toward cocaine cues, especially in the context of emotional distress.

The purpose of the present study was to examine the BDNF Val66Met polymorphism as a moderator of the relation between PTSD and cocaine-related attentional bias following trauma script exposure. We predicted that among CD patients with PTSD, Val homozygotes would exhibit greater cocaine-related attentional bias following trauma script exposure compared to Met carriers. Study findings may aid in the identification of a subset of PTSD-CD patients most at-risk for relapse.

The dot-probe task (described below), a commonly used measure of attentional bias, was used in the present study to assess cocaine-related attentional bias. This, in turn, is expected to increase cravings for cocaine and risk for treatment dropout and relapse. In support of this model, Tull, McDermott, Gratz, Coffey, and Lejuez (2011) found greater attentional bias to cocaine-related cues in CD patients with PTSD only after exposure to a trauma script. These findings support the idea that cocaine-related attentional biases in CD patients with PTSD may be more salient in the context of trauma-related emotional distress.

2. Method and Materials

2.1. Participants

Cocaine-dependent adults were recruited from a residential SUD treatment center located in the Southern United States. Eligible participants had to (a) have experienced a Criterion A traumatic event (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5]; American Psychiatric Association, 2013), (b) speak English, and (c) have no current psychosis or cognitive impairment (scores ≥ 24 on the Mini-Mental Status Examination [Folstein, Folstein, & McHugh, 1975]). Data were excluded from participants (a) who did not complete the second study session (n = 6), (b) for whom BDNF Val66Met genotype status was not determined due to sampling errors (n = 2), and (c) who exhibited inattentive or random responding to one or both of the dot-probe tasks (i.e., < 75% accuracy for any one cell; Ratcliff, 1993 [n = 10]). The final sample (N = 45; 19 women [42%]), had an average age of 32.1 years (SD = 9.9, range = 18 to 57). The majority of participants self-identified as Black/African-American (87%) and reported an annual income of less than $30,000 (59%).

2.2. Interview and Self-report Measures

2.2.1. Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND)

Current PTSD was assessed using the Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND; Tolin et al., 2018). The DIAMOND is a structured clinical interview that was designed to assess current and lifetime DSM-5 psychiatric disorders. The DIAMOND demonstrates good test-retest reliability (one-week retest), interrater reliability (κ = .62 to 1.00 depending on diagnostic category), and convergent and discriminant validity (Tolin et al., 2018). The DIAMOND was administered by bachelors- to PhD-level clinical assessors trained to reliability by the principal investigator (MTT). In the case of ambiguous responses, data were reviewed and discussed by the principal investigator and interviewer until a consensus was reached. The DIAMOND was used in the present study to assign participants to groups (No PTSD or PTSD).

2.2.2. Positive and Negative Affect Schedule

The Negative Affect (NA) subscale of the PANAS (Watson, Clark, & Tellegen, 1988) was used to assess NA reactivity to presentation of the trauma script. Participants rate the extent to which they are currently experiencing 10 forms of NA on a scale from 1 (very slightly or not at all) to 5 (extremely). The PANAS-NA subscale has exhibited adequate psychometric properties, including excellent internal consistency (Watson et al., 1988), criterion-related validity with measures of anxiety and depression, and measurement invariance across demographic
subgroups (i.e., age, gender; Crawford & Henry, 2004). The measure was administered before and after presentation of the idiographic trauma script. Internal consistency for the PANAS-NA scale was adequate at both pre- ($\alpha = .91$) and post-script ($\alpha = .95$).

### 2.3. Genotyping

DNA was isolated from saliva samples using the Invitrogen™ PureLink™ Genomic DNA Mini Kit. On average, each sample resulted in 3.5 $\mu$g of total DNA. All samples were normalized to 50 ng/$\mu$l to perform an initial quality control evaluation of DNA based on PCR amplification of the human $\beta$-actin gene. All samples generated a single band as visualized on 2% agarose gel stained with ethidium bromide. Subsequently, Taqman genotyping was performed using pre-designed Taqman SNP Genotyping Assay for BDNF Val66Met (rs6265, Cat.# 4351379). The assay is based on two allele-specific fluorescent probes (VIC = Allele 1 and FAM = Allele 2) that are amplified and detected using a Real-Time PCR system. Samples were prepared using iTaq™ Universal Probes Supermix and run with a Bio-Rad CFX96 Real-Time PCR instrument. Allele calls were made using Bio-Rad CFX Manager Software.

### 2.4. Trauma Scripts

As part of the DIAMOND, participants were tape recorded while answering questions regarding their most traumatic life event. During this interview, participants were instructed to use multiple sensory dimensions (e.g., thoughts, emotions, physical sensations, visual details) to describe their worst traumatic event. Research personnel used these recordings to create a personalized script using the participant’s own language. This method for generating personalized trauma scripts was developed by Lang and colleagues (see Lang & Cuthbert, 1984; Levin, Cook, & Lang, 1982) and has been used in previous studies of SUD patients with PTSD (e.g., Tull et al., 2011, 2018). This procedure has been found to reliably induce emotional responses across a range of populations (Lang et al., 1983; Orr et al., 1993; Pitman et al., 1987), and, of particular relevance to the present study, has been used to reliably elicit PTSD-related emotional responses in patients with PTSD and SUDs (Coffey et al., 2002; Saladin et al., 2003). Trauma scripts were approximately one minute in length, and the narrator was the same across all scripts.

### 2.5. Dot-Probe Task

The dot-probe task was presented on a laptop computer using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Stimuli consisted of 20 cocaine-related images (e.g., crack pipes) and 40 furniture images (Tull et al., 2013). At the start of each trial, a fixation cross appeared in the center of the screen for 500 ms, followed by a blank screen for 250 ms. Next, participants were shown two images side by side on the screen for 500 ms followed by a single dot in the location of one of the images. Participants were instructed to press an arrow key (left or right) on the computer keyboard to identify the position of the dot for each trial. The task consisted of 5 practice trials and 240 experimental trials. Of the experimental trials, 80 consisted of neutral-neutral image pairings, 80 consisted of cocaine-neutral pairings, and 80 consisted of cocaine-cocaine pairings. The 80 cocaine-neutral image pairs consisted of 40 congruent trials (CTs: the probe replaced the cocaine image) and 40 incongruent trials (ITs: the probe replaced the neutral image). The neutral-neutral and cocaine-cocaine image pairs served to increase task engagement and reduce expectations about image content for each trial. Neutral-neutral trials were used to create “Fake” TL-BS parameters (Zvielli et al., 2015). The order of stimulus presentation was randomized across participants.

### 2.6. Procedure

All study procedures received institutional review board approval. To limit the impact of cocaine withdrawal on study findings, participants were recruited no sooner than 72 hours after the time of admission. All participants took part in the study within their first two weeks of treatment (i.e., between days 3 and 14 of treatment). At the first session, participants provided informed consent, provided a saliva sample, and completed the DIAMOND. Before leaving the session, participants received $25 compensation and scheduled the second session, which took place approximately two days later.

A research assistant masked to patients’ PTSD status conducted the second session. At the second session, participants reported their level of craving (substance craving on a 0 to 10 scale) and completed the dot-probe task as a baseline measure of cocaine-related attentional bias. Afterwards, participants rated their NA, listened to the 1-minute tape-recorded trauma script, and then rated their NA again. They then completed the second dot-probe task. Participants were debriefed and provided with $10 compensation for completing the second session.

### 3. Results

#### 3.1. Preparation of Stimulus-Response Data

Consistent with Zvielli et al. (2015), trials with error responses, trials indicating anticipatory responding (response times [RTs] < than 200 ms), and outlier trials (RTs > 1,500 ms or > 3 SDs above a participant’s mean) were discarded (i.e., 3.58% of pre-script and 3.61% of post-script responses). A traditional total attentional bias score (i.e., static AB) was calculated by subtracting mean latencies on CTs from mean latencies on ITs (IT – CT) in neutral-cocaine pairings (Frewen, Dozois, Joanisse, & Neufeld, 2008). To calculate TL-BS, RTs of CTs were subtracted from temporally contiguous (matched within 5 trials) ITs (Zvielli et al., 2015). Specifically, each CT is matched with an IT that is as close in time as possible, and a difference score is created. For example, if trial #2 was a IT and trial #4 was a CT, the RT of trial #4 would be subtracted from the RT of trial #2 for that pairing. Mean TL-BS was calculated by summing all of the resultant absolute values for the temporally contiguous difference scores, and dividing this sum by the total number of scores. Consistent with Zvielli et al. (2015), we also calculated TL-BS Positive (i.e., individual differences in Mean TL-BS > 0 ms) and TL-BS Negative (i.e., individual differences in Mean TL-BS < 0 ms), which represent attention toward and away from cocaine stimuli, respectively. Additionally, we calculated a “Fake” TL-BS using only neutral-neutral trials, to ensure that any observed effects were due to the presence of cocaine stimuli rather than being a by-product of individual differences in responding (Zvielli et al., 2015).

#### 3.2. Preliminary Analyses

Considerable variation has been observed in BDNF Val66Met genotype status across populations, with Met allelic frequency often observed to be high in Asian populations, low to moderate in European (White) populations, and low in Central and South American, and African populations (Gonzalez-Castro et al., 2017; Pivac et al., 2009; Tsai, 2018). As such, with the majority of participants self-identifying as Black/African-American (87%), it was not surprising that Val/Val carriers were well represented in our sample (n = 31; see Table 1).^{1}

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^{1} Evidence suggests racial and ethnic differences in the frequency of the BDNF Val66Met polymorphism (Gonzalez-Castro et al., 2017; Pivac et al., 2009; Tsai, 2018), as well as potential differences in BDNF function based on sex and age. As such, we repeated our primary analysis including race, age, and sex as covariates in each regression model. Results were consistent with our initial analysis; statistically significant findings remained significant and
Table 1
Personalized Trauma Script Content by PTSD Status.

<table>
<thead>
<tr>
<th>Category</th>
<th>No PTSD (n = 28)</th>
<th>PTSD (n = 17 [n = 9 Val/Val])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accident</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Assault (physical or</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>weapon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual Assault</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Death/Injury to Other</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Natural Disaster</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Note. PTSD = posttraumatic stress disorder

Frequency counts for personalized trauma script content categories are provided in Table 1. Consistent with Tull et al. (2011), the results of a series of independent sample t-tests revealed that there were no statistically significant differences in our five attentional bias indices, prior to trauma script exposure, between those with (vs. without) PTSD, all ps > .05. Results of a dependent t-test showed that all participants reported a significant increase in NA from pre- (M = 15.07, SD = 6.52) to post-trauma script (M = 22.62, SD = 11.95), t(44) = −6.12, p < .001. As expected, participants with PTSD reported a significantly larger increase in NA from pre- to post-script (non-PTSD: M = 3.68 [SD = 5.89]; PTSD: M = 13.94 [SD = 7.77]), t(43) = −5.02, p < .001. Thus, pre- to post-script change in NA served as a covariate in our primary analysis (in addition to pre-script attentional bias). Additionally, self-reported substance use craving at the laboratory session was included in primary analyses as a covariate to ensure that differential levels of craving did not influence results.

3.3. Primary Analyses

The BDNF Val66Met genotype was dichotomized (1 = those with either the Val/Met or Met/Met genotypes [i.e., Met carriers]; 2 = those homozygous for the Val/Val genotype; see Felmingham et al., 2018; Park et al., 2017; Shen et al., 2018, for precedent in using this grouping approach) and served as the moderator variable in a series of regression models. Control variables (i.e., change in NA, pre-script attentional bias, craving) and the predictor (i.e., PTSD status) and moderator (i.e., BDNF) variables were mean centered and entered into the first step of each model (Aiken & West, 1991). The interaction term was calculated as the product of the moderator and predictor variables and entered into the second step of each model. Five attentional bias indices served as outcome variables in separate models (i.e., TL-BS Variability, TL-BS Positive, TL-BS Negative, Fake TL-BS, Static AB). Simple slopes analysis was used to examine significant interaction effects (Aiken & West, 1991).

As can be seen in Table 2, BDNF moderated the relation between PTSD status and TL-BS Variability (p < .001), TL-BS Positive (p < .01), and Static AB (p < .01), but did not moderate the relation between PTSD status and TL-BS Negative (p = .23) and Fake TL-BS (p = .41). Simple slopes analysis revealed a positive association between PTSD status and TL-BS Variability for those with BDNF Val/Val (β = .47, p = .002), but not for BDNF Met carriers (β = .17, p = .21; see Fig. 1). A similar pattern of effects was observed for the second significant interaction effect; a positive association was revealed between PTSD status and TL-BS Positive for those with BDNF Val/Val (β = .51, p = .004), but not for BDNF Met carriers (β = −.11, p = .49). Finally, simple slopes analysis revealed a positive association between PTSD status and static AB that trended toward significance for those with BDNF Val/Val (β = .34, p = .09), but not for BDNF Met carriers (β = −.29, p = .13).

(footnote continued)

nonsignificant findings were unchanged.

4. Discussion

This is the first study to examine the BDNF Val66Met polymorphism (i.e., Val/Val vs. Met carriers at locus 66) as a moderator of the relation between PTSD and cocaine-related attentional bias following trauma script exposure. As predicted, among CD patients with PTSD, those homozygous for the Val/Val genotype exhibited greater cocaine-related attentional bias following trauma script exposure than Met carriers. Specifically, greater temporal variability of cocaine-related attentional bias (i.e., TL-BS Variability) discriminated between PTSD-Val homozygotes versus PTSD-Met carriers. Importantly, TL-BS Positive, but not TL-BS Negative accounted for this effect, suggesting that the cocaine-related attentional bias that differentiates PTSD participants with the Val/Val genotype versus Met carriers is a bias toward, rather than away, from cocaine cues. Also of note, the interaction effect of interest did not predict the Fake TL-BS parameters (Zvielli et al., 2015), for which only neutral stimuli were presented. This finding increases confidence that the greater temporal variability in responding observed by those with PTSD and the Val/Val genotype is specific to cocaine stimuli and not merely the result of general variability in response times.

Although the interaction between PTSD and BDNF significantly predicted the traditionally calculated attentional bias score, neither of the simple slopes was significantly different from zero at p < .05 (i.e., a horizontal plane). The pattern of effects, however, is consistent with those in Fig. 1. These medium-sized simple effects may have reached statistical significance at p < .05 had the sample size been slightly larger. In any case, this finding is not surprising given the noted problems with calculating attentional bias as a static signal (e.g., poor reliability, difficulty replicating findings, small-medium effects). These findings highlight the importance of assessing attentional bias using a method that accounts for the temporal dynamics of this phenomenon. Potentially meaningful results may be obscured by failing to do so.

Taken together, results of this study suggest that among CD patients with PTSD, those with the Val/Val genotype are more likely to attend to cocaine-relevant stimuli in response to trauma reminders. This may be because Val homozygotes are more likely to exhibit synaptic modifications in the mesolimbic system that enhance dopaminergic neurotransmission induced by cocaine use (Tsai, 2007), thereby increasing the rewarding value of cocaine use. Consequently, for these individuals, cocaine-related cues may gain greater motivational significance due to their increased ability to predict reward. This, in turn, may increase the likelihood of attending toward cocaine cues in the context of trauma-related distress (Baker et al., 2004), ultimately increasing risk for relapse and/or treatment dropout. Additionally, for the broader population of individuals with CD (including those who are not in treatment), the Val/Val genotype may increase the likelihood of drug use maintenance and exacerbation.

Our study design precludes conclusions regarding the function of substance use in CD patients with PTSD who are Met carriers. Future research examining the effect of BDNF and PTSD on cocaine-related attentional bias in other contexts (e.g., positive emotion inductions, general life stress) may help clarify this issue. Such research would also aid in determining if our current findings are specific to trauma-related emotional distress or emotional distress in general. Although individuals with PTSD exhibit greater reactivity to personalized and standardized trauma-related cues in comparison to general negative emotion cues (Blanchard et al., 1996; Ehlers et al., 2010), it would be beneficial to examine cocaine-related attentional bias among CD patients with PTSD in the context of trauma-specific, general negative emotion, and neutral cues in future research.

Study limitations must be acknowledged. First, results from the present study cannot be used to determine whether cocaine-related attentional bias following trauma script exposure leads to relevant clinical outcomes because such outcomes were not assessed. Longitudinal study designs are needed to determine whether cocaine-
related attentional bias among CD patients with PTSD and the Val/Val genotype predict later treatment relapse, dropout, or other negative substance use outcomes. Second, the sample was comprised of CD patients in a residential SUD treatment facility, the majority of whom self-identified as African-American. Thus, study findings may not generalize to individuals in the general population or those from other racial/ethnic backgrounds who use cocaine. Likewise, although all participants were in the early phases of SUD treatment, differences in responses to this early stage of treatment could have influenced findings. Future research should attempt to replicate findings among community or outpatient samples of individuals with CD. In addition, we cannot generalize our findings to substance use more broadly due to our exclusive use of cocaine-related stimuli. It will be important to include other types of drug- and alcohol-related stimuli in future research to determine if the observed effects are consistent across substances and SUDs. Moreover, it may be important to include positively-valenced images with high arousal ratings that are not drug- or alcohol-related in future studies to ensure that the observed biases are substance-specific. Regarding the moderator, although it is standard practice to combine Met/Val and Met/Met genotypes into one group (Felmingham et al., 2018; Park et al., 2017), it may be of value to examine the relation between PTSD and trauma script-evoked cocaine-related attentional bias in each of the three genotypes (Val/Val, Val/Met, and Met/Met) in future research. Given that the Met/Met genotype is relatively rare, we did not have adequate representation of this genotype in our modestly-sized sample, thus preventing us from conducting these analyses (Shen et al., 2018). Future studies would require a significantly larger sample size to conduct this analysis, as well as provide validation of current findings. Thus, replication of these results within a larger sample size is recommended.

There is a critical clinical need to identify CD patients who are most at-risk for relapse, as well as to determine factors that may contribute to

Table 2

<table>
<thead>
<tr>
<th>Predictor</th>
<th>TL-BS Variability</th>
<th>TL-BS Positive</th>
<th>TL-BS Negative</th>
<th>Fake TL-BS</th>
<th>Static AB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔR²</td>
<td>Step 2 β</td>
<td>ΔR²</td>
<td>Step 2 β</td>
<td>ΔR²</td>
</tr>
<tr>
<td>Step 1</td>
<td>.66***</td>
<td>.58***</td>
<td>.39***</td>
<td>.56***</td>
<td>.42***</td>
</tr>
<tr>
<td>Initial Craving</td>
<td>.05</td>
<td>.15</td>
<td>.05</td>
<td>.11</td>
<td>.16</td>
</tr>
<tr>
<td>NA Change</td>
<td>-.01</td>
<td>-.09</td>
<td>-.30</td>
<td>-.17</td>
<td>.38*</td>
</tr>
<tr>
<td>T1 Bias</td>
<td>.85***</td>
<td>.81***</td>
<td>.53***</td>
<td>.64***</td>
<td>.59***</td>
</tr>
<tr>
<td>PTSD</td>
<td>.15</td>
<td>.20</td>
<td>.06</td>
<td>.04</td>
<td>.04</td>
</tr>
<tr>
<td>BDNF</td>
<td>-.09</td>
<td>-.13</td>
<td>-.04</td>
<td>-.04</td>
<td>.21</td>
</tr>
<tr>
<td>Step 2</td>
<td>.09***</td>
<td>.09**</td>
<td>.02</td>
<td>.01</td>
<td>.09**</td>
</tr>
<tr>
<td>PTSD x BDNF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. N = 45. TL-BS = trial-level bias score; Positive = TL-BS toward cocaine stimuli; Negative = TL-BS away from cocaine stimuli; Fake TL-BS = TL-BS generated from neutral trial pairs (used to ensure observed effects are not simply a function of differences in variability of responding); Static AB = traditional calculation of attentional bias; Initial Craving = self-reported substance craving on a 0 to 10 scale; NA change = change in negative affect from pre- to post-script presentation; T1 Bias = attentional bias indice from the first dot-probe administration that corresponds to the outcome variable in each model (control variable); PTSD = post-traumatic stress disorder; BDNF = brain-derived neurotrophic factor Val66Met genotype; PTSD x BDNF = interaction of interest.

*p < .05. **p < .01. ***p < .001.
this heightened risk. Results from the present study suggest that it may be important to assess for homozygosity of the Val allele at codon 66, especially among patients with PTSD, when attempting to identify CD patients who are at greatest risk for cocaine-related negative clinical outcomes. However, before this determination can be made, it will be important to examine whether cocaine-related attentional bias mediates the relationship of the PTSD-BDNF interaction to negative clinical outcomes in future research. Findings in support of this mediated moderation model would support the importance of assessing for the Val/Val genotype among CD patients with PTSD in order to alert clinicians to their heightened risk for negative clinical outcomes and suggest the need for a more personalized treatment approach. Such an approach could include training patients to flexibly disengage and shift attention from cocaine-related stimuli (e.g., attention retraining), thus reducing cocaine-related attentional dyscontrol and associated behaviors.

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