Stress responding and stress-related changes in cue reactivity in heavy smokers, problem gamblers, and healthy controls

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Abstract

Addictions, both substance and behavioral, have been conceptualized as involving similar biopsychosocial processes with different opportunistic expressions. A maladaptive stress response in combination with craving or urges to engage in the addictive behavior may be among the underlying factors common to behavioral and substance addictions. The current study compared the neuroendocrine (cortisol) and subjective responses to stress of gamblers and smokers to healthy controls. We assessed if participants responded differently to smoking or gambling cues before and after a psychosocial stressor. To this end, the subjective urges/cravings of all participants were measured in response to smoking or gambling cues versus neutral cues, once under normal conditions and again after exposure to a stressor. Salivary cortisol was measured prior to, immediately following, and ten minutes after conclusion of the stressor. Smokers and gamblers showed a similar blunted cortisol response to the acute stressor that differed from the control group's response. Following a stressor, subjective craving in smokers increased whereas gamblers' urges decreased. In smokers, a blunted cortisol and subjective stress response were related to increased urges. In contrast, for gamblers, changes in cortisol levels were unrelated to urges and higher subjective stress was associated with decreased urges. In conclusion, individuals with a substance and a behavioral addiction share common patterns of reactivity to stress. However, while the stressor enhanced cue-related craving in smokers, it generally had the opposite effect on gamblers. Further research is necessary to elucidate the complicated patterns of similarities and differences that underlie substance and behavioral addictions.

Keywords

Cortisol; craving; cue reactivity; gambling; nicotine; stress

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Authors Contribution

SEW and EW were responsible for the study concept and design. SEW, ZC, and LH contributed to the analysis of salivary samples. SEW completed the data analysis and EW aided in interpretation of findings. SEW and EW drafted the manuscript, and ZC provided critical revision of the manuscript. All authors have reviewed the manuscript and approved the final version for publication.

Introduction

Individuals struggling with addiction often display multiple behavioral and substance use related-patterns of excess. Emphasis has been placed on the intrinsically addictive nature of alcohol and illegal substances, but much less is known about behavioral addictions (e.g., excessive gambling). Identifying biopsychosocial processes common to all addictive behaviors may lead to a broader understanding of addiction (Shaffer, LaPlante, LaBrie, Kidman, Donato & Stanton 2004). To examine common factors, nicotine dependence and problem gambling are excellent candidates because they frequently co-occur (Griffiths, Wardle, Orford, Sproston & Erens 2010).

As stress has often been linked to addictive behaviors, the stress response may provide insight into disruptions caused by both substance and behavioral addictions. Sinha (2001) posits that a maladaptive stress response mediates the relationship between individual vulnerabilities to substance use and increased consumption. A vicious cycle develops and is perpetuated due to neuroadaptation to stress, which further exacerbates maladaptive stress reactions. This is consistent with research findings that the persistent abuse of substances such as nicotine dysregulates the basal and stress-reactive secretion of the steroid hormone cortisol (Lovallo 2006). Chronic dysregulation in turn leads to blunted cortisol secretion in the face of acute stress (Ginty, Jones, Carroll, Roseboom, Phillips, Painter & de Rooij 2014), which has been associated with increased severity of addiction and relapse following treatment (al' Absi 2006).

A blunted cortisol response has also been observed in behavioral addictions such as problem gambling (Paris, Franco, Sodano, Frye & Wulfert 2010), but only one experimental study to date has directly assessed cortisol reactivity in response to a stressor in problem gamblers (Maniaci, Goudriaan, Cannizzaro & van Holst 2017). Although problem gamblers displayed a similar pattern of arousal to stress as healthy controls, gambling disorder was related to decreased baseline levels of cortisol. As this study included only male gamblers in treatment, it remains to be demonstrated whether the findings generalize to a mixed-gender sample of community problem gamblers (Petry 2003).

Another phenomenon common to both behavioral and substance addictions is the experience of cravings or urges to engage in the behavior. These psychological reactions have often been measured using a cue reactivity paradigm where neutral environmental cues are repeatedly paired with the addictive behavior. Over time, these neutral cues begin to elicit reactions similar to those associated with using a substance (Carter & Tiffany 1999) or engaging in a behavioral addiction such as gambling (Wulfert, Maxson & Jardin 2009). Under real-world conditions, not only environmental but also internal cues such as stress-related negative feelings can become conditioned stimuli that elicit cravings (Stewart, de Wit, Eikelboom, Wit & Eikelboom 1984). These conditioning factors play a role in addiction. For example, individuals with higher reactivity to drug-related cues are more likely to relapse after successful treatment (Papachristou, Nederkoorn, Giesen & Jansen 2014). Similarly, individuals who confront stress-inducing situations experience greater cravings and are more prone to relapse (Doherty, Kinnunen, Militello & Garvey 1995;

Cooney, Litt & Morse 1997; Killen & Fortmann 1997). This phenomenon has also been demonstrated in the laboratory, where an acute stressor significantly increased cortisol levels and tobacco cravings and lowered participants' ability to resist smoking (McKee, Sinha, Weinberger, Sofuoglu, Harrison, Lavery & Wanzer 2011a).

If addiction is conceptualized as a disorder with different expressions or phenotypes (Shaffer *et al.* 2004), identifying common biopsychosocial processes involved in substance-related and behavioral addictions might lead to a broader understanding. To this end, we examined heavy smokers and problem scratch-off lottery gamblers for similarities and differences in psychological and hormonal reactions, particularly under conditions of high stress. We hypothesized that the reactions of smokers and gamblers would be similar to each other and show a blunted cortisol response compared to healthy controls. We also hypothesized that gamblers and smokers would show greater cue reactivity than controls and that stress would increase this effect.

Materials and Methods

Participants

Participants were recruited from the New York State capital region via ads in local newspapers, Google ads, Craigslist, and local flyers. Potential participants were screened over the phone to determine eligibility. Inclusion criteria included men and women who were 18 years old or older, could comprehend English, had a 8th-grade reading ability and were able to sign informed consent. Individuals with a past or current severe psychiatric diagnosis (psychosis, bipolar, dementia), a past-year history of alcohol or illicit drug abuse/dependence, and current treatment for smoking or gambling disorder were excluded. Scratch-off gamblers had to endorse a past year score of 4 on the South Oaks Gambling Screen (SOGS) (Lesieur & Blume 1987), a self-report instrument that corresponds with DSM-III criteria for pathological gambling, and report no smoking in the past year. We used a lower threshold of the SOGS for inclusion criteria as a cut-off score of 4 has been shown to yield better sensitivity without compromising hit rate and specificity (Stinchfield, 2003). Furthermore, the 5 cut-off was developed using DSM-IV-TR criteria for Pathological Gambling which has eliminated one of the ten previous criteria (i.e., illegal acts). For DSM-5, the diagnosis of gambling disorder requires four rather than five criteria (Rennert *et al.*, 2014). By using the lower score, we could recruit a group of scratch-off gamblers that were representative of individuals that may meet criteria for DSM-5 Gambling Use Disorder.

Smokers had to smoke a minimum of ten cigarettes daily and report no gambling in the past year. Control subjects must have neither smoked nor gambled in the past year. Eligible individuals were invited to the lab and informed that they would be compensated \$50 for their time and effort and be entered into a raffle for a \$100 prize.

One hundred participants were recruited from the community (34 scratch-off gamblers, 33 heavy smokers, 33 controls) and completed the study. Of those, eight were dropped from the analyses (1 control, 4 gamblers, 3 smokers) because they either endorsed both smoking and gambling within the past year or, if a gambler or healthy control, fell outside of the non-

smoking levels on the CO monitor. This left a final sample of 32 controls, 30 scratch-off gamblers, and 30 heavy smokers.

Self-Report Measures

Demographics and participant information.—Participants reported their gender, race/ethnicity, income, education, marital status and any current medications. A body mass index was calculated from their height and weight.

Gambling and smoking history.—Participants who gambled provided information on the average amount of money spent per week gambling and the frequency of gambling. Participants who smoked provided information on the average number of cigarettes per day.

Gambling severity.—The South Oaks Gambling Screen (SOGS) is the most widely used screen for problem and pathological gambling (Lesieur & Blume 1987). It consists of 20 yes/no items and yields a score from 0 to 20. Scores of 5 or higher identify probable pathological gambling; however, we used a cut-off score of at least 4 on the SOGS for reasons stated above. Gambling participants completed the past-year SOGS during the phone screen up to the point at which they met criteria for the study, and all participants completed the lifetime SOGS score after arrival to the laboratory. The sample's internal consistency for the lifetime SOGS score was $\alpha=.859$ (Cronbach's).

Smoking severity.—The Fagerstrom Test for Nicotine Dependence (FTND) is the most extensively used measure of nicotine dependence (Heatherton, Kozlowski, Frecker & Fagerstrom 1991). This self-report consists of six items that assess when, where, and how much one smokes. The FTND has acceptable internal consistency (Cronbach's $\alpha = .61$). Scores range from 0 to 10, with less than 4 suggesting minimal nicotine dependence, 4 to 6 moderate dependence, and 7 to 10 high dependence. All participants completed the FTND in the laboratory. The internal consistency for the FTND score was $\alpha=.833$ (Cronbach's).

Subjective stress.—A 5-point Likert scale was used to measure subjective stress throughout the procedures. Participants were asked to rate their current stress-related feelings from 1 (*very slightly or not at all*) to 5 (*extremely*).

General negative affect.—The Depression Anxiety Stress Scales (DASS) were used to assess the participants' general level of negative affect in the past two weeks (Lovibond & Lovibond 1995). The DASS is a 42-item questionnaire composed of three subscales that measure depression (e.g., "I couldn't seem to get any enjoyment out of things I did"), anxiety (e.g., "I had a feeling of shakiness [e.g., legs going to give way]"), and stress (e.g., "I found it hard to wind down"). Items are rated on a 4-point Likert scale from 0 (didn't apply to me at all) to 3 (applied to me very much or most of the time). The sample's internal consistency was $\alpha=.92$, $\alpha=.95$, and $\alpha=.94$ for the Anxiety, Depression, and Stress subscales, respectively.

Subjective cue reactivity.—Previous studies have established a well-documented ceiling effect on subjective reports of craving in smoking cue reactivity studies, particularly under conditions of nicotine deprivation (Sayette, Shiffman, Tiffany, Niaura, Martin & Shadel

2000). For nicotine-dependent individuals, even a brief period of abstaining (i.e., 30–40 minutes) may be enough to elicit a mild deprivation state (Hughes 1991). If we relied on the typical Visual Analogue Scale, craving scores in the heavy smoking group may reach an artificial ceiling and thus reduce the power to detect differences in the groups (Ray, Courtney, Bacio & MacKillop 2013). Sayette and colleagues (2000, 2001) addressed the ceiling effect by calculating a composite magnitude estimation score based on ratings from a baseline reactivity task. Participants first rated their baseline urge on a 1–100 Visual Analogue Scale (VAS). Following exposure to active cues, they were then asked to indicate on a scrollbar how much their craving had changed relative to the baseline, from the “greatest decrease ever experienced” (–50), to “remained the same” (1), to the “greatest increase ever experienced” (+50). The two scores were then multiplied to yield a composite score. Thus, the composite score included information for both the baseline level and the degree of change in urge ratings. By using the composite of both the baseline score and the amount of increase, we could then adjust for the effect of deprivation on self-reported craving. To reduce experimenter-induced expectancy bias, participants completed these urge ratings in an Excel file on the computer, rather than reporting them to the research assistant.

Cortisol Hormone Analyses

Saliva samples were collected as described in the Procedure section below. Cortisol was extracted from 400 μ L of the saliva samples, quality controls, and blank artificial saliva using butanol/ethyl acetate (1:1) mixture and re-suspended in 70 μ L of 0.02% NH_4OH , of which 30 μ L was analyzed on using a liquid chromatography tandem mass spectrometry (LC-MS/MS) system. Cortisol was separated by a Polaris C18-A column. The positive-ion multiple-reaction monitoring mode was used, and the ionization conditions were optimized with a flow-infusion analysis. Cortisol was detected by monitoring the m/z 363 $\rightarrow$ 121 transition for quantification and the m/z 363 $\rightarrow$ 91 transition as the qualifier; [2,3,4- $^{13}\text{C}_3$] cortisol internal standard was detected by monitoring the m/z 366 $\rightarrow$ 124 transition. The lower limits of quantification were determined to be 0.06 ng/mL. Intra-assay precisions (%CVs) were <10.4% and inter-assay precisions were 17.9%, 7.9% and 8.1%. The assay linear responses were obtained with $R^2=0.9996$ (0.024 – 200.00 ng/mL). Carryover and ion suppression were not observed.

Carbon Monoxide (CO) Breath Readings

Each participant, regardless of group, completed a breath test using a piCO+ Smokerlyzer (Bedfont Scientific) to verify smoking status. The CO breath monitor provides an immediate measure of the amount of CO parts per million (ppm) emitted when breathing. Readings of 0–6 ppm are indicative of a non-smoker, 7–10 of a light smoker, 11–15 of a moderate smoker, and 16 of a frequent smoker.

Stress Induction

The stress induction procedure consisted of a modified version of the Trier Social Stress Test (TSST) (Kirschbaum, Strasburger & Langkrar 1993). The TSST is comprised of a mock job interview in front of judges and a mental arithmetic task (serially subtracting 13 from 1022). The procedure has been described in detail elsewhere (Wemm & Wulfert 2017). The only

difference between the current study and the previous one was that the preparation period was extended from 3 minutes to 5 minutes in duration.

Cue Exposure

The first *in vivo* cue-reactivity exposure began with the neutral cues (control) followed by the active cues to reduce carryover effects (Sayette, Griffin & Sayers 2010). Both neutral and active cues were presented at random from the following combination of options: neutral: a box of pencils and an eraser or a pen and paper; smoking cues: a closed pack of their preferred cigarettes and a lighter or a single cigarette and an ashtray; for gambling cues: a scratch-off ticket and a penny or scratch-offs in a dispenser box and a quarter. Smokers only received the neutral and smoking cues, and gamblers received the neutral and gambling cues. One-half of the healthy control participants were exposed to the smoking cues, the other half to the gambling cues. For each of the cue exposures (first neutral, then active), participants were instructed to look at the cues (60 seconds), and then physically manipulate them (60 seconds). Immediately thereafter, the participants rated the magnitude of change in urge to smoke or gamble, respectively, relative to baseline. The second cue-reactivity exposure was conducted after the stress induction. The procedure was identical to the first one, except that the stimulus materials had been changed to avoid habituation.

Procedure

To control for the diurnal variation in hormone levels, the study was conducted between 3:00 PM and 7:00 PM. Participants were asked not to consume any food or beverages up to 90 minutes prior to the study. Participants' report of last use of food, alcohol, caffeine, and illicit substances was obtained to assess whether they followed these instructions. Cigarette smokers were asked to abstain from smoking approximately thirty minutes prior to participating in the study.

A schematic of the experimental procedures has been provided in Figure 1. Upon arrival at the laboratory, participants provided informed consent, gave a baseline rating of their subjective craving/urge to smoke or gamble, and then completed the subjective stress rating and self-report measures during a 10-minute acclimation period.

After 10 minutes the participants were led to another laboratory room to complete the first set of cue exposures and the stress rating. Participants were then led back to the original room and a third stress rating was obtained. After the 15 minutes ended, participants watched a relaxing movie for another 25 minutes. Approximately forty minutes after the first cue exposure, participants provided a stress rating and saliva sample to assess their pre-stress cortisol levels before they underwent the TSST. After the TSST, another saliva sample and a stress rating were obtained approximately 15 minutes after onset of the stressor. Immediately following, participants returned to the cue exposure room and completed the second cue reactivity procedure. At the end of this second cue exposure, participants provided a final stress rating and saliva sample at +25 minutes after the onset of the stressor and completed questionnaires. After the experiment, participants were debriefed and received compensation.

Analytic Plan

All statistical analyses were conducted with SPSS 21.0 and SAS v9.4. Planned covariates included in the model were BMI, medication status, and gender. Hypotheses were tested using linear mixed modeling to control for random variation in the starting point (random intercept) and random variation of time (random slope with unstructured covariance structure) when assessing the effects of the stressor or the cues on the dependent variables. Groups were coded as contrasts to first compare the control group to the gamblers and smokers, and then to compare gamblers to smokers. First, main effects were tested to assess the effects of group and time on the dependent variables of cortisol response and subjective response to stress. Next, the interaction effect of time by group was analyzed to determine if changes in cortisol and subjective response to the stressor varied by group.

The second objective of the study was to examine the impact of a stressor on cravings or urges. Linear mixed models were used to determine whether the group differed in cue-elicited subjective cravings/urges before and after an acute social stressor. As before, groups were coded using contrasts to first compare the control group to the addicted groups and then the gamblers to the smokers. As previous research has shown that stress in and of itself can induce craving (Tiffany 2010), we first compared the urges elicited solely by the stressor to the urges caused by the baseline cue reactivity task. Like before, the random effects included in this model were a random intercept and random slope for time with an unstructured covariance structure. In a separate model, we then assessed the effect of stress on cue reactivity by comparing the baseline response to the neutral and active cues to the response to these cues after the TSST. Instead of including a random slope of time in this model, we included the random slope for cue type (neutral, active) and exposure before and after the stressor with an unstructured covariance structure. Finally, with exploratory analyses, we assessed the relationship between baseline-corrected cortisol response and subjective stress level proximal to the urge ratings to predict cue reactivity. These models were conducted separately in gamblers and smokers to aid in interpretation. In these models, random intercept and random slopes for time and time-varying covariates (subjective stress) were estimated using unstructured covariance structures.

Data Screening

Four outliers in cortisol that fell more than three standard deviations from the mean were removed from the analyses. Cortisol values were positively skewed and kurtotic, so were logarithmically transformed.

Results

Baseline Measures

Participants' demographic information is shown in Table 1. ANOVAs and chi-square tests did not identify differences between groups in gender, race, ethnicity, age, education, BMI, and medication use (see Table 1); however, the three groups did differ in reported depression, anxiety, and stress symptoms. The DASS subscales were therefore included as covariates in the analyses to control for possible differences due to general negative affect. Gender, age, BMI, and medication use were also included to control for their potential

effects on the dependent variables. Baseline-corrected cortisol levels before the initial stressor and at the final time point were used for later analyses examining the association of cortisol with craving.

Cortisol and Subjective Response to Stress

Cortisol increased in response to the TSST, $b=.0048$, $t(167)=3.83$, $p<.001$, 95% CL[.0023,.0073], but the main effect of the group contrasts on cortisol levels was not significant ($p>.05$). When the interaction of time with the group contrasts was added to the model, controls displayed a steeper increase in cortisol than gamblers and smokers, $b=.007$, $t(165)=2.52$, $p=.013$, 95% CL[.0016,.0132], whereas the latter did not differ from each other, $b=.003$, $t(165)=0.81$, $p=.421$, 95% CL[−.0036,.0087] (see Fig. 2a).

Subjective Stress—Self-reported stress increased in response to the TSST, $b=.860$, $t(165)=8.71$, $p<.001$, 95% CL[.67, 1.05]. Controls reported less stress than gamblers and smokers, $b=−.73$, $t(77)=−3.28$, $p=.002$, 95% CL[−1.17, −.29], and gamblers reported less stress than smokers, $b=−.55$, $t(77)=−2.36$, $p=.021$, 95% CL[−1.01, −.086] (see Fig. 2b). The interaction effect of time with group contrasts was not significant ($p>.05$), indicating that the stress levels of all three groups increased similarly in response to the TSST.

Effect of Stress on Urges

Comparison of urges induced by stress to baseline cue reactivity—First, we compared baseline urges following neutral and active cues and urges following the stressor (immediately after the TSST, prior to cue exposure). The main effects of cue type and the groups were added first, followed by their interactions. Urge ratings differed by type of cue, $b=585.28$, $t(178)=4.29$, $p<.001$, 95% CL[316.18, 854.38], such that the active cues elicited the most craving, $M=623.78$ ($SE=126.38$), followed by stress, $M=376.41$ ($SE=139.78$), followed by the neutral cues, $M=1.27$ ($SE=78.14$). Controls reported fewer urges overall than gamblers and smokers, $b=−389.05$, $t(82)=−2.27$, $p=.023$, 95% CL[−730.07, −48.02]; the latter did not differ from each other ($p=.990$). Urges after each type of cue differed significantly between controls and the addicted groups in response to the active cues and stressor (active cues: $b=814.60$, $t(174)=−2.56$, $p=.011$, 95% CL[−1442.88, −186.33]; stressor: $b=−1353.71$, $t(174)=−3.96$, $p<.001$, 95% CL[−2027.89, −679.53]), as well as between gamblers and smokers specifically in response to the stressor, $b=−1494.07$, $t(174)=−4.27$, $p<.001$, 95% CL[−2184.71, −803.42], but not to the active cue, $p=.472$. As shown in Figure 3, smokers reported increased craving to both the stressor, $M=1366.83$, and the active cue, $M=1391.39$, compared to the neutral cue, $M=149.25$. In contrast, gamblers reported greater urges in response to the active cue, $M=922.67$, than the neutral cue, $M=28.57$, but reduced urges in response to the stressor than the neutral cue, $M=−159.17$. That is, active cues reliably provoked urges in gamblers and smokers. In contrast, stress in-and-of-itself was sufficient to elicit urges in smokers but not in gamblers.

Effect of stress on cue reactivity—The effect of the TSST was assessed by comparing responses to the active and neutral cues before and after the TSST. As before, we first assessed the main effect of group, cue and the stressor on urges/cravings; then, we added the corresponding two- and three-way interactions in a stepwise fashion. Active cues elicited

stronger urges than neutral cues, $b=706.36$, $t(90)=5.23$, $p<.001$, 95% CI[437.80,974.83], and cue-elicited urges were stronger after the TSST than before it, $b=178.33$, $t(89)=2.11$, $p=.038$, 95% CI[10.19,346.46]. Controls reported lower urges than smokers and gamblers, $b=-368.69$, $t(82)=-2.59$, $p=.011$, 95% CI[-651.72,-85.65].

When the two-way interactions were added to the model, the interaction of stress with the comparison of controls versus the addicted groups was significant, $b=-676.40$, $t(88)=-3.59$, $p<.001$, 95% CI[-1051.30,-301.49], as was the interaction of stress with the gamblers versus smokers comparison, $b=-793.57$, $t(88)=-4.11$, $p<.001$, 95% CI[-1177.61,-409.52]. The urges of the controls, $M=-3.14$, and gamblers, $M=-120.31$, were unaffected by the stressor, whereas smokers reported greater cravings after the stressor, $M=679.42$. The interaction of the comparison of controls to the addicted groups with cue type was significant, $b=-1195.65$, $t(89)=-3.92$, $p<.001$, 95% CI[-1802.31,-588.99], and gamblers did not differ from smokers in response to the cues ($p>.27$). Control subjects' urges following the active versus neutral cues did not differ, $M=42.83$; however, both gamblers, $M=894.10$, and smokers, $M=1242.14$, displayed greater urges to the active than the neutral cues.

Finally, the three-way interaction of the groups with stress and cue type was added to the model. The three-way interaction including the control versus addicted groups comparison was significant, $b=-779.33$, $t(88)=-2.47$, $p=.015$, 95% CI[-1405.18,-153.48], as was the three-way interaction with the comparison of gamblers to smokers, $b=1175.58$, $t(88)=-3.64$, $p<.001$, 95% CI[-1816.69,-534.46]. As shown in Figure 3, the stressor did not change gamblers' or control subjects' responses to the active or neutral cues; however, smokers reported greater cravings to the active cue following the stressor, $M=1094.47$. Smokers, therefore, showed a synergistic effect of stress on cue-elicited craving; whereas stress reduced the effect of cues on urges for gamblers.

Exploratory Analyses: Cortisol and Subjective Stress Association with Craving—Using similar models, we examined the association of the stress response (baseline-corrected cortisol level and subjective stress) with cravings/urges following the stressor. Since control subjects' urges were unchanged by exposure to the cues or the stressor, we only included gamblers and smokers in subsequent analyses to determine whether their urges/cravings were influenced by their subjective and hormonal responses to stress. Furthermore, we sought to isolate the putative mechanism that might be driving the differences between gamblers' and smokers' urges after the stressor. The main effect of change in cortisol did not predict urges in gamblers, $b=191.90$, $t(17)=1.01$, $p=.33$, but it did so in smokers, $b=-964.18$, $t(18)=-2.28$, $p=.035$. That is, a stress-induced blunted cortisol level was unrelated to the gamblers' urges, but it did predict increased cravings in smokers. Higher-order interactions of cortisol with pre- and post-stress and cue type neither predicted urges in gamblers (p 's $.32$) nor craving in smokers (p 's $.53$). The simple slopes of the association between cortisol at ± 2 SD and mean cortisol levels and urges have been graphed in Figure 4a.

However, in contrast to the cortisol response, subjective stress was associated with urges in both gamblers, $b=180.58$, $t(84)=2.08$, $p=.041$, and smokers, $b=-330.65$, $t(79)=-3.23$, $p=$

002, albeit in opposite directions (Fig. 4b). Higher levels of subjective stress were related to increased urges in gamblers, whereas lower levels were related to increased cravings in smokers. The non-significant interaction of stress with cue type and stress (smokers: p 's 10; gamblers: p 's .23) indicated that the relationship between subjective stress and urges was neither strengthened nor weakened by these variables.

Discussion

Consistent with previous research, we found that problem gamblers like heavy smokers display a blunted cortisol response to an acute stressor. An early explanation for this phenomenon in substance addictions was that repeated exposure to the substance resulted in a blunted cortisol response comparable to Cushing's disease (Margraf, Moyer, Ashford & Lavalley 1967; Rees, Besser, Jeffcoate, Goldie & Marks 1977). However, research involving behavioral addictions suggests otherwise, as a blunted response has also been shown in exercise addictions (Heaney, Ginty, Carroll & Phillips 2011) and problem gamblers (Paris *et al.* 2010). A more recent study reported no differences in cortisol levels between problem gamblers and healthy controls (Maniaci *et al.* 2017). These researchers examined male treatment-seeking pathological gamblers who engaged in a variety of gambling activities, and they did not include a comparison group of substance-addicted individuals, while we focused on non-treatment-seeking male and female problem gamblers who played scratch-off lottery tickets. It is possible that the pattern of results differs by type of gambler, given that coping with stress-related urges to gamble are most salient for scratch-off and slot machine gamblers (Suomi, Dowling & Jackson 2014). Future studies with individuals who engage in other modes of gambling should seek to elucidate this possibility.

Contrary to findings, we also had hypothesized that a psychosocial stressor would increase smokers' and gamblers' subjective cravings/urges to active cues, but we found that stress *enhanced* cravings only in cigarette smokers, whereas it *reduced* urges in gamblers. That is, while the stressor enhanced cue-related craving in smokers, it generally had the opposite effect in gamblers. The results for smokers are consistent with previous research (Heckman, Kovacs, Marquinez, Meltzer, Tsambarlis, Drobos & Brandon 2013), but the limited research linking self-reported stress and urges in gamblers is inconsistent with the current findings (de Castro, Fong, Rosenthal & Tavares 2007; Elman, Tschibelu & Borsook 2010). However, it must be considered that this research to date has been correlational and has relied almost entirely on self-report. The findings therefore provide no compelling information about causality or even directionality between stress and gambling behavior, and carry with them the limitations and possible biases involved in survey-based designs. The current study is the first to examine these relationships using an experimental design grounded in a laboratory-based cue reactivity paradigm, which enhances the credibility of the findings.

A closer inspection of how the biological (cortisol) and self-reported (subjective) levels of stress relate to cravings suggested a possible process underlying the differences between smokers and gamblers. A blunted cortisol response was related to increased cravings in smokers, consistent with previous research (al'Absi, Wittmers, Erickson, Hatsukami & Crouse 2003; al'Absi 2006), but was unrelated to urges in gamblers. When we examined the level of subjective stress proximal to the cue response, we found that a blunted stress

response was related to increased urges in smokers, whereas the opposite was true in gamblers. One possible reason for the discrepancy between smokers and gamblers in the stress-craving association may be related to the pharmacological effects of nicotine. Disruptions in reward and punishment processing that are a common feature in addiction may generally blunt the cortisol response (Ginty 2013); however, the link between a disrupted physiological stress response and craving may be enhanced by the pharmacological effects of nicotine on the dopaminergic system (al'Absi 2006). In contrast, there is evidence that dopaminergic changes, particularly in dopamine receptor availability noted in drug addictions, may not generalize to problem gambling (Clark, Stokes, Wu, Michalczuk, Benecke, Watson, Egerton, Piccini, Nutt, Bowden-Jones & Lingford-Hughes 2012). More research comparing substance and behavioral addictions is necessary to tease apart the pharmacological effects of drugs from the cumulative impact of the learned behavior.

Another plausible explanation for the differences between gamblers and smokers in the association between stress and craving may stem from the nature of the stressor used in this study. Gamblers' stress-induced cravings in real-world settings tend to be tied primarily to relationship problems and financial pressures which activate specific beliefs about gambling as a means to escape these specific psychosocial stressors (Sylvain, Ladouceur & Boisvert 1997). In contrast, the stress response observed in smokers in real-world settings is closely tied to cravings for a cigarette to calm one's nerves regardless of the specific nature of a stressor. In essence, stress is a complex construct, and the physiological responses to a stressor may vary dependent on the degree to which an individual interprets a stressor as being pertinent to their behavior. In future research with gamblers, we recommend comparing the effects of a general stress induction procedure with stressors more specifically tailored to problem gamblers, e.g., through an imagery-based script (McKee, Sinha, Weinberger, Sofuoglu, Harrison, Lavery & Wanzer 2011b). Future studies should also examine potential moderators, such as interoceptive awareness, tension reduction expectancies and the nature of the stressor.

When interpreting the results of the current study, certain limitations should be considered. One is the relatively small sample size and the resultant lack of power for some of the statistical tests. Another is the just-described possible problem related to the specific stressor used. However, the experimental stress induction in the present study is a considerable improvement over other research that has typically relied on retrospective self-reports with questionable validity when linking stress to urges to gamble. Possible additional methodological improvements could be obtained by conducting field research in a real-world gambling environment, or by using ecological momentary assessment, as this might allow us to better understand the types of stressors that motivate individuals to gamble. Once valid stressors have been identified, laboratory-based methods could be used to investigate their effects on urges and physiological responses.

Despite these limitations, the current findings nevertheless provide initial support for the presence of common biological processes in gamblers and smokers, particularly those pertaining to stress. The results suggest that specific physiological changes are not solely due to the pharmacological effects of substances, because some of the same changes can be

observed in substance-related and behavioral addictions. The study also suggests that stress may have different effects on cigarette cravings versus urges to gamble. However, we cannot rule out the possibility that the observed difference was due to a methodological artifact. As we delineated above, stress is a multi-faceted and complex construct, and with different stress induction procedures, or by including additional moderating variables, we might have been able to discover comparable effects of stress on gamblers' urges to gamble and smokers' cravings for a cigarette. Much research remains to be done to fully understand the complex relationships driving the similarities and differences between substance-based and behavioral addictions.

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Figure 1. Schematic of the study design. The timing of each measurement is indicated in minutes since beginning the study (top) and in minutes from the stressor (bottom). VAS=Visual Analogue Scale; ME=Magnitude Estimation.

Figure 2.

Cortisol and self-reported stress in response to the TSST. Lighter gray lines represent each participant's slope in response to the stressor, and the darker line indicates the group level change. Figure 2a shows change in log-transformed cortisol and Figure 2b represents individuals subjective stress ratings. All analyses controlled for age, medication status, gender, BMI, the DASS subscales.

Figure 3.

Urges in response to neutral cues, active cues, and after the stressor. Cue reactivity tasks are indicated if they occurred before or after the TSST. Figure 3c indicates the magnitude estimation in response to the TSST. Error bars represent the standard error of the mean.

Figure 4. Change in urges as a function of baseline-corrected cortisol response to the TSST and the subjective stress. The simple slopes are plotted at ± 2 SD and the average values for change in cortisol and subjective stress.

Table 1.

Demographics and descriptive statistics for the sample.

	Gamblers (n=30)	Smokers (n=30)	Controls (n=32)
<i>Demographics</i>			
Sex: Female <i>n</i> (%)	21 (72.4%)	14 (46.7%)	20 (62.5%)
Race: White <i>n</i> (%)	20 (69.0%)	18 (60.0%)	22 (68.8%)
Black/African American	4 (13.8%)	5 (16.7%)	6 (18.8%)
Other	2 (6.8%)	3 (10.0%)	2 (6.3%)
More than one	3 (10.3%)	2 (6.7%)	2 (6.3%)
Hispanic: <i>n</i> (%)	2 (6.9%)	3 (10.0%)	7 (21.9%)
Age: <i>M</i> (<i>SD</i>)	34.14 (15.06)	32.87 (12.01)	35.13 (16.27)
Education: Some High School <i>n</i> (%)	0 (0.0%)	2 (6.7%)	0 (0.0%)
High School/GED	6 (20.7%)	6 (20.0%)	0 (0.0%)
Some college	10 (34.5%)	10 (33.3%)	13 (40.6%)
Associate's	3 (10.3%)	4 (13.3%)	4 (12.5%)
Bachelor's	8 (27.6%)	5 (16.7%)	8 (25.0%)
Master's	2 (6.9%)	3 (10.0%)	7 (21.9%)
BMI: <i>M</i> (<i>SD</i>)	29.92 (7.26)	28.21 (7.88)	28.67 (7.04)
Medications: Yes <i>n</i> (%)	13 (55.2%)	10 (33.3%)	19 (59.4%)
<i>Gambling/Smoking Use Patterns</i>			
Number of days in past 90 days: <i>M</i> (<i>SD</i>)	27.62 (22.07)	84 (1.58)	--
Amount spent/smoked per day: <i>M</i> (<i>SD</i>)	\$28.52 (\$90.90)	13.58 (8.62)	--
Severity (SOGS/FTND): <i>M</i> (<i>SD</i>)	7.54 (4.28)	4.03 (2.51)	--
CO reading: <i>M</i> (<i>SD</i>) ^{**}	1.21(3.71)	37.5(40.76)	0.47 (.92)
<i>DASS Subscales</i>			
Depression: <i>M</i> (<i>SD</i>) [*]	11.82 (10.00)	11.00 (9.42)	5.37 (7.00)
Anxiety [*]	9.58 (8.85)	9.86 (9.52)	4.44 (5.82)
Stress ^{**}	17.36 (9.99)	13.48 (9.86)	7.63 (7.11)
<i>Baseline Measurements</i>			
Cortisol	.717 (.350)	.656 (.264)	.692 (.322)
Subjective Stress [*]	1.59 (1.12)	2.14 (1.43)	1.28 (.68)
Urge (first cue exposure) ^{**}	31.90 (28.28)	47.57 (27.84)	1.41 (2.12)
Urge (second cue exposure) ^{**}	27.93 (23.77)	62.20 (28.71)	2.25 (5.54)

Note:^{*}
p < .05^{**}
p < .001.

One gambler did not complete baseline measures and thus is not included in the demographics form. Chi-square analyses were used to determine group differences in sex, race, ethnicity, and education. One-way ANOVAs were used to determine group differences in age, BMI, CO monitor reading, the DASS subscales, and baseline urge and stress measures.