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HPA axis response to psychological stress and treatment retention in residential substance abuse treatment: A prospective study

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ABSTRACT

Introduction: Substance abuse treatment programs are often characterized by high rates of premature treatment dropout, which increases the likelihood of relapse to drug use. Negative reinforcement models of addiction emphasize an individual's inability to tolerate stress as a key factor for understanding poor substance use treatment outcomes, and evidence indicates that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis contributes to an individual's inability to respond adaptively to stress. The aim of the current study was to examine whether HPA axis response to stress is predictive of treatment retention among a sample of drug users in residential substance abuse treatment.
Method: Prospective study assessing treatment retention among 102 individuals enrolled in residential substance abuse treatment. Participants completed two computerized stress tasks, and HPA axis response to stress was measured via salivary cortisol at five time points from baseline (pre-stress) to 30 min post-stress exposure.
Results: The main outcome measures were treatment dropout (categorical) and total number of days in treatment (continuous). A significantly higher salivary cortisol response to stress was observed in treatment dropouts compared to treatment completers. Further, Cox proportional hazards survival analyses indicated that a higher peak cortisol response to stress was associated with a shorter number of days to treatment dropout.
Conclusions: Results indicate that a higher salivary cortisol level in response to stress is associated with an inability to remain in substance abuse treatment. These findings are the first to document a biological marker of stress as a predictor of substance abuse treatment dropout, and support the development and implementation of treatments targeting this vulnerability.

1. Introduction

An estimated 10–30% of individuals entering substance abuse treatment programs drop out prior to treatment completion, and the highest rates of treatment dropout occur in long-term residential treatment programs (Substance Abuse and Mental Health Services Administration, 2005a). This is of great public health significance given that more than 40% of individuals seeking substance abuse treatment nationwide receive care at residential facilities (Substance Abuse and Mental Health Services Administration, 2005b), and longer treatment duration is one of the strongest predictors of successful substance use outcomes (Simpson et al., 1997). Understanding the factors underlying an individuals' inability to remain in treatment is of particular importance in informing future treatment development efforts.

Of particular interest is the extent to which negative affective states play a role in treatment duration and subsequent substance use outcomes. Theoretical accounts of the underlying mechanisms responsible for relapse to drug use implicate negative reinforcement processes (Baker et al., 2004), which collectively emphasize that the motivational basis of addictive drug use is the reduction or avoidance of aversive internal states. In support of this theoretical approach, prospective studies indicate that individuals with an inability to tolerate affective distress are significantly more likely to dropout of residential substance abuse treatment (Daughters et al., 2005a), and have shorter abstinence durations across addictions (Brandon et al., 2003; Brown et al., 2002; Daughters et al., 2005b).

Previous studies examining an individuals' ability to tolerate affective distress have relied primarily on self-report and behavioral assessment approaches, yet evidence indicates that one's biological response to stress may also play a key role in substance use outcomes. The most commonly studied biological component associated with stress is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis, which controls the secretion of hormones from

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the pituitary gland and adrenal cortex, plays a central role in mediating the body's response to stress and is extremely sensitive to inputs from the limbic system and prefrontal cortex (Carmichael and Price, 1995; Sinha, 2001), two brain areas that are important in modulating reinforcement and motivational processes.

In animal models of substance use, a series of studies by Piazza and colleagues provide evidence to suggest that a dysfunctional HPA axis response to stress is associated with increases in self-administration of addictive substances (Piazza et al., 1991, 1996, 1998). Specifically, rats who respond to stressful stimuli with prolonged secretion of the HPA stress hormone (i.e., corticosterone), were more likely to self-administer amphetamines than those with lower level HPA reactivity (Piazza et al., 1991). Further, administration of corticosteroids to rats that were low level responders increased the risk that these rats would begin to self-administer amphetamines. Additional studies have demonstrated that drug experienced laboratory animals robustly reinstate drug seeking behavior after exposure to footshock stress and that these effects are mediated by the extrahypothalamic corticotrophin-releasing factor (CRF) and brain noradrenergic pathways (Shaham and Miczek, 2003). Studies with human cocaine users have corroborated animal studies in that increased stress-related corticotrophin and cortisol responses to an emotional imagery stressor have been associated with greater amounts of cocaine consumption per occasion at 90 days post-treatment (Sinha et al., 2006).

Taken together, biobehavioral studies examining an individual's response to stress provide support for the role of negative reinforcement processes in substance using behavior. These processes are also applicable to treatment retention, as behavioral assessments indicate that an inability to tolerate affective distress predicts premature substance abuse treatment dropout. However, important biological markers have yet to be examined as a concurrent risk factor for treatment retention. Thus, the aim of the current study was to examine whether HPA axis response to stress at treatment entry is predictive of treatment retention among a sample of drug users entering residential substance abuse treatment. In line with previous findings, it was hypothesized that higher salivary cortisol levels in response to stress would be significantly related to an inability to complete treatment.

2. Method

2.1. Sample

Study participants included individuals entering a residential drug treatment center in Northeast Washington, DC. Treatment at this center involves a mix of strategies adopted from Alcoholics and Narcotics Anonymous as well as group sessions focused on relapse prevention. Complete abstinence from drugs and alcohol (verified by a clean urine drug test) is required upon entry into the center and through the duration of the program, with the exception of nicotine; regular drug testing is provided and any drug or alcohol use results in immediate dismissal from the center. When needed, detoxification from an outside source is required prior to entry into the center; therefore, acute drug effects likely did not influence the current findings.

A total of 123 participants provided informed consent and were enrolled in the study. Of these, 18 were excluded for meeting criteria for DSM-IV psychosis ($n=4$), indicating use of corticosteroids ($n=4$), or providing undetectable salivary cortisol data ($n=10$). A total of three participants began study procedures and chose to stop participation because they preferred to attend treatment center activities (e.g., chorus practice). Thus, the data analysis for the current study is based on a sample of 102 participants. Participants were primarily male (81.4%, $n=83$) and ranged in age from 19 to 66 ($M=41.9$, $SD=10.8$). With regard to racial/ethnic background, 89.2% ($n=91$) of the participants were African American, 7.8% ($n=8$) were White, and 2.9% ($n=3$) were Hispanic/Latino. In terms of highest education level, 23.5% ($n=24$) reported less than a high school education, 34.3% ($n=35$) reported completing high school or obtaining a GED, and 42.2% ($n=43$) reported some college or technical school. The majority of the sample reported current unemployment (79.6%, $n=81$) and a household income of less than $20,000 a year (68.6%, $n=70$). Participants entered treatment under 30-day (47.1%, $n=48$), 60-day (33.3%, $n=34$), 90-day (2.9%, $n=3$), or 180-day (16.7%, $n=17$) contract lengths, with 55.9% ($n=57$) of the participants being legally mandated by the court to attend treatment by a pre-trial release to treatment program, in which drug offenders who are awaiting trial are granted the option to receive substance abuse treatment prior to their court appearance.

2.2. Procedure

All participants were approached on the Monday of their first week of treatment. After providing a complete description of the study to the subjects, written informed consent was obtained. All aspects of the study and the consent forms were approved by the University Institutional Review Board. Following informed consent, participants were administered the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1997, 2002) to assess Axis I psychiatric and substance use history and diagnoses, as well as Axis II borderline personality disorder and antisocial personality disorder. Residents were then scheduled for participation in an experimental stress session on the Tuesday evening following the Monday evening SCID-IV interview. All testing sessions were conducted between 6 and 8 pm to control for the effects of circadian variation in cortisol levels. Each testing session began with participants completing a 5-min deep breathing exercise for purposes of relaxation, followed by collection of a baseline salivary cortisol sample via the "passive drool" technique (Granger et al., 2006). Specifically, at each collection time point participants were instructed to spit into a straw to fill a cryovial (i.e., resealable plastic tube). Participants then completed the *Positive and Negative Affect Schedule* (PANAS; Watson et al., 1988) to assess baseline state negative mood. Two psychological stressor tasks were then administered (counterbalanced), after which salivary cortisol was immediately collected at 0, 10, 20, and 30 min post-stressor for a total of 5 salivary cortisol samples (including the baseline sample). Following completion of the computerized stressors, participants completed self-report questionnaires including demographic information, the *Multidimensional Personality Questionnaire-Negative Emotional Temperament* (MPQ-NEM; Tellegen, 1985) to assess trait level vulnerability to negative affect, a widely used smoking history questionnaire measuring smoking characteristics including smoking status (i.e., never smoker, ex-smoker, regular smoker) and the number of cigarettes per day when smoking daily (Heatherton et al., 1989), and a drug use history questionnaire to assess past year frequency of drug use across drug classes (Babor and Del Boca, 1992). Patients received payment in the form of grocery store gift cards for participation in the study. Participant status was followed up with the administrative offices of the treatment center to determine the number of days they remained in treatment and whether they completed their entire contract duration or dropped out prematurely.

2.3. Computerized psychological stress tasks

Two computerized psychological stress tasks were used to induce distress. Both tasks include forced failure which is recommended for inducing a cortisol response (Dickerson and Kemeny, 2004). We used a modified version of the Paced Auditory Serial Addition Task (PASAT-C; Lejuez et al., 2003) which has been used in previous research with substance users and demonstrated an ability to increase participant distress levels (Brown et al., 2002; Daughters et al., 2005b, 2008). For this task, numbers were sequentially flashed on a computer screen, and participants were asked to add the currently presented number to the previously presented number before the subsequent number appeared on the screen. If the participant failed to add the numbers before the presentation of the next number or gave an incorrect response, an explosion sound would occur. As the task was designed to limit the role of mathematical skill, the presented numbers only ranged from 0 to 20, with no sum greater than 20. Participants were told that their score increased by one point with each correct answer and that incorrect answers or omissions would not affect their total score. The task consisted of three levels of increasing difficulty, with the latencies between number presentations titrated based upon the participants' ability level. On the last level, the latency between number presentations is extremely short, making the task virtually impossible to complete successfully. During this final level, participants were informed that they could terminate exposure to the task at any time by clicking on a "Quit" button on the screen; however, an incentive to continue was provided such that they were told that the amount of money they would earn at the end of the session would depend upon their performance on the task.

We also used a computerized version of the Mirror Tracing Persistence Task (MTPT-C). As used previously with substance users to induce distress (Daughters et al., 2005a, 2008), participants were required to trace a red dot along the outline of a star using the computer mouse, with the mouse programmed to move the red dot in the reverse direction. Participants were told that their performance was measured based upon how far around the star they moved the red dot. If the participant moved the red dot outside of the outline of the star or if the participant stalled for more than 2 s, a loud buzz would sound and the red dot would return to the starting position. The outline of the star is extremely thin, making it virtually impossible to perform well on the task. Participants were told that they could end the task at any time by pressing any key on the computer, but that how well they did on the task would affect how much money they made.

The maximum duration of the final level was 5 min for both tasks, yet participants were not told the maximum duration prior to beginning the task. In line with previous studies using the PASAT-C and MTPT-C (Brown et al., 2002; Daughters et al., 2005a, 2008), we measured changes in distress using a four item scale consisting of self-reported anxiety, difficulty concentrating, irritability, and frustration, with