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Distress Tolerance among Substance Users is Associated with Functional Connectivity between Prefrontal Regions during a Distress Tolerance Task

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Abstract

Distress tolerance (DT), defined as the ability to persist in goal directed behavior while experiencing affective distress, is implicated in the development and maintenance of substance use disorders. While theory and evidence indicate that cortico-limbic neural dysfunction may account for deficits in goal directed behavior while experiencing distress, the neurobiological mechanisms of DT have yet to be examined. We modified a computerized DT task for use in functional magnetic resonance imaging (fMRI), the Paced Auditory Serial Addition Task (PASAT-M), and examined the neural correlates and functional connectivity of DT among a cohort of substance users ($n=21$; regular cocaine and nicotine users) and healthy controls ($n=25$). In response to distress during the PASAT-M, we found greater activation in *a priori* cortico-limbic network ROIs, namely the right insula, anterior cingulate cortex (ACC), bilateral medial frontal gyrus (MFG), right inferior frontal gyrus (IFG), and right ventromedial prefrontal cortex (vmPFC) significantly predicted higher DT among substance users, but not healthy controls. In addition, greater task-specific functional connectivity during distress between the right MFG and bilateral vmPFC/sgACC was associated with higher DT among substance users, but not healthy controls. The observed positive relationship between DT and neural activation in cortico-limbic structures, as well as functional connectivity between the rMFG and vmPFC/sgACC is in line with theory and research suggesting the importance of these structures for persisting in goal directed behavior while experiencing affective distress.

Keywords

Distress tolerance; substance use disorder; prefrontal cortex; emotion regulation; fMRI

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AUTHORSHIP CONTRIBUTION

SD, TR, and EAS were responsible for the study concept and design. JR, RB, and JY contributed to data acquisition and processing. SD, TR, and RB conducted the data analysis. SD, RB, and JY drafted the manuscript. TR and EAS provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

FINANCIAL DISCLOSURES

The authors have no financial interests to declare.

INTRODUCTION

Affective distress, which includes feelings such as anxiety, stress, and irritability, is often present in addicted individuals during an abstinence attempt (Baker, Japuntich, Hogle, McCarthy, & Curtin, 2006), with the severity of these symptoms reported to predict treatment outcome and relapse across drug classes (Mulvaney, Alterman, Boardman, & Kampman, 1999). Accordingly, negative reinforcement models of addiction collectively emphasize that the motivational basis of addictive drug use is the reduction or avoidance of aversive internal states (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004).

Behavioral laboratory paradigms that specifically capture the real-time avoidance of affective distress have been developed to test the theory that negative reinforcement mechanisms are associated with substance use frequency and relapse. These paradigms measure *distress tolerance*, defined as the ability to persist in goal directed behavior while experiencing affective distress. The distress tolerance laboratory paradigm involves participant engagement in and persistence on a task that gradually increases in difficulty, thereby increasing affective distress. The participant has the option to persist (for a mild incentive) or in contrast, to terminate the task, thereby escaping affective distress in the short-term but losing out on the reward in the long-term. In line with negative reinforcement models of drug use, low distress tolerance would be associated with a more rapid return to substance use in response to abstinence distress (i.e., to temporarily ameliorate the emotional discomfort). From this perspective, distress tolerance tasks effectively create a laboratory paradigm with high internal validity while creating a situation where affective distress during goal directed behavior and an opportunity for avoidance interact, allowing the participant to make the decision of persisting or terminating the task. Indeed, several findings converge to provide evidence of the utility of the distress tolerance paradigm in predicting substance use outcomes. Low distress tolerance, as measured with these paradigms, is associated with greater substance use frequency (Ali, Ryan, Beck, & Daughters, 2013; Quinn, Brandon, & Copeland, 1996), shorter abstinence duration (Brandon et al., 2003; Brown, Lejuez, Kahler, & Strong, 2002; Daughters, Lejuez, Kahler, Strong, & Brown, 2005), treatment dropout (Daughters, Lejuez, Bornoalova, et al., 2005; Tull, Gratz, Coffey, Weiss, & McDermott, 2013), and relapse (Brown et al., 2009; Strong et al., 2012).

The negative reinforcement model is in line with neurobiological conceptualizations of substance use disorder (SUD), such that chronic substance use leads to neuroadaptations and a chronic “negative affect” or psychologically distressed state during abstinence (Koob & Le Moal, 2001; Koob & Le Moal, 2008). Regulation of behavior in response to distress is theorized to be achieved in a top-down manner in which emotional salience is provided to prefrontal regions to ultimately guide and initiate appropriate goal-oriented behavior (Li & Sinha, 2008; Menon & Uddin, 2010; Sutherland, McHugh, Pariyadath, & Stein, 2012). In particular, the anterior cingulate cortex (ACC) and areas of the prefrontal cortex (PFC) are associated with cognitive control and evaluating and manipulating emotional information to guide planning and decision making. Indeed, chronic substance users evidence impaired functioning (Goldstein & Volkow, 2011) and hypoactivation (Hester & Garavan, 2004; Kaufman, Ross, Stein, & Garavan, 2003) in prefrontal regions, including impaired response inhibition, working memory capacity, and cognitive control (Ma et al., 2014).

Given the importance of inhibiting emotionally driven impulses and determining an appropriate behavioral response during successful abstinence, it is hypothesized that neural deficits may underlie low distress tolerance among substance users. To test this, we first validated a computerized distress tolerance paradigm modified for use in functional magnetic resonance imaging (fMRI). We then examined the neural mechanisms associated with distress tolerance among chronic substance users and healthy controls. It was hypothesized that reduced neural activation during the task within corticolimbic regions would uniquely predict distress tolerance among substance users. We also sought to determine the relationship between task-specific neural activity and distress tolerance. We hypothesized that increased functional connectivity between cortical and limbic regions would be associated with greater distress tolerance.

MATERIALS AND METHODS

Participants

Twenty-nine substance users (SU) and twenty-nine healthy control (HC) participants were recruited, provided IRB approved written informed consent, and participated in study procedures. Of these, 12 were excluded from analyses due to excessive head motion (SU $n=4$; HC $n=1$), behavioral noncompliance (SU $n=2$; HC $n=1$), and technical problems associated with the fMRI task (SU $n=2$; HC $n=2$). The final sample included 21 substance users (mean $\pm$ SD age=41.9 $\pm$ 6.9; 19 males; 19 African Americans, 1 Caucasian; IQ=101.8 $\pm$ 12.5) and 25 healthy controls (mean age=39.7 $\pm$ 8.2; 16 males; 21 African Americans, 4 White Caucasians; IQ=107.4 $\pm$ 13.1). All participants were right-handed, aged 18-55 years and recruited from the general population of Baltimore City and surrounding areas. Substance users were included if they reported regular cocaine (i.e., 2 times per week) and nicotine (i.e., daily smoker) use during the past year prior to participation, and did not meet DSM-IV criteria for current substance dependence on any other substance other than cocaine or nicotine. Healthy non-drug using participants did not meet DSM-IV criteria for any past or current substance abuse or dependence, nor any use of illicit substances in the past 30 days.

General procedure

The current report includes data that was part of a larger assessment battery. A pre-scan assessment included a test for current drug use (Triage®), alcohol use (breathalyzer), and pregnancy, the vocabulary portion of the *Wechsler Abbreviated Scale of Intelligence* (WASI-VIQ; Wechsler, 1999), *Fagerstrom Test for Nicotine Dependence* (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and a questionnaire assessing frequency of use in the past year across 11 drug classes. All substance users smoked a cigarette 60 minutes prior to entering the MRI.

Distress tolerance task

All participants completed the Paced Auditory Serial Attention Task for fMRI (PASAT-M), which was modified from the Computerized Paced Auditory Serial Addition Task (PASAT-C; Lejuez, Kahler, & Brown, 2003). A series of numbers flash on the screen one at a time and the participant must add the current number on the screen to the previously presented

number, and then use an MRI compatible joystick to indicate the correct answer before the subsequent number appears. Correct responses result in a pleasant bell sound and an increase in the participants' score, while incorrect and/or slow responses result in an explosion noise and a decrease in points. The volume is set at a constant level that was determined during pilot testing to be sufficiently loud to allow for participants to hear the task noises over the noise of the MRI scanner.

The block design of the PASAT-M task consisted of four phases (**Figure 1**): an *easy* phase, designed to control for cognitive and motor functioning, a *latency* test phase to determine skill level, a *distress* phase, designed to elicit affective distress, and a *distress tolerance* (DT) phase to measure DT (i.e., latency, in seconds, to task termination). For both the *easy* and *distress* phases there are a total of six 60-second activity blocks, beginning, ending and alternating with 35-second rest blocks, for a total of about 10 minutes. Following the easy phase, a five-minute *latency* test phase begins in order to determine each participant's individual skill level. Each time a participant responds correctly, the subsequent number appears 500 milliseconds faster. Conversely, each time a participant is too slow or chooses an incorrect response, the subsequent number appears 250 milliseconds slower. Skill level is calculated as the mean latency during this phase of the task. During the *distress* phase, the response time allotted for each number presentation is 2.5× faster than their skill level as determined during the latency phase. Participants are told that their performance during this phase will influence how much money they will receive at the end of the testing session. The task parameters and procedures in the *distress* phase are intended to maximize loss, repeated forced failure, and aversive negative performance feedback (i.e., constant explosion noises signaling failure, as well as a decreasing point meter). During the *DT* phase, the rate of number presentations is equal to the distress phase for a maximum of 10 minutes. Participants are instructed that they have the opportunity to win back points they may have lost during the *distress* phase, but that they will no longer lose points for 'incorrect' or 'too slow' responses, although the negative auditory feedback will still be presented. The removal of loss in this phase is designed to prevent participants from choosing to quit the task because it is an adaptive response to prevent further loss. Participants are again told that their performance will determine how much money they receive at the end of the session, but that they can press a button on the joystick at any time to end the task.

Although there are a total of four phases of the PASAT-M, the final phase (i.e., the DT phase) is intended as a behavioral measure of DT, measured as time in seconds to task termination. Self-report mood ratings are collected prior to the *easy* phase (Time 1), and post-easy phase (Time 2), *latency* test phase (Time 3), *distress* phase (Time 4), and *DT* phase (Time 5). Distress is calculated as the mean ratings of anxiety, frustration, irritability, and stress at each time point. Following the task, motivation to perform well during the task was assessed using a 10-point Likert scale ranging from "not at all motivated" to "extremely motivated".

Physiological data acquisition and analysis

Skin conductance response (SCR) and heart rate (HR) were recorded on a BIOPAC data acquisition system operating AcqKnowledge 4.1 at a sampling rate of 1 kHz/channel

(BIOPAC Systems, Inc., Goleta, CA). HR data was recorded using four Ag-AgCl electrodes placed in the chest area and SCR was recorded from the non-dominant index and middle fingers using two Ag-AgCl electrodes. HR and SCR (μmho) data were recorded continuously throughout the scan and analyzed as average values over the course of both the *easy* and *distress* blocks.

fMRI data acquisition and analysis

Whole-brain blood oxygenation level-dependent (BOLD) echo-planar imaging (EPI) data were acquired on a Siemens 3-T Magnetom Trio MR Scanner (Siemens, Erlangen, Germany) equipped with a 12-channel head coil. Thirty-nine 4 mm thick slices were obtained covering the whole brain using an acquisition plane approximately 30° axial-to-coronal from AC-PC (Deichmann, Gottfried, Hutton, & Turner, 2003). Imaging parameters were: repetition time (TR) of 2 s, echo time (TE) of 27 ms, field of view (FOV) of 220×220 mm, flip angle (FA) of 78°, and an in-plane resolution of 3.44×3.44 mm. In each scanning session, a whole-brain T1-weighted structural image (MPRAGE) was acquired for anatomical reference (1mm³ isotropic voxels, TR of 1.9 s, TE of 3.51 ms, FA of 9°).

The functional and anatomical data were pre-processed and analyzed using FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl) using FSL FEAT v. 6.00. Preprocessing included: motion correction with MCFLIRT, spatial smoothing with a Gaussian kernel of full-width half-maximum 5 mm, high-pass temporal filtering (Gaussian-weighted least squares straight line fitting with sigma = 100 s), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and skull stripping of structural images with BET. Functional scans were excluded if they displayed a relative mean displacement >0.3 mm in any plane. Registration of functional data to the T1-weighted anatomical slices and registration of structural images to the 2 mm Montreal Neurological Institute (MNI) standard-space template were done using FLIRT utilizing a 12-parameter affine transformation.

Individual time-series statistical analysis was carried out using FILM with local autocorrelation correction. A block design was utilized for both the *Easy* and *Distress* phases with the task block serving as the regressor of interest. The regressor was constructed as a block convolved with a hemodynamic response function that was modeled using a gamma function. A first-level analysis was conducted for each individual on each phase separately (*Easy* and *Distress*) using a general linear model (GLM) consisting of a contrast for each phase as [Easy – Rest] or [Distress – Rest]. The motion-correction time courses were included as covariates of no interest. For each individual, a fixed effects GLM was conducted to obtain a subtraction contrast consisting of neural activations associated with distress [(Distress - Rest) - (Easy - Rest)].

Regions-of-interest (ROIs) were identified *a priori* based on empirical and theoretical evidence for their association with response to stress paradigms and goal directed behavior (Hare, Camerer, & Rangel, 2009; Li & Sinha, 2008; Menon, 2011). These included the anterior cingulate cortex (ACC), amygdala, right insula, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), and frontal medial cortex (FMC), and were created as lateralized masks from both the Harvard-Oxford Subcortical and Cortical probabilistic atlases set at

10% and overlaid on the MNI152 standard-space T1-weighted average structural template image. Percent signal change was extracted from the contrast of parameter estimates [(Distress - Rest) - (Easy - Rest)] from each ROI utilizing featurquery and then entered in to SPSS Version 22 (Corp, Released 2013).

Data Analysis

Because the PASAT-M had not previously been imaged, our goal was first to validate that the task elicited distress by examining within and between group task-induced self-report, physiological, and neural responses to distress. Next, we constructed within and between group whole-brain activation maps, employing the contrast of [(Distress - Rest) - (Easy - Rest)], including demeaned values of relevant covariates, using FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 3.0$ and a (corrected) cluster significance threshold of $p = 0.05$. We used ANCOVA to examine between group differences in response to distress within our *a priori* ROIs. To determine if the effects of neural activation to distress on DT within ROIs were moderated by group, we used moderated ordinary least-squares regression analysis using the PROCESS macro in SPSS (Hayes, 2012).

We conducted a psychophysiological interaction (PPI) analysis (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) to explore task specific changes in functional connectivity. Specifically, we examined the impact of distress on the strength of time-course correlations between an empirically defined ROI with all other regions of the brain. The seed ROI was identified if (1) it was an *a priori* ROI, and (2) there were observed groups difference in task activation to distress [Distress-Rest]-[Easy-Rest]. Based on this criterion, the right MFG was chosen as the seed ROI (see **Figure 3** and **Table 3**). For each participant, the time-course of activity of the right MFG was extracted from each volume within a participant-specific mask of the seed region for both the *distress* and *easy* phases of the task. First level fixed-effects GLM analyses were conducted separately for the *distress* and *easy* runs and included three regressors: psychological (i.e., [Easy - Rest] or [Distress - Rest]), physiological (i.e., time-course of activation in the seed region for each volume for [Easy - Rest] or [Distress - Rest]), and PPI (i.e., interaction of psychological and physiological regressors). The PPI regressor provided the measure for brain regions whose correlation to the right MFG changed as a function of task state. A higher-level fixed effects GLM was then conducted for each individual to obtain a subtraction contrast consisting of activations in response to distress correlated with the right MFG activation (Distress PPI - Easy PPI). Utilizing the (Distress PPI - Easy PPI) contrast as a DV, a voxelwise multiple regression analysis was conducted consisting of four IVs: gender, group (i.e., substance user or healthy control), distress tolerance (DT), and the Group $\times$ DT interaction term. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.6$ and a (corrected) cluster significance threshold of $p = 0.05$.

RESULTS

Sample Characteristics

As indicated in **Table 1**, there were no group differences in age, ethnicity, or IQ. There were significantly more females among the healthy controls than the substance users. As such, gender was included as a covariate in all group analyses. Substance users reported additional use of alcohol, heroin, marijuana, ecstasy, PCP, and prescription opiates (**Table S1**).

Behavioral performance on the PASAT-M

Behavioral data for the PASAT-M is displayed in **Table 1**. Raw scores are reported for DT (i.e., total persistence time), although this variable was log transformed due to positive skew and all analyses were conducted on the log transformed scores. Substance users demonstrated significantly lower DT than controls. There were no group differences in performance or motivation. Partial correlation and ANCOVA, controlling for group status, demonstrated that DT was not associated significantly with age ($r = -.097$, $p = .53$), gender [$F(1,45) = 0.10$, $p = .76$], race [$F(1,45) = 3.13$, $p = .08$], IQ ($r = -.018$, $p = .91$), motivation ($r = -.185$, $p = .23$), task performance ($r = 0.164$, $p = .29$), or task order [$F(1,45) = 0.29$]. Among substance users, DT was also not associated with the number of days without cocaine use prior to the assessment ($M = 3.9 \pm 6.5$; $r = -0.093$, $p = .69$) or level of nicotine dependence (FTND; $r = -.216$, $p = .21$).

PASAT-M Task Effects

Self-report and physiological response to the PASAT-M—Self-report and physiological responses to the PASAT-M are reported in **Table 1**. Changes in self-reported distress, skin conductance response (SCR), and heart rate (HR) during the task were examined with group $\times$ time repeated measures ANCOVA, with gender as a covariate. There was a significant effect of time for self-report distress, SCR, and HR from pre-task through the distress phase and no significant group $\times$ time interaction effects. Taken together and by design, self-report and physiological indices indicate an increase in distress for both groups from the easy to distress phase of the task.

A priori ROI activation in response to the PASAT-M—Mean percent signal change in response to distress [(Distress - Rest) - (Easy - Rest)] within *a priori* ROIs are displayed in **Table 2** for substance users and healthy controls. Healthy controls displayed deactivation in the MFG, vmPFC, ACC, and left IFG, while showing increased activation in the right IFG, right insula and amygdala. In contrast, substance users displayed deactivation across all hypothesized ROIs. An ANCOVA examined between group differences in ROI response to distress, controlling for gender. Compared to controls, substance users had less activity in the right and left MFG and right IFG, and trended toward greater deactivation in the left IFG. Mean percent signal change during the baseline phase of the PASAT-M (Easy-Rest) within *a priori* ROIs is displayed in **Table S2**. Substance users demonstrated greater activation in the right insula, and less deactivation in the amygdala during the Easy phase of the task compared to healthy controls.

Neural response to distress, group, and distress tolerance—The interactive effect of neural response to distress and group on DT was estimated with separate OLS regression models predicting DT for each ROI, with group as the moderator and gender as a covariate. The interaction term was significant for models including the right insula, ACC, right amygdala, bilateral MFG, right IFG, and right vmPFC (**Table S3**¹). To further understand the nature of this moderation, conditional effects (“simple slopes”) of each ROI on DT were estimated for each group (**Table S4**). As illustrated in **Figure 2**, increased activation in response to distress was positively associated with DT among substance users, but not controls within the bilateral MFG, right insula, ACC, right IFG, and right vmPFC.

Whole brain neural activation in response to the PASAT-M—Exploratory whole brain neural activation as a result of distress during the PASAT-M was obtained with the contrast of [(Distress - Rest) - (Easy - Rest)]. As displayed in **Figure 3a-b** and **Table S5a-b**, healthy controls and substance users demonstrated a robust neural response to distress in multiple areas, with substance users displaying a more robust deactivation map, although similar regions were observed across both groups. Regressing group onto the contrast of [(Distress - Rest) - (Easy - Rest)] resulted in significant group differences (**Figure 3c** & **Table 3**), with the substance users displaying less activity than controls in the superior frontal gyrus, lateral occipital cortex, left occipital fusiform gyrus, right MFG, juxtapositional lobule cortex, precentral gyrus, and precuneus.

Functional connectivity and association with distress tolerance—The right MFG was chosen as a seed ROI for PPI functional connectivity analyses due to its concordance with our *a priori* ROIs, as well as its observed group difference in task activation to distress. The right MFG PPI voxel-wise multiple regression analysis on the Group $\times$ DT interaction term revealed that PASAT-M induced distress was negatively associated with right MFG functional connectivity in two clusters, one including the right SFG and one aligned with our *a priori* ROIs, namely the vmPFC and subgenual ACC (vmPFC/sgACC) (**Figure 4**, **Table S6**). Mean percent signal change in the vmPFC/sgACC was extracted for each participant and included in an OLS regression model predicting DT, with group as the moderator and gender as a covariate. The interaction term was significant [$\beta = 1.349$, $SE = 0.424$, 95% CI : 0.488, 2.211, $p < .01$] (**Table S7**). Conditional effects of the rMFG-vmPFC/sgACC connectivity strength on DT were estimated for each group using OLS regression. As illustrated in **Figure 5**, increased right MFG-vmPFC/sgACC connectivity in response to distress was associated with greater DT among substance users [$\beta = 1.065$, $SE = 0.250$, 95% CI : 0.558, 1.572, $p < .001$], but not controls [$\beta = -0.284$, $SE = 0.346$, 95% CI : -0.987, 0.419, $p = .417$].

DISCUSSION

In the current study, we modified a computerized distress tolerance task for use in fMRI in order to examine the neural correlates of distress tolerance among and between a healthy control and regular substance using sample. The PASAT-M differentiated healthy controls

¹Significant values in all models in Tables S3 and S4 were unchanged when including the mean percent signal change during the Easy-Rest contrast as a covariate.

from substance users on levels of distress tolerance, with substance users evidencing significantly lower distress tolerance, which is in line with previous research (Ali et al., 2013; Quinn et al., 1996). As predicted, among substance users, higher distress tolerance during the task was associated with increased neural activation in the right insula, ACC, bilateral MFG, right IFG, and right vmPFC, as well as increased functional connectivity during distress between the right MFG and a vmPFC/sgACC cluster. A ceiling effect for distress tolerance was observed among healthy controls, limiting the interpretation of between group differences in the relation between neural response to the task and distress tolerance.

PASAT-M as a measure of distress tolerance

As designed, the modified distress tolerance task elicited increases in self-report and physiological indices of distress in both groups, and engaged brain regions consistent with tasks designed to elicit distress among either substance users or healthy control samples (Dedovic et al., 2005; Dedovic et al., 2009; Gianaros et al., 2005; Sinha, Lacadie, Skudlarski, & Wexler, 2004). All participants demonstrated increased activation in motor planning and execution substrates (left precentral gyrus; Ulrich & Kiefer, 2015), as well as deactivation in areas associated with response inhibition and self-awareness (inferior frontal gyrus; Morin & Michaud, 2007; Swick, Ashley, & Turken, 2008), working memory and emotion processing (middle frontal gyrus; Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015), recognition memory (precuneus; Dörfel, Werner, Schaefer, Von Kummer, & Karl, 2009), and reward anticipation (caudate; Benningfield et al., 2014). This is in line with task demands, as the increased speed of number presentations and forced failure would be expected to accompany the increased frequency of motor responding with the joystick, as well as decreased anticipation of reward. Critically, substance users demonstrated greater deactivations than controls in regions associated with response inhibition and action monitoring (juxtapositional lobule cortex; Swann et al., 2012), attentional reorientation (middle frontal gyrus; Japee et al., 2015), and recognition memory (precuneus; Dörfel et al., 2009). This may reflect greater challenges for substance users in activating neural regions responsible for detecting and responding to task demands in an ongoing manner while experiencing affective distress. Support that these differences are not due to differences in task engagement is reflected in similar group responses of self-reported motivation, task behavioral data, and activation patterns in regions associated with motor attention, representation, and execution.

Neural indices of distress tolerance

The PASAT-M differentiated healthy controls from substance users on levels of distress tolerance, with substance users evidencing significantly lower distress tolerance, which is in line with previous research (Ali et al., 2013; Quinn et al., 1996). However, only among substance users did we observe regions of interest associated with distress tolerance, namely the right insula, ACC, right IFG, bilateral MFG, and right vmPFC. The positive association between distress tolerance and activation in the prefrontal cortex and ACC is in line with evidence indicating that emotion regulation processes depend upon these regions initiating inhibitory control, working memory, and goal directed behavior. As part of the salience network (SN), the right anterior insula plays a critical role in detecting and evaluating

stimuli in order to engage task oriented responding (Menon & Uddin, 2010; Sutherland et al., 2012), suggesting that reduced activation in the right insula may lead to less recruitment and engagement of prefrontal regions primarily responsible for cognitive control processes (Jha, Fabian, & Aguirre, 2004; Terasawa, Fukushima, & Umeda, 2013; Wheelock et al., 2014).

We also investigated whether task-related functional connectivity was associated with distress tolerance. An analysis of the psychophysiological interactions (PPI) using the right MFG as the seed region demonstrated a significant interaction between right MFG-vmPFC/sgACC connectivity and group in predicting distress tolerance, with follow-up analyses indicating that substance users with higher distress tolerance demonstrated greater functional connectivity during the distress phase of the task between the right MFG and vmPFC/sgACC. Both the subgenual ACC and vmPFC are associated with signaling emotional significance and goal valuation (Bechara, Damasio, Tranel, & Damasio, 1997; Roy, Shohamy, & Wager, 2012), while the MFG has an important role in emotion regulation via cognitive control in non-substance using (Phillips, Ladouceur, & Drevets, 2008), and substance dependent (Moreno-López et al., 2012) samples. Our finding is in line with theory suggesting impairment in the ability of substance users to exert emotion regulation and cognitive control in the face of distress via top down mechanisms. In particular, Maier et al. (2015) reported a positive correlation between perceived stress during an acute stressor prior to task onset, and functional connectivity between the dlPFC and vmPFC during successful self-control in a goal directed food choice task. Our finding extends this research by directly measuring task specific functional connectivity during a distress task in which the choice to quit a goal directed behavior (i.e., low distress tolerance) is measured.

Contrary to our working hypothesis, neural activation as a result of distress induced by the PASAT-M did not predict distress tolerance among healthy controls. Although task effects indicated elevations in distress and engagement on the task, a clear ceiling effect is noteworthy, such that the majority of healthy control participants persisted on the task for the entire duration of the distress tolerance phase, limiting the within group variability in levels of distress tolerance. The healthy controls evidenced significantly less deactivation in the bilateral MFG and significantly greater activation in right IFG during distress, which was not observed in the substance users and may reflect a more effective cortico-limbic response to distress in healthy controls. Given evidence of task effects on distress, as well as the ceiling effect in levels of distress tolerance, it is premature to conclude that neural response to distress is unrelated to distress tolerance within a healthy population. Moreover, the ability to accurately characterize group differences is compromised. Future studies are needed to determine if extending the duration of the distress tolerance phase will capture a greater range of levels of distress tolerance among healthy controls.

Limitations and future directions

A number of limitations are of note. Our sample included regular non-treatment seeking cocaine users who also reported daily cigarette use and use of additional substances on a weekly or less basis. In addition, our substance using sample was predominately male. As such, generalizability of our results is limited among treatment seeking substance users,

females, and individuals who regularly use other substances. Low distress tolerance is associated with additional psychopathology and related constructs other than substance use disorder (Zvolensky, Vujanovic, Bernstein, & Leyro, 2010). It will be important for future work to rule out additional variables contributing to the current findings. Moreover, it will be important to determine if these findings extend to other DT assessment paradigms (see Magidson, Ali, Linstead, & Daughters, 2013 for a review) as well as to investigate whether neural response to distress on the behavioral paradigms is associated with self-report indices of DT. Given the existing literature indicating the utility of behavioral measures of DT in predicting post-treatment relapse, a next step will be to examine the utility of the neural indices of distress tolerance in predicting treatment response. Despite these limitations, this study provides novel data on the neural mechanisms underlying distress tolerance among substance users, a construct implicated in the development and maintenance of multiple psychopathologies (Leyro, Zvolensky, & Bernstein, 2010).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Task design for the Paced Auditory Serial Addition Task distress tolerance task for fMRI (PASAT-M).

Figure 2.

Moderation of the effect of a prior ROI response to distress on distress tolerance (DT) by group. Points on graph reflect point estimate of conditional effect of ROI on DT (Mean $\pm$ 1 SD). Distress tolerance=persistence in seconds during the DT phase of the PASAT-M. r=right; l=left; ACC=anterior cingulate cortex; MFG=middle frontal gyrus; IFG=inferior frontal gyrus; FMC=frontal medial cortex.

Figure 3a-c.

PASAT-M response to distress [(Distress-Rest) – (Easy-Rest)] among (a) healthy controls, (b) substance users, and (c) the contrast of substance users < healthy controls. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 3.0$ and a (corrected) cluster significance threshold of $p = 0.05$.

Figure 4.

PPI Analysis. Interaction between Group and DT during PASAT-M distress [(Distress-Rest) – (Easy-Rest)] with the r MFG as the seed region. There was a significant negative interaction between the r MFG and a bilateral vmPFC/sgACC cluster and SFG. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.6$ and a (corrected) cluster significance threshold of $p = 0.05$. r=right; l=left; sgACC=subgenual anterior cingulate cortex; MFG=middle frontal gyrus; SFG=superior frontal gyrus.

Figure 5.

The effect of the vmPFC/sgACC cluster functional connectivity with rMFG on distress tolerance (DT) by group. Points on graph reflect point estimate of conditional effect of connectivity on DT (Mean $\pm$ 1 SD). Distress tolerance=persistence in seconds during the DT phase of the PASAT-M. vmPFC/sgACC functional connectivity with r MFG= the average rMFG-vmPFC/sgACC PPI beta coefficient during distress on the PASAT-M; r=right; l=left; vmPFC=ventromedial prefrontal cortex; sgACC=subgenual anterior cingulate cortex; MFG=middle frontal gyrus; *** $p < .001$.

Table 1

Group characteristics and self-report, behavioral, and physiological response to the PASAT-M.

		Substance Users (<i>n</i> =21)	Healthy Controls (<i>n</i> =25)	Statistic
Age		41.95 (6.95)	40.08 (8.03)	$F(2, 45)=0.42$
IQ		102.8 (12.5)	108.0 (13.2)	$F(2, 45)=2.15$
Gender (% male)		90.5	64.0	$\chi^2(1)=4.40^*$
Race (% Black/African American)		85.7	80.0	$\chi^2(1)=0.26$
Distress Tolerance (seconds)		389.9 (232.9)	487.6 (180.7)	$F(1, 45)=3.9^{*†}$
Performance (% Correct)		21.47 (9.05)	19.27 (10.21)	$F(1, 45)=.77$
Motivation to Perform Well (1-10)		8.15 (1.89)	8.16 (1.88)	$F(1, 45)=.01$
Self-Report Distress Rating	Pre-Easy Phase	22.93 (29.56)	10.16 (19.44)	$^a F(3, 132)=13.62^{***}$
	Post-Easy Phase	23.20 (27.86)	11.21 (19.01)	$^b F(1, 42)=2.30$
	Post-Latency Phase	29.86 (29.72)	22.94 (22.84)	$^c F(3, 126)=1.05$
	Post-Distress Phase	32.19 (30.82)	24.68 (27.22)	
Skin Conductance Response (μmho)	Easy Phase	6.71 (1.78)	5.54 (1.48)	$^a F(1, 42)=6.18^*$
	Distress Phase	7.08 (1.69)	5.59 (1.56)	$^b F(1, 42)=7.66^{**}$
				$^c F(1, 42)=3.91$
Heart Rate (bpm)	Easy Phase	70.71 (13.53)	91.19 (20.43)	$^a F(1, 42)=4.21^*$
	Distress Phase	73.74 (12.74)	97.81 (25.29)	$^b F(1, 42)=15.01^{***}$
				$^c F(1, 42)=0.03$

Note:

^a Main effect of time from pre-post task^b Main effect of group^c Group × Time interaction[†] Statistic based on log transformed values* $p < .05$ ** $p < .01$ *** $p < .001$.

Table 2

Group means for percent signal change among *a priori* regions of interest.

	Substance Users (<i>n</i> =21)	Healthy Controls (<i>n</i> =25)	<i>F</i> Statistic
r Insula	−0.145±0.363	0.069±0.506	2.70
r Amygdala	−0.195±0.814	0.124±0.933	2.07
l Amygdala	−0.363±0.880	0.109±1.269	1.54
ACC	−0.162±0.289	−0.019±0.372	2.10
r MFG	−0.439±0.555	−0.044±0.369	8.30 ***
l MFG	−0.443±0.546	−0.129±0.341	5.65 *
r IFG	−0.246±0.399	0.049±0.524	4.59 *
l IFG	−0.596±0.799	−0.230±0.527	3.47
r vmPFC	−0.176±0.997	−0.114±0.969	0.04
l vmPFC	−0.131±0.880	−0.126±0.686	0.00

r=right; l=left; ACC=anterior cingulate cortex; MFG=middle frontal gyrus; IFG=inferior frontal gyrus; vmPFC=ventromedial prefrontal cortex.

Note:

** $p < .01$

* $p < .05$

*** $p < .001$.

Table 3

Clusters and max Z-values in response to distress [(Distress-Rest)-(Easy-Rest)] for the contrast of Substance Users < Healthy Controls.

Deactivations	Voxels	<i>p</i>	Z-Max X (mm)	Z-Max Y (mm)	Z-Max Z (mm)
R. Superior frontal gyrus	466	2.71×10^{-5}	12	14	70
-Juxtapositional lobule cortex ^a					
-Bilateral precentral gyrus ^a					
L. Lateral occipital cortex	301	0.0008	-22	-70	40
-L. Precuneus ^a					
L. Occipital fusiform gyrus	292	0.0011	-34	-78	-16
R. Middle frontal gyrus	187	0.0143	30	8	60
-R. Superior frontal gyrus ^a					
R. Lateral occipital cortex	147	0.0472	28	-64	58
-R. Precuneus ^a					

Note:

^aRegions that also showed activation in the clusters.