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Blunted Reward Sensitivity and Trait Disinhibition Interact to Predict Substance Use Problems

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Abstract

Reward deficit models of addiction posit weaknesses in reward sensitivity to be promotive of substance dependence, while the externalizing spectrum model views substance problems as arising in large part from a general disinhibitory liability. The current study sought to integrate these perspectives by testing for separate and interactive associations of disinhibition and reward dysfunction with interview-assessed substance use disorders (SUDs). Community and college adults (N = 199) completed a scale measure of trait disinhibition and performed a gambling-feedback task yielding a neural index of reward sensitivity, the 'Reward Positivity' (RewP). Disinhibition and blunted RewP independently predicted SUDs, and also operated *synergistically,* such that participants – in particular, men – with high levels of disinhibition together with blunted RewP exhibited especially severe substance problems. Though limited by its cross-sectional design, this work provides new information about the interplay of disinhibition, reward processing, and gender in SUDs and suggests important directions for future research.

Keywords

Drug/Substance Problems; Rewards; Psychophysiology

Substance use disorders (SUDs) are prevalent in the United States and pose an enormous financial burden to society (e.g., over $200 billion in healthcare costs each year for alcohol use disorder [AUD] alone; Rehm et al., 2009). Because of this, substance-related problems have received a great deal of empirical attention. SUDs have been found to co-occur with

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Author Contributions

K.J.J. and C.B.B. developed the study concept, and performed the primary psychophysiological data processing under the supervision of J.R.Y. C.B.B. and J.R.Y. performed data collection under the supervision of N.C.V., J.F., and C.J.P. K.J.J. was primarily responsible for the data analysis, as well as initial drafting of the paper. Each author then contributed substantial revisions to the paper at various stages and in various capacities. G.H. provided particular expertise in reward sensitivity and psychophysiology, N.C.V. and J.F. provided expertise on the topic of disinhibition, and D.A.W. and B.D.B. provided specific expertise in substance abuse, all contributing critical revisions to the framing of the paper. C.J.P. served as the senior author on the paper, overseeing all aspects of the work from all authors and significantly influencing K.J.J.'s conception, data analysis, and writing of the paper.

other externalizing disorders involving weak impulse control and poor affect regulation (e.g., child conduct disorder, attention deficit disorder, adult antisocial personality; Krueger, Markon, Patrick, Benning, & Kramer, 2007; Young, Stallings, Corley, Krauter, & Hewitt, 2000), and evidence points to a common dispositional factor accounting for this comorbidity (Krueger, 1999; Krueger et al., 2002). Termed “disinhibition” in the general psychopathology literature (Gorenstein & Newman, 1980; Patrick et al., 2013b; Sher & Trull, 1994), or “common addiction liability” in the SUD literature (Hicks, Iacono, & McGue, 2012; Vanyukov et al., 2012), this dispositional factor is strongly heritable (Krueger et al., 2002; Young et al., 2000) and appears related to dysfunction in frontal-control (‘executive’) systems of the brain (Venables et al., 2018; Young et al., 2009).

Although disinhibition is strongly correlated with SUDs, it relates in similar strong ways to other externalizing conditions (e.g., conduct disorder and adult antisocial personality; Krueger et al., 2002; Yancey, Venables, Hicks, & Patrick, 2013), as would be expected of a general liability factor. This raises the intriguing question of whether other dispositional factors might combine with disinhibition to shape its expression toward problematic use of substances (Patrick, Venables, Foell, & Worthy, 2016). Relevant to this, considerable evidence exists for reward-related mechanisms in SUDs (Baler & Volkow, 2006; Karoly, Harlaar, & Hutchinson, 2013). One theoretical view holds that *hyper*sensitivity to naturally-occurring rewards promotes drug-taking by enhancing gratification-seeking behaviors generally (Bijttebier, Beck, Claes, & Vandereycken, 2009; van Hemel-Ruiter, de Jong, Ostafin, & Wiers, 2015). By contrast, another perspective is that *impairments* in sensitivity to natural reward that predate substance exposure contribute to the development of drug sensitization at points of use, and in turn, to substance dependence (e.g., Blum et al., 2000; Blum, Oscar-Berman, Demetrovics, Barh, & Gold, 2014). Using novel assessment methods to quantify trait disinhibition and reward sensitivity, the current study evaluated whether these two dispositional factors relate separately, and possibly in an interactive manner, to SUD symptomatology.

Trait Disinhibition

There is appreciable comorbidity among different disorders involving weak impulse control, including child disruptive disorders, adult antisocial personality, alcohol abuse/dependence, and other substance use disorders (Krueger, 1999; Sher & Trull, 1994). Evidence indicates that disorders of these types share a common heritable basis that accounts for their high overlap and mutual relations with disinhibitory traits (Krueger et al., 2002). This common trait-liability factor, termed ‘disinhibition’ (Krueger et al., 2007; Patrick et al., 2013; Young et al., 2009), shows distinct neural correlates – the best-established being reduced amplitude of P3 brain response to salient stimuli in visual processing tasks (Brislin et al., in press; Nelson, Patrick, & Bernat, 2011; Patrick et al., 2006). In addition, trait disinhibition has correlates in the task-behavioral domain – relating in particular to the common performance component of cognitive control tasks (e.g., Stroop, stop-signal, anti-saccade) that has been shown to index executive functioning (Miyake & Friedman, 2012; Young et al., 2009). Of note, relations of these neural and behavioral variables with trait disinhibition largely reflect shared genetic influence (Yancey et al., 2013; Young et al., 2009). The implication is that the general factor that underlies impulse disorders reflects a coherent neurobehavioral trait

dimension. Further consistent with the idea of trait disinhibition as a liability factor, scores on this dispositional factor prospectively predict externalizing disorder outcomes, including substance problems (Iacono, Malone, & McGue, 2008; Tarter, Kirisci, Habeych, Reynolds, & Vanykov, 2004).

Importantly for purposes of the current work, trait disinhibition can be measured effectively through self-report – using a brief scale measure of externalizing proneness composed of items from the Externalizing Spectrum Inventory (ESI; Patrick, Kramer, Krueger, & Markon, 2013a), a questionnaire instrument developed to assess disinhibitory problems and traits. Scores on this ESI Disinhibition (ESI-DIS) scale correlate substantially (>.6) with externalizing psychopathology symptoms as assessed by interview (Patrick et al., 2013b), largely as a function of genetic variance in common between the two (Yancey et al., 2013). Additionally, ESI-DIS scores correlate reliably with brain-response and task-performance indicators of externalizing psychopathology (Patrick et al., 2013b; Venables et al., 2018), also largely as a function of shared genetic variance (Yancey et al., 2013; Young et al., 2009). These consistent, converging lines of evidence indicate that ESI-DIS can be used to index the broad neurobehavioral propensity toward externalizing problems.

Reward Sensitivity and SUDs

A critical unanswered question is what other factors shape general disinhibitory liability in the direction of substance use problems, as opposed to other clinical outcomes (e.g., antisocial conduct, attentional problems). Converging lines of evidence indicate that dysfunction in reward circuitry of the brain is distinctively involved in SUDs (see, e.g., Baskin-Sommers & Foti, 2015; Patrick et al., 2016). However, there are differing perspectives on the nature of the relationship between reward dysfunction and substance problems. One is that individual differences in sensitivity of the brain's reward system confer *liability* to SUDs. As noted earlier, there are two opposing variants of this perspective. One is that *over*sensitivity to rewards results in enhanced gratification-seeking including heightened proclivities toward use of substances (Urošević et al., 2014). Support for this position is provided by work showing that reward *hyper*sensitivity contributes to initial substance involvement (e.g., van Hemel-Ruiter et al., 2015). However, a complicating factor in this literature is that reward sensitivity has frequently been operationalized in a manner that overlaps with disinhibitory liability – through use of scale measures of behavioral approach/activation (e.g., Alloy et al., 2009; Norbury & Husain, 2015) that include items related to excitement- or sensation-seeking tendencies – known to operate as indicators of trait disinhibition (Cloninger, 1987; Krueger et al., 2007; Sher & Trull, 1994). This raises the possibility that observed overresponsiveness to rewards in these studies could be a reflection of disinhibitory propensity.

An opposing perspective, however, is that *hypo*sensitivity to natural rewards leads to increased drug seeking, in order to compensate for a lowered hedonic equilibrium. This view, known as the reward deficiency hypothesis (Blum, Cull, Braverman, & Comings, 1996; Bowirrat & Oscar-Berman, 2005), posits that reduced reward sensitivity leads to increased drug seeking behavior and additionally to a higher relative-reinforcing value of the hedonic effects of drug consumption (i.e., relative to the lowered 'resting' hedonic state) –

leading to escalating dependence on drug consumption. Along similar lines, behavioral economic theories conceive of addiction as a 'reward pathology' entailing a lack of engagement with and enjoyment of natural rewards in comparison to pharmacologic rewards (Bickel, Jarmolowicz, Mueller, & Gatchalian, 2011; Bickel, Johnson, Koffanus, MacKillop, & Murphy, 2014; Joyner, Acuff, Meshesha, Patrick, & Murphy, 2018). Considerable experimental evidence supports this reward hyposensitivity perspective. For example, neuroimaging work by Andrews and colleagues (2011) has shown blunted nucleus accumbens activation during a reward task in the children of alcoholics. Other work, utilizing event-related brain potentials (ERPs), has demonstrated blunted cortical reactivity to visual depictions of naturally-rewarding stimuli (e.g., erotic, food, action IAPS pictures) in heavy substance users compared to healthy subjects (Lubman et al., 2009). Research employing EEG/ERP methodology has also reported evidence for reduced reward-related processes in individuals with addictions to specific substances, including alcohol (Kamarajan et al., 2012) and cocaine (Parvaz et al., 2015).

Yet another notable perspective on the role of reward sensitivity in substance use problems is that diminished sensitivity to rewards – in particular, naturally occurring (non-substance) rewards – is an emergent *consequence* of continued excessive substance use. This perspective, termed the allostatic model of addiction, is supported by extensive research evidence (e.g., Koob & LeMoal, 2001; 2008; Koob & Volkow, 2010). It posits that the brain's reward system undergoes a reduction in its capacity to respond to naturally-occurring rewards as an individual progresses from initial to more severe substance dependence. This occurs because of the brain's neuroadaptation to the recurring physiological effects of the substance on the reward system; upon cessation of use, the addicted individual becomes susceptible to relapse because the reward system remains overresponsive to substance-related cues and hyporesponsive to naturalistic reward cues.

These contrasting theoretical perspectives highlight the need for further research on the relationship between disinhibitory propensity and reward sensitivity and how these characteristics relate to substance problems. As noted in the preceding section, the ESI-DIS scale provides an efficient and effective measure of disinhibitory tendencies corresponding to general externalizing liability. We next consider a brain measure that has proven effective for indexing sensitivity to naturally-occurring (i.e., non-substance) rewards: the Reward Positivity.

The Reward Positivity

The Reward Positivity (RewP; Hajcak Proudfit, 2015) is an ERP component that shows particular promise for indexing sensitivity to rewarding outcomes. The RewP is evident as a relative positivity in the ERP waveform that peaks approximately 300 ms following feedback denoting gain as compared to loss outcomes. This difference has been shown to correlate positively with self-reported reward sensitivity, and with behavioral preference for previously rewarded options (Bress & Hajcak, 2013). Other work (Cherniawsky & Holroyd, 2013) has shown the magnitude of RewP response to be dependent on the immediacy of reward, with the level of response enhanced for immediate compared to future rewards. Additionally, there is considerable evidence for blunted RewP response in depressed

individuals (Hajcak Proudfit, 2015), including work demonstrating that low-magnitude RewP in adolescent girls prospectively predicts the later onset of major depressive episodes (Bress, Smith, Foti, Klein, & Hajcak, 2012; Nelson, Perlman, Klein, Kotov, & Hacjak, 2016).

These lines of evidence indicate that the magnitude of RewP response indexes sensitivity to rewarding outcomes (Hajcak Proudfit, 2015). Consistent with this view, research using functional magnetic resonance imaging (fMRI) combined with ERP recording has shown a robust association between magnitude of RewP response and functional activation in reward-related brain regions (i.e., the ventral striatum and medial prefrontal cortex; Becker, Nitsch, Miltner, & Straube, 2014; Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). Given evidence for the striatum as a locus of dysfunction in reward processing associated with addiction (Volkow, Wang, Fowler, Fomasi, & Telang, 2011), the RewP holds promise as an index of reward sensitivity in studies of substance problems.

Current Study

The current study was undertaken to provide new insight into the critical question of how trait disinhibition and reward sensitivity relate, individually and jointly, to substance use problems. A major innovation of our study is that we operationalized these two dispositional constructs in distinct neurobehavioral terms (Patrick et al., 2013b). Specifically, we quantified trait disinhibition using a scale measure (i.e., ESI-DIS) that relates reliably to brain and task-behavioral indicators of this hypothesized liability factor (Venables et al., 2018; Yancey et al., 2013; Young et al., 2009), and we assessed reward sensitivity using a neural measure (i.e., RewP) that has strong validity for indexing hedonic response capacity (Hajcak Proudfit, 2015). In undertaking this initial examination of how these two dispositional factors relate to substance use problems, we utilized a non-treatment-seeking sample – consisting mainly of young adults – exhibiting substance problems of a less severe nature (i.e., regular use to moderate symptoms of dependency). To enhance generalizability, we recruited both from a university population and from the surrounding urban community. Our aim was to gather initial empirical data pertaining to the role of disinhibition and reward sensitivity in problematic substance use, at levels below severe dependence.

Our specific study hypotheses were as follows:

(1) Trait disinhibition: Based on abundant existing evidence, including prior work using the ESI-DIS scale (Patrick et al., 2013a; Yancey et al., 2013), we predicted that disinhibitory propensity as indexed by this scale would show a robust positive association with substance use problems as assessed by clinical interview.

(2) Reward sensitivity: We hypothesized that neural sensitivity to reward, operationalized as RewP (i.e., augmented cortical reactivity to gain versus loss outcomes in a choice-feedback task), would also show a significant association with substance problems. However, in this case, the existing literature supports viable alternative hypotheses regarding the directionality of this relationship. On one hand, based on the idea that reward hypersensitivity promotes use of substances as a manifestation of high gratification-seeking (van Hemel-Ruiter et al., 2015; Urošević et al., 2014), a positive association could be

expected. If this were the outcome, a further question would be whether this positive association reflects the overlap between reward sensitivity and reward-related aspects of trait disinhibition (e.g., excitement- or sensation-seeking); this could be clarified by evaluating whether scores on ESI-DIS and RewP reflect unique or overlapping variance in SUDs.

By contrast, based on the reward deficiency hypothesis (Blum et al., 1996), which posits that *hypo*sensitivity to natural reward enhances attraction to drugs and pleasure derived from their use, a negative relationship between RewP response and substance problems would instead be predicted – and this was our favored hypothesis. Indeed, the allostatic model of addiction would predict a negative association between the two as well – though our hypothesis was predicated mainly on the reward deficiency perspective, given the non-clinical nature of our study sample and the moderate rather than severe levels of substance problems within this sample. It is also possible that these hypotheses are not mutually exclusive – i.e., that the relationship between reward sensitivity and SUDs may be non-linear, such that both extreme hypo- or hyper-sensitivity are associated with greater severity of SUDs.

(3) Interaction between trait disinhibition and reward sensitivity: Additionally, we evaluated the possibility that aberrant reward sensitivity (as indexed by RewP) would interact with disinhibitory liability (as indexed by ESI-DIS) to predict substance use problems. This hypothesis was based on prior work theorizing that the presence of reward system dysfunction in conjunction with high disinhibitory liability results in maximal proneness to substance problems (Patrick et al., 2016; see also Karoly et al., 2013). In addition, we examined gender as a further moderator of the disinhibition and reward sensitivity interaction. [1]

Method

Participants—Participants were 201 community (36%) and undergraduate student (64%) adults (n = 100 [50.3%] females) between the ages of 18 and 47 (M = 20.9 years, SD = 4.3). Two participants declined to report their gender, leaving a sample of N = 199 for study analyses. This sample size yields > 80% power to detect correlations at or above .2, the level of association that has been found for RewP magnitude with other psychopathological outcomes in prior work (i.e. Foti & Hajcak, 2009; Bress & Hajcak, 2013). Participants were recruited through advertisements on campus and online, and completed an online questionnaire protocol prior to lab testing. Representation of high disinhibitory liability in the sample was enhanced by prioritizing recruitment of individuals falling within the upper quartile of the score distribution for the ESI-DIS scale. The test sample was largely Caucasian (79%), with some representation of minority populations (12% African-American, 5% Asian-American), consistent with the racial composition of the larger Tallahassee area from which the sample was recruited. As such, the race variable was coded as White versus non-White for subsequent analyses. Study participants were compensated $10 per hour or with class credit for their voluntary participation. All study procedures were

[1]While we did not *a priori* hypothesize a gender moderation effect, we tested it in response to the suggestion of a helpful anonymous reviewer.

approved beforehand by the Florida State University Institutional Review Board, and all participants gave written informed consent prior to commencement of data collection.

Measures

Substance Use Disorder Symptoms: Lifetime symptoms of SUDs were assessed according to criteria specified in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association [APA], 2000), using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2002). Interviews were performed by clinical psychology graduate students who had undergone specialized training in diagnostic interviewing. Following procedures used in prior published work (e.g., Iacono, Carlson, Taylor, Elkins, & McGue, 1999; Nelson, Strickland, Krueger, Arbisi, & Patrick, 2016), symptom ratings for each case were assigned using a consensus decision-making process overseen by a clinically-trained academic psychologist (senior author, Christopher J. Patrick). The diagnostic interviews were videotaped, and the first author independently coded a 10% (n = 20) random subsample of participants for SCID symptoms of alcohol and substance use disorders (ICC = .99).

Though substance use was assessed only at time of test and was not employed as a criterion for selection, a considerable portion of study participants exhibited some level of substance problems. Considering symptoms across all substance types, 44.2% (n = 88) reported experiencing one or more symptoms of AUD or another SUD. According to current diagnostic (DSM-5; APA, 2013) specifications, 9.0% of participants exhibited ‘mild’ symptomatology (2-3 symptoms), 6.5% exhibited “moderate” symptomatology (4-5 symptoms), and 17.1% exhibited ‘severe’ symptomatology (6+ symptoms). With respect to alcohol use disorder specifically, 8.5% fell into the mild range (2-3 symptoms), 7.5% fell into the moderate range (4-5 symptoms), and 8.0% fell into the severe range (6+ symptoms). For cannabis use disorder, 4.0% fell into the mild range, 6.0% fell into the moderate range, and 6.0% fell into the severe range. Rates of symptomatology for drug of other types were low. To create a single index of substance problems for use in our main analyses, symptom-count scores for abuse and dependence were summed across alcohol, cannabis, opioids, cocaine, hallucinogens, sedatives, and stimulants. The mean SUD symptom composite count for participants in the study was 2.63 (SD = 4.46, range = 0 to 21).

Trait Disinhibition: Trait disinhibition was quantified using a scale developed to index the general disinhibitory factor of the Externalizing Spectrum Inventory (ESI; Krueger et al., 2007; Patrick, Kramer, Krueger, & Markon, 2013a), a questionnaire that assesses impulse control problems of various types and traits associated with such problems. The Disinhibition (DIS) scale used in the current study comprised 30 items from the ESI reflecting problematic impulsiveness, irresponsibility, impatience, lack of planning, alienation, and thievery (see Yancey et al., 2013), with no inclusion of items pertaining to substance use or problems. Scores on this ESI-DIS scale correlate reliably with brain and task-behavioral indicators of disinhibitory liability (Venables et al., 2018; Yancey et al., 2013). Cronbach’s alpha (α) for this scale in the current study sample was .89; the corresponding greatest lower bound (GLB) value (see McNeish, 2017) was .94. The average

score (quantified from 0 to a maximum of 1) for current study participants was .19 (*SD* = .14; range = .00 to .73). The full ESI-DIS item set is available in the Supplemental Materials.

Neural Assessment of Reward Sensitivity: Task Description and Procedure: Participants completed a simulated gambling task that has frequently been used to assess the Reward Positivity (RewP; Hajcak Proudfit, 2015). The task involved a sequence of 40 trials in which two doors were presented side by side and participants were instructed to choose which one they thought would result in winning money. The participant's choice between the two doors (via button-press) was followed by an inter-stimulus interval of 1000 ms, after which a feedback cue appeared denoting the outcome of the choice. Outcomes were predetermined such that on half of the trials, positive feedback was given via a green arrow pointing upwards, signaling a $0.50 gain. On the other half of trials, negative feedback was given via a red arrow pointing downwards, signaling a $0.25 loss. Gains were twice the magnitude of losses, in line with work demonstrating losses to be roughly twice as salient as gains (Tversky & Kahneman, 1992). The feedback cue was presented for 2000 ms. Participants received gain feedback on exactly 50% of trials. The intertrial interval was 1500 ms. (For further details regarding task procedures, see Hajcak Proudfit [2015].)

Neurophysiological Data Recording and Reduction

Data were collected using two computers running simultaneously, the first utilizing E-Prime software (MEL Software, Inc.) to control stimulus presentation, and the second using Neuroscan Acquire software to record physiological data. Electroencephalographic (EEG) activity was measured using a 128-channel elastic Neuroscan Quik-Cap, with sintered Ag-AgCl electrodes positioned according to the Neuroscan Nonstandard Layout (NSL) system, and electrode impedances were kept below 10 KOhms during recording. To capture vertical and horizontal electrooculographic (EOG) activity, electrodes were positioned above and below the left eye (VEOG), and adjacent to the outer canthi of the two eyes (HEOG).

The raw EEG signal was bandpass-filtered online from .05 – 200 Hz, and digitized at 1,000 Hz. Data were collected using an online reference at the vertex site and re-referenced offline to averaged mastoids. Continuous EEG recordings were segmented into 3,000-ms epochs for each task trial (1,000 ms pre-stimulus to 2,000 ms post-stimulus) through use of Neuroscan Edit software (version 4.5, Neuroscan, Inc.). Eyeblink artifacts were corrected using the algorithm developed by Semlitsch, Anderer, Schuster, and Presslich (1986). Data were subsequently processed in Matlab (Mathworks, Inc.) to down-sample the EEG signal to 128Hz (through use of an antialiasing filter) and to remove trials in which signal activity exceeded a range of ±75μV during the 3,000-ms epoch of interest; the number of trials omitted on this basis was small (*M* = 0.53 per subject, *SD* = 1.33). If more than half the trials were omitted for a particular electrode, that electrode's activity was replaced with the average activity for the electrodes surrounding it.

Quantifying the Reward Positivity (RewP)—Trial-level data were averaged separately within the two feedback conditions (gain, loss). Gain and loss feedback-elicited ERPs were quantified separately as the mean activation between 200 – 350 ms following onset of the feedback stimulus, relative to a 200-ms baseline preceding feedback stimulus onset. In line

with previous published work (e.g., Hajcak Proudfit, 2015), the RewP was quantified as the difference in average ERP signal amplitude for gain trials minus loss trials during the 200 – 350 ms window following feedback onset. Average ERP waveform plots for gain and loss feedback trials are presented in Figure 1, along with a topographic plot of the scalp distribution of the RewP difference score. The RewP difference waveform exhibited a frontocentral distribution as in prior work, and analyses for the current study focused on RewP quantified at NSL electrode site 63 (analog Cz). The amplitude scores for gain and loss trials were highly reliable (Spearman-Brown corrected split-half *r*s = .89 and .90 for gain and loss, respectively) and, consistent with prior work (Levinson et al., 2017), the RewP difference score evidenced lower split-half reliability ($r = .36$). The mean magnitude of RewP response for participants in the current study was 3.03 μV ($SD = 4.16$).

Data Analyses

Bivariate correlations and zero-inflated negative binomial (ZINB) regression models were used to evaluate study hypotheses. ZINB models were employed in order to address zero-inflation of scores for the AUD/SUD symptom composite, that is, the sizable proportion of study subjects who reported no symptoms of AUD/SUD.[2] Further, the AUD/SUD symptom composite was over-dispersed, meaning that the variance exceeded the mean. While linear regression analysis is generally robust to departures from normality (Gelman & Hill, 2006), ZINB models are statistically preferable for testing effects on criterion measures that demonstrate a high proportion of zero-score values. ZINB models have two parts: (1) a zero-inflation model, which aims to predict "structural" zeros (i.e., excess zeros beyond the level expected in a negative binomial distribution) in a logistic regression-like manner – with a *positive* coefficient for the predictor variable indicating *higher* levels of the predictor being associated with a greater likelihood of a *zero,* as opposed to a non-zero value, on the criterion; and (2) a count model, which evaluates the extent to which predictors account for variance across the distribution of the count variable according to a negative binomial distribution, conditional on the presence of non-zeros (i.e., coefficients are interpreted similarly to OLS regression betas).

To address study hypotheses 1 and 2, pertaining to associations of ESI-DIS and RewP response (respectively) with SUD symptomatology, ZINB models controlling for age, gender, race, and recruitment source are reported for predicting an overall SUD composite, reflecting abuse and dependence symptoms (computed as a total symptom count score) for AUD and illicit drugs (i.e., other SUDs). To test for synergy between trait disinhibition and neural reward sensitivity in predicting SUD symptomatology (hypothesis 3), we used another ZINB model in which age, gender, race, recruitment source, ESI-DIS, RewP magnitude, the ESI-DIS × RewP interaction, the ESI-DIS × Gender interaction, the RewP × Gender, and the ESI-DIS × RewP × Gender interaction were entered as predictors of SUD

[2]While there are different types of zero-inflated models, including zero-inflated negative binomial, zero-inflated poisson, and negative binomial hurdle, these models can be compared on the basis of their AIC and BIC fit statistics using Vuong's (1989) Z test. The Vuong test indicated that a zero-inflated Poisson, a zero-inflated negative binomial, and a negative binomial hurdle model all fit better than their non-zero-inflated Poisson and negative binomial regression counterparts, supporting the need to account for zero-inflation in the DV. In the current dataset, the zero-inflated negative binomial model exhibited superior fit relative to both the zero-inflated Poisson (Vuong $Z = 3.00$, $p = .001$) and negative binomial hurdle models (Vuong $Z = 3.01$, $p = .001$). Accordingly, zero-inflated negative binomial models were used for all analyses involving the SUD symptom composite.

symptomatology. All interactions were computed as the product of their respective mean-centered lower-order terms, and were probed by manipulating the centering point for the moderating variable and re-computing interaction terms as appropriate. A table showing correlations among all study variables can be found in the Supplemental Materials.

Results

Hypothesis 1: Trait Disinhibition and SUD Symptoms

Replicating findings from previous research, scores on the ESI-DIS scale showed a robust positive association with the composite index of SUD symptomatology in the ZINB model (zero-inflation component, $B = -9.29$ [$Z = -4.21$], $p < .001$; count component, $B = 2.14$ [$Z = 3.43$], $p < .001$) when controlling for age, gender, race, and recruitment source.[3] This indicates that disinhibition operated both to differentiate individuals who showed no SUD symptomatology and, conditional on having some SUD symptomatology present, predicted the severity of that symptomatology. See Table 1 for full ZINB model results. ESI-DIS scores did not correlate significantly with RewP response magnitude ($r = -.10$, $p = .15$).

Hypothesis 2: RewP Response and SUD Symptoms

Controlling for age, gender, race, and recruitment source, a significant *negative* association was evident for RewP magnitude with SUD symptomatology (zero-inflation component, $B = -.10$ [$Z = -1.02$], $p = .31$; count component, $B = -.07$ [$Z = -2.40$], $p = .02$), indicating that reward ***hypo***sensitivity was related to greater substance problems.[4] However, this relationship was specific to the count component of the model, such that RewP magnitude did not operate to differentiate individuals without SUD symptomatology, but rather, conditional on individuals having some SUD symptoms, it predicted the severity of that SUD symptomatology (see Table 1 for full ZINB model results).

Because the RewP is computed as a difference score, a follow-up ZINB analysis was used to evaluate the contributions of gain-trial activation and loss-trial activation to SUD symptomatology. Mutual ('cooperative'; Paulhus, Robins, Trzesniewski, & Tracy, 2004) suppression was evident in the predictive relations for trials of each type, with magnitudes of association for each increasing, in opposite directions, when controlling for covariance with the other. When entered alone, gain trials (zero-inflation component, $B = .00$ [$Z = .22$], $p = .82$; count component, $B = -.02$ [$Z = -1.13$], $p = .26$) and loss trials (zero-inflation component, $B = .00$ [$Z = .07$], $p = .94$; count component, $B = .01$ [$Z = .31$], $p = .76$) did not predict SUD symptomatology, but when entered together, both gain (zero-inflation component, $B = .01$ [$Z = .24$], $p = .81$; count component, $B = -.08$ [$Z = -2.97$], $p = .003$) and loss trials (zero-inflation component, $B = -.00$ [$Z = -.09$], $p = .93$; count component, $B = .08$ [$Z = 2.69$], $p = .007$) showed significant associations with SUDs. This outcome indicates that RewP effects in the current work are driven by the *net difference* in activation for trials of the two types.

[3] In an OLS regression analysis controlling for age, gender, race, and recruitment source, ESI-DIS also showed the same robust positive association with the SUD symptom composite ($\beta = .49$, $p < .001$).

[4] In an OLS regression controlling for age, gender, race, and recruitment source, RewP magnitude also showed the same negative association with the SUD symptom composite ($\beta = -.16$, $p = .019$).

A further question was whether non-linearity was present in the relationship between RewP and SUD symptoms (i.e., whether both reward hypo- and hypersensitivity were related to more severe SUD). A further ZINB model analysis suggested this was not the case. Controlling for age, gender, race, and recruitment source, the RewP-squared term (zero-inflation component, $B = .00$ [$Z = .17$], $p = .87$; count component, $B = .01$ [$Z = 1.60$], $p = .11$) was not significantly associated with SUDs beyond the linear RewP term (zero-inflation component, $B = -.09$ [$Z = -.90$], $p = .37$; count component, $B = -.09$ [$Z = -2.64$], $p = .008$). Thus, it was concluded that reward hyposensitivity exhibits a linear association with SUD symptomatology.

Hypothesis 3: Interaction between RewP and Disinhibition in Predicting SUD Symptoms

Turning to study hypothesis 3, a ZINB analysis was conducted to test for interactive associations of ESI-DIS, RewP response, and gender with overall SUD symptoms, when controlling for age, race, and recruitment source. In the zero-inflation portion of the model, only race ($B = 1.37$ [$Z = 2.52$], $p = .02$; non-White participants more likely to be zeros) and ESI-DIS ($B = -9.36$ [$Z = -4.33$], $p < .001$) emerged as significant predictors of which participants would be "structural zeros" on the SUD composite. In the count portion of the ZINB model for the same predictors, recruitment source ($B = .47$ [$Z = 2.13$], $p = .03$; community participants more likely to exhibit more severe SUDs), ESI-DIS ($B = 1.31$ [$Z = 2.17$], $p = .03$), RewP ($B = -.05$ [$Z = -2.40$], $p = .02$), and the three-way ESI-DIS × RewP × Gender interaction ($B = .68$ [$Z = 2.67$], $p = .008$) emerged as significant predictors (see Table 2 for detailed ZINB model results).[5]

To clarify the source of the interaction effect, follow-up ZINB models were first probed across genders; given that the three-way interaction, as noted, emerged as significant in the count component of the model (i.e., it was predictive of severity of SUDs, conditional on having at least some SUD symptomatology), the analysis for each gender focused on this component of the model. For males, a robust two-way ESI-DIS × RewP interaction was evident ($B = -.40$ [$Z = -2.25$], $p = .02$), but this two-way interaction did not emerge as significant for females ($B = .28$ [$Z = 1.55$], $p = .12$). The two-way interaction effect for males was probed by examining the relationship between RewP and SUD symptoms for participants scoring high (one *SD* above the sample mean) versus low on ESI-DIS (one *SD* below the mean). A significant *negative* association between RewP and SUD symptomatology was evident at high levels of ESI-DIS ($B = -.09$ [$Z = -2.51$], $p = .01$), but not at low levels of ESI-DIS ($B = .02$ [$Z = .40$], $p = .69$).

Collectively, the results of these ZINB modeling analyses demonstrate a significant *negative* association between RewP magnitude and SUD symptomatology in both men and women, with ESI-DIS exerting a moderating effect on this association among men but not women. These results are depicted graphically in Figure 2, in which the RewP/SUD-symptom relationship is plotted by disinhibition score level for male and female participants separately.

[5]In an OLS regression controlling for age, race, recruitment source, and lower-order interaction terms, the three-way ESI-DIS, RewP, and gender interaction was also significant ($\beta = .172$, $p = .003$).

Discussion

Substance use problems are characterized by both inhibitory control deficits and reward system dysregulation (Baskin-Sommers & Foti, 2015; Karoly et al., 2013). In line with prior work, the results of the current study indicated that trait disinhibition was robustly associated with substance use problems (Hypothesis 1). It is important to note that disinhibition as assessed by the ESI-DIS scale is not interchangeable with psychological concepts such as trait impulsivity or self-control. The construct assessed by the ESI-DIS scale is specifically the heritable liability for externalizing problems; scores on this scale correlate substantially with problems of this type, largely as a function of shared genetic influence (Yancey et al., 2013), and they correlate as well with brain and behavioral variables that operate as genetic markers (endophenotypes) for externalizing liability (Yancey et al., 2013; Young et al., 2009). Though the ESI-DIS scale contains no items pertaining to alcohol or drug use, it correlates substantially – as shown in the current work – with SUD symptomatology, and this association can be attributed mainly, on the basis of findings from prior work (Yancey et al., 2009; see also Hicks, Krueger, Iacono, McGue, & Patrick, 2004), to heritable externalizing liability.

Along with corroborating this predictive relationship for disinhibition with SUD symptoms, the current study demonstrated both a separate main effect and an interactive association for the construct of reward sensitivity. Of note, reward sensitivity was operationalized using a neurophysiological measure, the RewP, which has shown validity in clinical as well as experimental studies (Hajcak Proudfit, 2015). The RewP was unrelated to ESI-DIS scores, indicating that it taps an aspect of reward sensitivity distinct from excitement- or sensation-seeking. In line with the reward hyposensitivity variant of Hypothesis 2, RewP response evinced a negative (rather than positive) relationship with substance use problems. Additionally, among male participants in the current sample, reward sensitivity and trait disinhibition operated synergistically in predicting substance problems: Males high in trait disinhibition (as indexed by ESI-DIS) and low in reward sensitivity (as indexed by RewP) showed greatly amplified levels of SUD symptomatology (Figure 2, left plot). The fact that this interaction effect was not significant for female participants could indicate a gender-based difference in the interplay between low reward sensitivity and high disinhibition in contributing to SUD symptomatology – perhaps related to the differential role of heritable biological factors in substance problems among men as compared to women (Bierut et al., 1998; Han, McGue, & Iacono, 1999; Hicks et al., 2007; Hopfer, Crowley, & Hewitt, 2003; van den Bree, Johnson, Neale, & Pickens, 1998), or gender differences in the relationship between substance use patterns and occurrence of problems (Brady & Randall, 1999; Tuchman, 2010). However, the three-way interaction effect was not predicted *a priori*, and the lack of a significant interaction for female participants could alternatively reflect a lack of statistical power, attributable to reduced sample size in the analyses by gender. Research with larger samples will be needed to corroborate the finding of a three-way interaction and clarify whether the synergy between low reward sensitivity and disinhibition in predicting substance problems is specific to men, or simply more pronounced in males than in females.

Based on research demonstrating that RewP covaries negatively with depressive symptomatology, this measure has been interpreted as indexing the capacity for hedonic

response (Carlson et al., 2011; Hajcak Proudfit, 2015). In this context, our finding of a significant main effect of reduced RewP magnitude on SUD symptomatology, not moderated by gender, therefore suggests that *reduced* capacity for hedonic response is associated with heightened proclivities toward substance problems. Further, the above-noted RewP × Disinhibition × Gender interaction indicates that, within the current study sample, participants with the highest levels of SUD symptomatology were men exhibiting weak inhibitory control in combination with attenuated brain response to reward. More broadly, the current work illustrates the value of moving toward operationalizing reward sensitivity in a way that incorporates neurophysiological indicators – by showing how assessing reward sensitivity in this way can disentangle it from trait disinhibition, allowing its unique predictive relationship with SUD symptomatology (and its interplay with disinhibition) to be discerned.

Implications for Understanding Proneness to Substance Problems

Our results align with the reward hyposensitivity hypothesis as opposed to the reward hypersensitivity perspective. However, there are two major variants of the hyposensitivity hypothesis, with different etiological and developmental implications. One of these, the *reward deficiency hypothesis* (Blum et al., 1996; Blum et al., 2000), posits reward hyposensitivity as a dispositional liability for substance dependence and other addictions (e.g., compulsive gambling). The other, the *allostatic load hypothesis* (e.g. Koob & LeMoal, 2008; Koob & Volkow, 2010), holds that reward hyposensitivity arises as a result of repeated and severe substance use. Given the cross-sectional nature of our design, the current findings cannot distinguish between these alternative perspectives. Considering the relative youthfulness of our study participants and their non-treatment-seeking status, it seems more plausible to suppose that our results reflect dispositional factors operative at earlier stages in the progression toward substance addiction, rather than consequences of sustained heavy use. The fact that RewP operates as an index of trait liability for depression, showing reduced magnitude in pre-symptomatic offspring of parents with histories of clinical depression (Kujawa, Hajcak Proudfit, & Klein, 2014) and prospectively predicting onset of depression (Nelson et al., 2016), lends credibility to the idea that reduced RewP magnitude in the current study was indicative of a dispositional impairment in hedonic response capacity. However, it is also possible that both variants of reward hyposensitivity mechanisms play a role in the observed negative association of RewP with substance problems – i.e., individuals with low dispositional reward sensitivity may experience a greater hedonic ‘lift’ from substances that promotes recurrent heavy use, and this recurrent use may operate to exacerbate their pre-existing insensitivity to natural reward. Systematic longitudinal work will be required to confirm that deficits in RewP response evident before the onset of substance use predict increased levels of SUD symptomatology later in life, particularly when accompanied by high levels of trait disinhibition.

The current work also may serve as a bridge between behavioral economic theories of addiction (e.g., Bickel et al., 2014) and the impaired response inhibition and salience attribution (I-RISA) model of addiction (e.g., Goldstein & Volkow, 2002) when considered from a trait dispositional perspective. While the I-RISA focuses on lack of inhibitory control over response to substance-related reward, behavioral economic models emphasize that the

lack of sensitivity to, and availability of (e.g., Acuff et al., 2018; Joyner et al., 2016), alternative (substance-free) rewards serve to increase the relative valuation of substance-related reward. The current work highlights the interplay between the impaired inhibitory control component of the I-RISA and the impaired substance-free reward sensitivity element of behavioral economic models. The current work is also broadly consistent with classic work on the biological bases of personality dimensions related to impulse control and positive affectivity (e.g., Cloninger, 1986) that have been shown to predict substance misuse in a similar fashion (for a review, see Finn, 2002). For example, Colder & Chassin (1997) reported findings indicating that impulsivity exacerbated the effect of low positive affectivity on alcohol use and problems among adolescents, similar to our findings of heightened disinhibition and blunted neural reward sensitivity combining to predict substance problems in younger adults.

Also similar to the current findings, Joyner and colleagues (2018) reported that a family history of alcohol misuse, which has been shown to broadly confer disinhibitory liability (Bornovalova et al., 2010; Hicks, South, Dirago, Iacono, & McGue, 2009; Hicks, Iacono, & McGue, 2012), moderated the relationship between substance-free experience of reinforcement and alcohol problems. Among individuals with a positive family history of alcohol use in this study (i.e., those at heightened risk for disinhibitory problems), a negative relationship was evident between level of substance-free reinforcement and alcohol problems; conversely, individuals without a positive family history evidenced no such association (Joyner et al., 2018). Thus, the current work connects with existing published work and highlights the value of considering the moderating role of constructs related to disinhibition when studying SUDs.

A further implication of the current work is that evaluations of risk for SUDs are likely to benefit from measurement of reward sensitivity in conjunction with disinhibitory liability and gender. Across male and female participants, reduced reward sensitivity (as indexed by RewP magnitude) predicted greater SUD symptomatology, distinct from the predictive effect for trait disinhibition. The implication is that assessment of reward sensitivity can provide information about risk for, or mechanisms contributing to, substance problems beyond that provided by assessment of trait disinhibition. In the case of women, relationships for these two variables with SUD symptoms appeared additive (Figure 2, right plot), such that an assessment indicating low reward sensitivity would be informative independently of assessed level of trait disinhibition. For males on the other hand, a finding of low reward sensitivity would need to be interpreted *in relation to* assessed level of trait disinhibition. That is, if an individual were found to be low in disinhibitory liability, lack of reward sensitivity could not be relied upon to augment prediction of risk or inform understanding of reasons for substance problems; however, for individuals exhibiting modest or higher levels of trait disinhibition, knowledge of reward sensitivity status would be valuable for gauging risk and informing understanding of the bases of problems.

Limitations and Future Directions

Some limitations of the current work warrant comment. As already mentioned, the cross-sectional nature of the study limits our ability to distinguish the reward deficiency and

allostatic load hypotheses. Systematic longitudinal research will be critical for clarifying the role of disinhibitory liability and reward sensitivity at different points along the path from initial use to severe dependence on substances. A second limitation is that the sampling strategy we used resulted in limited representation of heavy substance users, as indicated by the percentages of participants who endorsed diagnostic symptoms of SUDs and the level of symptomatology evident in those who did. Future research is needed, therefore, to replicate the current results in samples exhibiting clinically-severe substance problems (e.g., addiction clinic patients). However, for samples that exhibit low rates of substance use symptomatology, the use of zero-inflated analyses is recommended. Additionally, data for nicotine use disorder were not collected in the current study, and thus it will be particularly valuable to evaluate in future work whether our findings generalize to nicotine problems.

Another limitation of the current work is that the psychological bases of the observed effects for reward sensitivity are unclear, since this construct was operationalized using a neurophysiological measure alone. Given that the meaning of a measured variable is revealed by its network of relations with other measured variables (i.e., its ‘nomological network’; Cronbach & Meehl, 1955), it will be valuable in future work to identify variables from other assessment domains (including self-report and task performance) that (a) correlate with RewP, and (b) help to account for RewP’s associations (both main and interactive) with substance problems. Along with helping to clarify the basis of observed relations for indicators like RewP, systematic work directed at delineating a nomological network that includes addictive symptomology along with indices of disinhibitory liability and reward sensitivity from multiple domains can form the basis for an integrated, neuroclinical assessment framework for SUDs (Kwako et al., 2016; for an illustration focusing on trait disinhibition, see Venables et al., 2018).

In addition, further work is needed to clarify the neural bases of the RewP response itself, and to clarify what specific aspect(s) of reward processing it taps. Basic neuroscience research has identified different components of reward processing, commonly referring to as “liking,” “wanting,” and “learning,” that are mediated by distinct neural circuits (e.g. Berridge, Robinson, & Aldridge, 2009). Drawing on this evidence, the National Institute of Mental Health’s Research Domain Criteria framework (RDoC; Kozak & Cuthbert, 2016) includes distinct reward subprocesses in its Positive Valence Systems domain. The RewP has been characterized as relating most to initial reward responsiveness, or “liking” (Baskin-Sommers & Foti, 2015), but this perspective remains to be substantiated empirically. Research utilizing neuroimaging methodology (to quantify reactivity in specific neural structures) in conjunction with ERP measurement (to index RewP response) will be of particular value for addressing questions regarding the neural substrates for RewP.

Conclusion

While acknowledging the foregoing limitations, the current paper provides evidence for a distinct role of reward processing deficits in SUD symptomatology. Through use of a well-established neurophysiological measure, we were able to quantify reward sensitivity separately from trait disinhibition – and demonstrate a role for both in predicting substance problems. This research has important implications for understanding motivational factors

that operate to shape the expression of general disinhibitory liability in the direction of addictive behaviors specifically (Patrick et al., 2016). Our work also has clear relevance to major scientific initiatives aimed at advancing neurobiological conceptualizations and assessments of mental health problems (Kozak & Cuthbert, 2016; Kwako et al., 2016).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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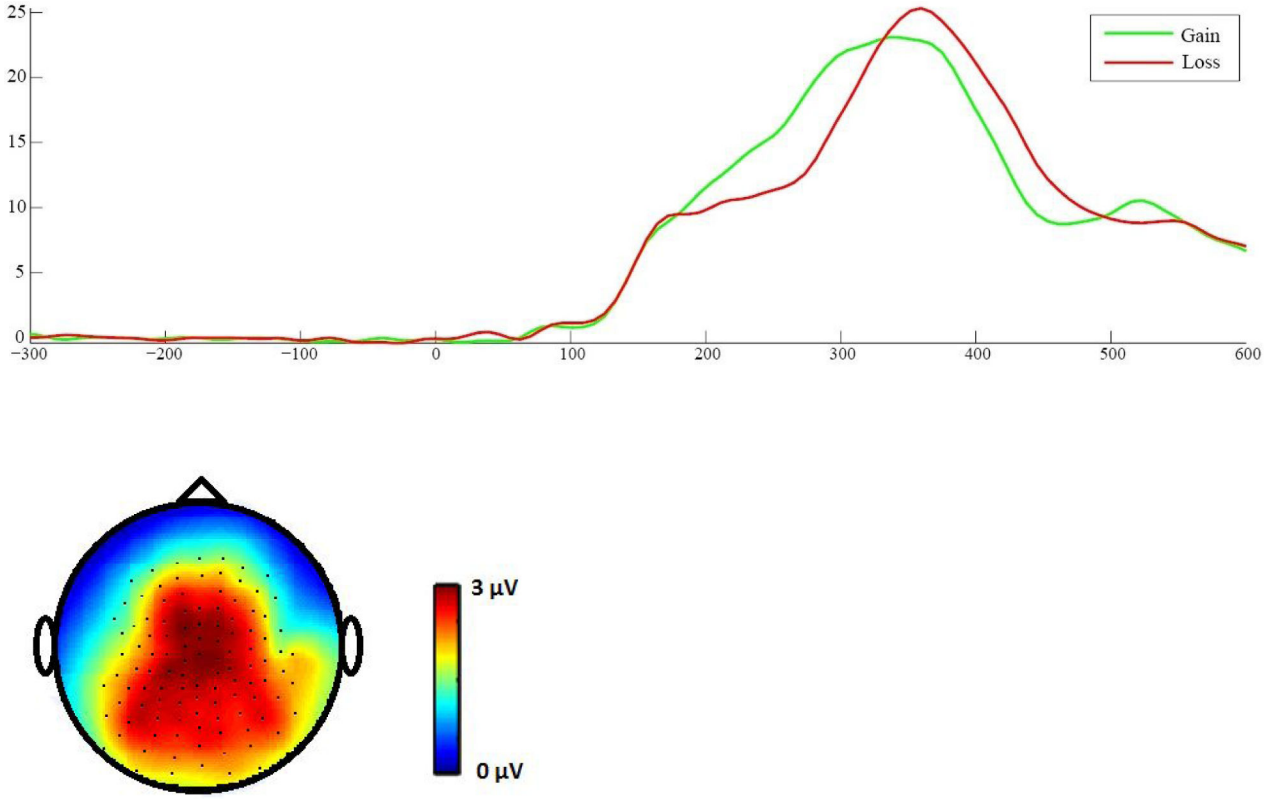

Figure 1.

Waveform plot and scalp topography of the mean event-related brain response to cues signaling gain versus loss outcomes in the choice-feedback task. The shaded region of the waveform plot indicates the scoring window for the RewP response, which was quantified as mean signal activity for gain trials minus mean activity for loss trials. The topographic map depicts variations in the magnitude of the RewP response across different scalp recording sites.

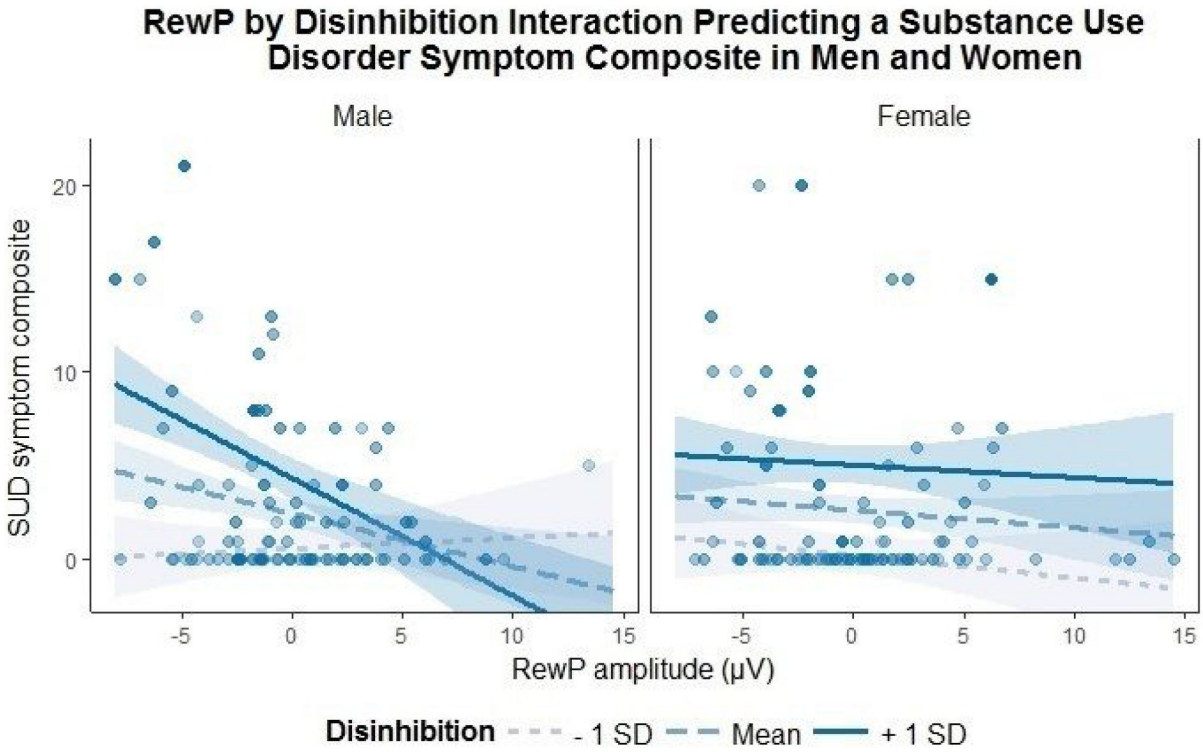

Figure 2.

Depiction of associations for trait disinhibition (operationalized using the ESI-DIS scale) and neural reward sensitivity (indexed via the RewP) with substance use disorder (SUD) symptoms, in male (left plot) and female (right plot) study participants. The effect of RewP response on SUD symptomatology is plotted as a function of variations in ESI-DIS score level. Plotted points appear in continuous shadings of blue, with darker levels denoting increasing levels of trait disinhibition; regression lines are shown for levels of ESI-DIS corresponding to 1 *SD* below the sample mean (−1 *SD*), at the mean, and 1 *SD* above the mean (+1 *SD*). Shaded regions around each regression line reflect 95% confidence intervals.

Table 1.

Main Effects for Trait Disinhibition and RewP Magnitude in Predicting SUD Symptomatology within Separate Zero-Inflated Negative Binomial (ZINB) Models

	Count Model				Zero-Inflation Model			
Disinhibition Main Effect	**Unstd. B**	***SE B***	***Z*-value**	***p*-value**	**Unstd. B**	***SE B***	***Z*-value**	***p*-value**
Age	.01	.02	.70	.49	−.14	.12	−1.17	.24
Race (white vs. non-white)	−.15	.27	−.56	.57	**1.43**	**.56**	**2.55**	**.01**
Recruitment source (college vs. community)	**.44**	**.22**	**2.00**	**.046**	−.22	.48	−.46	.65
Gender (male vs. female)	−.12	.21	−.55	.58	−.03	.41	−.06	.95
Disinhibition	**2.14**	**.62**	**3.43**	**<.001**	**−9.29**	**2.21**	**−4.21**	**<.001**
RewP Main Effect								
Age	.03	.03	1.17	.24	**−1.30**	**.47**	**−2.75**	**.006**
Race (White vs. non-White)	−.12	.36	−.33	.74	**2.81**	**1.15**	**2.43**	**.02**
Recruitment source (college vs. community)	.17	.30	.57	.57	**−2.97**	**1.32**	**−2.24**	**.03**
Gender (male vs. female)	.29	.28	1.01	.31	1.71	.96	1.78	.07
RewP	**−.07**	**.03**	**−2.40**	**.02**	−.10	.10	−1.02	.31

Note. N = 199. RewP = Reward Positivity; SUD = Substance Use Disorder; Unstd. = unstandardized. In the zero-inflation component of each model, the likelihood of the dependent variable having a 'true zero' value is being predicted; thus, the direction of the Z-value (+/−) is reversed from the intuitive direction of effect for the variable. Significant ($p < .05$) regression coefficients, and their associated Z-values, are bolded.

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Table 2.

Interaction effects for Trait Disinhibition, RewP Magnitude, and Gender in Predicting SUD Symptomatology within a Zero-Inflated Negative Binomial (ZINB) Model

	Count Model				Zero-Inflation Model			
Variable	**Unstd. *B***	***SE B***	***Z*-value**	***p*-value**	**Unstd. *B***	***SE B***	***Z*-value**	***p*-value**
Age	.01	.02	.75	.45	−.11	.07	−1.47	.14
Race (White vs. non-White)	−.17	.25	−.67	.50	**1.37**	**.55**	**2.52**	**.01**
Recruitment source (college vs. community)	**.47**	**.22**	**2.13**	**.03**	−.24	.46	−.52	.60
Disinhibition	**1.31**	**.60**	**2.17**	**.03**	**−9.36**	**2.16**	**−4.33**	**<.001**
RewP	**−.05**	**.02**	**−2.40**	**.02**	−.01	.05	−.18	.86
Gender (male vs. female)	.00	.21	.02	.98	.01	.40	.02	.98
Disinhibition × RewP	−.06	.13	−.49	.63	.30	.50	.59	.55
Gender × Disinhibition	.28	1.19	.23	.82	−.71	4.09	−.17	.86
Gender × RewP	−.03	.04	−.70	.48	−.05	.10	−.45	.65
Gender × Disinhibition × RewP	**.68**	**.25**	**2.67**	**.008**	.62	1.02	.61	.54

Note. $N = 199$. RewP = Reward Positivity; SUD = Substance Use Disorder; Unstd. = unstandardized. In the zero-inflation component of the model, the likelihood of the dependent variable having a 'true zero' value is being predicted; thus, the direction of the Z-value (+/−) is reversed from the direction of effect for the variable. Significant ($p < .05$) regression coefficients, and their associated Z-values, are bolded.