

## Post-traumatic stress symptoms in pathological gambling: Potential evidence of anti-reward processes

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(Received: October 30, 2016; revised manuscript received: January 22, 2017; accepted: January 29, 2017)

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**Background:** Excessive gambling is considered to be a part of the addiction spectrum. Stress-like emotional states are a key feature both of pathological gambling (PG) and of substance addiction. In substance addiction, stress symptomatology has been attributed in part to “anti-reward” allostatic neuroadaptations, while a potential involvement of anti-reward processes in the course of PG has not yet been investigated. **Methods:** To that end, individuals with PG ( $n = 22$ ) and mentally healthy subjects ( $n = 13$ ) were assessed for trauma exposure and post-traumatic stress symptomatology (PTSS) using the Life Events Checklist and the Civilian Mississippi Scale, respectively. **Results:** In comparison with healthy subjects, individuals with PG had significantly greater PTSS scores including greater physiological arousal sub-scores. The number of traumatic events and their recency were not significantly different between the groups. In the PG group, greater gambling severity was associated with more PTSS, but neither with traumatic events exposure nor with their recency. **Conclusions:** Our data replicate prior reports on the role of traumatic stress in the course of PG and extend those findings by suggesting that the link may be derived from the anti-reward-type neuroadaptation rather than from the traumatic stress exposure *per se*.

**Keywords:** trauma, sensitization, cross-sensitization, addiction, craving, relapse

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### INTRODUCTION

Classified as a “Substance-Related and Addictive Disorder” in the Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th edition (American Psychiatric Association [APA], 2013), gambling disorder is characterized, similarly to all addictive disorders, by stress-like emotional states. In substance addiction, this type of symptomatology has been attributed to “anti-reward” allostatic neuroadaptations, wherein ongoing drug consumption provides momentary relief but contributes to the “spiraling distress cycle” (Goldstein & McEwen, 2002; Koob & Le Moal, 2001) involving an outpouring of stressogenic corticotropin-releasing factor, norepinephrine and dynorphin that progressively worsen the clinical condition by increasing the state averseness and craving, eventually evolving into a *bona fide* addiction (Koob & Le Moal, 2008). Anti-reward research in human gamblers is, however, limited in part by a lack of animal models and of a laboratory-based formulation of the “stress” construct.

Stress may indeed be defined from the cognitive, emotional, endocrinological, psychophysiological, neurobiological, and molecular standpoints (to name a few). Here, we respond to this question by considering stress from the psychopathological standpoint by adopting post-traumatic stress symptomatology (PTSS) as its valid version. Although only one of many legitimate ways that “stress”

might be conceptualized, this approach has several advantages. First, it is clearly defined using the post-traumatic stress disorder diagnostic criteria (DSM-IV-TR; APA, 2000). Second, it rests on a firm clinical foundation (e.g., Holley, Wilson, Noel, & Palermo, 2016; Moscarello, 1990). Third, the link between anti-reward and chemical addictions has been extensively documented (e.g., Koob & Le Moal, 2008).

The goal of this study was to begin addressing potential pathological gambling (PG) anti-reward processes by measuring PTSS and traumatic stress exposure with the Life Events Checklist (LEC; Weathers et al., 2013) and the Civilian Mississippi Scale (CMS; Lauterbach, Vrana, King, & King, 1997; Vreven, Gudanowski, King, & King, 1995). Unconfounded by exogenous neurotoxicity, PG offers a unique opportunity to test whether a purely behavioral addiction is accompanied by PTSS, which have not yet been investigated in this patient population.

The value of using the proposed procedures is a more conclusive interpretation of the findings. Assuming an etiological link between traumatic stress exposure and subsequent

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symptomatology, if PG patients display increases in PTSS in response to similar levels and recency of trauma, it may be concluded that heightened stress is not secondary to environmental factors, and a case for primary anti-reward alterations in stress processing is supported. Conversely, if PTSS in PG patients is not elevated relative to the measures of traumatic exposure, it may be suggested that primary stress mechanisms are intact in PG, and that stress measurements are elevated in conjunction with environment-derived pressures.

## METHODS

Study participants were individuals with PG ( $n = 22$ ) and healthy subjects ( $n = 13$ ) who volunteered to participate in a study on the neurobiology of gambling, the results of which are reported elsewhere (Elman, Tschibelu, & Borsook, 2010). The diagnoses were made by a research psychiatrist using a best-estimate format based on the Structured Clinical Interview for DSM-IV-TR (SCID; First, Williams, Spitzer, & Gibbon, 2007), clinical history, and available informants. PG subjects endorsed a mean of 7.3 [standard deviation ( $SD$ ) = 1.2] out of 10 DSM-IV-TR diagnostic criteria. Their comorbid psychiatric diagnoses included: two subjects with a history of major depressive disorder, in full remission for at least 1 year, two subjects with cocaine dependence in full sustained remission, two subjects with alcohol dependence in full sustained remission, one subject with bulimia nervosa, purging type but free from any bingeing or purging episodes for at least 3 months, one subject with intermittent explosive disorder, and one subject who was taking bupropion for smoking cessation. The control subjects were free from any type of gambling problems; they had no psychiatric history as determined by the SCID. All individuals were in good physical health as ascertained by the Cornell Medical Index-Health Questionnaire (Brodman, Erdmann, Lorge, Wolff, & Broadbent, 1951).

The LEC (Weathers et al., 2013) is a 17-item self-report measure of potentially traumatic events including natural disasters, exposure to warfare, robbery involving a weapon, physical abuse, and sexual assault. For each event, respondents are asked to provide information regarding whether the event happened to oneself, was witnessed, was learned about, whether one was not sure, or whether the event did not apply to oneself, as a gauge of the impact of the event. The CMS (Lauterbach et al., 1997), originally designed with 35 items for combat-related PTSD, was administered in its 39-item civilian format (Keane, Caddell, & Taylor, 1988). Items are rated on a 5-point Likert scale and summed to yield a continuous measure of PTSD symptom severity. Both tools are validated in addictive behaviors (Back, Brady, Sonne, & Verduin, 2006; Berenz et al., 2016; Freeman & Kimbrell, 2004; Michaels et al., 2000). Moreover, the latter tool has a convergent validity with neurobiological indices of anti-reward in the form of noradrenergically mediated physiological arousal sub-scores (Back et al., 2006).

Descriptive statistics,  $t$ -tests, and correlations were computed using SPSS 23.0. The bootstrap technique (Davidson & Hinkley, 1997), using the boot package (Canty & Ripley, 2010) in R 3.1.2 (R Core Team, 2014), was applied for the determination of 95% confidence intervals (CI) for

correlations. All analyses were two-tailed;  $t$ -tests did not assume equal variances; significance for all tests was defined as  $p < .05$ . Group data were summarized as mean  $\pm$   $SD$ .

## Ethics

All subjects gave written informed consent to a protocol approved by the McLean Hospital Institutional Review Board.

## RESULTS

Participants with PG were not significantly different from healthy controls with respect to age ( $45.0 \pm 10.1$  years vs.  $40.3 \pm 13.8$  years;  $t_{19,7} = -1.02$ ,  $p = .321$ ), race (white/non-white = 10/12 vs. 9/4;  $\chi^2_1 = 1.86$ ,  $p = .172$ ), gender distribution (male/female = 13/9 vs. 8/5;  $\chi^2_1 = 0.02$ ,  $p = .886$ ), or years of education ( $14.6 \pm 3.0$  vs.  $14.9 \pm 1.4$ ;  $t_{32,0} = 0.38$ ,  $p = .706$ ).

While not meeting diagnostic threshold for the current PTSD diagnosis according to the SCID, pathological gamblers had greater PTSS (heightened mean CMS scores) than healthy controls [29.9 vs. 4.38,  $\Delta = 25.5$ , 95% CI = (14.6, 36.5),  $p < .001$ ]. Moreover, pathological gamblers had significantly higher mean arousal sub-scores than controls [13.1 vs. 6.38,  $\Delta = 6.66$ , 95% CI = (2.90, 10.4),  $p < .001$ ]. On the other hand, no significant group differences were detected in the LEC number of traumatic events [3.68 vs. 2.31,  $\Delta = 1.37$ , 95% CI = (-1.79, 4.54),  $p = .383$ ] nor in mean years since last trauma [11.5 vs. 11.9,  $\Delta = -0.43$ , 95% CI = (-9.51, 8.65),  $p = .921$ ].

Among PG subjects, there was a significant correlation between gambling severity (reflected in the number of PG DSM-IV-TR symptoms) and the PTSS scores [ $r = .567$ , 95% CI = (0.251, 0.888),  $p = .006$ ]. However, no significant correlation was detected between gambling severity and number of traumatic events [ $r = -.311$ , 95% CI = (-0.638, 0.008),  $p = .159$ ] nor years since the last trauma [ $r = -.308$ , 95% CI = (-0.821, 0.145),  $p = 0.264$ ].

## DISCUSSION

The major finding of this study is that, in comparison with healthy controls, patients with PG have both greater traumatic stress symptomatology and higher physiologic arousal sub-scores in the face of similar trauma exposure. Our findings are consistent with other reports of heightened trauma symptomatology including co-occurring PTSD in up to 34% of PG patients (Ledgerwood & Petry, 2006; Taber, McCormick, Russo, Adkins, & Ramirez, 1987). Previous research has also linked gambling behaviors with both stress (Elman et al., 2010) and with hyperarousal (e.g., Daghestani, Elenz, & Crayton, 1996).

The association of gambling severity and traumatic stress symptoms may be consistent with the incentive sensitization theory of addiction (Robinson & Berridge, 2003), which distinguishes between sensitization and cross-sensitization. The former term typically refers to a situation in which prior exposure to one stimulus (e.g., gambling) increases subsequent response to itself (e.g., urges), whereas the latter may

be defined by the enhancement of gambling urges following prior stress exposure and *vice versa*. The sensitized gambling responses in PG may thus confer greater prominence to traumatic stress symptomatology, whereas stress causes more gambling and additional worsening of PG symptoms.

Although among correlated factors, we cannot determine which is primary and which is secondary using a cross-sectional design, our findings could be relevant to understanding and predicting relapse. After a long period of abstinence, delivery of a priming dose of an addictive drug can re-establish drug self-administration in laboratory animals (McFarland & Kalivas, 2001). This effect is elicited even when the drug used for priming is drawn from a different class than the self-administered substance. If the neural circuitry underlying this reinstatement plays a role in PG and in traumatic stress, then it is possible that traumatic stress exposure could trigger reinstatement of gambling in abstinent PG individuals. Such cross-sensitization would be bi-directional (i.e., those who resume gambling may also have a resurgence of traumatic stress symptoms).

In some instances, it might be possible to postulate specificity of the cross-sensitization and anti-reward mechanisms. Their dissociability is supported by the involvement of different neuroanatomical and neurochemical characteristics such as limbic structures, which contribute to an outpouring of norepinephrine and other stressogenic hormones for the former versus mesolimbic dopaminergic nuclei and related circuitry for the latter (Elman & Borsook, 2016). An alternative, continuum-type interpretation is that anti-reward is a specific form of cross-sensitization. While the cross-sensitization encompasses multiple stimuli other than stress (e.g., various classes of addictive substances), anti-reward is limited to aversive emotional states. In keeping with the latter assumption, a key element of anti-reward (i.e., physiologic arousal; Koob, 2009; Koob & Le Moal, 2008) has here been shown to be elevated in PG patients.

The findings of this study should be considered within the context of certain limitations. First, the CMS does not measure the duration of traumatic stress symptoms, a limitation which could have been addressed using the Clinician-Administered PTSD Scale (Weathers, Keane, & Davidson, 2001). Second, although *a priori* emphasis was placed on the self-reported psychosocial symptoms and no objective indices (e.g., endocrine measures or brain activation) were obtained to quantify stress responses, these findings may provide a foundation for further, more rigorously designed projects. Third, the age and ethnic distributions were somewhat different between groups; however, adjusting for these potential confounders did not alter any of our conclusions. Fourth, the sample size was small; however, using more robust non-parametric tests (Mann–Whitney *U* instead of *t*-test and Spearman’s rho instead of Pearson product-moment correlation) did not change any of the conclusions.

Fifth, exigencies of subject recruitment did not allow the exclusion of all factors that could confound the proposed study’s results. For example, the presence of major depression as well as cocaine and alcohol dependence even more than 1 year prior to the study may alter the brain’s stress system, as might the current use of bupropion. Given the substantial comorbidity of PG with major depression (Getty,

Watson, & Frisch, 2000) in conjunction with cocaine (Konkoly Thege, Hodgins, & Wild, 2016) and alcohol (Petry, Stinson, & Grant, 2005) dependence, however, implementing these as exclusion factors would have ruled out a high percentage of subject candidates as to make recruitment unfeasible. Even if adequate subjects were recruited with these constraints, the resultant groups would likely be unrepresentative of the universe of PG subjects. However, we have attempted to balance the recruiting efforts with pragmatics by excluding so called “endogenous” depression and ongoing substance dependence. By doing so, we believe that we made reasonable compromises between diagnostic pureness and feasibility. Finally, this study was solely focused on PG, so it remains uncertain whether the data are generalizable to other types of behavioral addictions (e.g., food, internet, or sex). Thus, future research may be enriched by examining PTSS and trauma exposure in other types of addicted patients.

Our findings may have diagnostic implications by pointing to a potential clinical marker. This is important because PG is devoid of objective symptoms of addiction, for example, intoxication, needle marks, or positive urine toxicology findings. Also, if the potential stress-related PG vulnerability factor could be confirmed in longitudinal trials, it might be used to screen patients at risk for the development of PG. In a study of pathological gamblers, gambling behavior significantly decreased upon completion of PTSD treatment with prolonged exposure therapy with concurrent naltrexone (Najavits et al., 2013). The suggestion is that treatment of trauma symptomatology can positively impact treatment for PG. Thus, patients found to possess high vulnerability for developing PG might be counseled to avoid gambling (primary prevention), or targeted for early intervention even in the presence of mild trauma symptoms (secondary prevention).

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*Funding sources:* This research was supported by the grant 1 I01 CX001118-01A2 from the Veterans Health Administration.

*Authors’ contribution:* CLG coordinated data analyses and wrote the manuscript. RWN provided statistical analyses and their interpretations. AAS helped with writing the manuscript and data interpretation. IE designed the study, supervised the work of co-authors, and finalized the manuscript.

*Conflict of interest:* There were no conflicts of interest on the part of any of the authors.

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