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Developing a laboratory model of smoking lapse targeting stress and brief nicotine-deprivation

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Abstract

Stress plays a significant role in the maintenance of, and relapse to smoking. The current study aims to develop a human laboratory model examining stress-precipitated tobacco lapse following brief nicotine deprivation. Daily smokers ($n = 48$; 50% female) who were nicotine deprived for 3 hours received a personalized imagery induction (stress or neutral, within-subject, counterbalanced) on two separate days. Following imagery induction, participants were instructed that they could smoke or receive monetary reinforcement (\$0.25, \$0.50, \$1.00; between-subject) for every 5 minutes they chose to delay tobacco self-administration during a 50-minute delay period. After the delay period, participants engaged in a 1-hour ad-libitum smoking period. Tobacco craving and mood were assessed throughout. The primary aim was to determine if stress imagery would reduce the ability to resist following a brief nicotine deprivation in a laboratory setting. A secondary goal identified which level of monetary reinforcement highlighted the effect of stress on reduced ability to resist smoking (i.e., resisting ~25 min of the 50-min window). Overall, stress versus neutral imagery decreased the ability to resist smoking, increased craving and negative mood states, decreased positive mood, but did not change ad-libitum smoking. Increased monetary reinforcement increased the ability to resist smoking. Planned-comparisons examining lapse behavior within each monetary condition demonstrated that \$0.50 produced the only significant difference between stress and neutral imagery, demonstrating target model behavior. Findings highlight that stress negatively impacts smoking lapse behavior and can be effectively modeled in the human laboratory with a brief, three-hour deprivation window.

Keywords

smoking; lapse; relapse; stress; human laboratory; craving; mood

Cigarette smoking is one of the most significant public health risks in the United States (U.S. Department of Health and Human Services, 2014) and worldwide (World Health Organization, 2017). Nicotine use disorder is associated with health costs, workplace losses (e.g., decreased productivity, sick days), and consequences of secondhand exposure.

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Intervention efforts have been focused at many levels: national campaigns, institutional approaches such as “smoke free” workplaces, insurance agency incentives to non-smokers, and effective pharmacological and behavioral treatments. Despite these many effective intervention strategies, smoking remains a prevalent and serious concern. Nicotine use disorder is a chronic relapsing disorder and most quit attempts are unsuccessful (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005; Centers for Disease Control and Prevention, 2002).

Stress is one of the most commonly cited triggers for smoking relapse by individuals with tobacco dependence (Baer & Lichtenstein, 1988; Baer et al., 1989; McKee et al., 2003; McKee et al., 2011). Research ranging from lab-based animal studies to epidemiological studies have supported the primary role of stress in the maintenance of and relapse to tobacco use (Richards, Stipelman, Bornovalova, Daughters, Sinha, & Lejuez, 2011). Despite the well-established link between stress and smoking behaviors, the point at which people smoke the first cigarette during a quit attempt is less clearly understood. In particular, it is well understood that nicotine withdrawal symptoms are a primary factor that prevent individuals from sustaining a quit attempt. In addition to the crucial role of understanding stress in relapse, it is essential to understand the interplay of stress and nicotine withdrawal in the decision to smoke during a quit attempt. Early withdrawal symptoms are evident within 3-4 hours of last intake of nicotine (Morrell, Cohen, & al'Absi, 2008), and continue to peak throughout the first 1-3 days (Hughes & Hatsukami, 1986). Early withdrawal symptoms are primarily affective in nature and include anxious and depressed moods and cravings (Morrell, Cohen, & al'Absi, 2008), whereas later withdrawal symptoms include an intensification of those psychological symptoms as well as physiological symptoms such as restlessness, difficulty sleeping, and headaches. Dismantling and modeling the points at which an individual makes the decision to smoke a cigarette are key in developing intervention strategies.

Human laboratory models developed by McKee and colleagues (2011) have been used to examine the impact of stress and negative affect on smoking lapse behavior. A novel human laboratory model of stress-precipitated nicotine lapse developed by McKee and colleagues (2011) was originally conducted with an overnight (15-hour) nicotine deprivation window followed by an ability to resist smoking task. The model includes exposure to stress and neutral imagery, immediately followed by a delay period of up to 50 minutes during which participants are provided money for every 5 minutes that they resist smoking. After participants make the decision to smoke, they are then provided 8 cigarettes for a 60-minute ad-libitum period during which they are provided a set amount of money from which they must pay for every cigarette they choose to smoke. The degree of nicotine deprivation is a crucial factor in laboratory study development, as that window of time can be varied to induce differing levels of withdrawal. Findings from this work showed that laboratory induced stress can be used as a model for studying the key points at which individuals with tobacco use disorders choose to smoke the first cigarette after a period of overnight deprivation. This human laboratory model of stress- precipitated tobacco lapse has been used to effectively screen medications thought to target stress-precipitated smoking (McKee et al., 2015, Verplaetse et al., 2017). It is important to note that prior research suggests that the use of negative mood induction in the laboratory leads to a significantly shorter time to first

cigarette after stress exposure for women as compared to men (Weinberger & McKee, 2011). Additionally, many prior works have found that negative affect is reported more often by women as a reason to smoke (Cepeda-Benito & Reig-Ferrer, 2000; Rundmo et al., 1997). Despite the effectiveness of this laboratory model in demonstrating the ability to resist smoking in response to a personalized stress induction, questions remain regarding whether the length of nicotine deprivation could be shortened for more direct translation to shorter periods of deprivation which are consistent with early withdrawal symptoms (e.g., depressed and anxious moods), but not physiological nicotine withdrawal symptoms.

The current trial is an adaptation of McKee and colleagues' (2011) human laboratory model of stress-precipitated tobacco lapse that examines the use of an abbreviated nicotine deprivation time period. The purpose of the current study was to determine the effectiveness of a brief 3-hour nicotine deprivation time period in combination with stress in precipitating smoking lapse behavior. If found effective in demonstrating an induction of stress-precipitated tobacco lapse during a laboratory session, this briefer deprivation period provides: (1) a deprivation period that is analogous with early psychological withdrawal symptoms and cravings but not physiological withdrawal; and (2) a cost-effective and controlled monitoring of a briefer deprivation period which will reduce non-compliance due to problems with ensuring overnight smoking deprivation.

The current within-subject study design examined the effect of a stress induction (i.e., personalized stress or neutral imagery, order counterbalanced) combined with brief nicotine deprivation on smoking lapse behavior. Following stress or neutral imagery, participants could choose to smoke or receive monetary reinforcement for every 5 minutes they delayed tobacco self-administration (\$0.25, \$0.50, \$1.00) during a 50-minute delay period. The primary aim of the study is to determine if stress imagery reduces the ability to resist (i.e., decreased latency in minutes to the first cigarette during the delay period), and increased number of cigarettes smoked during the ad-libitum period, as compared to neutral imagery. A secondary goal of this study was to identify the level of monetary reinforcement needed so that smokers, on average, delay smoking for approximately half of the delay window (i.e., ~25 minutes of the 50-minute window) to maximize the separation in smoking delay following stress and neutral imagery. In subsequent investigations, this "target model behavior" will limit potential floor or ceiling effects when examining whether pharmacological and behavioral interventions increase or decrease the ability to resist smoking (see McKee 2009; 2012). We predicted that stress would decrease the ability to resist smoking, increase ad-libitum smoking, increase craving and negative mood, and decrease positive mood.

Method

Participants

Participant eligibility criteria included: 18-60 years of age, smoked at least 10 cigarettes per day for the past year, and had urine cotinine levels greater than 150 ng/mL. Exclusions from participation included: current Axis I disorders with the exception of tobacco dependence and DSM-IV alcohol abuse, positive urine drug screen for any illicit substances, engagement in smoking cessation treatment during the past 6 months, or contraindications for smoking

because of medical conditions (e.g., hypertension, asthma, chronic obstructive pulmonary disease) as described through self-report.

Of the 100 participants who consented to the study; 57 were eligible and 48 (24 females; 24 males) completed the study. The average age of participants was 33.31 (SD = 11.31) years. Participants were primarily Caucasian/White (58.3%) or African-American/Black (33.3%). 91.7% percent of participants reported completion of high school or the equivalent and 45.9% reported at least some college education. Participants reported drinking alcohol approximately 3.79 times per month (SD = 5.25). Participants smoked on average 16.13 (SD = 9.13) cigarettes per day, had been daily smokers for 15.87 (SD=4.63) years, had baseline carbon monoxide (CO) readings of 26.46 ppm (SD = 14.12), and average Fagerstrom Nicotine Dependence Scores (FTND; Heatherton et al., 1991) of 6.42 (SD = 2.25; range of possible scores from 1-10).

Design

The study is a mixed within- and between-subject design to test the effects of personalized stress and neutral imagery on the ability to resist smoking and subsequent ad-libitum smoking following a 3-hour period of nicotine deprivation. The personalized imagery condition (stress versus neutral) was a within-subjects factor and monetary reinforcement (\$0.25, \$0.50, \$1.00) was a between-subjects variable (see McKee, 2009; McKee et al., 2011). Study sessions included an intake session, a script development session, and two laboratory sessions (stress versus neutral - counterbalanced across laboratory sessions).

Procedures

Intake sessions—The current study was approved by the Yale School of Medicine Human Investigation Committee. Participants' understanding of the study and procedures was ensured through detailed review with study staff and a brief quiz to ensure understanding. Written informed consent was provided by all participants. The Structured Clinical Interview for DSM- IV (First et al., 1995) was conducted during the intake session to screen for inclusion (nicotine dependence) and exclusion (any other Axis I disorder). A self-report assessment battery was then completed by all participants to assess current and past smoking behaviors.

Script development session—Prior to the laboratory sessions, all participants met with a clinical psychologist to develop stress and neutral imagery scripts (see Sinha, 2009). Stress scripts were developed using a personally experienced stressor during the past 6 months. To be used for the personalized stress guided imagery script, participants were asked to describe stressors that were rated as 8 or higher on a 10-point scale (1 = “not stressful at all”; 10 = “the most stress you recently felt in your life”). Neutral scripts were based on the participants' descriptions of a neutral situation. All scripts were then audiotaped for use in the laboratory session.

Laboratory sessions—Participants completed two 6-hour laboratory sessions at the Yale Center for Clinical Investigation. Stress and neutral imagery were provided in separate

laboratory sessions, approximately 1 week apart, and the order of imagery presentation was randomized. A timeline of study procedures is depicted in Figure 1.

Baseline assessment and 3-hour deprivation period: Participants arrived at the laboratory at 9:00am. At this time, baseline self-reports (craving, mood, and withdrawal) and breath CO monitoring were completed. Participants smoked 1 cigarette of their preferred brand at 10:00am to standardize the time of their last cigarette, prior to the start of the nicotine deprivation period.

Personalized imagery procedure: At 1:00pm participants were instructed by the research assistant that “You will soon hear a situation being described to you. Your task is to close your eyes and imagine yourself in the situation being described, as if it were happening right now. Allow yourself to become completely involved in the situation, by involving your mind and body in actually doing what is being described. Continue imagining for as long as you can!” The research assistant then plays the personalized mood induction recording (stress or neutral) on a digital audio-recorder. The audiotaped script was approximately 5 minutes in length.

50-minute delay period: At 1:10pm, after the personalized imagery, participants were informed “You may start smoking at any time between now and 2pm. For each 5 minutes that you can delay smoking, you will earn (\$0.25, \$0.50, \$1.00) for a maximum of (\$2.50, \$5.00, \$10.00, respectively). Continue imagining the situation just described to you for as long as you can.” Participants were provided with a tray containing 8 cigarettes of their preferred brand and an ashtray. The time in minutes that the participant resisted smoking was recorded (0-50 minutes).

60-minute ad-libitum smoking period: The ad-libitum period began immediately after the delay period terminated and lasted for 60 minutes. The delay period was terminated at the decision to smoke and the self-administration began once the participant started to smoke the 1st of up to 8 cigarettes. They were also provided with a smoking tab (\$4.00) at the start of the ad-libitum period. At the beginning of the ad-libitum period participants were instructed that they “*may smoke as little or as much of these cigarettes as you wish during the next 60 minutes. For each cigarette you smoke, it will cost you \$0.50 of your \$4 smoking tab.*”

Discharge: Participants were discharged from each laboratory session at 3:15pm, regardless of when they terminated their delay period. They were informed of this at the start of the laboratory session to avoid having the potential reinforcement of early dismissal factor into their decisions during the laboratory session. Money earned during the smoking delay period and any unused portion of the smoking tab from the ad libitum period was paid to the subjects at the completion of each laboratory session. At the end of the study, subjects were mailed a check compensating them for their study participation (\$368).

Timing of assessments: Tobacco craving and emotion ratings were assessed pre- and postimagery, end of delay, and at 30 and 60 minutes into the ad-libitum period (see Figure 1).

Measures

Biochemical verification of smoking behavior: Baseline assessments of breath CO, breath alcohol, plasma cotinine and nicotine levels, urine drug screens, urine pregnancy screen, and vitals were obtained. A Vitalograph Breath CO (Vitalograph, Inc.) instrument was used for detection of carbon monoxide.

Subjective measures: Tobacco craving was assessed using the 10-item Tiffany Questionnaire of Smoking Urges-Brief (QSU-Brief; Cox et al., 2001) which assesses craving as related to positive (Factor 1) and negative (Factor 2) reinforcement on a VAS scale (scores range 1 - 100). Positive and negative emotions were rated on the Differential Emotion Scale (DES; Izard, 1972), a 30-item VAS scale (scores range 1- 100). Current nicotine withdrawal symptoms were assessed using the 8-item Minnesota Nicotine Withdrawal Scale (MNWS; score range 0 - 32; Hughes and Hatsukami, 1986).

Statistical Analyses—Outcomes of modeled-smoking lapse behavior (i.e., latency to onset of smoking) and number of cigarettes smoked during the ad-libitum period were each examined using multivariate analyses of variance of mixed design (within: personalized stress versus neutral imagery; between: monetary condition of (\$0.25, \$0.50, \$1.00). For the latency to onset of smoking, planned a priori contrasts examined stress versus neutral imagery contrasts within each monetary condition. Secondary outcomes of mood and cravings were examined using multivariate analyses of variance with imagery condition (stress versus neutral) and time (pre-imagery, post-imagery, end of delay, 30 minutes into ad-libitum, and 60 minutes into ad-libitum) both as within factors. Analyses were initially run with the inclusion of monetary factor as a between factor, however, there were no significant interactions for the secondary outcomes and thus it was removed from the final secondary models. To examine the reported withdrawal symptoms following the brief 3- hour deprivation window, a multivariate analysis of variance with imagery condition (stress versus neutral) and time (start of study session/pre-deprivation, and immediately prior to imagery) was run. We also explored gender as a between-subject variable across the primary analysis. As no significant effects of gender were demonstrated, we did not retain gender in the final models.

Results

Modeled-Smoking Lapse Behavior

Participants were less able to resist smoking (i.e., shorter latency to start smoking) in the stress condition ($M = 29.40$, $SE = 3.43$) compared with the neutral condition ($M = 31.02$, $SE = 3.42$; $F = 9.60$, $p < .01$). There was a significant main effect of monetary condition ($F = 5.75$, $p < .01$; see Figure 2), but there was not a significant interaction between monetary condition and imagery condition ($F = 1.57$, $p = .22$). Planned a-priori contrasts determined a significant difference between latency to start smoking in the stress versus neutral condition for the \$0.50 monetary level ($p < .05$), but not the \$0.25 or \$1.00 monetary levels.

Ad-Libitum Smoking

There was not a significant main effect of personalized imagery condition ($F=0.07, p=.79$) on the primary outcome of number of cigarettes smoked during the ad-libitum session. Most participants smoked ($n=36; 75\%$), and the percentage who smoked in the stress (81.2%) and neutral (75.0%) conditions were not significantly different.

Craving Reactivity

Participants reported higher levels of craving for positive reinforcement ($F=10.40, p<.01$) and negative reinforcement ($F=7.30, p<.01$) across study time-points (see Figures 3a and 3b) when exposed to the personalized stress script. Cravings related to both positive and negative reinforcement increased immediately following the personalized stress script and decreased from the decision to smoke until the end of the laboratory session.

Mood Reactivity

There was a significant interaction between personalized imagery condition and time for both negative mood ($F=13.30, p<.01$) and positive mood ($F=3.59, p=.02$; see Figures 4a and 4b). Negative mood increased following exposure to the personalized stress imagery and decreased after the decision to smoke through the end of the laboratory session. Positive mood decreased following personalized stress imagery and increased following the decision to smoke until the end of the laboratory session.

Withdrawal

Withdrawal was analyzed at two timepoints: baseline (9:00am) and immediately prior to the start of the imagery procedure (1:00pm). There was only a marginal main effect of time on self-reported withdrawal symptoms ($F=4.11, p=.05$). There was not a significant interaction between time and condition ($F=0.46, p=.50$). Withdrawal symptoms did not significantly differ from the start of the deprivation time period (stress: $M=4.03, SD=4.85$; neutral: $M=4.19, SD=4.53$) to the start of the imagery procedure (stress: $M=5.97, SD=5.53$; neutral: $M=5.97, SD=5.23$), suggesting that individuals were not reporting symptoms of withdrawal at the beginning of the stress (or neutral) induction as designed. The most frequently reported symptom was craving with 94.9% of participants reporting at least slight cravings, and only 15.4% of participants reporting “severe” cravings for cigarettes.

Discussion

The present study used a human laboratory model of stress-induced smoking lapse behavior following an observed 3-hour deprivation window. Participants were exposed to both personalized stress and neutral scripts during laboratory sessions and smoking behavior following imagery exposure was recorded. Prior research by McKee and colleagues (2011) has found that this model of laboratory-based stress exposure is effective in impairing the ability to resist smoking for individuals who are nicotine dependent subsequent to an overnight (15-hour) deprivation. The primary aim of the present study was to determine if personalized stress imagery exposure would reduce participants' ability to resist cigarette smoking following a brief period of nicotine deprivation. Present findings show that stress

significantly decreased the participants' ability to resist smoking even after this brief nicotine deprivation. These findings extend McKee's earlier model development work (2011) by showing that the physiological withdrawal associated with overnight nicotine deprivation is not required to induce stress-precipitated smoking behaviors. In the present study, increases in nicotine withdrawal were small, with the primary symptom reported by participants after the 3-hour deprivation being cravings for cigarettes. Short (3-hour) - and longer (15-hour) - deprivation periods in laboratory models of stress-induced smoking can provide critical information in understanding the decision to smoke under differential effects of withdrawal states (i.e., early, psychological symptoms versus physical and psychological symptoms, respectively). The brief 3-hour deprivation window in the present study increased psychological symptoms of withdrawal such as craving, but did not elicit physical withdrawal symptoms.

Secondary Aims

A secondary goal of this study was to identify the level of monetary reinforcement needed so that smokers, on average, delay smoking for approximately half of the delay window (i.e., ~25 minutes of the 50-minute window) to maximize the separation in smoking delay following stress and neutral imagery. In the current study, we determined that the \$0.50 monetary condition was the only condition to produce a significant difference in smoking lapse behavior between the stress and neutral conditions and demonstrated 'target model behavior'. The \$0.50 reinforcement level balanced out the incentive value to smoke produced by combining stress with 3 hours of nicotine deprivation, such that participants delayed for about half of the 50-minute window. Lower (\$0.25) and higher (\$1.00) levels of reinforcement, produced floor and ceiling effects respectively, masking the effects of stress on smoking lapse behavior. We have seen similar ordered effects of monetary reinforcement in our other model development studies (McKee 2009; McKee et al., 2011; 2012). Interestingly, 'stronger' precipitants of relapse require greater levels of reinforcement to produce 'target model behavior'. For example, 15 hours of deprivation combined with stress requires \$1.50 per 5-minute delay to produce 'target model behavior' (see McKee et al., 2011) versus the \$0.50 level demonstrated in the current study.

An additional secondary aim of the present study was to determine if the number of cigarettes smoked during the ad-libitum smoking period was higher in the stress condition as compared to the neutral condition, and this was not supported. Consistent with McKee and colleagues' earlier work (2011), the number of cigarettes smoked did not differ between the stress and neutral conditions. Taken together with the finding that stress decreased the ability to resist smoking, these results suggest that stress plays an important role in the initial decision to smoke following deprivation but does not seem to influence smoking behavior after the initial cigarette is smoked. Additionally, the majority of participants who made the decision to smoke chose to smoke only 1 or 2 cigarettes during the ad-libitum period, suggesting that there was a floor effect for this data. Further, it is likely that the 'smoking-tab' contributed to this floor effect in that participants were motivated monetarily to avoid smoking. Twenty-five percent of participants did not smoke during the ad-libitum period, and this is consistent with prior studies with longer deprivation windows and a smoking tab (see McKee et al., 2011) suggesting the lack of smoking may be due more to the tab than the

brief deprivation. Future studies could remove the smoking tab which may increase the variability in the number of cigarettes smoked, thus increase sensitivity to manipulations.

Analyses examined participants' ratings of cravings and both negative and positive mood across study time points. With regard to cravings, both positive (e.g., smoking would be enjoyable) and negative (e.g., smoking would make me feel less stressed) reinforcement was examined. Craving, or desire to use a substance, is a good predictor of use behaviors and is often evident before use behavior occurs. Thus, self-reported cravings provide useful information about the decision to smoke timeline, and the identification of the timing of craving onset may provide insights into when and how to intervene in the decision to smoke. In the present study, participants experienced a greater increase in both the positive and negative reinforcement aspects of craving immediately following the stress exposure as compared to the neutral condition. Self-reported cravings decreased immediately upon the decision to smoke a cigarette, and remained low for the ad-libitum smoking period during which cigarettes remained available. These findings are notable in that the increase in craving following stress exposure was evident even though the period of nicotine deprivation was substantially shorter than earlier studies (i.e., McKee et al., 2011). Another important factor in understanding the points at which intervention could occur to prevent smoking behavior is the mood response to a situation. Negative mood followed a similar pattern to cravings in this study as it increased in response to the stress script, decreased following the decision to smoke, and remained low throughout the ad-libitum period. In general, positive mood also followed the expected pattern, with a decrease in positive mood following stress (but not neutral) exposure.

Limitations—There are several limitations to the current study that should be noted. First, although the small sample size is consistent with other laboratory based studies that employ within subject designs, the sample size does limit the generalizability of the findings to populations unlike the present sample. A second limitation of the present study is that the participants recruited were non-treatment seeking. Although the enrollment of non-treatment seeking participants may lead to less motivation to engage in resisting smoking during the lab, previous work (McKee et al., 2011) has shown that the monetary reinforcement used in the present study is effective in increasing motivation to engage in resisting smoking. Further, the significant differences with regard to time to resist smoking between stress and neutral imagery conditions suggests that we were able to effectively engage participants in the imagery task. A third limitation to the findings is that all participants were heavy, daily smokers, and further research is needed to understand the impact of brief nicotine deprivation on smoking lapse behavior in individuals who smoke less cigarettes and/or less frequently throughout the day.

Conclusions

In sum, the current study has extended McKee and colleagues (2011) earlier work towards the development of a laboratory model of stress-precipitated smoking lapse by using a brief, 3-hour deprivation as compared to the 15-hour nicotine deprivation window employed in prior studies to model lapse behavior. While stress reduced the ability to resist smoking overall, planned comparisons identified that the \$0.50 condition was the only monetary

condition to result in a significant difference between stress and neutral conditions demonstrating ‘target model behavior’. Our findings demonstrate that early psychological symptoms of withdrawal, in the absence of physiological withdrawal symptoms, can be used in the laboratory to elicit stress induced smoking behaviors. Daily cigarette smokers often experience frequent periods of abstinence similar to the 3-hour deprivation in this study and understanding smoking in response to these brief deprivation windows may provide crucial information on why some individuals are able to quit smoking while others are not. There is strong evidence for the link between stress and smoking, and laboratory based models of stress exposure are key to the development and testing of interventions designed to target stress-reactivity.

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Figure 1. Study Session Timeline

Figure 2. Ability to Resist Smoking: Minutes in the Delay Period. * $p < .05$ of stress vs neutral, within timepoints.

Figure 3.

a. Craving Factor 1 - Positive Reinforcement Across Timepoints by Condition.

b. Craving Factor 2 - Negative Reinforcement Across Timepoints by Condition. * $p < .05$ of stress vs neutral, within timepoints.

Figure 4.

a. Changes in Positive Mood Across Study Timepoints by Condition.

b. Changes in Negative Mood Across Study Timepoints by Condition. * $p < .05$ of stress vs neutral, within timepoints.