Neural Correlates of Stress Predict Future Cocaine Use

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Abstract

Cocaine use disorder has wide-ranging social, economic, and health-related consequences, including changes to the neural stress networks that may be linked to deficits in goal-directed behavior. Distress tolerance (DT), or the ability to withstand negative affect during goal-directed activities, is implicated in maintaining substance use disorders. Low distress tolerance (measured behaviorally) has been linked to worse treatment outcomes, shorter abstinence attempts, and more days of substance use. Daughters et al. (2016) validated a measure of DT (the Paced Auditory Serial Addition Task, or PASAT) for an fMRI scanner to examine the neural correlates of DT. As a follow up, the current study used longitudinal data from a sample of 24 regular cocaine and nicotine users to determine if the neural correlates associated with stress could be used to predict future substance use 30 days post-scan. There was a positive correlation between the percentage of days used crack/cocaine and the bilateral amygdala activation in response to stress. This is in line with prior studies regarding the implication of the hyperactivation of the amygdala in anxiety and increased substance use frequency. Future research should utilize a treatment-seeking population of cocaine users to determine whether neural regions linked to DT can predict treatment outcomes and relapse frequency to potentially find biomarkers to target with treatment.

Neural Correlates of Stress Predicts Future Substance Use for Crack/Cocaine Users

Across the United States, over 1.5 million people have used cocaine in the past month, with approximately 16.60% of adults reporting lifetime cocaine use (Center for Behavioral Health Statistics and Quality, 2016). In 2014, approximately 913,000 people in the US met DSM-V criteria for cocaine use disorder (National Institute for Drug Abuse [NIDA], 2016). While many people start using to feel the increased energy and euphoria that cocaine may bring, cocaine is a powerful stimulant and the addictive nature of the drug can lead to long-term substance use (NIDA, 2016). This long-term cocaine use presents with several possible side effects including impaired judgment, irritability, malnourishment, and the risk of overdosing (NIDA, 2016). Drug misuse has wide ranging medical consequences, ranging from increased cancer risk, cardiovascular disease, kidney damage, liver damage, and increased mortality rates (NIDA, 2016). From an economic perspective, substance abuse costs the nation more than 484 billion dollars, which is significantly more than diabetes or cancer (NIDA, 2005). The clear negative impact of substance use helps validate the need for continued research into the addictive nature of drugs and how neural changes can influence continued use despite negative consequences. Specifically, we hope to eventually find biomarkers that can be used as targets for intervention as well as predictors of treatment outcomes and relapse prevention.

Distress and Negative Affect Related to Substance Use Relapse

Despite the numerous consequences present with cocaine use, cocaine use disorder has one of the higher relapse rates and treatment dropouts among drug classes (Dutra et al., 2008). One of the factors affecting relapse rates is thought to be exposure and reactivity to stress, suggesting that individuals with higher levels of affective distress during withdrawal have more relapse events and fewer days to first cocaine use (McKay et al., 1999; Miller & Westbrook,

1996; Sinha, 2001). One of the main underlying theories for the high rates of relapse in substance use disorders is the negative reinforcement model. Negative reinforcement refers to removing an aversive stimulus to continue or increase a response or behavior (Koob, 2013). For substance use, the withdrawal symptoms that occur during an abstinence attempt act as negative reinforcement mechanisms to continue use and perpetuate the relapse cycle (Koob, 2013). The model focuses on negative affect as the main mechanism for the negative reinforcement of drug addiction, since negative affect is a constant withdrawal element across drug classes (Baker, 2004). Drug users try to avoid the stressful negative internal states by continuing to use drugs, often without awareness (Erb, 2009; Baker, 2004). As levels of the drug drop in their body, they become more motivated to seek drugs through withdrawal-based learning and prior affective-ameliorating learning (Baker, 2004). When a drug user attempts to quit, the negative affect that comes when drugs are no longer in the system can be debilitating and too uncomfortable to handle. This can lead to the user breaking the abstinence attempt and using drugs to decrease negative affect (Sinha et al., 2006; Baker et al., 2006). This vicious cycle of drug use and negative affect perpetuates the substance use and makes quitting incredibly difficult and provides the motivational basis for continuing use (Baker, 2004).

Severity of negative affect is a predictor of relapse and treatment outcome among substance users (Mulvaney, Alterman, Boardman, & Kampmann, 1999). This relationship indicates the importance of looking at the differing vulnerabilities to negative affect in substance users to determine who is more susceptible to relapse. One way to measure the avoidance of negative affect is through a laboratory distress tolerance task, which can serve as a proxy for negative reinforcement behavior. Measures of distress tolerance, defined as the ability to persist in goal-directed behavior while experiencing distress, can help ellucidate the differences between

substance users in their ability to resist negative affect and pursue successful treatment outcomes (Ali, Seitz-Brown, & Daughters, 2015; Daughters, Lejuez, Kahler, Strong, & Brown, 2005a).

Negative Affect Relating to Distress Tolerance

Distress tolerance can be defined as the tendency to pursue a goal even when discomfort (physical or psychological) is present (Ali et al., 2015; Brown et al., 2009). For substance users, distress tolerance can be defined as how well a person is able to tolerate negative affect, or the negative emotions that come with withdrawal associated with the maintenance of substance use disorders (Baker et al., 2006; Daughters et al., 2005a). Low distress tolerance indicates that a person would be unlikely to persist in a task or activity that is uncomfortable or difficult because they have an inability to tolerate negative affect and would rather avoid the situation, even if that results in consequences. High distress tolerance indicates that a person would be more likely to persist on uncomfortable or difficult tasks, like persisting through negative affect during a withdrawal attempt (Brown et al., 2009; Quinn, Brandon, & Copeland, 1996). Distress tolerance has been linked to the maintenance of several pathologies, including substance use disorder (Leyro, Zvolensky, & Bernstein, 2010). Based on the theory of negative reinforcement and affective distress, substance users with lower distress tolerance would be associated with a faster return to substance use during an abstinence attempt, as they would have more difficulty resisting the negative affect (Brown, Lejuez, Kahler, & Strong, 2002). Several prior studies looked at the impact of low distress tolerance on treatment outcomes and relapse rates, and found consistent relationships between low distress tolerance and negative outcomes. Smoker populations who were unable to maintain abstinence for short periods of time had shorter task persistence on a distress tolerance task versus a smoker population with sustained abstinent periods. It was hypothesized that the immediate users had lower distress tolerance and increased

response to avoid negative affect (Abrantes et al., 2008; Brandon et al., 2003; Brown et al., 2002; Brown et al., 2009). Additionally, low distress tolerance measured through laboratory paradigms in substance users has been associated with greater substance use frequency (Quinn et al., 1996; Ali et al., 2013), relapse (Brown et al., 2009), shorter abstinence frequency (Daughters et al., 2005b), and higher treatment dropout (Daughters et al., 2005a). While these studies show evidence for low distress tolerance impacting substance use outcomes, understanding the neural mechanisms underlying stress pathways and DT is key to finding potential markers of substance use frequency and relapse.

Neural Stress Indices Impacted by Substance Use

The neural changes associated with substance users have been linked back to the negative reinforcement model, such that substance users tend to develop a chronic negative affect throughout their use which increases their proclivity to relapse (Koob and Le Moal, 2001; Sinha, 2001). There is evidence that these neural changes occur in cortico-striatal pathways, and may underlie the deficits in inhibitory control, working memory, and regulating distress states that can contribute to continued substance use (Li & Sinha, 2008; Ma et al., 2014). A main processing center of central executive functions is thought to be the right medial frontal gyrus (MFG) and other prefrontal cortical regions (Goldstein & Volkow, 2011). These areas have found to be hypoactivated in cocaine users, which may underlie the cognitive deficits present that make substance users more susceptible to relapse and drug use (Hester & Garavan 2004; Kaufman et al. 2003; Li & Sinha, 2008). Regulation of the prefrontal cortical regions is thought to be driven by three main regions: the insula, the amygdala, and the anterior cingulate cortex (ACC). Dysregulation in insula activation patterns has been associated with relapse in substance users and increased anxiety symptoms, suggesting that dysfunction in the ability to recruit

congnitve resources may be involved in substance use (Menon & Uddon, 2010; Paulus & Stein, 2006). Additionally, removal of insula in nictone users via lesion led to decreased urge to smoke and decreased relapse rates (Naqvi, Rudrauf, Damasio, & Bechara, 2007). Based on these studies, the insula is thought to be a key neural region for conscious interoception and cue-induced urges, and may recruit prefrontal cortical regions to make plans and direct attention towards obcuring drugs during periods of stress (Naqvi & Bechara, 2009). The amygdala is thought to have a role in conditioned-cued relapse (See, Fuchs, Ledford, McLaughlin, 2003) and attending to negative emotionally salient stimuli during stress situations (Hermans et al., 2014; Menon, 2015). Hyperactivation in the amygdala in substance users has been associated with emotional abnormalities and increased crack/cocaine length of use (Crunelle et al., 2015; Li & Sinha, 2008).

More recent studies have begun to look at connectivity patterns between and within three main networks in substance users. These networks include the central executive network (CEN), the default mode network (DMN), and the salience network (SN). Many of the regions of interest (ROIs) that were just examined in substance users are implicated in these pathways and give us a deeper understanding of how the regions may be working together to maintain substance use disorders during stress.

Neural Stress Networks

The framework for thinking about stress pathways as resting state networks was described by Menon and Uddin (2010), where they propose that the insula acts as a hub to recruit other neural resources to respond to salient stimuli, like stressors. The insula, anterior cingulate cortex, and amygdala act as a ‘salience network’ that recognizes and identifies important stimuli, and determines their strength and nature (Craig 2009; Menon, 2015; Seeley et al., 2007). The

two other essential networks (central executive network and default mode network) are ideally switched 'on' or 'off' based on the activation of the insula (Menon & Uddin, 2010; Sridharan et al., 2008). The salience network and central executive network (CEN) tends to become active during working memory and goal-directed behavior under stress, while the default mode (DMN) is generally deactivated relative to baseline (Greicius et al., 2003; Menon & Uddin, 2010). The DMN is active during self-monitoring and autobiographical functions (Spreng et al. 2009). The CEN includes the right medial frontal gyrus (MFG) and the posterior parietal cortex (PPC) as main ROIs, while the DMN involves the posterior cingulate cortex (PCC), the right inferior frontal gyrus (rIFG), and the ventromedial prefrontal cortex (vmPFC) (Menon, 2011).

Prior research has shown changes in connectivity between and within these three networks occur in substance users, which could underlie their deficits in resisting stress during an abstinence attempt (McHugh, Gu, Yang, Adinoff, & Stein, 2016). Additional research has shown that increased salience network activity in the amygdala and insula has been linked to anxiety disorders, supporting the idea that additional salience network involvement can be maladaptive in some cases (Paulus and Stein, 2006; Stein, Simmons, Feinstein, & Paulus, 2007). Within the executive control network, cocaine users with decreased intrinsic connectivity had fewer days of abstinence, suggesting that they could not recruit enough cognitive resources to withstand distress (McHugh et al., 2016). Substance users often fail to deactivate the DMN, which then affects the attentional resources they can allocate towards the CEN (Lerman et al., 2014; Mayer et al., 2013). Based on the importance of distress tolerance in abstinence attempts, it was hypothesized that there may be neural indices underlying the behavioral proxy of distress tolerance that that can contribute to vulnerability of negative affect during abstinence attempts among substance users.

Neural Indices of Distress Tolerance

To continue to pursue potential biomarkers and relapse prevention targets, Daughters et al. (2016) looked for neural regions associated with distress tolerance during a stress-inducing task to identify underlying differences between controls and substance users. In order to study DT neurally, the PASAT task was validated for an MRI scanner (PASAT-M) in the same study design as this study. The study compared regular cocaine and nicotine users (n=21) and control subjects (n=25) without group differences in age, ethnicity, and IQ. The PASAT-M results validated the task for the scanner via increases in self-report and physiological measures of distress (such as self-report distress ratings, skin conductance response, and heart rate) from the easy portion of the task to the distress portion of the task (Daughters et al., 2016; Dedovic et al., 2005). Additionally, both groups displayed increased activation in motor planning and execution regions (left precentral gyrus; Ulrich & Kiefer, 2015), and decreased activation in response inhibition (inferior frontal gyrus; Morin & Michaud, 2007), reward anticipation (caudate; Benningfield et al. 2014) and working memory and emotional processing (middle frontal gyrus; Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015). These activation patterns follow task demands of increased motor response and decreased reward expectancy as the task continues and gets more difficult (Daughters et al., 2016). Substance users displayed greater deactivation compared to controls in the juxtapositional lobule cortex (Swann et al., 2012), implicated in response inhibition and action monitoring, as well as the middle frontal gyrus for attentional reorientation (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015) and the precuneus for recognition memory (Dörfel et al., 2009). This potentially means that substance users have difficult activating neural regions that help respond to task demands while under distress

(Daughters et al., 2016). Overall, substance users experienced lower distress tolerance compared to healthy controls, in line with prior research (Ali et al., 2013, Daughters et al., 2016).

After the validation of the PASAT-M, ROIs were selected *a priori* based on prior theory and empirical evidence of their involvement in stress pathways and goal directed pathways. These regions included the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), amygdala, right insula, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), ventromedial prefrontal cortex (vmPFC) and posterior parietal cortex (PPC) (Li & Sinha, 2008; Menon, 2011; Daughters, et al., 2016). Activation in these ROIs was measured using the subtraction logic of [(Distress-Rest)-(Easy-Rest)] for both substance users and controls. Healthy controls showed decreased activation in the MFG, vmPFC, ACC, and left IFG, as well as increased activation in the right IFG, right insula, and amygdala. As a contrast, substance users displayed deactivation across all *a priori* ROIs (Daughters et al., 2016). Additionally, substance users showed a significant association between increased activation in bilateral MFG, right insula, ACC, right IFG, and right vmPFC and increased distress during the task. Control subjects did not display this association. The prefrontal cortex and ACC are involved in inhibitory control and working memory, and the association suggests that working memory and inhibitory control are important in emotional regulation when under distress (Sutherland et al., 2012). The right insula is part of the salience network that detects novel stimuli and recruits other areas to respond (Naqvi & Bechara, 2009). This potentially reflects substance users with low distress tolerance having greater difficulty recruiting emotional regulation neural regions during distress (Daughters et al., 2016). Overall, these findings fit in with the prior studies examining networks implicated in stress, and indicate that differences in activation between regions within these networks can underlie differences in ability to persist through distress towards a goal. Decreased recruitment of

salience network and central executive regions was associated with lower DT, suggesting that substance users with lower DT have more difficulty recruiting and engaging cognitive control mechanisms during stress than substance users with higher DT (Daughters et al., 2016).

Gaps in Research

Based on the prior research, I propose a continuation of the study completed by Daughters et al. (2016) to continue looking at distress tolerance and activation in neural stress pathways in substance users. While this paper found evidence for neural indices of DT and validated the PASAT-M, there was not any predictive data analyzed. I will utilize the neural indices associated with stress and look at their ability to predict substance use frequency at a follow-up appointment. This is a useful goal as a preliminary analysis of the predictive ability of neural ROIs involved in the stress pathway, and will allow us to better understand if neural indices associated with stress can act as significant future targets of relapse prevention. Since we eventually hope to find neural indices that predict relapse and can be used as treatment targets, determining the relationship between neural activation in stress pathways and future substance use frequency is a useful first step.

Current Study

Existing literature has indicated that behavioral measures of DT can be used to predict future substance use among cocaine users. We now propose examining the utility of using neural indices activated during a stressful task to predict substance use at a follow-up appointment 30 days post-scan. Based on theory that the regions within salience network are activated in response to distressing stimuli, we would expect an increase in activation in these regions during stress to be associated with more days of substance use at follow-up (Menon, 2015). Since we recruit the resources of the central executive network during goal-directed behavior, it is

expected that decreased neural activation during stress in areas associated with the central executive network regions will result in more days used crack/cocaine because fewer resources are being allocated towards these regions (Lerman et al., 2014). Additionally, we expect that increased activation during stress in regions associated with the default mode network would result in more days used crack/cocaine. An increase in activation of regions within the DMN indicates that fewer resources are being allocated towards goal-directed behavior and cognitive control in CEN regions, which may also lead to increased rumination and negative thoughts during the stressful task (Lerman et al., 2014).

Hypotheses/Aims:

Aim: To examine if neural response to distress predicts frequency of future crack/cocaine substance use.

H1. Crack/cocaine users with lower neural activation in the PPC and MFG ROIs will have more days of crack/cocaine use 30 days post-scan.

H2. Crack/cocaine users with higher neural activation in the amygdala, insula, ACC, IFG, PCC, and vmPFC will have more days of crack/cocaine use 30 days post-scan.

Method

Participants

A total of thirty-one substance using (SU) participants were recruited from Baltimore City and the surrounding area and provided verbal and written consent based on the IRB of NIDA. To be considered for the study, participants must be right-handed, between the ages of 18 to 55 years old, and in good health. Participants were recruited from residential areas in the general Baltimore City area and were generally non-treatment seeking. Substance users were

eligible if they reported regular cocaine (i.e. ≥ 2 times per week) use during the past year prior to participation, as well as daily nicotine use. Substance users also could not meet DSM-IV criteria for current substance dependence on any other substance other than cocaine or nicotine. Participants were also excluded based on MRI requirements, and could not have metallic devices, claustrophobia, or other issues that would prevent them from entering the scanner. Participants were excluded if they were pregnant, had major medical illnesses, had neurological issues, had any current psychiatric disorders, had an IQ less than 85 as measured by the Wechsler Abbreviated Scale of Intelligence (WASI) vocabulary subtest, or were intoxicated/had a positive drug screen at the time of the assessment.

In the current study, six participants were excluded from analyses because of excessive head motion or technical problems associated with the scan (n=4) or if they were nonsmokers (n=2), for a final sample of 24 participants. The sample was predominantly male (92%) with an average age of 40.17 years (SD=8.41) ranging from 23 to 50 years. The sample was also predominantly Black/African American (71%), followed by Caucasian (25%), and one participant who reported 'Other'. 42% of the sample was unemployed, 29% of the sample was working part-time at the time of the baseline, 25% were working full-time, and 4% of participants were students. In regards to substance use, 75% reported past year cocaine or crack use at least 2-3 times per week and had an average score of 3.67 (SD=1.91) out of possible score of 7 on the Fagerstrom Test of Nicotine Dependence (FTND). Participants had an average IQ of 102.31 (SD=12.63) as measured by the WASI. This study is interested in substance use during the first 30 days after the assessment (i.e., 1-month follow-up). The retention rate from the baseline assessment to the one-month follow up (FU1) was relatively high (83%).

Procedure

Participants initially were screened over the phone and then in person at NIDA. Participants were given a medical examination, a pregnancy test, a urine drug screen, and a Breathalyzer. Additionally, the Wechsler Abbreviated Scale of Intelligence (WASI) was administered to check for IQ eligibility using the vocabulary subtest. Participants were asked for contact information and given an MRI screening form for safety regarding the MRI machine. If participants were qualified, they were taken to a mock MRI scanner to assess their comfort level. Participants were also given a computer administered Structured Clinical Interview for DSM-IV, which assessed for Mood Disorders, Anxiety Disorders, Substance Use Disorders, Psychotic Symptoms, Somatoform Disorders, and Eating Disorders. The Substance Use Disorder section included questions to assess abuse and dependence across all drug classes. If participants met all eligibility criteria, they were considered for the study and could schedule their baseline assessment (BLA). At the baseline assessment, participants signed for informed consent and participated in a brief medical screen including a urine screen, Breathalyzer, and pregnancy test. The tasks to be completed in the scanner were described in detail, and participants practiced the distress tolerance task until they demonstrated competence. Participants were then placed in the MRI scanner and completed several tasks, including the distress tolerance task. Following the scanner, participants were given a battery of self-report and interview measures. The entire appointment lasted around 6 hours. There were follow-up appointments one month (FU1), 3 months (FU3), 6 months (FU6), and 12 months (FU12) post-baseline, but this study is only considering data from FU1. The follow-up procedure was very similar to baseline assessments. They participated in a medical screen, a urine test, a Breathalyzer, and a pregnancy test, the fMRI scanning session, and a battery of self-report and interview measures.

Measures

The battery of measures utilized in this study assessed demographic characteristics, problems related to substance use, levels of affect and distress, and emotional regulation skills via self-report.

Time Line Follow Back. A clinician administered the Time Line Follow Back (TLFB) at baseline and all follow up assessment to assess and quantify recent drug use. It is a widely used measure for assessing substance use with high test-retest reliability, high validity, and agreement with urinalysis results (Fals-Stewart et al., 2000). The clinician uses calendars marked with the dates of assessments to recount the number of days used and the amount of each substance used across the time period. The time period for the 1-month follow-up assessment was from the baseline assessment to FU1, including the date of the assessments. Participants were asked specifically to recount their alcohol, cocaine, heroin, and marijuana use and the amount used on each day within the assessment period was recorded. Substance use frequency at the 1-month follow-up was calculated as the percentage of days used in the past 30 days prior to the assessment for 'crack/cocaine use'.

Self-report measures. A number of self-report measures were administered to account for potential covariates, namely, variability in cognitive ability (IQ), impulsivity, mood (depressive symptoms, anxiety symptoms), emotion regulation, substance use behavior, and demographics. Basic demographic information including age, income, education, and socioeconomic status was collected via self-report. The vocabulary portion of the Wechsler Abbreviated Scale for Intelligence (WASI) was administered for screening purposes to assess IQ (Wechsler, 1999). The Barratt Impulsivity Scale (BIS) was used to assess impulsivity across three domains: non-planning, attentional, and motor. The BIS consists of 30 questions on a four-

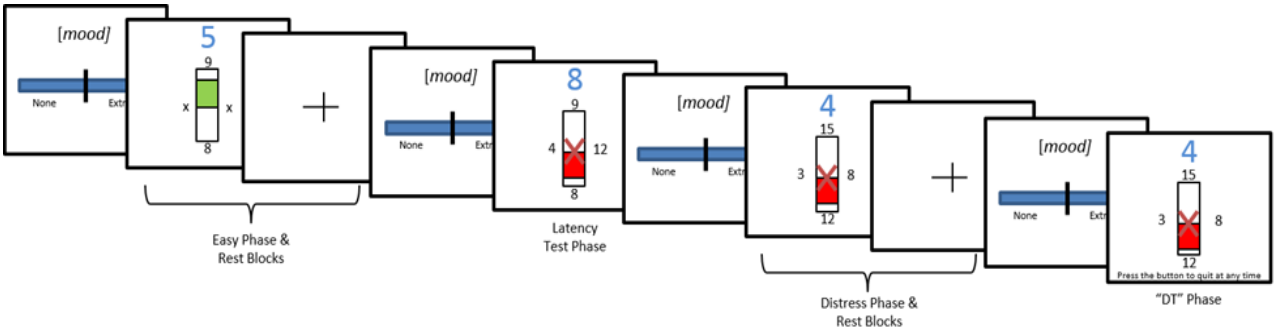
point Likert scale, and has high internal consistency across a diverse population of subjects (Patton et. al., 1995). The scale ranged from 1 (rarely/never true) to a 4 (almost always true) and assessed impulsiveness across different situations, with a higher composite score indicating higher impulsivity. The Beck Depressive Inventory (BDI-II) assessed current depressive symptoms over the past seven days through a 21-item questionnaire. The rating scale ranged from 0-3, with a summary score range of 0-63 (Beck, 1993). The Beck Anxiety Inventory (BAI) assessed current anxiety severity over the past seven days through a 21-item inventory with ratings on a 0-3 scale. The summary scores range from 0-63 (Beck, 1996). The BDI and BAI have discriminant validity among patients with depression and anxiety, and are seen as valid and reliable assessment tools across populations (Beck, 1993 & Beck, 1996). The Short Inventory of Problems (SIP) was used to look at problems from substance use across different life domains. The SIP domains include physical, interpersonal, intrapersonal, impulse control, and social responsibility. The questionnaire is a 15-item self-report measure asking about the frequency of consequences faced on a 0-3 scale (never, once or twice a month, twice a week, daily) with a total composite range of 0-45 (Bender et al., 2007). The Drug Use Questionnaire (DUQ) was used to assess crack/cocaine use over the past year to confirm that participants were regular crack/cocaine users. The frequency of use at the time when they were using most was measured on a six-point scale: ‘never’, ‘one time’, ‘monthly or less’, 2 to 4 times a month’, ‘2 to 3 times a week’, and ‘4 or more times a week’ (Grant, Contoreggi, & London, 2000). The Fagerstrom Test of Nicotine Dependence (FTND) was utilized to measure smoking status and confirm all substance users were also smokers. The severity of use is measured on a scale from 0-7, and this measure has high validity across populations for physical nicotine use (Fagerstrom, 2012).

Distress tolerance task. The distress tolerance task used in this study is called the

PASAT-M or Paced Auditory Serial Addition Task for fMRI (Figure 1; Daughters et al., 2016). The PASAT, or Paced Auditory Serial Addition Task, is a common task used to study distress tolerance in substance use populations (Lejuez, Kahler, & Brown, 2003). The task consists of a series of flashing numbers, and participants must add the number shown currently to the prior number shown, and select the correct answer using a joystick before the next number appears (Daughters et al., 2016). There are four possible answer choices shown, and the participant must move the joystick in the direction of the correct answer. When the participant gives a correct answer, their score will increase and they will hear a bell. When the participant gives an incorrect answer or answers too slowly, their score will decrease and they will hear a loud explosion sound. There were four phases of the PASAT-M, with mood ratings between each phase to assess affective distress. The easy phase was first, and was used as a control measure to keep the affective distress at a minimum. It consisted of six 60-second activity phases, with 35-second breaks in between the activity phases. The latency phase was second and was designed to determine the baseline skill level of that participant. It lasted for 5 minutes straight, and the numbers appeared faster with every correct response and slower with incorrect responses. This phase calculates the mean latency of the participant, which is utilized in the subsequent rounds. The third phase was the distress phase, which presents the numbers at a 2.5X faster pace than the latency phase. It is designed to induce affective distress and create aversive situations through the loud explosions. Participants are told that their performance during this round will influence the amount of money they win at the end of the task. The final phase is the phase that is actually measuring distress tolerance, or goal-directed behavior while experiencing affective distress. The DT phase can last up to ten minutes, but participants are instructed that they can quit at any time. Participants are told they are winning back earnings they lost in the distress phase, and will no

longer lose money or points for incorrect or slow answers. This rationale is to ensure participants do not quit to prevent further loss, but are continuing to engage in goal-directed behavior. This final phase is the construct of distress tolerance that we use for behavioral data, and is measured by the time it takes for the participant to quit the task.

Figure 1. Task design for the Paced Auditory Serial Addition Task distress tolerance task for fMRI (PASAT-M). Reprinted with permission from Daughters et al., (2016).



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 2s, echo time (TE) of 27ms, field of view (FOV) of 220x220mm, 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 ($1mm^3$ isotropic voxels, TR of 1.9s, TE of 3.51ms, FA of 9). The functional and anatomical data were pre-processed and analyzed using FMRIB's Software Library (FSL; ww.fmrib.ox.ac.uk/fsl) using FSL FEAT v. 6.00. Further details on preprocessing steps are reported in Daughters et al., 2016.

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)] (Daughters et al., 2016).

Regions-of-interest (ROIs) were identified *a priori* based on empirical and theoretical evidence for their associating 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), posterior cingulate cortex (PCC), amygdala, right insula, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), and ventromedial prefrontal cortex (vmPFC), 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 featquery and then entered in to SPSS Version 22 (Corp, Released 2013).

Analytic plan. Preliminary data analyses included distributional properties of the dependent and independent variables. Variables demonstrating skew and/or kurtosis were transformed for subsequent analyses. These variables included distress tolerance, BAI, BDI, and

percentage of days used alcohol at baseline. The means and standard deviations for demographics, substance use variables, and participant characteristics were determined. The correlations between substance use frequency variables and potential covariates were run to look for any additional factors that may be contributing to the correlation between ROI activations in response to distress and substance use frequencies. To test the main hypotheses, correlations between percent signal change in *a priori* ROIs and the substance use frequency variable were run, partialing out any significant covariates.

Results

Participant characteristics are reported in Table 1, and include demographic variables, past 30 day crack/cocaine and alcohol use frequency, cognitive ability (IQ), impulsivity, mood (depressive symptoms, anxiety symptoms), emotion regulation, and distress tolerance. Covariates were determined by examining their relationship to our primary outcome variable, namely 30-day crack/cocaine use frequency, and are presented in Table 1 as well. Distress tolerance, BDI, BAI, and percentage days used alcohol at baseline were positively skewed and therefore log transformed for all analyses. The variable significantly associated with the substance use frequency at FU1 was the percentage of days used crack/cocaine in the 30 days prior to the baseline assessment (r=.902, p=.000).

Neural response to stress as predictors of future substance use

Partial correlations were calculated between percent bold signal change in a priori ROIs during distress and substance use frequency at FU1, partialing out the contribution of the significant covariate. The substance use outcome of interest was percentage of days used crack/cocaine in the 30 days before FU1. The results of the correlations are shown in Table 2.

1-month follow up. There was a significant positive association between 30-day crack/cocaine use and the right (r=.597, p=0.007) and left (r=.544, p=.016) amygdala, and approached significance with the right vmPFC (r=.510, p=.052) and the right anterior insula (r=.447, p=.055). These are illustrated in Figures 2a-d.

Discussion

In the current study, we utilized the activation in neural indices during distress to predict future substance use frequency in crack/cocaine users at 30 days post-scan. After controlling for the amount of crack/cocaine use prior to baseline, we conducted correlations between the predetermined neural indices associated with distress and future substance use frequency.

There were several significant relationships present in these correlations. The two statistically significant relationships present included the activation in the right and left amygdala and substance use frequency. In support of the working hypothesis, greater activation in the left and right amygdala was associated with greater percentage of days used crack/cocaine at FU1. The right anterior insula was also approaching a positively significant relationship with the substance use frequency. Previous research suggests that the amygdala is a region that controls motivation and emotional inputs to the anterior insula (Menon, 2011), while the insula plays a major role in switching between distinct brain networks across task paradigms and stimulus modalities (Sridharan, 2008). This result has been supported by previous studies regarding dysfunction in the amygdala and insula being linked to greater anxiety (Paulus and Stein, 2006; Stein, Simmons, Feinstein, & Paulus, 2007) and greater substance use frequency (Crunelle et al., 2015).

Additionally, greater activation in right vmPFC was associated with greater percentage of days used crack/cocaine, which matched the direction of the initial hypothesis. The vmPFC is

thought to mediate aspects of emotional dysregulation in substance users (Sutherland et al., 2012). Increased activation could also indicate greater rumination/negative thoughts about self during task and daily activities, perpetuating the cycle of drug use by maintaining negative affect and negative self-thoughts (Mayer, Wilcox, Teshiba, Ling, Yang, 2013).

These results are in line with expected activations in the networks associated with stress as well. We did not find any significant findings in regards to activation in the central executive network regions, where we expected to find decreased activations associated with cognitive control deficits. Two regions within the salience network (bilateral amygdala and right anterior insula) were associated with greater frequency of use at follow-up. Although activation of the salience network during stress results in greater cognitive control and increased ability to persist towards a goal in healthy controls (Menon & Uddin, 2008), substance users displayed greater days of substance use with increased amygdala and insula function. One potential explanation that can help explain this difference is that the amygdala and insula, although activated during stress, may be recruiting the wrong resources and strengthening connections that are maladaptive. The increased salience network activation could instead be recruiting additional default mode network regions, which may lead to difficulty with cognitive control and remaining abstinent (McHugh et al., 2014). Additionally, studies conducted by Hermans et al. (2014) suggest that stress responses tend to reallocate resources to the salience network, resulting in decreased executive control network function. When the stressor is removed, they argue that this relationship is once again reversed to normalize long-term functioning. However, if a substance user is consistently experiencing chronic negative affect, there could potentially be long term changes resulting in increased activation of the salience network in response to stress like shown here (Hermans et al., 2011; Hermans et al., 2014). We also found close to significant activations

in the vmPFC, which is linked to the default mode network. This supports the prior explanation regarding the recruitment of the DMN instead of the CEN by the salience network. The increased default mode activation could be inhibiting the central executive network from recruiting the proper cognitive resources when persisting through an abstinence attempt (Leyman et al., 2014).

Activation in both the insula and the vmPFC were found to be positively associated with distress tolerance in Daughters et al. (2016), and now illustrate nearly significant positive relationships with substance use frequency at 1-month follow-up. This supports the main aim of the paper, suggesting that regions associated with DT can act as predictors for future experiences of substance users. However, the directions of our correlations are opposite compared to the findings presented previously. Based on behavioral research, we would expect lower activation in regions associated with DT to be associated with greater substance use frequency (Quinn et al., 1996; Ali et al., 2013), but our results showed the opposite finding. One potential explanation is that the sample of substance users was not attempting to quit or cut down on their substance use, so the higher activation in DT regions they experienced did not accurately predict the substance use frequency for this reason. There was also an absence of significant findings within the right MFG, a region found to be highly significant with distress tolerance in Daughters et al. (2016). One potential explanation is the substance users in this sample are not trying to quit, so the underlying neural regions associated with DT are not influencing their decision to quit or continue using. A treatment-seeking population would be expected to have lower activation in DT regions associated with frequency of crack/cocaine use at follow-up, but the measure of DT that we are using may not be useful as a proxy for negative reinforcement in predicting future behaviors of non-treatment seeking samples.

The results of this study are in line with the negative reinforcement theory of substance use disorder, suggesting that greater negative affect and increased response to stress during abstinence attempts leads to increased substance use frequency (Baker, 2004). Activation patterns within neural pathways associated with stress were able to predict future substance use, indicating that greater activation in stress related regions can be maladaptive for substance users and may underlie the difficulties of abstinence.

Limitations and future directions:

A number of limitations are of note. Our sample size was small, and the relatively low retention rate at follow-ups limited the analyses that we could conduct. The sample was also predominantly male and Black/African American, which makes the generalizability limited. The results cannot be generalized past crack/cocaine use disorder either, because many of the substance users only used crack/cocaine and did not meet criteria for other substance use disorders. Additionally, the sample was not treatment-seeking. Since the participants were not actively trying to quit using crack/cocaine, we cannot interpret and relationships between activation in neural indices and treatment outcomes or motivation to stop use. The participants may not be actively trying to reduce or stop their use in the month after their initial scan. The data also looked at activation in ROIs in isolation from one another, and did not utilize connectivity data to interpret the relationships between the networks. While we can show that activations in regions within the salience network can be associated with greater frequency of use, we cannot determine that activation within or between networks is directly associated with substance use.

There are many future directions that stem directly from this study. A logical next step from this study would be conducting a similar study utilizing longitudinal data 1-year post scan

to determine if the findings presented here still hold true. One of the key goals of future research would be looking at treatment outcomes in relation to the activation of neural indices of DT to predict treatment success and relapse frequency. Utilizing the fMRI task in a treatment-seeking population, as well as a non-treatment seeking population, to create comparisons in neural activations between groups would help elucidate the neural differences that could be underlying motivation to stop use. This would allow a better understanding of the neural networks that could be predicting treatment response and relapse rates in crack/cocaine users, which assists in the ultimate goal of increasing treatment success.

Despite the limitations in this study, it still provides a novel look at the predictive ability of neural indices involved in stress pathways regarding substance use frequency, and acts as a logical continuation of the findings of Daughter et al. (2016).

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