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A Systematic Review of Stress Physiology in Gambling Disorder and Problem Gambling

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Abstract

Purpose of Review Stress may contribute to the onset and symptoms of maladaptive gambling behaviour. However, minimal work investigates stress physiology in gambling populations. This review explores available research examining stress physiology in problem and disordered gambling.

Recent Findings Eighteen studies were included in the review. Acute stress and risky decision-making tasks were most often employed to examine stress physiology. Stress markers typically examined across studies included cortisol, adrenocorticotropic hormone, and heart rate measurements.

Summary Results indicate potential alterations in stress physiology among problem and disordered gambling populations, although studies were heterogenous. Patterns observed across studies suggest that in gambling populations: (1) basal stress markers do not differ from healthy individuals; (2) stress physiology is altered during risky decision-making and real-stakes gambling; and, (3) the physiological acute stress response is blunted. More research should seek to validate these findings to provide a comprehensive understanding of stress and its associated risks in problematic gambling.

Keywords Problem gambling · Gambling disorder · Stress physiology · Acute stress · Hypothalamic-pituitary-adrenal axis · Sympathetic nervous system

Background

Gambling is prevalent worldwide. While most people who gamble do so recreationally and do not experience significant negative personal consequences, some individuals develop symptoms of disordered gambling, which can progress into clinically defined gambling disorder (GD) [1]. GD is defined in the fifth edition of the *Diagnostic and Statistical Manual* (DSM-5) as a persistent and recurring pattern of gambling associated with substantial stress and functional impairment. GD is associated with negative long-term outcomes such as poorer health, relationship problems, poor work or school performance, financial issues, and suicidality. "Problem gambling" (PG) describes individuals who exhibit symptoms of disordered gambling that are not identified using formal diagnostic criteria or exist below the clinical threshold [2].

One critical aspect prevalent in GD is high stress, which contributes to the development and maintenance of GD; acute stress may increase gambling urges and gambling behaviour may be used to mitigate stress [3, 4]. Chronic stress may also increase susceptibility to maladaptive gambling and the rewarding value of gambling behaviours [5••, 6, 7]. Relapse likelihood may increase during stressful situations, making recovery more difficult [3]. Furthermore, stress can alter cognitive and neural function over time which could promote gambling fallacies such as the illusion of control [3, 4]. Certain forms of gambling, such as slot machines, rely on unpredictability and uncontrollability factors that may induce acute stress, such that the action of gambling itself can become a cue for stress, even for people who gamble recreationally [8].

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Acute stress induces a physiological response mediated by two systems: the hypothalamic-pituitary-adrenal (HPA) axis, and the sympathetic nervous system (SNS) [9]. The HPA axis drives the response from several hormones including corticotropin-releasing hormone (CRH), adrenocorticotropin hormone (ACTH), and cortisol, while the SNS initiates cardiovascular activity to increase heart rate and blood pressure [9, 10]. Other important physiological markers of stress include epinephrine, norepinephrine, and alpha-amylase [10, 11]. The physiological acute stress response maintains homeostatic balance; however, overactivation due to chronic stress disrupts this system over time [7]. Since stress is both a risk factor for developing GD and is enhanced by the disorder, individuals who display maladaptive gambling behaviour likely experience altered physiological acute stress activity. Therefore, the purpose of this review is to examine literature that describes physiological stress activity and reactivity in individuals with PG and GD. We discuss research investigating basal stress markers, acute stress effects, stress physiology during risky decision-making, and therapeutic and pharmaceutical considerations in PG and GD populations.

Methodology

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Database searches were done on PubMed, Web of Science, and PSYCInfo. Keywords used included "Stress", "HPA", "Cortisol", "ACTH", "CrH", "epinephrine", and "amylase" coupled with "gambling", "problem gambling", "gambling disorder", and "pathological gambling". Results were not restricted by year of publication or journal. The original inclusion criteria were that studies: (1) be peer-reviewed and accessible in English, (2) contain primary research involving human subjects (meta-analyses, systematic reviews, abstracts, and commentaries excluded) (3) include a comparison between a PG or GD population and a healthy control (HC) group, and (4) contain a biological measure of neuroendocrine stress function. After the search was completed, our criteria were expanded to include studies examining physiological stress markers in PG and GD without a HC group for comparison. Database searches and screening for studies took place between October 2022 and January 2023, and results were extracted thereafter.

Results

Our initial search generated 1024 results, 18 of which met our inclusion criteria (see Fig. 1). The results are organized across four main sections summarizing study findings on 1) basal and diurnal stress hormone measures; 2) the physiological stress response to gambling and other risky decision-making tasks; 3) direct acute stressor effects on stress hormones; and 4) therapeutic and pharmacological effects on stress hormones in GD. The study details are summarized in Tables 1 and 2.

Basal Stress Measures

While basal stress measures represent baseline physiological markers, diurnal activity follows a consistent circadian pattern. The "cortisol awakening response" (CAR) refers to the typical increase within 40 minutes of awakening, while the "diurnal cortisol slope" (DCS) is the subsequent decrease until nighttime [13]. The search identified three studies collecting basal stress markers, with one measuring diurnal cortisol activity (Table 1).

Geisel and colleagues [14] found no significant difference in basal levels of ACTH, cortisol, and copeptin (a marker of arginine vasopressin released as a stress hormone) between GD, Internet Gaming Disorder, and HC groups. However, lower cortisol levels were associated with greater GD severity. Another study [15] examined leptin, finding no significant differences between GD and HC groups. Although the GD group displayed a positive association between leptin and copeptin levels, leptin was not associated with ACTH or cortisol in either group, nor was it associated with self-reported gambling urges.

Roy and colleagues [16] measured diazepam binding inhibitor (DBI), a peptide implicated in depression, and CRH in individuals with GD, Major Depressive Disorder (MDD), and HCs. A trending larger range of DBI levels were observed in the HC group compared to the GD group, whereas the range of CRH levels trended greater in the GD group. Both groups displayed positive associations between DBI and CRH, although this correlation in the GD group was driven by individuals who were not depressed.

Wohl and colleagues [17] examined diurnal cortisol rhythms in university students classified as having recreational gambling (RG), PG or GD. All three groups showed the typical diurnal cortisol response, but the CAR was significantly larger in both the PG and GD groups compared to the RG group. Only at 330 minutes post-wakeup was there no difference in cortisol between groups.

Physiological Stress Activity During Risk-Taking

Five studies from our search examined the HPA axis and SNS activity under situations involving risky decision-making (Table 2).

Buchanan and colleagues [18] assessed diurnal cortisol profiles in comparison to performance on the Columbia Card task (CCT) and the Cups Task. Compared to HCs, the PG

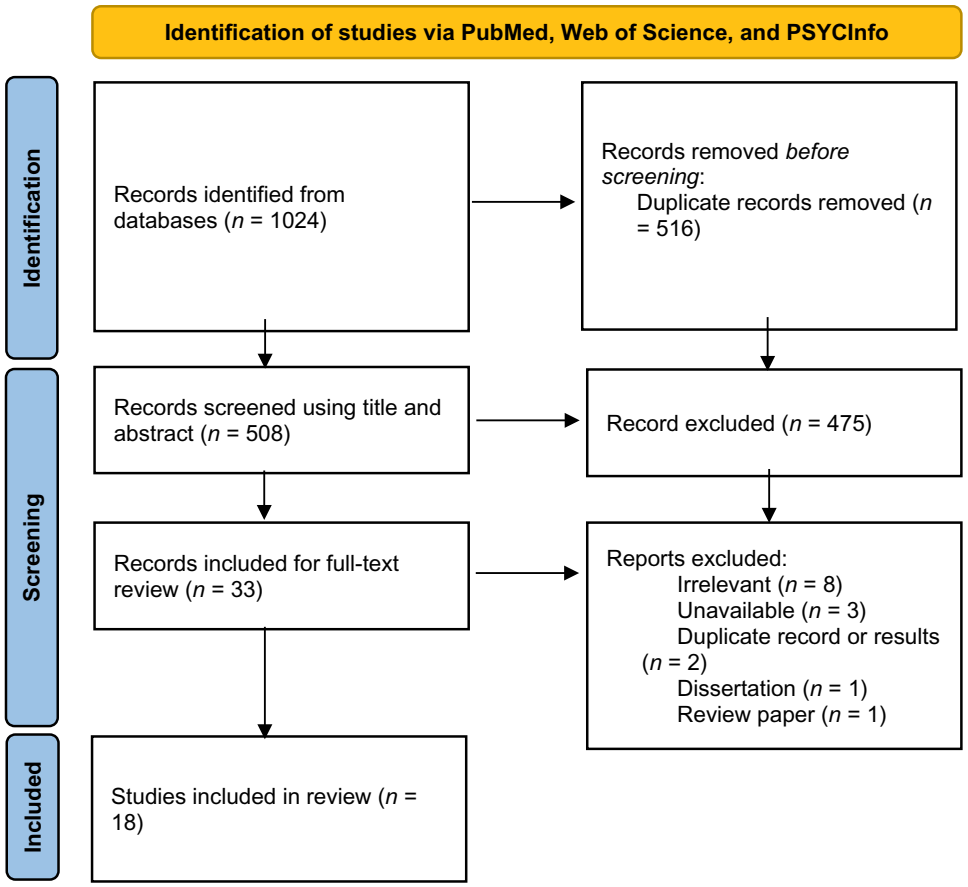

Fig. 1 A flowchart based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines representing the number of articles included in the review using set criteria. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

group displayed a flatter DCS and significantly lower early morning cortisol, but there were no differences right at waking, in the afternoon, or at bedtime. A lower CAR was associated with higher PG severity and riskier decisions in the "hot" CCT (targeting affectively driven decision-making), but not the "cold" CCT (relying on controlled decisions). Conversely, Cups Task performance yielded no significant relationships to cortisol or gambling pathology.

Labudda and colleagues [19] examined salivary cortisol and alpha-amylase (sAA) before and during the Computerized Game of Dice Task (cGDT) in GD versus HC groups. Although the GD group chose more disadvantageous alternatives on the cGDT than HCs, no significant differences in cortisol levels or sAA were identified between groups and no changes were observed throughout the task. In only the GD group, disadvantageous choices on the cGDT were negatively associated with sAA between baseline and task cessation.

Kruger and colleagues [20] examined plasma cortisol and heart rate activity when playing blackjack. In RG, PG, and GD groups, plasma cortisol and heart rate increased at the onset of gambling and declined at the end. These effects were more pronounced in conditions where participants gambled with their own money in a casino (experimental condition), than in a neutral laboratory setting without money (control condition). Furthermore, individuals rated as more impulsive had significantly greater heart rates during the experimental condition, but no cortisol differences.

Two methodologically similar studies by Meyer and colleagues [21, 22] also identified a relationship between physiological stress and real-stakes gambling. Meyer and colleagues [21] found significantly higher salivary cortisol levels and heart rates during the experimental compared to control conditions. GD severity negatively correlated with heart rate in only the control condition, with no effect on cortisol. Meyer and colleagues [22] also found that heart rate and norepinephrine levels increased more significantly in a PG compared to RG group during the experimental condition. Baseline epinephrine was comparatively greater in the PG group and remained elevated during the experimental condition, and ACTH, cortisol, and prolactin showed no significant main group differences.

Cue Reactivity and Cortisol

Paris and colleagues [23] applied an experimental protocol where GD and RG groups were presented videos of other people winning or losing money while gambling using their

Table 1 Summary of findings on baseline stress markers, therapeutic and pharmacological effects

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Geisel *et al.*, 2015	Copeptin, ACTH, cortisol	To examine basal HPA-axis markers across behavioural addictions	Male only • GD (n=14) • Mean age=35.4 • HC (n=13) • Mean age=35.2	GD was determined using DSM-IV and ICD-10 criteria • Participants completed PG-YBOCS to measure gambling severity • Blood samples collected between 9 and 10am	• No significant difference in copeptin, cortisol, and ACTH levels between GD and HC groups Cortisol was negatively associated with the following PG-YBOCS items and scores: • Time occupied by gambling • Associated distress with gambling • "Behaviour" subscale score • Total score
Geisel *et al.*, 2018	Leptin, copeptin, ACTH, cortisol	To compare leptin levels with cravings across behavioural addictions	Male only • GD (n=14) • Mean age=35.4 • HC (n=12) • Mean age=36.6	*Same as above*	• No significant difference in leptin levels between GD and HC groups • Leptin was significantly positively associated with copeptin levels in GD group • Leptin was not significantly correlated with PG-YBOCS, the frequency, or duration of GD
Roy *et al.* 1989	CRH, DBI	To investigate the relationship between DBI and CRH in a clinical population	Male only • GD (n=18) • HC (n=17)	GD was determined using DSM-III criteria • Cerebral spinal fluid was extracted through a lumbar puncture	• DBI levels ranged from 0.60–1.99pmol/ml in the HC group, and 0.6–1.56 pmol/ml in the GD group • CRH levels ranged from 22.3–61.6 pg/ml in the HC group, and 14.2–82.8 pg/ml in the GD group • DBI was significantly positively associated with CRH levels in HC group and GD participants not endorsing depression • This association was insignificant in GD participants endorsing depression

Table 1 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Wohl *et al.*, 2008	Cortisol	To examine if distress, depression, and impulsivity varies across the severity of gambling behaviour	• RG (n=66) • Mean age (male)=20.32 • Mean age (female)=19.7 • PG (n=51) and GD (n=8) • Mean age (male)=20.27 • Mean age (female)=20.61	Gambling severity was determined using DSM-IV criteria • Participants collected their own saliva samples upon wakeup (T0) and 0.5 (T1), 3.5 (T2), and 5.5 hours (T3) afterwards • Participants completed the BDI and BIS-11	Morning cortisol levels displayed typical diurnal patterns across all groups, increasing between waking and T1 and declining until T3 • The increase in cortisol was significantly greater in the PG and GD groups than in the RG group • Group differences in cortisol were significant at every time point except T3 • There was no main effects of sex on cortisol levels across any group • In only the GD group, morning cortisol was larger in females using oral contraceptives than those who did not • Cortisol was not significantly related to BDI or BIS-11 scores
Angelo *et al.*, 2013	ACTH, cortisol, prolactin	To investigate if physical activity is an effective treatment for stress in GD	Male and female GD (n=63) • Physical activity group (n=33) • Mean age=47.5 • No physical activity group (n=30) • Mean age=45.4	GD was determined using DSM-IV criteria • Participants either underwent treatment over 4 weeks (short) or 8 weeks (long) • Blood samples were collected before and after the physical activity treatment program • Gambling craving was measured using the PCS, CQ, and VCS	• Participants undergoing physical activity treatment displayed no significant changes in ACTH, cortisol, or prolactin following completion of the program • The change in craving was significantly positively correlated with the change in prolactin levels • Changes in craving were not associated with changes in ACTH or cortisol levels

Table 1 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Ramirez *et al.*, 1988	Cortisol	To explore the relationship between cortisol and depression in GD	Male only • GD (n=21) • Mean age=43.14	GD was determined using DSM-III criteria • Day 1: blood samples were collected at 8am and 4pm, and dexamethasone was administered at 11PM • n=11 participants received 2mg of dexamethasone, and n=10 participants received 1mg of dexamethasone • Day 2: blood samples were collected at 8am and 4pm Participants completed the BDI, as well as the MMPI to measure depression, psychasthenia, psychopathic deviancy, and schizophrenia	• Participants with greater morning cortisol had a steeper decline in cortisol by 4PM • Cortisol levels at 8am were moderately positively associated with MMPI (depression, psychasthenia, and schizophrenia) scores and BDI scores • Cortisol levels at 4pm were significantly negatively associated with MMPI (depression and psychopathic) scores and BDI scores • The change in cortisol between 8am and 4pm was significantly positively associated with MMPI (depression, psychopathic, and schizophrenia) scores, and moderately positively associated with the MMPI (psychasthenia) score
Pallanti *et al.*, 2006	Prolactin, cortisol	To examine the physiological stress response following serotonergic stimulation in GD	Male only • GD (n=26) • Mean age=35.3 • HC (n=26) • Mean age=31.6	GD was determined using DSM-IV-TR criteria • Participants received oral dose of m-cPP and a placebo pill, separated by 48 hours • Blood samples were collected at baseline and 90, 120, 180, and 210 minutes following drug administration • Participants completed the Y-BOCS-PG to measure gambling severity	• Both GD and HC groups showed significantly greater prolactin levels following m-cPP compared to placebo • The GD group displayed a significantly greater prolactin increase than the HC group at 180 and 210 minutes following m-cPP administration • Both GD and HC groups showed a significant increase in cortisol at 120 minutes following m-cPP administration • Cortisol levels did not significantly differ between groups • The increase in prolactin observed was significantly positively associated with Y-BOCS-PG scores

Table 1 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Moreno *et al*., 1991	Prolactin, cortisol	To examine differences in serotonergic activity following pharmacological stimulation between GD and HC groups	Male and female • GD (n=8) • HC (n=8)	GD was determined using DSM-III criteria • Participants were administered clomipramine • Blood samples were collected at baseline and 4 times over 2 hours following drug administration	• Prolactin levels were significantly greater in the HC group, 1 hour following clomipramine administration • The GD group displayed a trend toward lower baseline prolactin • The GD group displayed a trend toward a blunted prolactin response to clomipramine • Cortisol did not significantly differ between groups or following clomipramine administration

Table 1 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Zack *et al.*, 2015	Heart rate, SBP, DBP, cortisol	To examine differences in the stress response to amphetamines in GD versus HC groups	Male only • GD (n=12) • Mean age=32.7 • HC (n=11) • Mean age=34.5	GD was determined using DSM-IV criteria • Day 1: participants completed the Eysenck Impulsiveness Scale, Personality Inventory, and SOGS • Participants completed the Stop Signal Task, responding to specific stimuli and inhibiting their response when a specific tone played • Day 2: participants received an oral dose of amphetamine • Heart rate, blood pressure, and blood samples were collected at baseline and up to 210 minutes following drug administration	• Both groups displayed an increase in cortisol following amphetamine administration, but this was significantly lower in the GD group from baseline to peak levels • Both groups displayed an increase in heart rate following amphetamine administration, but the GD group displayed a significantly larger decrease after 90 minutes • The GD group had significantly lower SBP from baseline to 120 minutes following amphetamine administration, and significantly decreased while the HC group's remained stable • Both groups displayed increasing DBP until 120 minutes following amphetamine administration, but the GD group displayed significantly lower DBP, except from 120–210 minutes, where it was significantly greater • Heart rate and DBP were oppositely correlated in HC (positively correlated) versus GD (negatively correlated) groups • In the GD group, heart rate was negatively associated with SOGS scores and negatively correlated with the Stop Signal Task response time (i.e., better inhibition) • In the HC group, heart rate and SBP were positively correlated with Stop Signal Task response time (i.e., worse inhibition)

Abbreviations: *ACTH* Adrenocorticotropic hormone, *HPA* hypothalamic-pituitary-adrenal, *GD* pathological gambling, *HC* healthy control, *PG-YBOCS* Yale–Brown Obsessive–Compulsive Scale for Pathological Gambling, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, *ICD-10* International Classification of Diseases 10th Revision, *CRH* Corticotrophin-releasing hormone, *DBI* Diazepam binding inhibitor, *DSM-III* Diagnostic and Statistical Manual of Mental Disorders Third Edition, *RG* recreational gambling, *PG* problem gambling, *BDI* Beck Depression Inventory, *BIS-11* Barratt Impulsiveness Scale-11, *PCS* Pennsylvania Craving Scale, *CQ* Craving Questionnaire, *VCS* Visual Craving Scale, *MMPI* Minnesota Multiphasic Personality Inventory, *DSM-IV-TR* Diagnostic and Statistical Manual of Mental Disorders Text Revision Fourth Edition, *m-cPP* meta-chlorophenylpiperazine, *Y-BOCS-PG* Yale Brown Obsessive Compulsive Gambling Scale, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 2 Summary of findings on risk- and stress-driven effects on stress physiology

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Buchanan *et al.*, 2020	Cortisol	To explore diurnal cortisol activity and its relationship to risky decision-making	Male and female • PG (n=30) • Mean age=45.63 • HC (n=29) • Mean age=42.70	PG was determined using the NODS screener • Saliva samples were collected at awakening and 30, 45, and 180 minutes post-awakening, and at bedtime Participants completed The Cups Task: participants can pick between certain and uncertain choices, with alternating trials of gains (winning money) and losses (losing money) Participants completed CCT: an online card game where participants choose to flip cards which have varying levels of points to gain or lose • The "hot" version requires participants to choose their starting card and continue to individually chose cards (affective) • The "cold" version requires participants to choose the number of cards to select before flipping them (deliberate)	• The PG group displayed significantly lower cortisol at 30 and 45 minutes following waking, and a flattened total diurnal cortisol slope • Cortisol levels did not significantly differ between groups at waking, 180 minutes post-wakeup, or at bedtime • The cortisol awakening response, but not the diurnal cortisol slope, was significantly negatively associated with NODS scores • A flattened cortisol awakening response was significantly associated with greater risk-taking on the CCT, with a particularly large effect in the "hot" version • No significant effects or relationships were identified between cortisol activity and performance on the Cups Task
Labudda *et al.*, 2007	Cortisol, alpha-amylase	To investigate the relationship between physiological stress and decision-making	Male only • GD (n=22) • Mean age=40.45 • HC (n=19) • Mean age=42.89	GD was determined using ICD-10 and DSM-IV criteria • Saliva samples were collected at baseline and 10, 20, and 30 minutes following baseline A computerized Game of Dice task was completed: • Participants guess a potential combination of numbers (single, two, three, or four numbers) that will be thrown on dice, each of which is associated with varying gains or losses (shown following each throw) A neutral task and subjective stress scale were administered afterwards	• Cortisol and salivary alpha-amylase levels did not significantly differ between groups • Changes in alpha-amylase between baseline and task completion were significantly negatively associated with disadvantageous choices made in the GD group, but cortisol was unrelated to task performance • Subjective stress was significantly associated with baseline cortisol in the HC group, but not the GD group • Subjective stress was not significantly associated with alpha-amylase at any point in either group

Table 2 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Kruger *et al.*, 2005	Cortisol, heart rate	To examine the physiological stress response to real-life gambling	Male only • RG (*n*=15) • Mean age=43.9 • PG (*n*=4) and probable GD (*n*=9) • Mean age=42.1	Gambling status was determined using the SOGS • The EIS measured impulsivity • Participants played a game of blackjack for 90 minutes with real money at stake (experimental session), and a card game with no money in a neutral environment (control session) • Blood samples were collected at baseline and 30, 60, and 90 minutes into playing blackjack, and heart rate was collected at baseline and continuously throughout the session	• Heart rate significantly increased throughout the experimental condition compared to the control condition, and declined after its completion • Plasma cortisol significantly increased at the onset of the experimental condition and remained greater than in the control condition throughout, but was not significantly different at baseline or following task completion • Heart rate significantly increased following the onset of the experimental condition in high and low impulsivity groups, and decreased after completion of gambling • The high impulsivity group had a significantly greater baseline heart rate measurement • Cortisol significantly increased at gambling onset and continuously decreased throughout the session in both impulsivity groups, with no significant between-group differences in cortisol
Meyer *et al.*, 2000	Cortisol, heart rate	To examine the physiological stress response to real-life gambling	Males only (mean age=44.5) • RG (*n*=5) • emerging GD (*n*=3) • medium GD (*n*=1) • severe GD (*n*=1)	Gambling severity was determined using a 20-item questionnaire • Participants played a game of blackjack with real money at stake (experimental session), and a card game with no money in a neutral environment (control session) • Saliva samples were collected at baseline, 30 and 60 minutes into playing, and after task cessation; heart rate was collected at baseline and continuously throughout the session	• Heart rate was significantly greater during the experimental compared to control condition, but was significantly higher at baseline in the control condition • Salivary cortisol was significantly higher in the experimental compared to control condition at 60 minutes and following completion of gambling • Gambling severity was negatively correlated with heart rate across all time points in the control condition, but unrelated to heart rate in the experimental condition • Gambling severity was not significantly related to cortisol in either condition

Table 2 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Meyer *et al.*, 2004	Heart rate, epinephrine, norepinephrine, ACTH, cortisol, prolactin	To examine how real-life gambling impacts physiological stress activity	Male only • PG (n=14) • Mean age=42.1 • RG (n=15) • Mean age=43.9	• Gambling severity was determined using SOGS and a 20-item German quesionnaire ("Kurzfragebogen zum Glu ¨cksspielverhalten") • Participants played a game of blackjack using real money (experimental condition) or a game of cards with no money (control condition) • Heart rate was collected throughout the session and following task completion • Blood samples were collected at baseline and 30, 60, and 90 minutes into gambling, and following task completion	• Heart rate significantly increased during the experimental condition in both groups, but was higher in the PG compared to RG group • No significant between-group differences in heart rate were observed in the control condition • Epinephrine increased throughout the experimental condition in the RG group and declined at the end, but was elevated at baseline and remained elevated in the PG group • Norepinephrine increased in both groups during the experimental condition, but was elevated in the PG group in both conditions • ACTH and cortisol increased in the experimental condition across both groups, while cortisol showed a significantly greater increase at the onset of gambling in the PG group • Prolactin did not significantly differ between conditions or groups
Paris *et al.*, 2010	Cortisol	To investigate how different gambling cues alter cortisol activity	Male and female • GD (n=21) • RG (n=21)	Gambling severity was assessed using NODS and SOGS • Participants watched a video of other people gambling using their preferred method (i.e., someone who often uses slot machines watched a video of someone playing on slots) • Both winning and losing scenarios were observed • Participants also watched people riding a rollercoaster as a neutral exciting condition • Salivary cortisol was collected at baseline, after watching both gambling videos, and after the rollercoaster video	• The RG group displayed higher levels of cortisol after all videos compared to baseline levels • Cortisol did not significantly differ across all time points in the GD group • Males had higher baseline cortisol levels than females, but no significant differences were observed at any other time point

Table 2 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Wemm *et al.*, 2020	Cortisol	To investigate how a psychosocial stress affects cortisol and gambling urges	Male and female • PG (n=30) • Mean age=34.14 • HC (n=32) • Mean age=35.13	Gambling severity was determined using SOGS • Participants completed the TSST where they performed a mock interview and mental math tasks in front of a panel of people • Saliva samples were collected directly before, directly after, and 20 minutes following stress exposure • Participants rated subjective stress on a 5-point likert scale	• Cortisol increased for both groups following the TSST, with no significant main group differences • The HC group had a significantly steeper increase in cortisol following the stressor than the PG group • Changes in cortisol were not significantly related to gambling urges in the PG group
Maniaci *et al.*, 2018	Cortisol, heart rate	To examine physiological stress activity in response to psychosocial stress	Male only • GD (n=35) • Mean age=36.34 • HC (n=30) • Mean age=37.60	Gambling severity was assessed using the SOGS and CIDI • Participants completed the Trier Social Stress Test (TSST) • Salivary cortisol and heart rate were collected at baseline, during TSST prep, onset of TSST speaking, directly post-TSST, and 20 and 40 min post-TSST	• Cortisol and heart rate significantly increased during the task and declined after completion in both groups • There were no significant group differences in cortisol levels; however, a trend toward greater levels of cortisol was observed in the GD compared to control group at 0 and 20 minutes post-TSST • A significant negative correlation was observed between GD duration and baseline cortisol, such that individuals who have had a diagnosis for longer had lower levels of baseline cortisol • No significant relationship between gambling duration and heart rate was observed

Table 2 (continued)

Citation	Stress marker	Purpose	Sample Characteristics	Relevant Study Protocol	Summary of Findings
Steinberg *et al.*, 2011	SBP	To explore differences in psychological stress reactivity and different addictive cues between those with alcohol and/or gambling problems and healthy controls	Male only • PG (*n*=12) • Mean age=36.4 • PG+AUD (*n*=12) • Mean age=40.3 • HC (*n*=16) • Mean age=36.4	Gambling severity was determined using SOGS • Participants underwent a psychological stressor where they listened to white noise through headphones under two conditions: • "U-noise" = uncontrollable white noise • "C-noise" = controllable white noise • In both conditions, subjects had to repeat back a sequence of mouse clicks and were told it would stop the noise (however, this only worked in the C-noise condition) • An emotional Stroop task followed by an affective go/no-go task using gambling-related words were administered following stress exposure • Participants drank either placebo beer or soda before the go/no-go task • SBP was obtained at baseline, before beverage consumption, and at the end of the session	• Baseline blood pressure did not significantly differ between PG and HC groups, but was significantly greater in the PG+AUD group • Stress exposure (U-noise) significantly increased blood pressure in the HC group • Conversely, stress exposure significantly lowered SBP in both PG and PG+AUD groups, such that: • PG displayed the greatest reduction in SBP in the U-noise + placebo conditions compared to the C-noise + soda condition • PG+AUD had the greatest reduction in SBP in the U-noise + soda compared to the C-noise + soda condition

Abbreviations: *PG* problem gambling, *NODS* National Opinion Research Center DSM-IV Screen for Gambling Problems, *CCT* Columbia Card Task, *ICD-10* International Classification of Diseases 10th Revision, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, *GD* pathological gambling, *RG* recreational gambling, *EIS* Eyesynk Impulsivity Score, *SOGS* South Oaks Gambling Screen, *TSST* Trier Social Stress Test, *CIDI* Composite International Diagnostic Interview, *SBP* systolic blood pressure, *AUD* alcohol use disorder

preferred method (e.g., slot machine, sports betting, etc.) (Table 2). Both groups rated "winning" and "neutral exciting" videos as more exciting than "losing" videos; however, only the RG group displayed cortisol increases following all three video presentations.

Physiological Response to Acute Stress

Three studies examined the physiological response to acute stress (Table 2). Wemm and colleagues [24••] administered the Trier Social Stress Test (TSST), a well-validated psychosocial stressor [25], to PG, heavy smoking, and HC groups; all displayed a cortisol rise, but HCs had a steeper increase compared to the PG group. An exploratory analysis showed that cortisol changes among the PG group were unrelated to gambling urges. Maniaci and colleagues [26] applied a similar protocol with the addition of measuring heart rate variability and also found TSST-increased cortisol levels and altered heart rate variability in both HC and GD groups. Conversely, there were no group differences over time, but the GD group showed a trend of greater salivary cortisol immediately and 20 minutes following task cessation compared to HCs.

Steinberg and colleagues [27] employed a psychological stress paradigm, with "uncontrollable noise" to induce acute stress. Participants with combined PG and Alcohol Use Disorder (PG+AUD) had significantly greater baseline systolic blood pressure (SBP) compared to PG and HC groups. Following acute psychological stress, both gambling groups displayed significantly decreased SBP while HCs had increased SBP. This effect was most pronounced in the PG group after receiving placebo beer, and greatest in the PG+AUD group when participants drank soda.

Therapeutic and Pharmacological Effects on Stress Markers in GD

Various interventions are used to treat GD, such as cognitive behavioural therapy and motivational interviewing [28], both of which are well-validated across many studies, including when they are combined [29]. Five studies extracted in this review explore therapeutic and pharmaceutical effects on stress physiology in GD (Table 1).

Angelo and colleagues [30] studied the efficacy of a short versus long physical activity program among individuals with GD. There were no significant changes in ACTH, cortisol, or prolactin following completion of the program, regardless of its duration. However, trending changes in prolactin levels were significantly associated with self-reported gambling craving.

Four studies measured stress marker changes following drug administration. Ramirez and colleagues [31] found that dexamethasone, an anti-inflammatory drug [32], did not alter cortisol activity in individuals with GD. Pallanti and colleagues [33] identified increased cortisol in both GD and HC groups and comparatively greater prolactin increases in the GD group following administration of a serotonin receptor agonist, meta-chlorophenyl piperazine (m-CPP). Moreno and colleagues [34] reported decreased prolactin in GD, but not HC groups, following clomipramine (serotonin reuptake inhibitor) administration, but no changes in cortisol. Zack and colleagues [35] administered amphetamine which increased cortisol and heart rate in both GD and HC groups, albeit with a blunted increase in cortisol and stronger subsequent heart rate decline in the GD group.

Discussion

This review aimed to examine acute stress physiology in GD and PG groups; however, only three studies met our original inclusion criteria, providing somewhat inconsistent results. Therefore, the criteria were subsequently broadened to include any study examining physiological stress activity in gambling populations.

Physiological Response to Acute Stress

While few studies to date have implemented an acute stressor in PG populations, the 2 studies identified in our review did not detect group differences with controls [24••, 26]. However, Wemm and colleagues demonstrated a blunted cortisol response over time in the PG group, relative to the healthy controls. Notably, the blunted cortisol response did not differ from a smoking control group in the same study.

Steinberg and colleagues [27] extended these findings, as both PG and PG+AUD participants displayed blunted cardiovascular activity compared to HCs following acute stress. Nevertheless, it must be noted that Steinberg and colleagues provided a placebo (non-alcoholic beer) to participants, which may have resulted in an expectancy effect [36]. Altogether, the blunted acute stress reactivity findings further replicate blunted cortisol responses reported in cocaine use disorder [37], opiate use disorder [38], chronic cannabis use [39], alcohol and combined alcohol and stimulant dependency [40, 41], and recently in internet addiction [42]. These findings are important as blunted responses further relate to stress appraisal [43], and behavioural motivations for drugs [44].

The growing literature across addictive disorders suggests that blunted responses may relate to HPA-axis alterations that either pre-exist (e.g., due to chronic stress) or relate to other specific addiction processes, rather than a direct effect of substances. Larger longitudinal studies comparing across groups may shed more light on these mechanisms.

Baseline Stress Physiology

The limited studies examining basal stress activity identified no differences in baseline levels of cortisol, copeptin, ACTH, CRH, and DBI between GD and HC groups [14–16]. Nevertheless, most basal samples were collected without control for diurnal fluctuations, thereby making firm conclusions difficult to draw regarding baseline stress activity in this population. Contradictory findings across studies in CAR may be due to the sample ages and chronicity of GD [17, 18], as dampened cortisol activity may be associated with a longer disorder duration [26].

Physiological Stress Activity During Risk-Taking

The finding of a blunted CAR in individuals with GD with more affectively driven risky decisions made on the CCT [18] can be understood in context with the underlying neural circuitry impacting cortisol activity. Previous research elucidates a relationship between cortisol activity and brain regions facilitating emotional processing and executive control; both human and preclinical studies have identified increased activation of the amygdala and prefrontal cortex in response to acute stress [45–47]. Rapid hydrocortisone administration, which stimulates cortisol, increases amygdala activity and errors in response to negative-affective stimuli in an emotional Stroop Task [45]. This suggests that endogenous cortisol stimulation activates key regions implicated in emotional processing, which subsequently produces a negative emotional bias and reduces executive control. Disruptions to executive control networks are further supported by Yuen and colleagues [46] who showed that greater plasma cortisol was associated with increased glutamatergic activity in the prefrontal cortex of stressed rats. In humans with GD, a yohimbine infusion generating an acute physiological stress response produces greater left amygdala activation compared to HC groups [47]. Stress-induced cortisol activity therefore impacts emotional processing and executive control through related brain regions, and this might be particularly impacted in people with PG or GD. Emotionally driven disadvantageous decisions made in GD may therefore be mediated by cortisol effects exerted onto these limbic regions.

Relatively consistent physiological findings were observed across four PG studies investigating how gambling with or without risk impacts stress markers. Real-stakes gambling, relative to no-stakes gambling, reliably produced a greater stress response through increased heart rate, norepinephrine, and cortisol [20, 21]. The cortisol and heart rate response were also greater in PG compared to RG groups in real-stakes gambling [22]. While Labudda and colleagues [19] observed no differences in cortisol or sAA between PG and HC groups, this study did not apply a real-stakes gambling task. In sum, this research provides consistent evidence of heightened stress reactivity in PG populations when exposed to gambling that mimic real-life scenarios. Given cortisol interactions with executive control networks described above, an important future research direction is better understanding the arousal and decision-making interactions in specific gambling scenarios.

Paris and colleagues [23] examined stress reactivity to gambling cues, rather than direct participation. Interestingly, these findings showed a blunted cortisol response when observing videos of other people gambling in the PG group compared to HCs. One possible interpretation of these results could relate to the perceived outcome of risk and decisions related to gambling in those with PG. Perhaps watching individuals gamble from a secondary perspective does not produce arousal in the way personal real-stakes gambling does, as the risk of negative consequences is mitigated, similar to in controlled no-stakes gambling. However, this is not well-explored and thus more work should seek to understand the mechanisms that drive increased versus blunted stress and how the context of gambling influences this in individuals with PG and GD.

Therapeutic and Pharmacological Considerations Regarding Stress Markers in GD

Most studies examining therapeutic treatment applications in GD use pharmaceuticals. Angelo and colleagues [30] employed a physical activity program among a treatment-seeking GD group, finding no significant changes in ACTH, cortisol, or prolactin. These findings contrast with research showing that exercise enables individuals with substance use disorders (SUDs) to effectively cope with daily stressors without substances, reduce feelings of tension and fatigue, and decrease stress reactivity [48]. Although Angelo and colleagues [30] did not observe significant changes following the intervention, exercise should not be ruled out as a viable treatment for GD. Other findings show reductions in GD severity and craving following exercise treatment in a GD population, and a program completion rate of 81.63% of participants [49]. Therefore, more work should expand on its effects on stress in GD.

Findings from Ramirez and colleagues [31] also directly contradicted similar research conducted in other clinical populations. There were no identified changes in diurnal cortisol following dexamethasone administration in GD populations. Conversely, similar doses of dexamethasone have successfully blunted cortisol activity in people with heavy smoking or tobacco and individuals with Binge Eating Disorder [50, 51]. Like Angelo and colleagues, Ramirez did not use a HC group for comparison. Thus, while it is unclear why dexamethasone or exercise produced no significant changes observed in other addictive disorders,

more research is required to understand their true effects in these populations.

Zack and colleagues [35] found between-group differences in HPA axis and SNS activity, with a blunted cortisol increase and more rapid heart rate decline in the GD group following amphetamine administration. These effects were attributed to lower baseline cardiovascular measures in the GD group compared to controls, potentially indicative of chronic stress effects in this population. Pallanti and colleagues [33] found no between-group differences in cortisol following m-CPP administration, but increased prolactin in only the GD group. Similarly, Moreno and colleagues [34] found no differences in cortisol levels from clomipramine administration between groups, but significantly lower prolactin in the GD group. Since both m-CPP and clomipramine increase the functional activity of serotonin, these results might suggest a relationship between the serotonergic system and GD. Although it is unclear whether serotonergic systems are hyperactive or hypoactive in this population, serotonin appears to induce a disruption to maintenance of homeostatic balance that is facilitated by prolactin [52].

Limitations

The research reviewed in this paper came with significant limitations, including small sample sizes (mostly < 30 participants per group), which reduces the rigor. Another significant limitation is accounting for co-occurring conditions; only 7 of 18 studies explicitly controlled for other psychiatric disorders. SUDs such as nicotine and tobacco use disorders, AUD, and other SUDs frequently co-occur with GD, and the presence of psychiatric conditions significantly increases the odds of disordered gambling [53, 54•, 55]. Altered HPA axis activity has also been observed in people with heavy use of heroin, cocaine, alcohol, and stimulants [40, 41, 56–58]. Thus, limited research observing stress reactivity in GD and PG populations could be driven by SUDs that were not controlled in studies in this review. Similarly, mood disorders are common in individuals with GD [53]. Other research has found altered cortisol and heart rate activity in mood disorders such as MDD, MDD with psychotic features, and Bipolar Disorder compared to healthy individuals [59, 60]. Therefore, findings discussed in this review should be understood considering other potential mood conditions that may impact them.

Lastly, these limitations may be further compounded by sex- and gender-related differences; 12 of 18 studies discussed in this review included only male participants. Although males generally have higher GD rates [61], previous research also identifies sex differences in stress physiology. For example, research conducted in MDD and Generalized Anxiety Disorder populations finds that only females displayed different area under the curve in cortisol compared to HC groups [62]. Differences are also observed in SUDs, such that males with combined SUDs have greater cortisol activity in response to psychosocial stress than females [37]. Previous work has even highlighted different stress-driven motivations for gambling between sexes, as females are more likely to report gambling to relieve stress and anxiety than males and often report greater past-week mood disturbances than males [63, 64]. Thus, the current state of the research on stress physiology provides little insight into important sex differences.

Conclusion

This systematic review elucidated a need for more research surrounding stress physiology in gambling populations. Due to greatly limited research exploring acute stress reactivity in GD and PG populations, inclusion criteria were expanded to allow studies generally exploring physiological stress activity. Studies discussed in this review came with significant limitations, including small and mostly male samples with limited control for relevant co-occurring conditions. While it is difficult to draw concrete conclusions from these findings due to their heterogeneity, some themes can be identified. First, the acute stress response may be blunted in PG and GD populations. However, these findings were only consistent across two of three studies, with notable confounds. Nevertheless, findings to date suggest that basal stress measures do not differ between PG/GD populations and healthy groups. Diurnal activity, however, appears more frequently altered amongst gambling populations, but the direction of change is unclear. Failure to control for diurnal fluctuations in studies extracting basal measures may potentially explain null findings. Risky decision-making and gambling may more reliably alter stress activity in PG/GD populations, particularly in real-stakes situations. In neutral lab settings and second-hand viewings, differences are largely mitigated between PG/GD and HC groups. Considering the diverse methodologies employed in treatment intervention studies, general conclusions cannot be drawn from the existing work. Thus, future research should seek to validate acute stress findings, explore their relationships to decision-making and associated neural circuits, examine further basal stress activity, and investigate potential therapeutic options targeting stress systems in GD and PG populations.

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the the review and conceptualized the work contained in the current manuscript. All authors provided critical feedback and shaped the research, approach and interpretation of the findings, and approved the final article.

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•• Of major importance

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