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Imagery Scripts and a Computerized Subtraction Stress Task Both Induce Stress in Methamphetamine Users: A Controlled Laboratory Study

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Abstract: Patients treated for methamphetamine (MA) dependence have a high rate of relapse, and stress is thought to play a key role. We sought to develop a computerized procedure for experimentally inducing stress in MA users. In a within-subjects design, we compared a computerized subtraction stress task (SST) to personalized stress-imagery scripts and a control condition (neutral imagery) in 9 former MA users, recruited in San Francisco in 2006–2007. We assessed blood hormone levels, anxiety and craving for MA on visual analog scales, and the Positive and Negative Affect Schedule and made linear mixed-effects models to analyze the results. Both the SST and stress scripts were effective in inducing self-report markers of stress in MA users. Because the SST is easily reproducible and requires less time of staff and participants, it may be a useful alternative for measuring stress reactivity in drug users.

Keywords: methamphetamine, stress, addiction, relapse, computerized task

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Background

Patients treated for dependence on methamphetamine (MA) and other substances have a high rate of relapse, and stress is widely believed to play a key role.¹⁻³ Stress in this context is quantified based on major life events, such as loss of employment, as well as less severe but more frequent stressors (“hassles”), such as conflicts with co-workers. Hassles appear to be better predictors of psychological symptoms than major life events.⁴ Repeated exposure to drugs of abuse has long been associated with altered responses to stress,⁵⁻⁷ and these responses contribute to addiction.⁸ Stress is thought to contribute to relapse by activating the hypothalamic-pituitary-adrenal axis and by altering activity in extended basal forebrain extrahypothalamic brain regions involved in addiction, including the amygdala and nucleus accumbens.^{2,9-12}

Evidence that stress contributes to drug use has been seen in clinical populations. For example, Brown et al¹³ found that pre-treatment and post-treatment measures of psychosocial stress were related to alcohol relapse. They reported that 40% of subjects’ pre-treatment stressors were associated with alcohol use, and subjects who experienced severe life stressors during the three month trial were more likely to relapse. Likewise, in a sample of 64 smokers in a smoking cessation program, scores on the 4-item version of the Perceived Stress Scale correlated with rate of smoking two months later.¹⁴ In 30 subjects receiving methadone for opiate dependence in an outpatient setting, “everyday hassles” at baseline predicted the extent of illicit drug use over the subsequent 12 weeks.¹⁵ In a study of 113 alcohol dependent individuals, conflict and low cohesion in the family environment, but not life-changing events, were found to predict level of drinking at follow-up 18 months later.¹⁶ In a prospective study of individuals on methadone maintenance,¹⁷ relapse to heroin use was associated with elevations in stressful life events compared to baseline assessment.

However, not all studies of clinical populations have detected a relationship between stress and relapse. A single past-month measure of perceived stress in 70 subjects on methadone maintenance did not predict the proportion of urine samples positive for illicit drugs over the subsequent 3 months.¹⁸ In a sample of 221 subjects in treatment for nicotine (N = 68), alcohol (N = 85), or opiate (N = 72) dependence, Hall et al found that neither “everyday hassles, mood, nor

withdrawal predicted use in the subsequent week.¹⁹ In a similar design with 104 cocaine-dependent subjects, “hassles” were not predictive of a first relapse, although elevated mood was associated with less drug use.¹⁹ This could be the result of incomplete clinical data, and measurements too infrequent or insensitive to detect fluctuating stress levels.

Controlled laboratory experiments may therefore be more sensitive in determining the influence of stress on drug use. Both animal and human laboratory studies support the role of stress in contributing to drug abuse. Behavioral stress in animals has been shown to facilitate self-administration of morphine^{20,21} and cocaine.²²⁻²⁴ Stress has also been shown to reinstate drug-seeking behavior in alcohol-²⁵, nicotine-²⁶, heroin-²⁷, and cocaine-experienced animals.²⁸

Human laboratory studies have primarily induced experimental stress with either personalized stress imagery or public performance of a difficult task. In these laboratory studies, stress is typically defined as changes in physiological (heart rate), hormonal (cortisol), and/or self-report (negative affect and drug craving) measures. For example, Sinha and colleagues²⁹ developed a stress-imagery (SI) procedure in which participants are asked to describe stressful situations that are later replayed to facilitate imagination of the situation. In cocaine users, a personalized SI task increased cocaine craving as well as heart rate, salivary cortisol and self-report anxiety when compared to neutral imagery.²⁹ Harris et al³⁰ used the Trier Social Stress Test (TSST) and Sinha et al’s SI procedures to induce stress in cocaine and methamphetamine users.

Although the data support a relationship between stress and drug use, there are significant gaps in our understanding of how stress interacts with withdrawal, craving, and negative affect to increase risk of relapse in the day-to-day lives of those attempting to quit using drugs. One challenge in closing these gaps is the time needed to implement SI procedures. We therefore sought to develop a computerized procedure that we hypothesized would be comparable to a widely used SI method in inducing stress in MA users.

Methods

Participants

Nine individuals with history of MA-dependence were enrolled in the study, which was approved by the California Pacific Medical Center Institutional



Review Board. Participants were required to have no reported MA use in the last 30 days to reduce the risk that the study procedures would contribute to, or be influenced by, drug use. Other exclusion criteria included: DSM-IV diagnosis of severe major depression, severe posttraumatic stress disorder, mania, or hypomania within the last 90 days; lifetime history of schizophrenia, schizophreniform, or schizoaffective disorder; inability to comfortably abstain from tobacco for the duration of the experimental sessions; positive urinalysis result for any drug of abuse or breathalyzer positive for alcohol; pregnancy; a recent major negative life event (e.g., death of a loved one); use of oral contraceptives, antidepressants, beta blockers, corticosteroids, antipsychotics, or sedative-hypnotics in the preceding week; body weight of less than 50 kg or body mass index of less than 18 kg/m²; hemoglobin levels of less than 13.5 g/dL; and current DSM-IV dependence on any substance other than nicotine or MA.

Procedures

Subjects took part in three experimental procedures: subtraction stress task (SST), SI, and neutral imagery.

The three conditions were administered in random order during each of up to three sessions that occurred at one-week intervals. All sessions began at approximately 1 p.m. to control for time of day effects on hormonal response.

The SST consists of five minutes of serial subtraction problems. Subjects have three seconds to respond to each of the 100 problems. Subjects begin the task with potential compensation of \$50.00 and lose \$0.50 for each incorrect response. The current amount earned is displayed on the screen. Visual feedback (updated amount of potential compensation) and audio feedback (“wrong!”) are provided after each incorrect response (see Fig. 1). Each minute, the subtrahend changes based on the number of correct answers provided: poor performance will lead to an easier subtrahend (e.g., ‘subtract by two’), while good performance will lead to a more challenging subtrahend (e.g., ‘subtract by seventeen’); changes are made with a target performance rate 50% of problems correct.^{31,32} The SST was programmed using E-prime (Psychology Software Tools, Inc. Pittsburgh, PA).

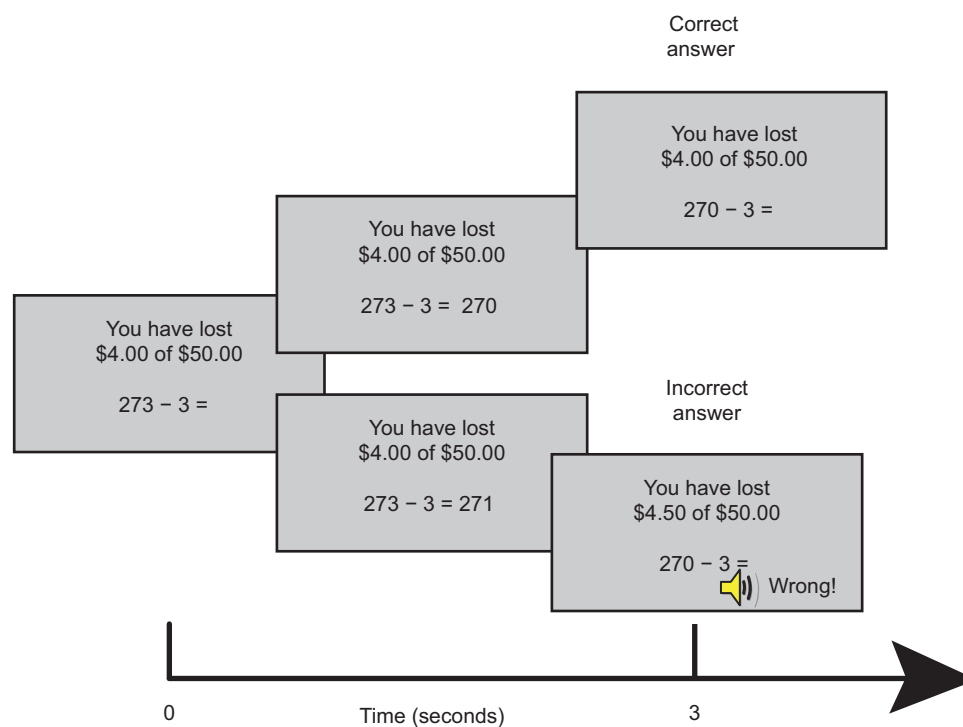


Figure 1. Subtraction stress task example.

Note: Example views of the computerized SST. If a correct response to a subtraction problem is entered within 3 seconds, the next screen will show the next subtraction problem in the series and no loss of earnings. If an incorrect or no response is entered, subjects hear the word “Wrong!” and the next screen will show the next subtraction problem in the series and a loss of \$0.50 to earnings.



For the SI task, using procedures developed by Sinha³³, subjects first completed a preparatory session for procedure familiarization and development of stress³³ and neutral-relaxing scripts.³⁴ Before developing the stress script, subjects verbally scored their identified stressful situation on a 0–10 scale (0 = “not at all stressful” and 10 = “the most stressed you got recently”), and continued with script development if they rated the situation as 8 or above. Subjects described the circumstances of the stressful situation, including location, time of day, persons present, conversation, physical sensations, thoughts, and emotional reactions. From these descriptions, five-minute scripts were developed by a psychiatrist or psychotherapist.

Once the stress script was developed, two independent raters assessed the level of its stressful and emotional content. Neutral scripts were considered acceptable if subjects viewed them as neutral or relaxing. Audio recordings were made of the scripts, to be played back to the subject during the experimental sessions. Upon completing script development, subjects received imagery-response training and relaxation training, and were instructed to practice relaxation at home. They were also familiarized with the equipment, questionnaires, and data-collection procedures; an intravenous catheter was placed and blood sample drawn to prepare them for these procedures.

Self-report measures and circulating hormone concentrations were collected immediately before and 0, 15, and 30 minutes after each condition. Self-report responses were assessed with MA craving and anxiety visual analog scales (VAS) and the Positive and Negative Affect Schedule (PANAS). On the MA Craving VAS, subjects rated their peak craving for MA on a 100 mm scale, ranging from “no craving for MA” to “greatest craving for MA ever experienced”. We have found this measure to be an excellent predictor of MA use.³⁵ Likewise, on the Anxiety VAS, subjects rated their anxiety on a 100 mm scale ranging from “no anxiety” to “most anxiety ever experienced”. The 20-item PANAS measures positive and negative affect by having subjects rate, on a 5-point Likert scale (from 1 = “Very slightly to not at all” to 5 = “Extremely”), to what extent they feel ten positive emotions (e.g., “Interested”, “Enthusiastic”, and “Alert”) and ten negative emotions (e.g., “Distressed”, “Ashamed”, and “Irritable”).³⁶ We collected

blood samples via intravenous catheter and assayed plasma or serum, as appropriate, for epinephrine (EPI), norepinephrine (NE), dopamine (DA), prolactin, adrenocorticotrophic hormone (ACTH), and cortisol, using high performance liquid chromatography, electrochemical detection, immunochemiluminometric assay, immunoassay, and radioimmunoassay methods, respectively (Nichols Institute, San Juan Capistrano, CA). Hemoglobin levels were measured after each of the first two experimental sessions to ensure subjects had not become anemic. Subjects with levels lower than 12.5 g/dL were excluded from further participation.

Analysis

To determine the relative efficacy of the SST and SI for inducing stress, we made linear mixed-effects models in which baseline-corrected stress measures were predicted by stress condition and time. For outcomes where both stress condition and time were significant predictors, we compared the conditions at individual timepoints using post-hoc *z*-tests. For models with only a significant effect of stress condition, we constructed new models predicting peak changes by stress condition and used post-hoc *z*-tests to compare the individual stress conditions.

Results

Participants

We enrolled nine subjects (5 male, 4 female) with a median age of 37 years (range: 26–49). Median time since last use of MA was 460 days (range: 65 days to 12 years). Five subjects reported smoking as their usual route of administration, 3 reported intravenous use, and 1 reported intranasal use. Of the 9 subjects, 5 completed all 3 sessions, 2 completed 2 sessions, and 2 completed 1 session, for a total of 21 sessions. One was excluded after their first session due to low hemoglobin levels; two were discontinued because of scheduling conflicts; and one due to use of exclusionary medications. (A tenth subject’s data were not used due to the lack of meeting criteria for stressful content in the personalized SI script).

Self-report effects

VAS anxiety was significantly predicted by both condition ($F_{2,172} = 12.14$, $P < 0.0001$) and time ($F_{2,172} = 19.16$, $P < 0.0001$). Both the SST and



SI scripts increased VAS anxiety relative to control immediately after the intervention (SST vs. control: $z = 6.306$, $P < 0.0001$; SI vs. control: $z = 4.945$, $P < 0.0001$), but not at later timepoints (see Fig. 2). The effects of SST and SI on VAS anxiety were not significantly different from each other at any timepoint. VAS MA craving was significantly predicted by the SI condition alone ($F_{2,172} = 6.22$, $P = 0.003$). In post-hoc tests, the SST significantly increased craving over control ($z = 2.44$, $P = 0.038$), an effect mainly driven by two individuals.

PANAS negative affect was significantly predicted by condition ($F_{2,172} = 12.61$, $P < 0.0001$) and time ($F_{2,172} = 18.72$, $P < 0.0001$). Post-hoc tests indicated that both SST and SI increased negative affect relative to control immediately after the intervention (SST vs. control: $z = 6.457$, $P < 0.0001$; SI vs. control: $z = 4.569$, $P < 0.0001$), but not at later timepoints. The effects of SST and SI on negative affect were not significantly different from each other at any timepoint (see Fig. 3). Positive affect was not significantly predicted by condition. No self-report responses differed by session.

Physiological effects

NE levels were significantly predicted by condition alone ($F_{2,169} = 7.65$, $P = 0.008$). Post hoc tests indicated that only the SST increased NE over neutral imagery ($z = 2.51$, $P = 0.032$). Cortisol, EPI, prolactin, DA, and ACTH levels were not significantly predicted by condition.

Discussion

We describe a computerized procedure for inducing stress in drug users and compared it to a commonly used personalized stress-script paradigm. Both the SST and the SI paradigm were effective in inducing self-reported stress response in abstinent MA users. These responses did not differ by session i.e, they appeared to be repeatable. Simplicity of administration is an advantage of the SST: preparation for the SST involves approximately five minutes for explanation of the task and a one-minute practice session; these tasks can be conducted by a research assistant. In contrast, preparation for the SI involves an interview to elicit the stressful experience, imagery training, imagery practice, script development, rating of the script by two independent raters, and script recording; approximately 120 minutes of time from Masters-level clinicians is required. Because the SST

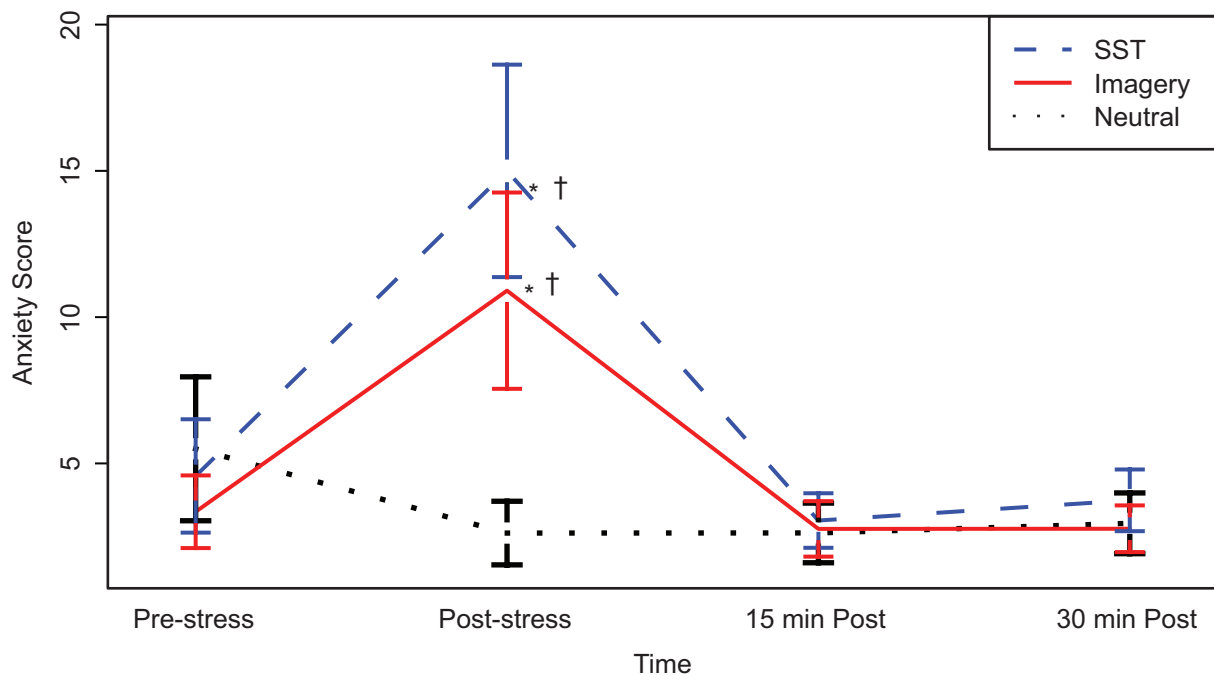


Figure 2. Stress script and SST effects on anxiety.

Notes: Both imagery stress scripts and SST significantly increased anxiety immediately post-stressor.

*—significantly different than baseline ($P < 0.05$); †—significantly different than control ($P < 0.05$).

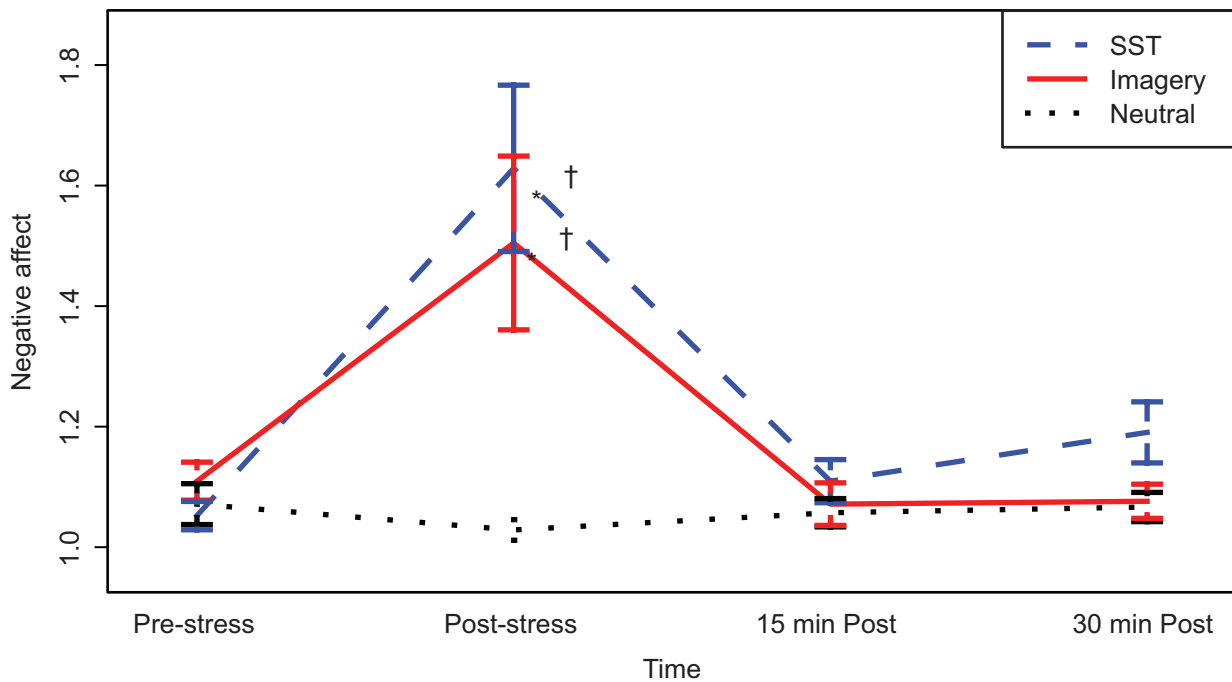


Figure 3. Stress script and SST effects on negative affect.

Notes: Both imagery stress scripts and SST significantly increased negative affect immediately post-stressor.

*—significantly different than baseline ($P < 0.05$); †—significantly different than control ($P < 0.05$).

involves a simple, replicable paradigm requiring less time of staff and participants, it may be a useful alternative to a stress-imagery procedure for measuring stress reactivity in drug users.

This is the first report of a computerized stress-induction procedure in an MA-using sample. We induced self-report anxiety and negative affect in our participants with both this procedure and the SI task. However, in contrast to past findings with cocaine and alcohol, we detected increased craving only in post-hoc analysis.^{7,29,33,37,38} Because our sample was small, caution should be used in drawing inferences from our failure to detect changes in craving. However, if confirmed, differences may be due to our participants' length of abstinence. Both Sinha et al's and Harris et al's participants were current users, while our participants had all been abstinent for at least 2 months. The two individuals with elevated craving scores in our study were also the two with the least amount of time since last MA use (65 and 145 days, respectively). Alternatively, the lack of significant changes in craving might be due to differences between cocaine and MA users. Harris et al, using the same SI procedure that we used, found that cocaine users had a much larger increase in craving than did MA users.³⁰

We found hormonal responses to stress to be more limited than the self-report responses. There was a small increase in NE, but no change in other measured hormones. Other studies have reported similar discrepancies between hormonal and either self-report or physiological measures of stress.^{31,39} For example, Harris et al also did not detect a change in cortisol after either SI or the TSST.³⁰ Discrepancies between hormonal and self-report responses to stress (e.g.,⁴⁰) could be explained by attenuated HPA hormonal response in chronic drug users.³⁹ If true, validated self-report or interview assessments may be the most fruitful measures of stress in drug users.

Limitations

This study had several limitations. First, the small sample size may have limited our ability to detect an effect of stress condition on hormonal stress response measures. The small sample size also precludes assessment of potential gender differences in stress responses that have been shown in other studies.⁴¹ Also, further research with current users and studies where stress is induced in naturalistic settings could help to further validate these findings.



Conclusions

Stress plays a key role in ongoing drug use and therefore represents a potential target for pharmacotherapy development. Testing the ability of medications to block responses to stress in laboratory-based trials is therefore important. Repeatable stress procedures such as the SST enable efficient assessment of stress responsivity in within-subject designs. In this paper, we described a novel computerized implementation of stress-inducing task that may offer advantages over personalized stress script procedures.

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Disclosures

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