STRESS REACTIVITY AND RISKY DECISION-MAKING

ACUTE PSYCHOSOCIAL STRESS REACTIVITY AND RISKY DECISION-MAKING IN GAMBLING DISORDER

By Fiza Arshad, B.Sc. (hons.)

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree of Master of Science.

McMaster University

Master of Science (2018)
McMaster University
Neuroscience

TITLE: Effects of acute psychosocial stress induction on risky decision-making in Gambling Disorder

AUTHOR: Fiza Arshad, B.Sc. (hons.) (McMaster University)

SUPERVISOR: Dr. Iris M. Balodis

NUMBER OF PAGES: xii, 88

Lay Abstract

Gambling Disorder (GD), the first non-substance-based ("behavioural") addiction, may also encompass dysregulated stress responses, including different levels of biomarkers cortisol and alpha-amylase (a proxy measure of the hormone norepinephrine), and impaired risky decision-making. To date, few studies investigate the effects of acute stress on these biomarkers and risky decision-making in those with GD. This thesis explores psychosocial stressor-induced release in biomarkers and its effects on risky-decision-making. In addition, those with GD also experience gambling urges, which can influence subsequent gambling behaviour. Other potent motivators for gambling include wanting to escape negative emotions and boredom; therefore, understanding the effects of stress reactivity in GD are of great importance. The findings have broader implications for informing the neurobiology of stress processing, decision-making and motivation, as well as in guiding potential treatment options and strategies.

.

Acknowledgements

First of all, I would like to thank my supervisor, Iris Balodis, for her time and guidance. I have learned a lot in your supervision over the past two years and am incredibly grateful for all of the different training opportunities you've provided. This includes practical laboratory experience in conducting experiments, writing and thinking critically about research, as well as in translating this knowledge to concerned users. Thank you, Dr. Balodis – your efforts have not been wasted!

Secondly, to my committee members, James MacKillop and Margaret McKinnon, thank you for your kind support, advice and encouragement. To Dr. MacKillop, thank you for asking critical questions that got me thinking about statistics and research design, and for always stopping by to ask after my well-being on days where research participants were being difficult. To Dr. McKinnon, thank you for prompting me to take a macroscopic view of my work; and especially for your bold words to help boost my self-esteem up.

To the post-doctoral candidates, research assistants and students – Jackie Hudson, Kiran Punia, Lana Vedelago, Candice Graydon, Katherine Naish, Emily Vandehei, Justin Scherrer, and Jessica Gillard – thank you for your encouragement, support and kind ears! To Jackie Hudson, a warm thank you for lending an ear and for being a friend.

A special thanks to my friends for their encouragement and for lending helpful ears, and another to my family, especially my Mum, who has been a pillar of support, strength and wisdom, motivating me to persevere and ride out both the highs and the lows in a bold and humble way. To my brother Hassan, who has helped me edit my work multiple times over, I owe you.

Table of Contents

List of Figures

CHAPTER 1

CHAPTER 2

List of Tables

CHAPTER 2

List of Abbreviations and Symbols

ACC: Anterior Cingulate Cortex
BART: Balloon Analogue Risk-taking Task
DA: Dopamine
dlPFC: Dorsolateral Prefrontal Cortex
GAS: General Adaptation Syndrome
GD: Gambling Disorder
GUS: Gambling Urge Scale
HC: Healthy Control
HPA: Hypothalamic Pituitary Adrenal
IGT: Iowa Gambling Task
mPFC: Medial Prefrontal Cortex
NE: Norepinephrine
OFC: Orbitofrontal Cortex
PFC: Prefrontal Cortex
POMS: Profile of Mood States
PrG: Problem Gambling
SOGS: South Oaks Gambling Screen
SAM: Sympathoadrenal Medullary
TSST: Trier Social Stress Test
vmPFC: Ventromedial Prefrontal Cortex

Declaration of Academic Achievement

The author is responsible for conducting the literature review presented in Chapter 1, and for interpretation and write-up. For the manuscript-in-preparation included in Chapter 2, the author is responsible for data analysis, interpretation and write-up of this thesis, including the manuscript in-preparation for submission. Data was collected and entered by research assistants at Yale University in New Haven.

Preface

The following thesis consists of one manuscript intended for publication in a scientific journal. Chapter 2 includes a manuscript titled “Acute Psychosocial Stress & Risky Decision-making in Gambling Disorder” which will be submitted to the journal *Psychoneuroendocrinology*. The author of this thesis was responsible for data analysis and manuscript preparation. Experimental design, data collection and entry were done at Yale University, as part of a larger project by the thesis supervisor and her collaborator, who are third and second authors of the paper, respectively.

CHAPTER 1: GENERAL INTRODUCTION

In this dissertation, I explore the effects of acute stress induction on risky decision-making in Gambling Disorder. The first chapter reviews acute stress reactivity and risky decision-making. Following this, the second chapter describes an original investigation of acute stress reactivity and risky decision-making in Gambling Disorder.

Acute Stress Reactivity

An adaptive response to stress is important for the survival of the organism. Typically, it leads to physiological responses, such as an increased release of glucocorticoids and heart rate (Lovallo, 2004). Such biological reactions – termed the fight or flight response by Walter B. Cannon – help the body maintain homeostasis (Cannon, 1929). In this scenario, "stress" – physical, biological or psychological - is good as it supports natural selection of an organism. For example, a state of threat can reduce risk-taking by potentially enhancing the processing of loss information (Clark et al., 2012). In an evolutionary and ecological context, this has important implications towards promoting survival of an organism as the enhancement of negative stimuli can promote risk averse behaviour, ultimately guiding the selection of safe actions. However, a stressor can also be negative and can lead to increased vulnerability towards health-related problems (DeLongis, Folkman, & Lazarus, 1988), including addiction (Goeders, 2003). As such, it is important to introduce a working definition of stress so as to better understand the associated physiological effects it may have.

Physical stress can be defined as the tension caused by an external force (stressor) that challenges the system, leading to disequilibrium (Lovallo, 2004); whereas, psychological stress includes socio-evaluative and uncontrollable components (Dickerson & Kemeny, 2004) that may not necessarily be caused by an external force. As defined by the General Adaptation Syndrome (GAS), physical stress leads to a set of specific and non-specific responses to reinstate homeostasis (Selye, 1950). It activates the hypothalamic pituitary adrenal (HPA) axis, the cardiovascular system, and the sympatho-adrenal-medullary (SAM) system (Lovallo, 2004), helping the organism adapt to changing environments, a process termed allostasis (Sterling & Eyer, 1988). Gradually, constant activation of these physiological mechanisms involved in the stress response take a significant toll on the body, placing an allostatic load on the system (McEwen & Stellar, 1993). In order to cope with the stressor, physical or psychological, the individual engages in cognitive appraisal, where active monitoring of the environment is followed by evaluation and deployment of appropriate coping mechanisms or behaviour (Lovallo, 2004), with the goal being to remove the stressor or reduce the physiological and negative emotional influences.

Over time, chronic allostasis or inefficiently executed allostasis can lead to "allostatic overload", which is better defined as "the price the body pays for being forced to adapt to adverse psychosocial or physical situations" (McEwen, 2002). The allostatic overload (AOL) hypothesis further defines this at a physiological level where chronic activation of the HPA and SAM axes is proposed to lead to a gradual dysregulation in the said systems, in itself becoming a source of chronic stress (see **Fig.** 1). Over time, this

type of stress can influence behaviour and cognition (Arnsten, 2009; Lupien, McEwen, Gunnar, & Heim, 2009), possibly through the differential effects of stress-induced release of glucocorticoids, such as cortisol, and catecholamines – norepinephrine (NE) and dopamine (DA) - on stress-signalling pathways (Arnsten, 2009). In particular, these glucocorticoids and catecholamines are proposed to have an inverted U-shaped effect on the physiology and function of the prefrontal cortex (PFC), in line with the inverted U-hypothesis (Lovallo, 2011), where both extremely high and low levels contribute to impairments (Arnsten, 2009; Lupien et al., 2009).

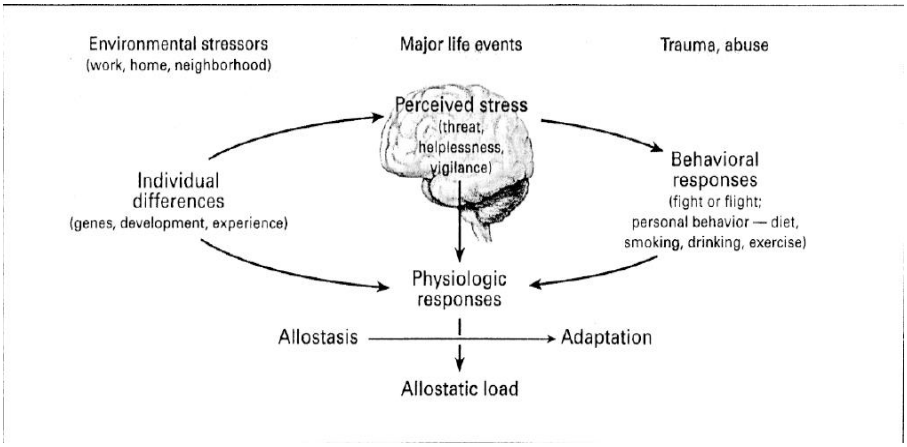

Figure 1 Allostatic Load Model. Sustained allostatic load process leads to allostatic overload that may have negative consequences. Taken from McEwen (2000).

In particular, the AOL hypothesis has been used to explain stress-related negative consequences in mood disorders, such as posttraumatic stress disorder and depression, and substance use disorders, such as cocaine and nicotine dependency (Koob & Le Moal, 2001; McEwen, 2000, 2002). Despite its apparent popularity in explaining the contributions of social, environmental and genetic factors, it does not address the resultant directionality of dysregulated physiological stress reactivity in altered allostatic states.

Secondly, it does not make a distinction between adaptive versus maladaptive outcomes, in particular as it relates to increased and decreased reactivity. The inverted U-hypothesis partly addresses the former criticism; however, it is inconsistent with work where high levels of cortisol are evolutionarily adaptive (Erickson, Drevets, & Schulkin, 2003; van Honk, Schutter, Hermans, & Putman, 2003). Therefore, a newer model is needed to predict diminished or exaggerated physiological stress reactivity that is in line with both negative and positive health consequences.

More recently, the Deficient Biological Stress Reactivity (DBSR) hypothesis (see **Fig.** 2) has been proposed where altered stress reactivity, described using the inverted U-function, may be an indicator of poor or good health depending on the outcome (Carroll, Ginty & Phillips, 2016). This is consistent with Erickson and colleagues' (2003) contention of cortisol having differential effects on the neural regions involved in its regulation in healthy versus psychiatric populations. Under DBSR, altered physiological reactivity is seen as a biomarker of dysregulation in brain areas involved in motivation and autonomic control (see **Fig.** 2B), such as the amygdala and the PFC, potentially as result of early life adversity and genetic inheritance (Carroll et al., 2016). The PFC, a neural region rich in glucocorticoid, adrenergic and corticotropin-releasing-hormone receptors, is involved in stress responsivity (Arnsten, 2009; Chiba et al., 2012; Jaferi & Bhatnagar, 2007). For instance, cortisol, a regulatory hormone involved in HPA-axis-related modulation of this stress response via a negative feedback mechanism (Lovallo, 2004), acts on glucocorticoid receptors in the PFC (Arnsten, 2009). The tenacity of the

stressor may progressively alter the levels of cortisol, leading to impairments within the HPA axis.

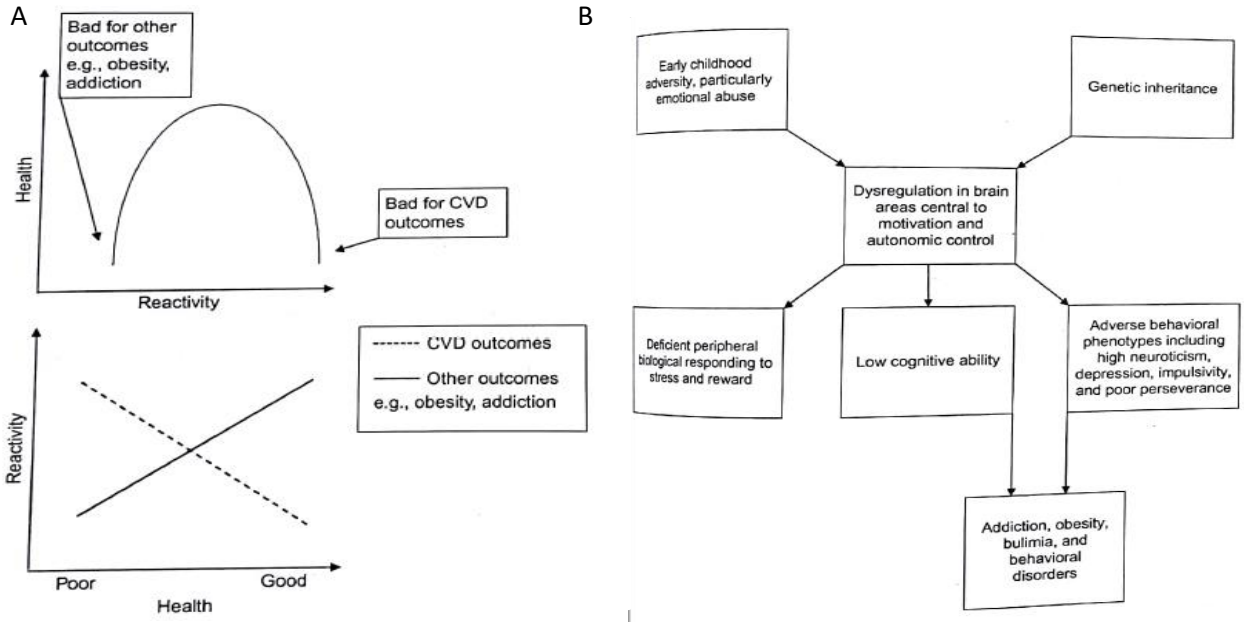

Figure 2 Deficient Biological Stress Reactivity Hypothesis. (A) Deficient stress reactivity, defined by the inverted U function, is outcome-dependent; (B) and is proposed to be a biomarker of dysregulation of motivation and autonomic control processes.

In addition, epinephrine and NE, indicators of SAM axis activity, also modulate the stress response (Vollmer, 1996). For NE activity, levels of salivary α-amylase are used as a proxy measure that is indicative of SAM axis activity (Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004; Thoma, Kirschbaum, Wolf, & Rohleder, 2012). Psychological stress can reliably induce increases in salivary cortisol (Kirschbaum, Pirke, & Hellhammer, 1993) and α-amylase levels (Rohleder et al., 2004; Thoma et al., 2012). Past work shows stressor-induced independence in the release of these biomarkers at specific time points (Nater et al., 2006); however, evaluation of large scale temporal dynamics reveal positive and negative correlations at several time lags throughout a stress

paradigm (Engert et al., 2011). They found α-amylase positively predicted cortisol levels around 14 minutes later, which predicted the inverse release of α-amylase around 14 minutes later, and this predicted the inverse release of cortisol levels around 42 minutes later. This provides preliminary evidence of a possible temporal relationship between these two biomarkers. In addition, the structural proximity and the functional interactions between the adrenal cortex and the medulla (Ehrhart-bornstein & Bornstein, 2008) show the HPA and SAM axes may be inter-independent as Engert and colleagues (2011) reveal possible psychosocial stressor-induced cross-talk between the two.

In populations with substance use addiction, both the HPA (Koob & Kreek, 2007), and SAM axes activities (Koob, 1999), appear to be dysregulated. This is evidenced by higher basal levels of corticotropin and blunted cortisol reactivity to stress cues in treatment-engaged alcohol-dependent patients when compared to healthy control participants (Sinha et al., 2011), and reduced cortisol reactivity in these patients relative to social drinkers (Sinha et al., 2009). Although there is a lack of comparative work with healthy participants investigating SAM activity, stressor-induced increases in NE and cortisol have been reported in cocaine dependent individuals (Sinha et al., 2003). Together, these findings are largely consistent with the DBSR hypothesis that proposes diminished stress reactivity to be a biomarker of a wider dysregulation of the autonomic and motivational processes involved in addiction (Carroll et al., 2016; Koob, 1999; Koob & Le Moal, 2001). This assertion may include non-addicted individuals who show increased reactivity; for example, heavy drinkers demonstrate greater cortisol, as well as systolic, and diastolic, blood pressure when compared to light drinkers (Thayer, Hall,

Sollers, & Fischer, 2006). Here, increased reactivity may not be a good health indicator (refer to **Fig.** 2) as the study did not measure for a possible diagnosis and the heavy alcohol use group likely includes both clinical and non-clinical participants. A lack of correlation between alcohol use and levels of cortisol, and the attenuation of one with heart rate variability (Thayer et al., 2006), further corroborates the potential confound in these findings. Alternatively, it may reflect a transition point where alcohol use has started to lead to physiological alterations in some individuals. The relationship between substance use and stress may be bi-directional, and dependent on clinical severity, as alcohol use, for example, decreases the subjective experience of stress in problem drinkers (Zack et al., 2011). Further, cannabis users, who were also not assessed for a clinical disorder, instead show blunted cortisol reactivity (Cuttler et al., 2017). These dissimilar results on cannabis versus alcohol use show pathways to addiction may differ, emphasizing the importance of investigating the underlying physiological responsivity of substance use and risk-taking behaviours.

Indeed, there is also some evidence for altered psychophysiological stress responses in Gambling Disorder (GD), the first non-substance-based ("behavioural") addiction in the Diagnostics and Statistical Manual on Mental Disorders (APA, 2013), which is characterized by persistent and recurrent gambling behaviour that leads to clinical impairment or distress. Gambling activates the HPA, cardiovascular, and SAM systems, observed through respective increases in cortisol levels and heart rate in recreational gamblers (Meyer et al., 2000), and in levels of NE and DA (Meyer et al., 2004) in problem gamblers (PrG; a sub-clinical form of problematic gambling), especially

in those with high levels of impulsivity (Krueger, Schedlowski, & Meyer, 2005). Others solely using a GD population find decreased cue-induced levels of cortisol when compared to recreational gamblers (Paris, Franco, Sodano, Frye, & Wulfert, 2010), reduced basal levels of cortisol and heart rate (Zack et al., 2015), and lower levels of α-amylase following a decision-making task (Labudda, Wolf, Markowitsch, & Brand, 2007) relative to healthy participants. In addition, blunted stressor-induced cortisol reactivity and cardiovascular responsivity is observed in individuals with disordered eating (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012) and exercise dependency (Heaney, Ginty, Carroll, & Phillips, 2011). These findings further emphasize the utility of the DBSR hypothesis in elucidating stress reactivity underlying pathological behavioural responses.

One shortcoming in gambling research is combining PrG and GD groups; the lack of differentiation between these populations is important because there are observed differences in the personality traits, such as in impulsivity and emotional vulnerability, between PrG and GD (Bagby et al., 2007). In addition, the severity of gambling problems correlates with clinical, neurobiological and physiological dimensions of gambling, such as impulsivity (Alessi & Petry, 2003; Krueger et al., 2005), executive function, including perseverative performance (Brevers et al., 2012) and advantageous decision-making (Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2005), mesolimbic reward system activity (Reuter et al., 2005), as well as with levels of cortisol (Maniaci, Goudriaan, Cannizzaro, & van Holst, 2018) and DA (Boileau, Payer, Chugani, Lobo, Behzadi, et al., 2013; Boileau, Payer, Chugani, Lobo, Houle, et al., 2013). Therefore, it is important to investigate physiological alterations in GD, without the potential confounding influence

of PrG under the assumption problematic gambling occurs on a continuum. It is highly likely that the extent of the observed psychophysiological and behavioural impairments, often related to the clinical severity of the gambling problems, also plays an important role in maintaining the pathophysiology of this disorder.

Risky Decision-making

Evolutionarily, decision-making, defined as the ability to weigh different options based on the cost-benefit valuation of a choice and of the associated outcomes, is important to guide action selection in order to adapt to the environment, ultimately promoting survival (O'Doherty, Cockburn, & Pauli, 2017). According to Dual-Process theories of decision-making, there are two systems involved – "hot" versus "cold" (Phelps, Lempert, & Sokol-Hessner, 2014), with each playing a differential functional role and involving different neural circuitries.

"Hot" decision-making, also known as emotional decision-making, is automatic and explorative, and it involves neural regions of the limbic system, such as the amygdala and the medial PFC (mPFC) (Phelps et al., 2014). This type is also known as decision-making under ambiguity as it incorporates implicit learning and precludes knowledge of different options (Brand, Labudda, & Markowitsch, 2006). Accordingly, the Somatic Marker Hypothesis (SMH), a popular hypothesis emphasizing the role of emotional processing on choice behaviour, proposes somatic markers signals from the body regulate adaptive decision-making (Damasio, 1996). These somatic markers act as biasing signals that track different response options; for example, the anticipatory skin conductance

responses guide learning different deck contingencies on the Iowa Gambling Task (IGT) (Bechara et al., 1997). The IGT, a reliable and well-validated decision-making task (Buelow & Suhr, 2009), is commonly used to explore implicit learning and decision-making across different decks where each deck is associated with differential probabilities and magnitudes of receiving a reward or a punishment (Bechara, Damasio, Damasio, & Anderson, 1994). Traditionally, the classic 'ABCD' version of the IGT includes five blocks of twenty trails each (100 trials in total). In this version, selections from disadvantageous decks A and B produce high, immediate reward but higher penalties; whereas, selections from the advantageous decks C and D are associated with small immediate rewards but lower penalties. The decks also differ in the frequency of losses: decks A and D are associated with frequent losses of smaller magnitude, whereas decks B and C are related to infrequent losses of greater magnitude.

The implicit learning process on the IGT involves learning action-outcome contingencies and reflects a personalized process dependent on the time it takes to learn as well as on individual reward sensitivities (Bull, Tippett, & Addis, 2015; Franken & Muris, 2005). Once an individual has learned the different deck contingencies on the IGT, other additional factors – not entirely congruent with SMH - may influence task performance, such as reversal learning and risk-taking (Dunn, Dalgleish, & Lawrence, 2006). Indeed, others show a distinct divide in conceptual factors influencing performance on early versus later trials of the IGT (Brand et al., 2006; Brand, Recknor, Grabenhorst, & Bechara, 2007). Performance on early trials, termed decision-making under uncertainty (or 'pre-learning' usually on Blocks 1-3), is in line with the SMH and

not contingent upon knowledge of reward or punishment schedules associated with each deck (Brand et al., 2006; Buelow & Blaine, 2015).

Performance on later trials of the IGT, termed decision-making under risk (or 'post-learning' usually on Blocks 4 & 5), occurs after having learned the outcomes associated with the different deck contingencies (Brand et al., 2006; Buelow & Blaine, 2015). Risky - also termed "cold" under Dual Process theories - decision-making involves rational processing and exploitative behaviour (O'Doherty et al., 2017; Phelps et al., 2014). This type involves higher-order cognitive brain processing areas, such as the PFC and the dorsolateral PFC (dlPFC) (Phelps et al., 2014). Although not entirely independent of SMH, it has also been associated with executive function, such as response perseveration (Brand et al., 2007) and working memory, (Brevers et al., 2012) unlike decision-making under uncertainty, which may rely more heavily on somatic markers and sensitivity to reward versus punishment (Bechara, Tranel, & Damasio, 2000; Dunn et al., 2006). Given the discussion so far, there are evident conceptual and experimental heterogeneities associated with the IGT. Indeed, poor performance on the IGT has also been hypothesized to be due to: reward hypersensitivity, myopia for the future, or hyposensitivity to punishment (Bechara et al., 2000; Dunn et al., 2006; Steingroever, Wetzels, Horstmann, Neumann, & Wagenmakers, 2013). As such, Clark and Manes (2004) further suggest preference for high risk behaviour may also underlie these differences; indeed, in animal models, inactivation of the PFC, a critical region involved in impaired IGT performance (Bechara et al., 1994), differentially alters risky decision-making (St. Onge & Floresco, 2010). Inactivation of the mPFC impairs

assessment of risky choices in a probabilistic discounting task; whereas, that of the orbitofrontal cortex alters response latencies (St. Onge & Floresco, 2010). Likewise, reward and punishment sensitivities as measured on the IGT may be different from risk-taking propensities.

Therefore, the Balloon Analogue Risk-taking Task (BART), another distinct measure of risky-decision-making (Buelow & Blaine, 2015), is used to explore increased propensity towards engagement in risky behaviour (Lejuez et al., 2002). The BART is a validated task with ecological validity that correlates with real-world risk-taking behaviours, smoking status, number of drug classes tried, and the total score on the gambling attitudes and beliefs scale (Lejuez et al., 2003, 2002; Lejuez, Simmons, Aklin, Daughters, & Dvir, 2004). Each trial includes a simulated balloon on the screen whereby the participants are asked to pump the balloon by clicking a button to earn virtual money. With each pump, the participant earns a reward of 5 cents, that is added on to a temporary bank, until a specific threshold when the balloon explodes or when the amount earned is collected. This breakpoint differs for each balloon across various contingencies ranging from 1-128 to 1-32 and 1-8 pumps. After each non-exploding balloon trial, the probability that the balloon will explode on the following trial increases. Therefore, each successive pump confers both greater risk and reward, where the ratio between the two decreases differentially for each balloon with a specific breakpoint. As such, the BART is better able to fractionate risky decision-making into different conceptual intricacies, including risk, reward and loss sensitivities.

Since the neurobiology of addiction overlaps with decision-making and reward pathways (Goldstein & Volkow, 2002; Phelps et al., 2014; Wise, 1996), including the PFC, the amygdala, and the striatum, it is important to explore these impairments in populations with addictions as they may help predict relapse. For example, patients with alcohol use disorders who relapsed took higher risks and made more disadvantageous selections on the IGT when compared to non-relapsed patients (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce, 2005). Further, similar to patients with lesions to the ventromedial PFC (vmPFC) and the amygdala (Bechara, Damasio, Damasio, & Lee, 1999; Bechara et al., 2001, 2000), and to those with brain injury associated lesions that are not restricted to the vmPFC, (Balagueró, Vicente, Molina, Tormos, & Roig Rovira, 2014), substance users (Bechara et al., 2001; Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2005; Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006), and those with GD (Cavedini, Riboldi, Keller, D'Annucci, & Bellodi, 2002; Goudriaan et al., 2005; Linnet, RØjskjÆr, Nygaard, & Maher, 2006), also show decision-making impairments on the IGT.

In particular, individuals with PrG show impairments in decision-making under risk on the IGT, potentially due to higher risk acceptance (Brevers et al., 2012). Indeed, those with GD show impairments in different lower-order components that contribute towards overall decision-making, including chasing behaviour, delay aversion and risk-taking (Kräplin et al., 2014). Work on the BART in GD and substance use populations is limited; however, patients with frontal lobe injury make decreased number of overall pumps (Balagueró et al., 2014). This is indicative of decreased reward-seeking choices

(Bogg, Fukunaga, Finn, & Brown, 2012) and increased loss aversion (Fukunaga et al., 2012). This also shows impaired BART function is particularly relevant as GD is also related to altered PFC function (Cavedini et al., 2002; Potenza, Leung, et al., 2003; Reuter et al., 2005); however the directionality of the effect may differ as past work using other decision-making tasks as reviewed earlier show increased risk-taking in the GD population.

Acute Stress Reactivity and Risky Decision-making

In healthy populations, cortisol regulates internal energy states in a circadian manner, as well as adaptation to environmental stimuli through its positive influences on arousal, attention and in the maintenance of a sustained fear response (Erickson et al., 2003). Indeed, high basal cortisol levels are associated with decreased risky decision-making in a gambling task (van Honk et al., 2003), and acute, psychosocial stress also leads to less risky decision-making when losses are involved (Pabst, Brand, & Wolf, 2013), as well as better response inhibition (Schwabe, Höffken, Tegenthoff, & Wolf, 2013). This reflects the utility of this hormone in helping to balance sensitivities towards reward and punishment (van Honk et al., 2003) and promoting adaptive behaviour. Together, these findings are consistent with the DBSR hypothesis as it proposes outcome-dependent health-related implications of deficient stress reactivity.

The DBSR hypothesis posits reduced stress reactivity and unstable affect regulation increase the probability of risk-taking, increasing the risk of addiction (Carroll et al., 2016). As reviewed earlier, diminished stress reactivity, proposed to underlie

addicted populations, is a biomarker of the dysregulation of brain regions involved in autonomic control and motivation (see **Fig.** 2). Both the PFC and the amygdala are neural regions involved in stress reactivity, including NE-mediated autonomic control (Arnsten, 2009; Koob, 1999), decision-making (Antoine Bechara et al., 1999; Phelps et al., 2014), and altered reward processing underlying the neurobiology of addiction (Wise, 1996). In addition, Koob and Le Moal's (2001) proposal of re-defining allostasis within an addictions' framework provides further corroboration of this hypothesis. They propose new reward setpoints, a result of dysregulated reward circuits and the recruitment of stress responsivity systems, is characteristic of an allostatic state in the brain's reward system. In particular, addiction marks an imbalance between the a-process, also known as the activational motivational process, and the b-process, the counteradaptive opponent process, which includes an already altered reward system as well as the activation of the stress responsivity axes (Koob and Le Moal, 2001). Moreover, Koob and Kreek (2007) posit these dysregulated motivational processes in the addiction cycle includes the HPA axis, which then facilitates the extrahypothalamic stress neurocircuit (see **Fig**. 3). This neuroadaptive perspective differs from the DBSR in two key ways. First, the DBSR hypothesis considers prior environmental and genetic factors that may influence frontolimbic function underlying altered autonomic and motivational processes. Secondly, it describes altered reward and stress responsivity as a resulting biomarker (refer to **Fig.** 2), in contrast to Koob and Le Moal (2001) where stress systems are recruited after transitioning to addiction. These criticisms show that Koob and Le Moal's (2001) and Koob and Kreek's (2007) propositions give the neurobiology of stress and

reward a distinct treatment dependent on the addiction cycle; whereas, under the DBSR hypothesis, both of these constructs share common neural circuitry. Finally, it is a relatively more useful model in predicting stress-induced reactivity and its relationships with risk-taking in addiction populations. As such, the DBSR hypothesis offers a common theoretical basis – dysregulated autonomic control and motivational processes - for work on stress and decision-making processes in addiction.

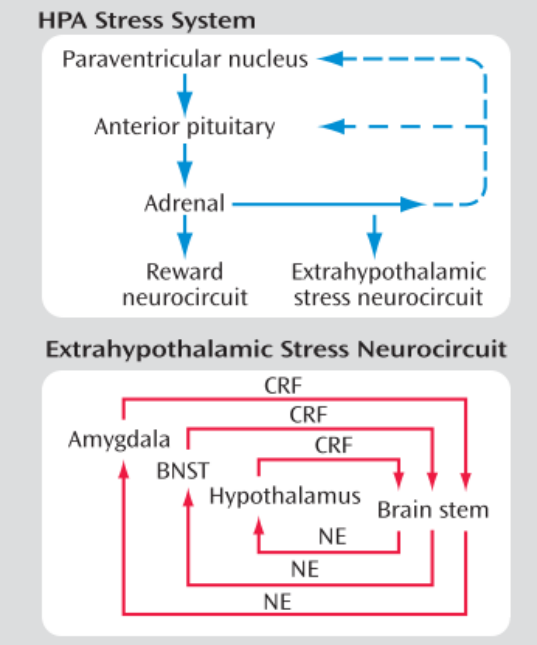

Figure 3 Stress Systems Involved in the Addiction Cycle. The HPA axis feedbacks to regulate itself, activates the reward circuit and facilitates the extrahypothalamic stress neurocircuit. CRF = corticotropin-releasing factor; BNST = bed nucleus of the stria terminalis, NE = norepinephrine. Taken from Koob and Kreek (2007).

Acute psychosocial stress impairs decision-making, such that stressed participants take longer to learn the IGT (Preston, Buchanan, Stansfield, & Bechara, 2007), with increasingly elevated levels of cortisol leading to poorer performance in males (van den Bos, Harteveld, & Stoop, 2009). The induction of acute stress is also linked to

dysregulated reward processing, as particularly evidenced by decreased differential activity within the dorsal striatum and orbitofrontal cortex in response to rewarding versus punishing outcomes (Porcelli, Lewis, & Delgado, 2012), and reduced risk-taking under a state of threat due to enhanced processing of loss-related information (Clark et al., 2012). Although the effects of acute stress induction on decision-making have not been explored in the PrG or the GD populations, physiological studies have explored basal reactivity in relation to decision-making in the former population. Decreased anticipatory heart rate when selecting from advantageous decks, and after having won or lost on the IGT (Goudriaan et al., 2006), and an association between increased α-amylase reactivity post task with a decreased number of risky decisions, (Labudda, Wolf, Markowitsch, & Brand, 2007) are observed in those with GD. Combined, the literature reviewed so far emphasizes the utility and novelty of exploring acute stress induction in relation to the distinct phases of decision-making in GD.

According to the DBSR hypothesis, the relationship between stress and addiction may be bi-directional; chronic stress promotes substance use, and in turn, substance use alters stress responsivity through its effects on the body's stress systems (Goeders, 2003; Sinha, 2008). For example, early life stressors may lead to a dissociation between executive function and reward processing pathways, which may then increase propensity towards risk-taking behaviours and reduce impulse control, potentially prompting substance use and risky behaviours (Carroll et al., 2016; Watt, Weber, Davies, & Forster, 2017). Exploring altered decision-making processes under an acute stress induction

paradigm may inform on the proposed underlying dysregulation in autonomic control and motivational processes.

Bibliography

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental Disorders. Text Revision.* (5th ed). American Psychiatric Association.

Alessi, S. M., & Petry, N. M. (2003). Pathological gambling severity is associated with impulsivity in a delay discounting procedure. *Behavioural Processes*, *64*(3), 345–354. https://doi.org/10.1016/S0376-6357(03)00150-5

Areny Balagueró, M., Vicente, M. J., Molina, A. G., Tormos, J. M., & Roig Rovira, T. (2014). Balloon Analogue Risk Task to assess decision-making in Acquired Brain Injury. *Int.J.Psychol.Res*, *9*(1), 30–39.

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews. Neuroscience*, *10*(6), 410–422. https://doi.org/10.1038/nrn2648

Bagby, R. M., Vachon, D. D., Bulmash, E. L., Toneatto, T., Quilty, L. C., & Costa, P. T. (2007). Pathological gambling and the five-factor model of personality. *Personality and Individual Differences*, *43*(4), 873–880. https://doi.org/10.1016/j.paid.2007.02.011

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damageto human prefrontal cortex. *Cognition*, *50*(1–3), 7–15. https://doi.org/10.1016/0010-0277(94)90018-3

Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *19*(13), 5473–5481. https://doi.org/0270-6474/99/19135473-09$05.00/0

Bechara, A., Damasio, H., Tranel, D., Damasio, A. R., Bushnell, M. C., Matthews, P. M., & Rawlins, J. N. P. (1997). Deciding Advantageously Before Knowing the Advantageous Strategy. *Science*, *275*(5304), 1293–1295. https://doi.org/10.1126/science.275.5304.1293

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S. W., & Nathan, P. E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, *39*(4), 376–389. https://doi.org/10.1016/S0028-3932(00)00136-6

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*, *123*(11), 2189–2202. https://doi.org/10.1093/brain/123.11.2189

Bogg, T., Fukunaga, R., Finn, P. R., & Brown, J. W. (2012). Cognitive control links alcohol use, trait disinhibition, and reduced cognitive capacity: Evidence for medial prefrontal cortex dysregulation during reward-seeking behavior. *Drug and Alcohol Dependence*, *122*(1–2), 112–118. https://doi.org/10.1016/j.drugalcdep.2011.09.018

Boileau, I., Payer, D., Chugani, B., Lobo, D., Behzadi, A., Rusjan, P. M., … Zack, M.

(2013). The D2/3 dopamine receptor in pathological gambling: A positron emission tomography study with [11C]-(+)-propyl-hexahydro-naphtho-oxazin and [11C]raclopride. *Addiction*, *108*(5), 953–963. https://doi.org/10.1111/add.12066

Boileau, I., Payer, D., Chugani, B., Lobo, D. S. S., Houle, S., Wilson, A. A., … Zack, M. (2013). In vivo evidence for greater amphetamine-induced dopamine release in pathological gambling: a positron emission tomography study with [(11)C]-(+)-PHNO. *Molecular Psychiatry*, *19*(12), 1–9. https://doi.org/10.1038/mp.2013.163

Bowden-Jones, H., McPhillips, M., Rogers, R., Hutton, S., & Joyce, E. (2005). Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(3), 417–420. https://doi.org/10.1176/appi.neuropsych.17.3.417

Brand, M., Labudda, K., & Markowitsch, H. J. (2006). Neuropsychological correlates of decision-making in ambiguous and risky situations. *Neural Networks*, *19*(8), 1266–1276. https://doi.org/10.1016/j.neunet.2006.03.001

Brand, M., Recknor, E. C., Grabenhorst, F., & Bechara, A. (2007). Decisions under ambiguity and decisions under risk: Correlations with executive functions and comparisons of two different gambling tasks with implicit and explicit rules. *Journal of Clinical and Experimental Neuropsychology*, *29*(1), 86–99. https://doi.org/10.1080/13803390500507196

Brevers, D., Cleeremans, A., Goudriaan, A. E., Bechara, A., Kornreich, C., Verbanck, P., & Noél, X. (2012). Decision making under ambiguity but not under risk is related to problem gambling severity. *Psychiatry Research*, *200*(2–3), 568–574.

Buelow, M. T., & Blaine, A. L. (2015). The Assessment of Risky Decision Making : A Factor Analysis of Performance on the Iowa Gambling Task , Balloon Analogue Risk Task, and Columbia Card Task. *American Psychological Associaton*, *27*(3), 777–785. https://doi.org/10.1037/a0038622

Buelow, M. T., & Suhr, J. A. (2009). Construct validity of the Iowa gambling task. *Neuropsychology Review*, *19*(1), 102–114. https://doi.org/10.1007/s11065-009-9083-4

Bull, P. N., Tippett, L. J., & Addis, D. R. (2015). Decision making in healthy participants on the Iowa Gambling Task: New insights from an operant approach. *Frontiers in Psychology*, *6*, 391. https://doi.org/10.3389/fpsyg.2015.00391

Carroll, D., Ginty, A. T., & Phillips, A. C. (2016). The Behavioral, Cognitive, and Neural Correlates of Deficient Biological Reactions to Acute Psychological Stress. In *Stress: Concepts, Cognition, Emotion, and Behavior* (pp. 187-194).

Cavedini, P., Riboldi, G., Keller, R., D'Annucci, A., & Bellodi, L. (2002). Frontal lobe dysfunction in pathological gambling patients. *Biological Psychiatry*, *51*(4), 334–341. https://doi.org/10.1016/S0006-3223(01)01227-6

Chiba, S., Numakawa, T., Ninomiya, M., Richards, M. C., Wakabayashi, C., & Kunugi, H. (2012). Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *39*(1), 112–119. https://doi.org/10.1016/j.pnpbp.2012.05.018

Clark, L., Li, R., Wright, C. M., Rome, F., Fairchild, G., Dunn, B. D., & Aitken, M. R. F. (2012). Risk-avoidant decision making increased by threat of electric shock. *Psychophysiology*, *49*(10), 1436–1443. https://doi.org/10.1111/j.1469-8986.2012.01454.x

Clark, L., & Manes, F. (2004). Social and emotional decision-making following frontal lobe injury. *Neurocase*, *10*(5), 398–403. https://doi.org/10.1080/13554790490882799

Cuttler, C., Spradlin, A., Nusbaum, A. T., Whitney, P., Hinson, J. M., & McLaughlin, R. J. (2017). Blunted stress reactivity in chronic cannabis users. *Psychopharmacology*, *234*(15), 2299–2309. https://doi.org/10.1007/s00213-017-4648-z

DeLongis, a, Folkman, S., & Lazarus, R. S. (1988). The impact of daily stress on health and mood: Psychological and social resources as mediators. *Journal of Personality and Social Psychology*, *54*(3), 486–495. https://doi.org/10.1037/0022-3514.54.3.486

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, *130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

Dunn, B. D., Dalgleish, T., & Lawrence, A. D. (2006). The somatic marker hypothesis: A critical evaluation. *Neuroscience and Biobehavioral Reviews*, *30*(2), 239–271. https://doi.org/10.1016/j.neubiorev.2005.07.001

Ehrhart-bornstein, M., & Bornstein, S. R. (2008). Cross-talk between Adrenal Medulla and Adrenal Cortex in Stress. *Annals of the New York Academy of Sciences*, *1148*(1), 112–117. https://doi.org/10.1196/annals.1410.053

Engert, V., Vogel, S., Efanov, S. I., Duchesne, A., Corbo, V., Ali, N., & Pruessner, J. C. (2011). Investigation into the cross-correlation of salivary cortisol and alpha-amylase responses to psychological stress. *Psychoneuroendocrinology*, *36*(9), 1294–1302. https://doi.org/10.1016/j.psyneuen.2011.02.018

Erickson, K., Drevets, W., & Schulkin, J. (2003). Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neuroscience and Biobehavioral Reviews*, *27*(3), 233–246. https://doi.org/10.1016/S0149-7634(03)00033-2

Franken, I. H. A., & Muris, P. (2005). Individual differences in decision-making. *Personality and Individual Differences*, *39*(5), 991–998. https://doi.org/10.1016/j.paid.2005.04.004

Ginty, A. T., Phillips, A. C., Higgs, S., Heaney, J. L. J., & Carroll, D. (2012). Disordered eating behaviour is associated with blunted cortisol and cardiovascular reactions to acute psychological stress. *Psychoneuroendocrinology*, *37*(5), 715–724. https://doi.org/10.1016/j.psyneuen.2011.09.004

Goeders, N. E. (2003). The impact of stress on addiction. *European Neuropsychopharmacology*, *13*(6), 435–441. https://doi.org/10.1016/j.euroneuro.2003.08.004

Goldstein, R. Z., & Volkow, N. D. (2002). Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex. *Amer*, *159*(October), 1642–1652. Retrieved from http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.159.10.1642

Goudriaan, A. E., Oosterlaan, J., de Beurs, E., & van den Brink, W. (2006). Psychophysiological determinants and concomitants of deficient decision making in pathological gamblers. *Drug and Alcohol Dependence*, *84*(3), 231–239.

Goudriaan, A. E., Oosterlaan, J., De Beurs, E., & Van Den Brink, W. (2005). Decision making in pathological gambling: A comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. *Cognitive Brain Research*, *23*(1), 137–151. https://doi.org/10.1016/j.cogbrainres.2005.01.017

Heaney, J. L. J., Ginty, A. T., Carroll, D., & Phillips, A. C. (2011). Preliminary evidence that exercise dependence is associated with blunted cardiac and cortisol reactions to acute psychological stress. *International Journal of Psychophysiology*, *79*(2), 323–329. https://doi.org/10.1016/j.ijpsycho.2010.11.010

Jaferi, A., & Bhatnagar, S. (2007). Corticotropin-releasing-hormone Receptors in the Medial Prefrontal Cortex Regulate Hypothalamic-Pituitary-Adrenal Activity and Anxiety-Related Behaviour Regardsess of Prior Stress Experience. *Brain Research*, *1186*, 212–223. https://doi.org/10.1016/j.immuni.2010.12.017.Two-stage

Kirschbaum, C., Pirke, K.-M., & Hellhammer, D. H. (1993). The "Trier Social Stress Test" - A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology*, *28*, 76–81.

Koob, G. F. (1999). Corticotopin-Releasing Factor, Norephinephrine, and Stress. *Biological Psychiatry*, *46*(9), 1167–1180. https://doi.org/10.1016/j.bbagen.2009.07.018

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, *24*(2), 97–129. https://doi.org/10.1016/S0893-133X(00)00195-0

Koob, G., & Kreek, M. J. (2007). Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *American Journal of Psychiatry*, *164*(8), 1149–1159. https://doi.org/10.1176/appi.ajp.2007.05030503

Kräplin, A., Dshemuchadse, M., Behrendt, S., Scherbaum, S., Goschke, T., & Bühringer,

G. (2014). Dysfunctional decision-making in pathological gambling: Pattern specificity and the role of impulsivity. *Psychiatry Research*, *215*(3), 675–682. https://doi.org/10.1016/j.psychres.2013.12.041

Krueger, T. H. C., Schedlowski, M., & Meyer, G. (2005). Cortisol and Heart Rate Measures during Casino Gambling in Relation to Impulsivity. *Neuropsychobiology*, *52*(4), 206–211. https://doi.org/https://doi.org/10.1159/000089004

Labudda, K., Wolf, O. T., Markowitsch, H. J., & Brand, M. (2007). Decision-making and neuroendocrine responses in pathological gamblers. *Psychiatry Research*, *153*(3), 233–243. https://doi.org/10.1016/j.psychres.2007.02.002

Lejuez, C. W., Aklin, W. M., Jones, H. A., Strong, D. R., Richards, J. B., Kahler, C. W., & Read, J. P. (2003). The Balloon Analogue Risk Task (BART) differentiates smokers and nonsmokers. *Experimental and Clinical Psychopharmacology*, *11*(1), 26–33. https://doi.org/10.1037//1064-1297.11.1.26

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., … Brown, R. a. (2002). Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology. Applied*, *8*(2), 75–84. https://doi.org/10.1037/1076-898X.8.2.75

Lejuez, C. W., Simmons, B. L., Aklin, W. M., Daughters, S. B., & Dvir, S. (2004). Risk-taking propensity and risky sexual behavior of individuals in residential substance use treatment. *Addictive Behaviors*, *29*(8), 1643–1647. https://doi.org/10.1016/j.addbeh.2004.02.035

Linnet, J., RØjskjÆr, S., Nygaard, Jø., & Maher, B. A. (2006). Episodic chasing in pathological gamblers using the Iowa gambling task. *Scandinavian Journal of Psychology*, *47*(1), 43–49. https://doi.org/10.1111/j.1467-9450.2006.00491.x

Lovallo, W. R. (2004). *Stress and Health: Biological and Psychological Interactions*. SAGE Publications.

Lovallo, W. R. (2011). Do low levels of stress reactivity signal poor states of health? *Biological Psychology*, *86*(2), 121–128. https://doi.org/10.1016/j.biopsycho.2010.01.006.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Maniaci, G., Goudriaan, A. E., Cannizzaro, C., & van Holst, R. J. (2018). Impulsivity and Stress Response in Pathological Gamblers During the Trier Social Stress Test. *Journal of Gambling Studies*, *34*(1), 147–160. https://doi.org/10.1007/s10899-017-9685-3

McEwen, B. S. (2000). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsychopharmacology*, *22*(2), 108–124. https://doi.org/10.1016/S0893-133X(99)00129-3

McEwen, B. S. (2002). The neurobiology and neuroendocrinology of stress implications for post-traumatic stress disorder from a basic science perspective. *Psychiatric Clinics of North America*, *25*(2), 469–494. https://doi.org/10.1016/S0193-953X(01)00009-0

McEwen, B. S., & Stellar, E. (1993). Stress and the Individual. *Archives of Internal Medicine*, *153*(18), 2093–2101.

Meyer, G., Hauffa, B. P., Schedlowski, M., Pawlak, C., Stadler, M. A., & Exton, M. S. (2000). Casino gambling increases heart rate and salivary cortisol in regular gamblers. *Biological Psychiatry*, *48*(9), 948–953. https://doi.org/10.1016/S0006-3223(00)00888-X

Meyer, G., Schwertfeger, J., Exton, M. S., Janssen, O. E., Knapp, W., Stadler, M. A., … Krüger, T. H. C. (2004). Neuroendocrine response to casino gambling in problem gamblers. *Psychoneuroendocrinology*, *29*(10), 1272–1280. https://doi.org/10.1016/j.psyneuen.2004.03.005

Nater, U. M., La Marca, R., Florin, L., Moses, A., Langhans, W., Koller, M. M., & Ehlert, U. (2006). Stress-induced changes in human salivary alpha-amylase activity - Associations with adrenergic activity. *Psychoneuroendocrinology*, *31*(1), 49–58. https://doi.org/10.1016/j.psyneuen.2005.05.010

O'Doherty, J. P., Cockburn, J., & Pauli, W. M. (2017). Learning, Reward, and Decision Making. *Annual Review of Psychology*, *68*(1), 73–100. https://doi.org/10.1146/annurev-psych-010416-044216

Pabst, S., Brand, M., & Wolf, O. T. (2013). Stress effects on framed decisions: there are differences for gains and losses. *Frontiers in Behavioral Neuroscience*, *7*, 142. https://doi.org/10.3389/fnbeh.2013.00142

Paris, J. J., Franco, C., Sodano, R., Frye, C. A., & Wulfert, E. (2010). Gambling Pathology is Associated with Dampened Cortisol Response Among Men and Women. *Physiological Behaviour*, *76*(2), 211–220. https://doi.org/10.1007/s11103-011-9767-z.Plastid

Phelps, E. a, Lempert, K. M., & Sokol-Hessner, P. (2014). Emotion and Decision Making: Multiple Modulatory Neural Circuits. *Annual Review of Neuroscience*, 263–290. https://doi.org/10.1146/annurev-neuro-071013-014119

Porcelli, A. J., Lewis, A. H., & Delgado, M. R. (2012). Acute stress influences neural circuits of reward processing. *Frontiers in Neuroscience*, *6*(NOV), 1–9. https://doi.org/10.3389/fnins.2012.00157

Potenza, M. N., Leung, H.-C., Blumberg, H. P., Peterson, B. S., Fulbright, R. K., Lacadie, C. M., … Gore, J. C. (2003). An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *The American Journal of Psychiatry*, *160*(11), 1990–1994. https://doi.org/10.1176/appi.ajp.160.11.1990

Preston, S. D., Buchanan, T. W., Stansfield, R. B., & Bechara, a. (2007). Effects of

anticipatory stress on decision making in a gambling task. *Behavioral Neuroscience*, *121*(2), 257–263. https://doi.org/10.1037/0735-7044.121.2.257

Reuter, J., Raedler, T., Rose, M., Hand, I., Gläscher, J., & Büchel, C. (2005). Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience*, *8*(2), 147–148. https://doi.org/10.1038/nn1378

Rohleder, N., Nater, U. M., Wolf, J. M., Ehlert, U., & Kirschbaum, C. (2004). Psychosocial stress-induced activation of salivary alpha-amylase: An indicator of sympathetic activity? *Annals of the New York Academy of Sciences*, *1032*(1), 258–263. https://doi.org/10.1196/annals.1314.033

Schwabe, L., Höffken, O., Tegenthoff, M., & Wolf, O. T. (2013). Stress-induced enhancement of response inhibition depends on mineralocorticoid receptor activation. *Psychoneuroendocrinology*, *38*(10), 2319–2326. https://doi.org/10.1016/j.psyneuen.2013.05.001

Selye, H. (1950). Allergy and the general adaptation syndrome. *British Medical Journal*, *1*(4667), 1383–1392. https://doi.org/10.1159/000227975

Sinha, R. (2008). Chronic Stress, Drug Use, and Vulnerability to Addiction Rajita. *Annals of the New York Academy of Sciences*, *1141*, 105–130. https://doi.org/10.1196/annals.1441.030.Chronic

Sinha, R., Fox, H. C., Hong, K. A., Bergquist, K., Bhagwagar, Z., & Siedlarz, K. M. (2009). Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. *Neuropsychopharmacology*, *34*(5), 1198–1208. https://doi.org/10.1038/npp.2008.78

Sinha, R., Talih, M., Malison, R., Cooney, N., Anderson, G. M., & Kreek, M. J. (2003). Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology*, *170*(1), 62–72. https://doi.org/10.1007/s00213-003-1525-8

St. Onge, J. R., & Floresco, S. B. (2010). Prefrontal cortical contribution to risk-based decision making. *Cerebral Cortex*, *20*(8), 1816–1828. https://doi.org/10.1093/cercor/bhp250

Steingroever, H., Wetzels, R., Horstmann, A., Neumann, J., & Wagenmakers, E. J. (2013). Performance of healthy participants on the Iowa Gambling Task. *Psychological Assessment*, *25*(1), 180–193. https://doi.org/10.1037/a0029929

Thayer, J. F., Hall, M., Sollers, J. J., & Fischer, J. E. (2006). Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. *International Journal of Psychophysiology*, *59*(3), 244–250. https://doi.org/10.1016/j.ijpsycho.2005.10.013

Thoma, M. V., Kirschbaum, C., Wolf, J. M., & Rohleder, N. (2012). Acute stress responses in salivary alpha-amylase predict increases of plasma norepinephrine. *Biological Psychology*, *91*(3), 342–348.

https://doi.org/10.1016/j.biopsycho.2012.07.008

van den Bos, R., Harteveld, M., & Stoop, H. (2009). Stress and decision-making in humans: Performance is related to cortisol reactivity, albeit differently in men and women. *Psychoneuroendocrinology*, *34*(10), 1449–1458. https://doi.org/10.1016/j.psyneuen.2009.04.016

van Honk, J., Schutter, D. J. L. G., Hermans, E. J., & Putman, P. (2003). Low cortisol levels and the balance between punishment sensitivity and reward dependency. *Neuroreport*, *14*(15), 1993–1996. https://doi.org/10.1097/01.wnr.0000091690.72892.ec

Verdejo-Garcia, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Decision-Making and the Iowa Gambling Task: Ecological validity in individuals with substance dependence. *Psychologica Belgica*, *46*(1–2), 55. https://doi.org/10.5334/pb-46-1-2-55

Watt, M. J., Weber, M. A., Davies, S. R., & Forster, G. L. (2017). Impact of juvenile chronic stress on adult cortico-accumbal function: Implications for cognition and addiction. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *79*, 136–154. https://doi.org/10.1016/j.pnpbp.2017.06.015

Wise, R. A. (1996). Neurobiology of Addiction. *Neurobiology of Addiction*, *6*, 243–251. https://doi.org/10.1016/B978-0-12-419239-3.X5036-X

Zack, M., Boileau, I., Payer, D., Chugani, B., Lobo, D. S., Houle, S., … Kish, S. J. (2015). Differential cardiovascular and hypothalamic pituitary response to amphetamine in male pathological gamblers versus healthy controls. *Journal of Psychopharmacology*, *29*(9), 971–982. https://doi.org/10.1177/0269881115592338

Zack, M., Woodford, T. M., Tremblay, A. M., Steinberg, L., Zawertailo, L. A., & Busto, U. E. (2011). Stress and alcohol cues exert conjoint effects on go and stop signal responding in male problem drinkers. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *36*(2), 445–458. https://doi.org/10.1038/npp.2010.177

CHAPTER 2

Arshad,F., Potenza, M. N., & Balodis, I. M. (in preparation for submission). Effects of Psychosocial Stress Induction on Risky Decision-making in Gambling Disorder

PSYCHOSOCIAL STRESS AND RISKY DECISION-MAKING IN GAMBLING DISORDER

Arshad, F.[1], Potenza, M. N.[2], & Balodis, I. M.[1,2*] (in preparation for submission). Effects of Psychosocial Stress Induction on Risky Decision-making in Gambling Disorder

[1]Peter Boris Centre for Addictions Research, Department of Psychiatry and Behavioural Sciences, McMaster University, Hamilton, ON, Canada; [2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

*corresponding author: balodisi@mcmaster.ca

Abstract

Gambling activates the hypothalamic-pituitary-adrenal and sympathoadrenal medullary (SAM) axes as evidenced by increased levels of cortisol in recreational gamblers, and in norepinephrine in problem gamblers. Further, Gambling Disorder (GD), the first non-substance related disorder in the DSM-V, is linked with stress-related conditions and psychiatric disorders. Few studies investigate interactions between stress reactivity and decision-making in GD; therefore, this study explored the effects of acute psychosocial stress induction on risky decision-making. Twenty-eight healthy control participants (HC) and 38 individuals with GD completed the Balloon Analogue Risk-taking Task (BART) and Iowa Gambling Task (IGT) following a stressor. Saliva samples, used to assess biomarkers cortisol and α-amylase, and gambling urge measures were collected at baseline, post-stressor and post-task. Results show stressor-induced increase in self-reported mood disturbance in the HC group from baseline, but not in the GD group. Stressor-induced cortisol reactivity, however, did not differ between or within groups. Unexpectedly, the stressed GD group showed reduced α-amylase reactivity following the stressor, and this decrease was significantly greater relative to the stressed HC group. The stressed GD group also made significantly less risky choices on the BART, relative to the non-stressed GD group. Further, increased α-amylase reactivity correlated with increased risky decision-making (blocks 4 and 5) on the IGT in this group. The GD group did not report stressor-induced changes in gambling urges. Overall, the differential effects of acute stress in GD is indicative of altered SAM function,

possibly a result of norepinephrinergic dysfunction, that may be suggestive of changes in risk/reward appraisal and dysregulated motivational processes.

Keywords: Psychosocial Stress, Decision-making, Risk-taking, Uncertainty, Iowa Gambling Task, Balloon Analogue Risk-taking Task, Cortisol, Alpha-amylase, Trier Social Stress Test

1. Introduction

Gambling Disorder (GD), the first non-substance-based (i.e. behavioural) addiction in the DSM-5, affects approximately 1% of the population (Williams, Vohlberg, & Stevens, 2012), and is characterized by persistent and recurrent gambling behaviour that leads to clinically relevant distress or impairment (APA, 2013). Individuals with GD report a lower quality of life and a less healthy lifestyle, such as lack of exercise, increased smoking rates, and limited access to medical services (Black, Shaw, McCormick, & Allen, 2013), comorbid stress-related psychiatric disorders, such as depression and anxiety (el-Guebaly et al., 2006; Hodgins & el-Guebaly, 2010), and cardiovascular diseases, including tachycardia and angina (Morasco et al., 2006), as well as higher relationship and personal distress in concerned significant others (Hodgins, Shead, & Makarchuk, 2007). Moreover, coping with negative emotions is a motivator underlying gambling behaviour in those with GD (Ledgerwood & Petry, 2006), consistent with the gambling pathways model where the emotionally-vulnerable sub-group gambles to self-medicate (Blaszczynski & Nower, 2002; Valleur et al., 2016). Comparatively, inducing sadness leads to increased persistence on a simulated slot machine task in recreational gamblers (Devos, Clark, Maurage, & Billieux, 2018). The association of depressive symptoms and self-reported baseline stress reactivity with a faster relapse rate further underscore the importance of exploring stress reactivity in GD (Daughters et al., 2005).

Gambling behaviour increases levels of cortisol and heart rate in recreational gamblers (Meyer et al., 2000), and increases norepinephrine (NE) and dopamine in problem gamblers (Meyer et al., 2004). Cortisol, an indicator of Hypothalamic-Pituitary-

Adrenal (HPA) axis function, and NE, a measure of Sympathetic-Adrenal-Medullary (SAM) system, modulate the physiological stress response (Vollmer, 1996; Lovallo, 2004). According to the Deficient Biological Stress Reactivity (DBSR) hypothesis, the inverted U-shaped function underlying stress reactivity is linked with wider health and behavioural outcomes, where reduced stress reactivity and unstable affect regulation may increase risk-taking, possibly posing a risk for addiction (Carroll, Ginty & Phillips, 2016). In those with an addiction, diminished reactivity, proposed to underlie risk for addiction, is seen as a biomarker of a broader dysregulation in brain areas involved in motivation and autonomic control (Carroll et al., 2016). In those with GD, altered psychophysiological reactivity, such as amphetamine-induced decreases in levels of cortisol and heart rate (Zack et al., 2015), are reflective of HPA and SAM axes impairments.

Cortisol's activity functions as a feedback mechanism in the PFC, involved in stress reactivity and decision-making (Lovallo, 2004; Radley, Arias, & Sawchenko, 2006; St. Onge & Floresco, 2010); whereas, norepinephrine (NE) plays a regulatory role in both the PFC and the amygdala, a region involved in motivation and emotional processing (Arnsten, 2009; G. F. Koob, 1999). In substance use addiction, both the PFC and the amygdala are also involved in dysregulated reward-related and motivational processes, and in impaired decision-making (Bechara, Damasio, Damasio, & Lee, 1999; Koob & Kreek, 2007; Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006; Wise, 1996). In this way, and consistent with the DBSR hypothesis, altered stress and arousal processing,

in particular in response to an acute stressor, may further influence pre-existing impairments in autonomic control, motivation, and decision-making.

Anticipatory stress induction enhances the processing of loss information and reduces risk-taking (Clark et al., 2012), and stress-induced release of cortisol and α-amylase (a proxy measure of NE (Nater & Rohleder, 2009)), also leads to less risky decision-making when losses are involved (Pabst et al., 2013). Further, those with GD show impairments in decision-making and learning deck contingencies as well as reward and punishment sensitivities on the Iowa Gambling Task (IGT) (Cavedini, Riboldi, Keller, D'Annucci, & Bellodi, 2002; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006; Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2005; Linnet, RØjskjÆr, Nygaard, & Maher, 2006), a well-validated decision-making task commonly used to explore implicit learning and decision-making (Bechara et al., 1994; Buelow & Suhr, 2009). This is similar to patients with ventromedial PFC lesions (Bechara, Tranel, & Damasio, 2000), those with brain injury (Balagueró, Vicente, Molina, Tormos, & Roig Rovira, 2014), substance users (Bechara et al., 2001; Goudriaan et al., 2005), and those with an alcohol use disorder (Bowden-Jones et al., 2005). The IGT explores both decision-making under uncertainty and under risk (Brand et al., 2006, 2007), reflecting a distinct divide in conceptual factors influencing performance on early versus later trials consistent with Dual Process theories of decision-making (Phelps et al., 2014). Performance on early trials, termed decision-making under uncertainty (or 'pre-learning'), is not contingent upon knowledge of reward or punishment schedules associated with each deck (Brand et al., 2006; Buelow & Blaine, 2015); whereas,

performance on later ones, termed decision-making under risk, occurs after having learned the outcomes associated with the different deck contingencies (i.e. post-learning) (Brand et al., 2006; Buelow & Blaine, 2015). It is particularly relevant to explore these facets of decision-making as high risk behaviour could underlie impaired IGT performance (Clark & Manes, 2004); in addition, problem gamblers show impairments in risky decision-making on the IGT (Brevers et al., 2012). Further, those with GD are impaired in different lower-order processes influencing risky decision-making, including delay discounting, chasing behaviour and risk-taking behaviour (Kräplin et al., 2014). As such, a distinct measure of risky decision-making, the Balloon Analogue Risk-taking Task (BART), a well-validated and reliable neurocognitive task, can be used to explore increased propensity towards engagement in risky behaviour (Buelow & Blaine, 2015; Lejuez et al., 2002). Although work examining BART performance in gamblers is limited, in healthy controls, the BART is used to explore reward-seeking (Bogg et al., 2012) and loss aversion (Fukunaga, Brown, & Bogg, 2012), thereby parsing out underlying processes contributing to risky decision-making.

In the only psychophysiological studies exploring decision-making in GD, decreased anticipatory heart rate when selecting from advantageous decks, and after winning or losing, as well as a relationship between increased α-amylase - a proxy measure of NE reactivity (Nater et al., 2006) - post task with a decreased number of risky decisions, are observed (Goudriaan et al., 2006; Labudda, Wolf, Markowitsch, & Brand, 2007). The relationships between altered basal psychophysiology and decision-making reflects the utility of investigating the effects of acute stress induction in GD as it may

reveal further impairments in decision-making. This could possibly be a result of altered stressor-induced shift in behavioural control from the PFC to the amygdala (Arnsten, 2009; Phelps, Lempert, & Sokol-Hessner, 2014), which is likely given ventromedial PFC and amygdala lesion patients show differential impairments in IGT performance (Bechara, Damasio, Damasio, & Lee, 1999). Work exploring stressor-induced impairments in decision-making and reward processing in healthy participants show stressed individuals take longer to learn reward contingencies (Preston, Buchanan, Stansfield, & Bechara, 2007) and show a lack of reward sensitivity (Porcelli et al., 2012). As such, exploring altered psychophysiology and decision-making in an acute stress induction paradigm is novel.

Stress exposure also leads to an increase in subjective anxiety and alcohol craving in cocaine dependent individuals (Sinha, Catapano, & O'Malley, 1999), and in 1-month, abstinent treatment-engaged alcohol dependent patients (Sinha et al., 2011). Given stress-induced and alcohol-induced craving significantly predict a shorter time to relapse (Sinha et al., 2011), and a greater number of self-reported daily psychosocial stressors predict gambling urges in those with GD (Elman, Tschibelu, & Borsook, 2010), it is worth exploring stressor-induced changes in these urges in a subset of this population.

The current study investigates the effects of acute, psychosocial stress, using the well-validated Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993; Nater et al., 2006), on decision-making. Given stressor-induced increase in cortisol and NE in treatment-engaged cocaine dependent patients (Sinha et al., 2003), and in cortisol in alcohol dependent patients (Sinha et al., 1999), it is expected the TSST will lead to

increase in both biomarkers in the stressed relative to the non-stressed GD group. Past work reports blunted stressor-induced cortisol reactivity in cannabis users (Cuttler et al., 2017) and in treatment-engaged patients with alcohol use disorder (Sinha et al., 2011), as well as decreased cortisol reactivity in these patients (Sinha et al., 2009). Gambling cue-induced decreases in levels of cortisol are also observed in those with GD (Paris et al., 2010). As such, it is predicted the stressed GD group will report decreased reactivity in both biomarkers, reflecting dysregulated HPA and SAM axes, when compared to the HC group. In line with the DBSR hypothesis, it is also expected acute stress will potentiate impairments in decision-making on the IGT and also increase risk-taking behaviour on the BART in the stressed GD group, relative to the stressed HC group and the non-stressed GD group.

Acute stressor induction will increase negative affect and gambling urges in the GD group, similar to stress-induced increases in subjective anxiety and in craving in substance use disorders (Sinha et al., 1999, 2009, 2011, 2003). It is also assumed these tasks act as gambling cues that are physiologically arousing based on their established ecological validity (Buelow & Suhr, 2009; Lejuez et al., 2002), and the positive correlation between less risky decision-making and task-induced α-amylase reactivity (Labudda et al., 2007). Therefore, increased gambling urges and biomarker reactivity is predicted in the non-stressed GD group. When compared to the non-stressed individuals in the GD group, those stressed will report relatively heightened gambling urges post tasks, similar to the additive effects of acute stress and cue induction on increased alcohol

and food craving in healthy participants (Amlung & Mackillop, 2014b; Stojek, Fischer, & MacKillop, 2015).

2. Methodology

2.1. Participants

The study includes 28 healthy control (HC) participants and 38 people with GD. All participants were recruited through flyers posted within the greater New Haven area and through online advertisements. Participants were administered the Structured Clinical Interview for Pathological Gambling (SCI-PG), in line with the DSM-IV criteria (Grant, Steinberg, Kim, Rounsaville, & Potenza, 2004), for a current and past GD diagnosis. In addition, gambling severity was assessed using the South Oaks Gambling Screen (SOGS). Exclusionary criteria included psychosis, movement-related disorder, neurological illness, psychiatric hospitalization, use of psychotropic medications in the last 6 months, and suicidality. Participants were screened for use of illicit substances and for other Axis I psychiatric and substance use comorbidities using the Structured Clinical Interview for Axis 1 Disorders (SCID-I). Participants were not excluded for Axis I, including mood and anxiety disorder, and substance use disorders (Dowling et al., 2015; El-Guebaly et al., 2006).

Following study completion, participants were debriefed and compensated for their time. All participants were tested between 08:00 and 18:00. This experimental protocol was approved by the Ethics Board at Yale University.

2.2. Psychosocial Stress Induction Procedure

The Trier Social Stress Test (TSST), a reliable and validated tool of inducing psychosocial stress was administered across HC and GD groups for 20-minutes (Kirschbaum et al., 1993). Individuals in the no stress condition completed crossword puzzles for 20 minutes instead of the TSST.

2.3. Measures

2.3.1. Self-report measures

2.3.1.1. South Oaks Gambling Screen (SOGS)

The SOGS is a robust and validated 20-item measure assessing gambling severity (Lesieur & Blume, 1987).

2.3.1.2. Profile of Mood States (POMS)

The POMS scale measures current mood states (McNair, 1971). Positive affect is assessed in the subscales Vigour, Friendliness and Elation subscales; and negative affect through the Tension-anxiety, Depression-dejection, Anger-hostility, Fatigue-inertia and Confusion-bewilderment subscales. Reactivity indices of the total mood disturbance (TMD) score, calculated by subtracting positive affect scores from negative affect, explored changes in subjective stress over time.

2.3.1.3. Gambling Urge Scale (GUS)

The GUS, a 6-item report with good psychometric properties, including reliability and predictive validity (Raylu & Oei, 2004), assessed gambling urges. Absolute values of the total GUS score measured changes in gambling urges over time.

2.3.2. Physiological measures

Saliva samples were collected at 3 different timepoints, (**Fig**. 1) by having the participants passively drool into a 5 ml polypropylene vial through a plastic straw. These samples were capped, labelled accordingly, and stored in a -20º freezer. Salivary cortisol levels were assayed using the ImmuChem Cortisol^{125} kit (MP Biomedicals, Solon, OH) and salivary α-amylase assayed using the enzyme-linked immunosorbent assay kit (ELISA, TX).

The changes in these biomarkers were assessed using percent change (Balodis, Wynne-Edwards, & Olmstead, 2010), one of the most representative indices of biomarker reactivity (Khoury et al., 2015). Percent change scores for cortisol and α-amylase were calculated using the following formula:

$$\Delta Biomarker_{(post-stressor)\%} = \frac{S_{post-stressor} - S_{baseline}}{S_{baseline}} * 100$$

$$\Delta Biomarker_{(post-task)\%} = \frac{S_{post-task} - S_{post-stressor}}{S_{post-stressor}} * 100$$

2.3.3. Neurocognitive Measures

Both tasks were presented in a randomized order.

2.3.3.1. Iowa Gambling Task (IGT)

The Iowa Gambling Task (IGT), a validated and reliable task with good construct validity (Buelow & Suhr, 2009), investigates implicit learning and decision-making as it factors reward probabilities and the uncertainty of receiving them (see Bechara, Damasio, Damasio, & Anderson, 1994). As described previously, selections from disadvantageous decks A and B produce high reward but higher penalties; whereas, selections from the advantageous decks C and D are associated with small immediate rewards but lower penalties. The decks also differ in the frequency of losses: decks A and D are associated with frequent losses, whereas decks B and C are related to infrequent losses.

The dependent variable on the IGT is the total IGT score calculated using the formula below:

$$IGT\ Score = [(C + D) - (A + B)]$$

In order to measure learning over time, analyses were run using the total IGT score across five blocks of 100 trials. In addition, since implicit learning of deck contingencies occurs predominantly during the first three blocks of trials and most participants have explicit knowledge of deck contingencies towards the end of block 3 (Bechara et al., 1997), analyses were also conducted by pre-learning (block 1-3) and post-learning (blocks 4-5) phases (Preston et al., 2007). This also allows for the exploration of decision-making under risk separate from that under uncertainty where implicit learning effects are more evident (Brand et al., 2007; Buelow & Blaine, 2015).

2.3.3.2. Balloon Analogue Risk-taking Task (BART)

The Balloon Analogue Risk-taking Task (BART), a well-validated measure of risky-decision-making, can be used to explore increased propensity towards engagement in risky behaviour (Buelow & Blaine, 2015; Lejuez et al., 2002). BART performance correlates with real-world risk-taking behaviours, smoking status, number of drug classes tried, risk-taking behaviour and the total score on the gambling attitudes and beliefs scale (Lejuez et al., 2003, 2002, 2004).

The computerized version of the BART includes 30 trials. Each trial included a simulated balloon on the screen whereby the participants were asked to pump the balloon by clicking a button to earn virtual money. With each pump, the participant earned a reward of 5 cents, which was added on to a temporary bank until a specific threshold when the balloon exploded. This breakpoint differed for each balloon across various contingencies ranging from 1-128 to 1-32 and 1-8 pumps. After each non-exploding balloon trial, the probability that the balloon would explode on the following trial increases. As such, each successive pump confers both greater risk and reward, where the ratio between the two decreases differentially for each balloon with a specific breakpoint. The BART score, calculated as the number of average adjusted pumps on non-exploding balloons, was used as the dependent variable.

2.4. Experimental Timeline

On the first visit, participants provided informed consent and completed a urine screen, breathalyzer, and CO screen to test for recent drug and alcohol use. Participants

were also administered the SCID-I and SCI-PG (for the GD group), and completed other self-report measures. On the second visit, participants underwent the experimental protocol, including administration of the TSST followed by the neurocognitive tasks (**Fig.** 1). To monitor respective changes in biomarkers, mood and gambling urges, saliva samples were collected, and POMS and GUS questionnaires administered (**Fig.** 1).

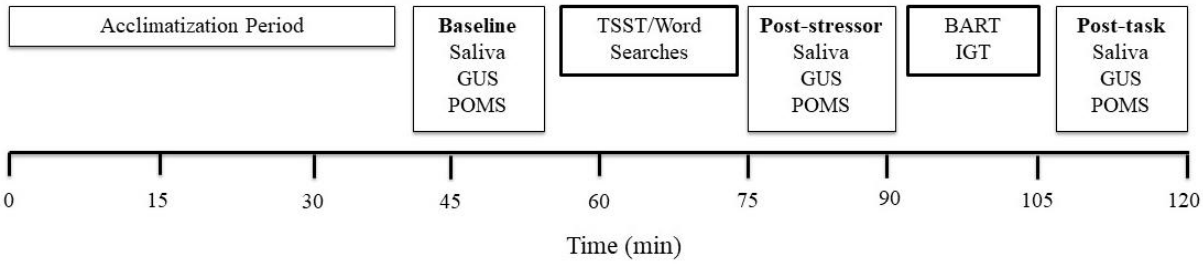

Figure 1 Active experimental protocol. GUS = Gambling Urge Scale; POMS = Profile of Mood States; TSST = Trier Social Stress Test; BART = Balloon Analogue Risk-taking Task; IGT = Iowa Gambling Task

2.5. Statistical Analyses

Data were analyzed using SPSS version 25.0. Between-group and within-group analyses explored differences across groups (i.e. GD vs HC) and stress (i.e. stress vs no-stress) conditions. Correlations examined relationships between some of the subjective, physiological and neurocognitive variables. Parametric tests were conducted on normally distributed data and non-parametric on non-normally distributed data.

3. Results

3.1. Participant Demographics

Participant demographic variables are presented in Table 1. A one-way ANOVA showed significant group differences on the following demographic variables – age, years

of education, and total SOGS score. The GD group was significantly older, ranging in ages 19 to 63, and the HC group, ranging between ages 18 to 56. One HC urine screen was positive for THC. Seventeen participants with GD and six in the HC group reported comorbid mood, anxiety, and substance or alcohol use problems (see Supplementary Materials). Consistent with previous studies, the GD group reported higher gambling severity.

	HC **n = 28**	**GD** **n = 38**	**Statistic**
Sex	M = 25; F = 3	M = 32; F = 6	$\chi^2 = 0.35$
Age*	31.04 ± 10.98	41.05 ± 13.00	$F_{(1, 64)} = 10.88$
Education (years)	14.18 ± 2.25	13.97 ± 1.92	$F_{(1, 64)} = 0.158$
SOGS**	1.20 ± 2.10	10.47 ± 4.92	Welch = 92.11
Smoking Status	9 Smokers	11 Smokers	$\chi^2 = 0.002$

Table 1 Demographics of HC and GD groups. *$p < 0.05$; **$p < 0.01$. M = Male; F = Female.

3.2. Subjective Effects

3.2.1. Profile of Mood States

Post-stressor

A 2 group (HC, GD) by 2 condition (stress, non-stress) ANOVA on $\Delta TMD_{post\text{-}stressor}$ did not reveal any main effect of group or a group by stress condition interaction; however, the main effect of stress condition was significant ($F_{(1, 61)} = 4.27$, $p < 0.05$, $\eta_p^2 = 0.065$), showing significantly higher TMD scores in the stressed condition (4.10 ± 2.61) when compared to the non-stressed condition (-2.03 ±1.80). In order to further parse out the effect of the stress condition, two post-hoc Bonferroni-corrected ANOVAs were conducted in the HC and GD groups. In the HC group, a main effect of stress ($F_{(1, 26)} = 6.14$, $p < 0.03$, $\eta_p^2 = 0.19$, see **Fig.** 2A) revealed the stressed participants (7.00 ± 13.4) reported significantly higher TMD when compared to the non-stressed participants (-2.27 ± 5.18); but, this effect was not present in the GD group ($F_{(1, 35)} = 0.64$, $p > 0.03$, $\eta_p^2 = 0.018$). For detailed analyses of the absolute TMD values, and of the different subscales, see Supplementary Materials.

Post-task

A 2 group (HC, GD) by 2 condition (stress, non-stress) ANOVA on $\Delta TMD_{post\text{-}task}$ showed a trend in the main effect of group ($F_{(1, 61)} = 3.88$, $p = 0.054$, $\eta_p^2 = 0.060$) and a main effect of the stress condition was significant ($F_{(1, 61)} = 6.45$, $p < 0.05$, $\eta_p^2 = 0.096$). There was no interaction between group and the stress condition ($p > 0.05$). In order see

in what group drove the main effect of the stress condition, two, Bonferroni-corrected, post-hoc one-way ANOVAs were conducted. This did not reveal any main effect of stress condition in the GD group ($F_{(1, 35)} = 1.99$, *p(uncorrected)* > 0.05, $\eta_p^2 = 0.054$, see **Fig.** 2B). In the HC group, a main effect of stress ($F_{(1, 26)} = 4.97$, *p(uncorrected)* < 0.05, $\eta_p^2 = 0.16$) revealed the non-stressed participants (-2.33 ± 7.54) reported a greater change in mood disturbance when compared to the stressed participants (-11.9 ± 14.4), following completion of the neurocognitive tasks. For detailed analyses of the absolute TMD values, and of the different subscales, see Supplementary Materials.

3.2.2. Gambling Urges

Since gambling urge scores are likely to be significantly differ between groups (Potenza, Steinberg, et al., 2003), the analyses focused on the specific effects of the stress manipulation in the GD group. A 2 condition (stressed, non-stressed) x 3 timepoints (baseline, post-stressor and post-task scores) repeated measures ANOVA in the GD group did not reveal a between-subjects effect of the stress condition ($F_{(1, 35)} = 1.64$, $p > 0.05$, $\eta_p^2 = 0.05$), a within-subjects effect of gambling urge ($F_{(1, 35)} = 1.64$, $p > 0.05$, $\eta_p^2 = 0.05$) or an interaction with stress ($F_{(1, 35)} = 1.64$, $p > 0.05$, $\eta_p^2 = 0.05$). In order to test our a priori predictions, two paired t-tests were conducted to explore changes in gambling urges from baseline to post-stressor, and from post-stressor to post-task, in the stressed condition. The third paired t-test explored changes in gambling urges from post-stressor to post-task in the non-stressed condition. These tests were not significant ($p > 0.05$).

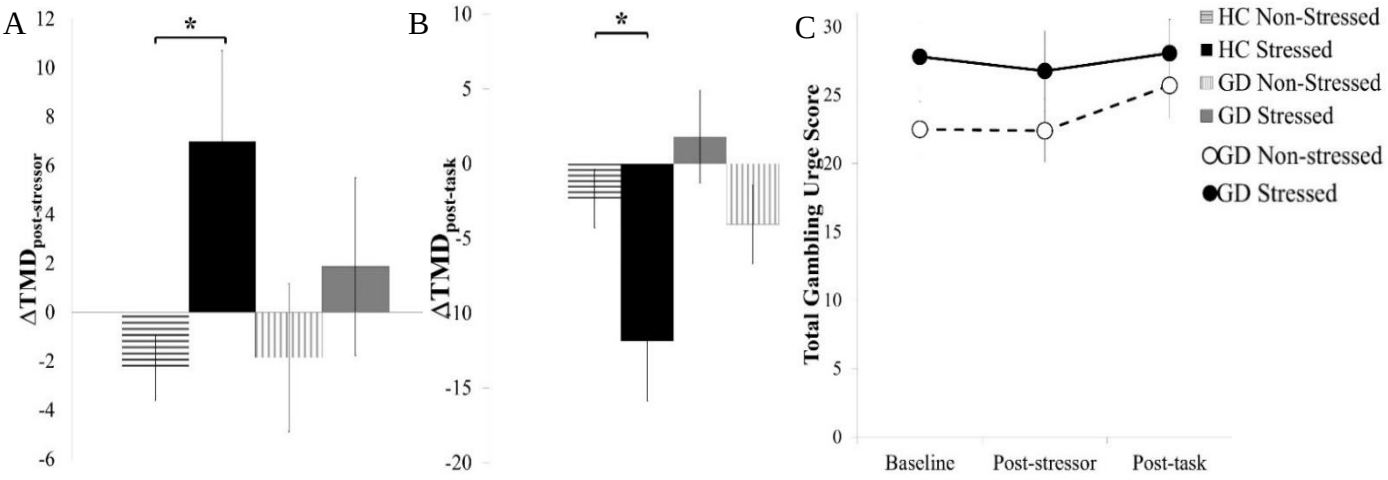

Figure 2 Self-reported total mood disturbance (TMD) and gambling urges across stressed conditions in HC and GD groups. (A) The stressed HC group reported significantly higher TMD score post-stressor and (B) significantly greater change in post-task TMD score when compared to the non-stressed group. (C) Gambling urge scores did not differ between stressed and non-stressed GD groups at baseline, post-stressor and post-task. $p < 0.05$

3.3. Physiological Measures

3.3.1 Cortisol

Post-stressor

To correct for non-normal distribution, the Mann U-Whitney test was conducted across the stress condition. Collapsed across groups, $\Delta cortisol_{post\text{-}stressor\%}$ (45.38 ± 63.17) was significantly (U = 318, $p < 0.01$, $\eta_p^2 = 0.12$, see **Fig.** 3A) higher in the stressed condition relative to the non-stressed condition (6.34 ± 32.89). To investigate our a priori hypotheses, two statistical tests were conducted to explore differences in $\Delta cortisol_{post\text{-}stressor\%}$ in the GD group, and within the stressed condition. The first Mann-U Whitney test, conducted in the GD group, showed $\Delta cortisol_{post\text{-}stressor\%}$ was marginally (U = 106, p = 0.052, $\eta_p^2 = 0.11$) higher in the stressed GD group (45.56 ± 68.19) when compared to the non-stressed GD group (4.04 ± 30.20). An additional Mann-Whitney U test, exploring the

effect of group in the stressed condition, was not significant ($p > 0.05$). Finally, a post-hoc, independent t-test in the HC group, conducted to explore the effects of the stressor manipulation, showed the stressed HC participants had greater cortisol increases (44.99 ± 55.75) when compared to non-stressed individuals (9.63 ± 37.32); however, $\Delta cortisol_{post\text{-}stressor\%}$ did not reach statistical significance by stress condition ($t = 1.93$, $p > 0.05$, $\eta_p^2 = 0.13$, **Fig.** 3A). The absolute levels of cortisol post-stressor were significantly different from those at baseline in the HC group (see Supplementary Materials).

Post-task

A 2 group (HC, GD) by 2 condition (stress, non-stress) ANOVA on $\Delta cortisol_{post\text{-}task\%}$ did not reveal any significant differences by group ($F_{(1, 35)} = 0.26$, $p > 0.05$, $\eta_p^2 = 0.004$), the stress condition ($F_{(1, 35)} = 0.95$, $p > 0.05$, $\eta_p^2 = 0.016$) or an interaction between the two ($F_{(1, 35)} = 0.95$, $p > 0.05$, $\eta_p^2 = 0.003$).

3.3.2 α-amylase

Post-stressor

To correct for non-normal distributions, Mann-Whitney U tests were performed. Collapsed across groups, $\Delta\alpha\text{-amylase}_{post\text{-}stressor\%}$ was significantly lower ($U = 763$, $p < 0.01$, $\eta_p^2 = 0.15$, see **Fig.** 3B) in the stressed condition (-14.60 ± 28.43) when compared to the non-stressed condition (17.90 ± 46.90). To explore our a-priori hypotheses, two additional, Bonferroni-corrected, Mann-Whitney U tests were conducted in the GD group and across the stressed condition. In the GD group, stressed individuals (-23.50 ± 25.38)

had a significantly lower $\Delta\alpha$-amylase$_{\text{post-stressor\%}}$ (U = 283, $p_{corrected} < 0.02$, $\eta_p^2 = 0.31$) when compared to non-stressed individuals with GD (17.46 ± 40.66). Within the stress condition, $\Delta\alpha$-amylase$_{\text{post-stressor\%}}$ was significantly greater in the GD group relative to the HC group (t = 2.11, $p_{uncorrected} < 0.05$, $\eta_p^2 = 0.14$). Further, to check for the effects of the stress manipulation, a post-hoc Mann-Whitney U test was conducted in the HC group. The stressed participants had a lower $\Delta\alpha$-amylase$_{\text{post-stressor\%}}$ (-4.40 ± 23.37) when compared to non-stressed HCs (7.49 ± 33.94); however, this difference was not statistically significant (U = 108, $p_{uncorrected} > 0.05$, $\eta_p^2 = 0.01$).

Post-task

To correct for non-normal distributions, Mann-Whitney U tests were performed. Collapsed across groups, $\Delta\alpha$-amylase$_{\text{post-task\%}}$ was significantly lower (U = 349, $p < 0.05$, $\eta_p^2 = 0.08$) in the stressed condition (43.40 ± 70.38) when compared to the non-stressed condition (8.812 ± 23.95). To explore our a-priori hypotheses, three additional Mann-Whitney U tests were performed in the GD group and within the stressed, and non-stressed, conditions. The stressed participants (55.25 ± 86.52) in the GD group had significantly higher $\Delta\alpha$-amylase$_{\text{post-task\%}}$ (U = 103, $p_{uncorrected} < 0.05$, $\eta_p^2 = 0.12$, see **Fig.** 3C) relative to the non-stressed individuals (9.26 ± 27.20). The $\Delta\alpha$- amylase$_{\text{post-task\%}}$ was not different across the stressed condition ($p > 0.05$).

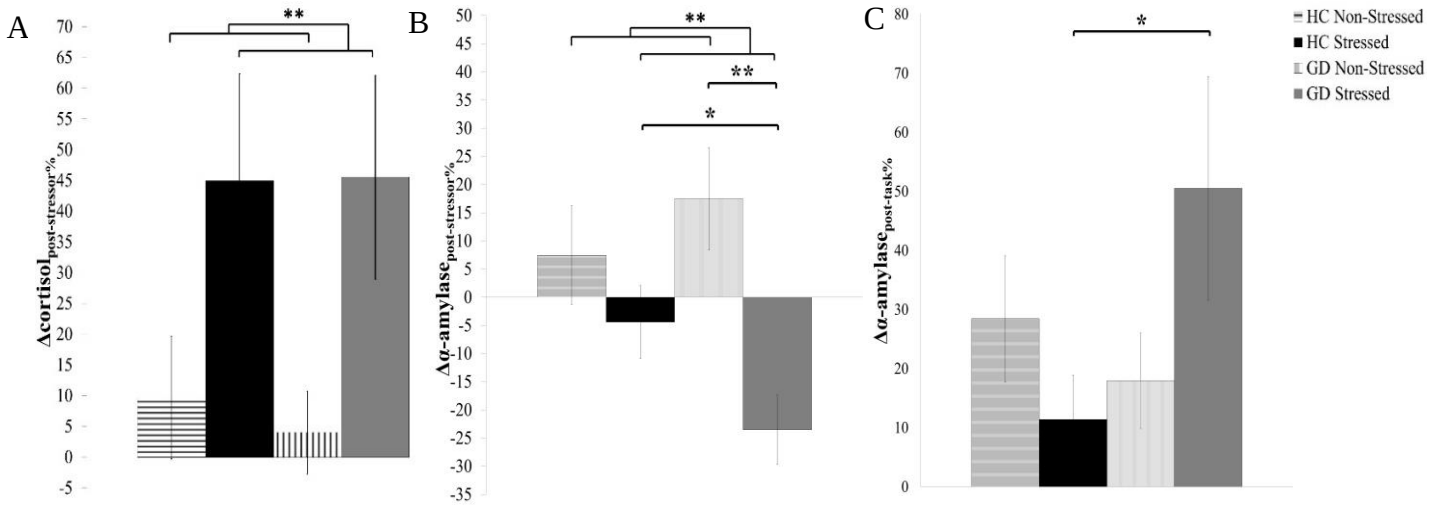

Figure 3 Stressor-induced reactivity across stressed and non-stressed conditions in HC and GD groups. (A) $\Delta cortisol_{post\text{-}stressor\%}$ is significantly higher in the stressed condition. (B) $\Delta\alpha\text{-}amylase_{post\text{-}stressor\%}$ was significantly lower in the stressed condition when compared to the non-stressed one, driven by lower reactivity in the stressed GD group when compared to the non-stressed one; stressed GD group had lower reactivity when compared to the stressed HC group. (C) $\Delta\alpha\text{-}amylase_{post\text{-}task\%}$ was significantly higher in the stressed GD group when compared to non-stressed GD group. *$p < 0.05$; **$p < 0.01$

3.4. Neurocognitive Tasks

Factoring the presentation order of the neurocognitive tasks did not have any significant effect on the BART and the total IGT scores so data was analyzed without task randomization.

3.4.1. BART Performance

A 2 group (HC, GD) by 2 condition (stress, non-stress) ANOVA did not reveal any main effect of group or the stress condition on BART score ($p > 0.05$). A significant interaction between group and stress condition was observed ($F_{(1, 61)} = 6.09$, $p < 0.05$, $\eta_p^2 = 0.09$). Given the interaction and in line with our a priori hypotheses, two separate one-way ANOVAs on the BART score were conducted in the HC and GD groups. This did not reveal a main effect of condition in the HC group ($p_{uncorrected} > 0.05$), but a main effect

of condition in the GD group ($F_{(1, 35)} = 4.43$, $p_{uncorrected} < 0.05$, $\eta_p^2 = 0.11$) showed stressed participants (28.21 ± 17.91) had a significantly lower BART score when compared to non-stressed ones (39.30 ± 13.98) (**Fig.** 4). Similarly, the total money earned was significantly lower in the stressed GD relative to the non-stressed GD group (see Supplementary Materials).

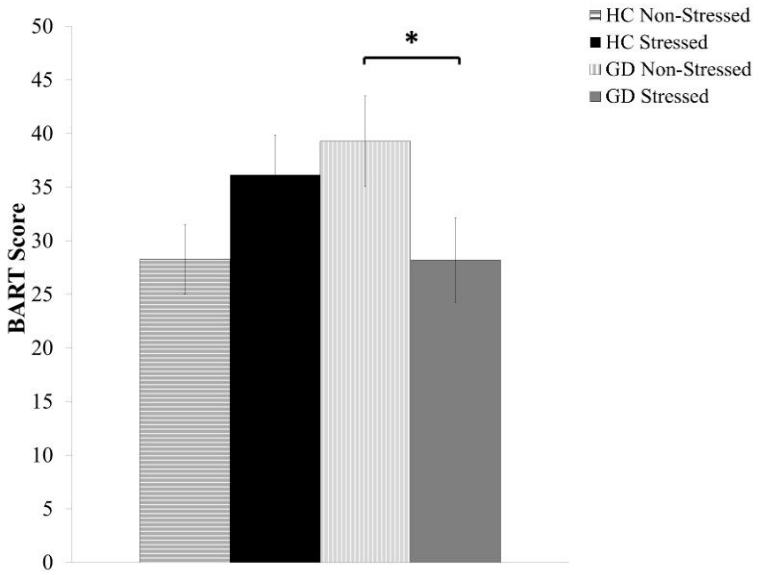

Figure 2 BART performance across stress conditions in HC and GD groups. The stressed GD group showed a significantly lower BART score relative to the non-stressed GD group. *$p < 0.05$

3.4.2. IGT Performance

3.4.2.1. Learning and Risky Decision-making

A 2 group (HC, GD) X 2 condition (stress, non-stress) x 5 IGT blocks repeated measures ANOVA did not reveal any main effects of group or condition or the interaction between the two on the IGT score ($p > 0.05$). A within-subjects effect of blocks ($F_{(3.10, 180)} = 5.03$, $p < 0.05$, $\eta_p^2 = 0.08$) showed IGT scores were significantly different across the

five blocks (**Fig.** 5A). Pairwise comparisons show IGT performance in block 1 is significantly lower when compared to blocks 3 and 4 ($p < 0.01$), but not block from blocks 1 and blocks 2 ($p > 0.05$).

To explore the disparate effects of risk-taking versus ambiguity, the blocks were divided into pre-learning and post-learning phases as done by Preston and colleagues (2007) previously. A 2 group (HC, GD) X 2 condition (stress, non-stress) x 2 phases (pre-learning, post-learning) repeated measures ANOVA did not reveal any main effects of phases or group, or an interaction ($p > 0.05$).

3.4.2.3. Frequency of Loss

Although there is a lack of a significant difference in IGT performance, the stressed group did show decreased risk-taking on the BART. Given increased reward hypersensitivity in problem gamblers and decreased loss aversion in GD (Gelskov, Madsen, Ramsøy, & Siebner, 2016; Hewig et al., 2010), we decided to analyze deck selections and the "*frequency-of-loss*" effect, which also drives learning deck contingencies on the IGT in healthy participants (Steingroever et al., 2013).

In order to explore this "*frequency-of-loss*" effect (Dunn et al., 2006), decks with high frequency (H_f) but low magnitude of punishment (A and C), and those with low frequency (L_f) but high magnitude of punishment (B and D), were combined. Two Bonferroni-corrected one-way ANOVAs revealed significant main effects of group on H_f ($F_{(1, 58)} = 6.24$, $p < 0.03$, $\eta_p^2 = 0.097$) and L_f ($F_{(1, 58)} = 6.24$, $p < 0.03$, $\eta_p^2 = 0.097$), but no main effects of stress condition or an interaction ($p > 0.05$). The HC group had a

significantly higher mean L_f score (50.32 ± 12.42) when compared to the GD group (41.94 ± 13.36); whereas, the GD group had a significantly higher mean Hf score (58.06 ± 13.36) when compared to the HC group (49.68 ± 12.42) (**Fig.** 5B).

Since the GD group preferred low loss frequency/high magnitude decks (decks B and D combined), and the stressed participants in this group made significantly lower number of selections from deck C (see Supplementary Materials), post-hoc t-tests were conducted to explore deck preferences in the stressed GD group (**Fig.** 5C). The participants made significantly higher selections (t = -3.29, p < 0.01, η_p^2 = 0.42) from deck B (32.29 ± 11.78) when compared to deck A (19.12 ± 10.65), and deck C (19.88 ± 9.23, t = 3.06, p < 0.01, η_p^2 = 0.38).

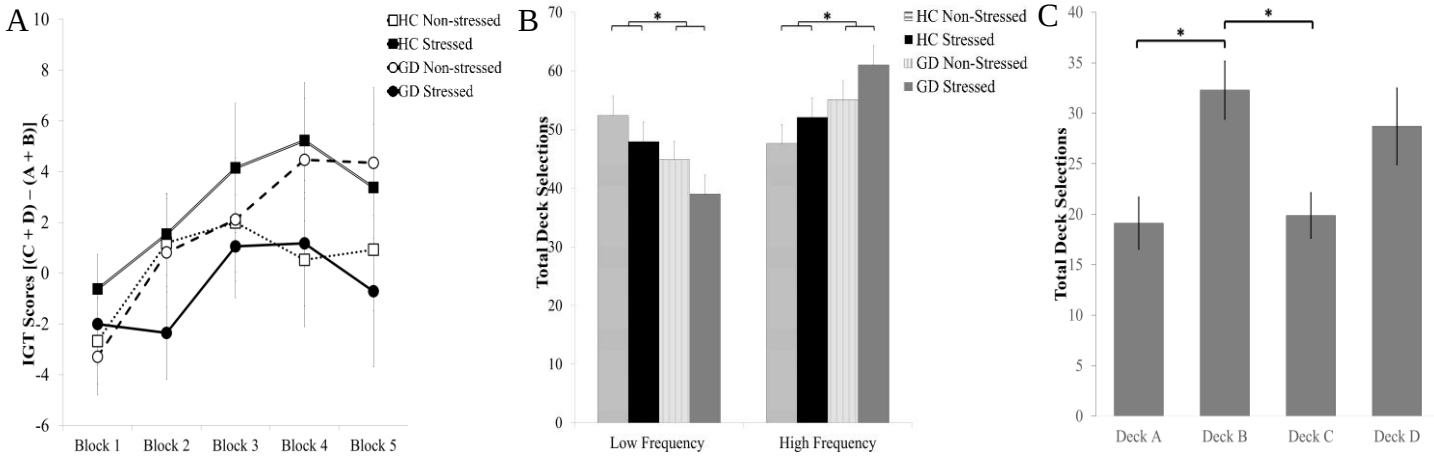

Figure 5 IGT Performance across stressed and non-stressed conditions in HC and GD groups. (A) IGT scores increased across 5 blocks but did not differ by group or condition. (B) GD group selected significantly more from low frequency decks (decks B and D combined), and HC group selected significantly higher from high frequency group (decks A and C combined). $p < 0.05$

3.6. Correlations

Pearson's r and Kendall's tau b correlations (for non-normal distributions) were conducted to explore relatonships of risky decision-making with TMD as well as with stressor and task induced reactivity in biomarkers. Additonal correlations between self-reported and biomarker reactivity are reported in Supplementary Materials.

In the stressed GD group, a higher total IGT score was significantly related to a lower BART score (r = -.0.564, $p = 0.018$, n = 17), an effect that was absent in the non-stressed GD group (**Fig.** 6A). Interestingly, the $\Delta\alpha\text{-amylase}_{\text{post-task\%}}$ in the stressed and non-stressed GD groups differed on the direction of their relationship with the IGT scores in the post-learning phase ("risky decision-making") (**Fig.** 6B). In the stressed GD group, higher IGT scores were significantly related to higher $\Delta\alpha\text{-amylase}_{\text{post-task\%}}$ ($\tau b = 0.390$, $p = 0.038$, n = 16); whereas, in the non-stressed group, a higher IGT score were significantly related to lower $\Delta\alpha\text{-amylase}_{\text{post-task\%}}$ ($\tau b = -0.466$, $p = 0.01$, n = 17). In particular, higher reports of $\Delta\text{TMD}_{\text{post-stressor}}$ was significantly associated with higher IGT scores in the post-learning phase in the stressed GD group ($\tau b = 0.402$, $p = 0.033$, n = 16, see **Fig.** 6C). A further exploratory analysis, examining whether gambling severity might relate to the effect of $\Delta\alpha\text{-amylase}_{\text{post-task\%}}$ on risky decision-making, demonstrated those who reported higher gambling severity had a significantly lower $\Delta\alpha\text{-amylase}_{\text{post-task\%}}$ in the stressed GD group ($\tau b = -.533$, $p = 0.01$, n = 14, see **Fig.** 6D).

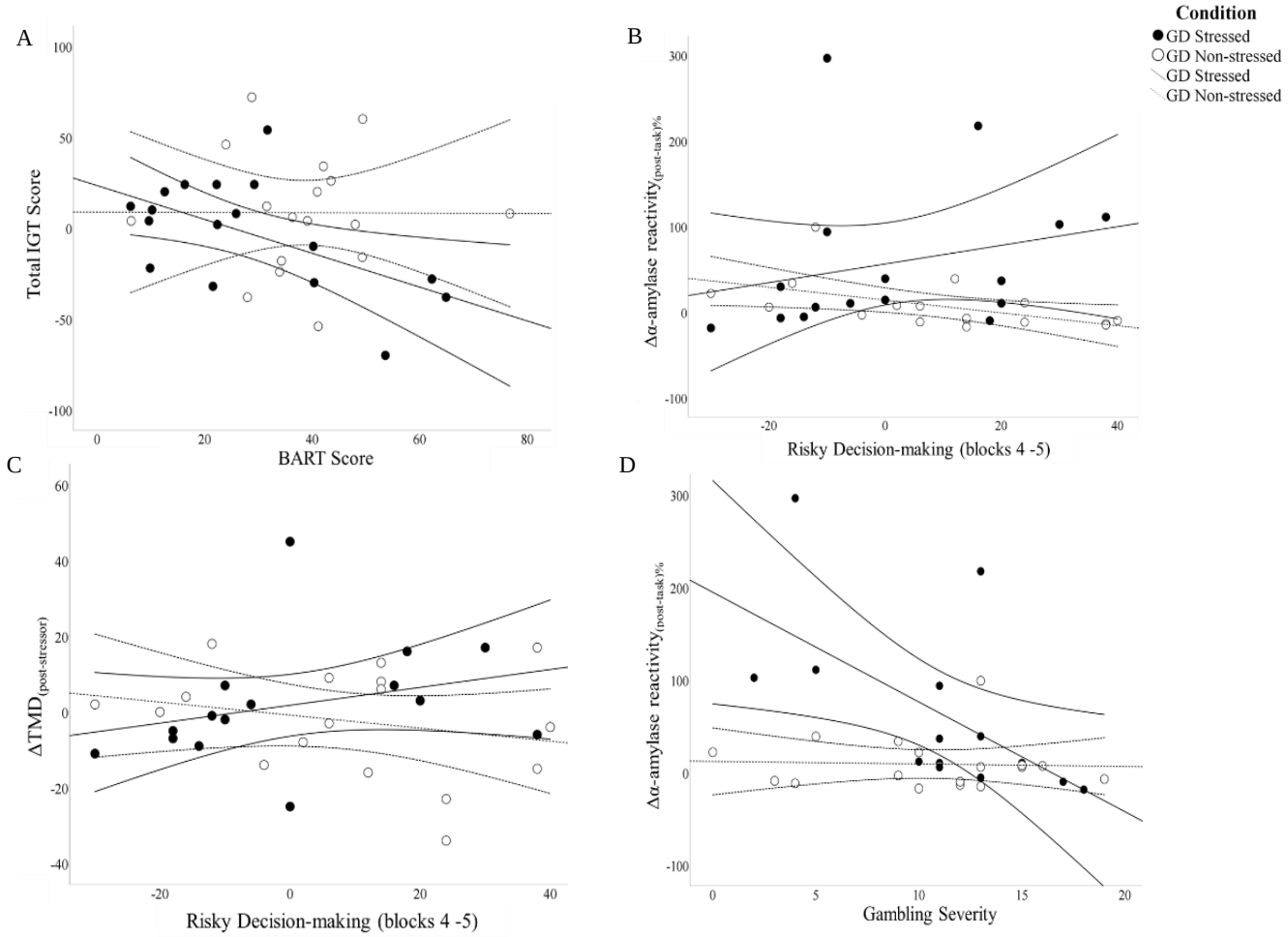

Figure 6 Correlation across stressed and non-stressed GD groups. TSST-induced alterations (A) higher BART score was significantly associated with a lower IGT score during risk decision-making. (B) IGT score in the post-learning phase was significantly related to lower Δα-amylase$_{post\text{-}task\%}$ in the non-stressed GD group, but higher Δα-amylase$_{post\text{-}task\%}$ in the stressed GD group. (C) those in the stressed GD group who reported higher ΔTMD$_{post\text{-}stressor}$ scored significantly higher in the post-learning phase. (D) Δα-amylase$_{post\text{-}task\%}$ correlated negatively with gambling severity in the stressed GD group.

4. Discussion

The current study explored the effects of acute psychosocial stress induction on subjective reports, physiological biomarkers, risky decision-making and gambling urges in those with GD. In the HC group, acute stress induction led to an increase in TMD in the stressed, relative to the non-stressed, participants; in contrast, the GD group did not

report any change in TMD across the stressed condition. On physiological measures, however, the stressed GD group did show a marginally heightened cortisol response, indicative of HPA reactivity, and an unexpected reduction in α-amylase, when compared to the non-stressed GD group. Although stressor-induced cortisol reactivity did not differ between groups, the GD group showed a greater decrease in α-amylase reactivity relative to the HC group. The study also found altered relationships between SAM-axis reactivity and risky decision-making (post-learning). Specifically, lower IGT score during this post-learning phase (i.e. blocks 4 & 5) correlated with higher α-amylase reactivity in the non-stressed GD group, an association that was reversed in the GD stressed group: greater α-amylase changes were related to riskier decision-making. Exploratory analyses also revealed higher gambling severity correlated with decreased α-amylase reactivity post-task in the stressed GD group. This stress reactivity relationship also extended to subjective measures; greater TMD change post-stressor was related to less risky decision-making in the stressed GD group. Finally, although the GD and HC groups did not differ overall on BART and IGT performance, the stressed GD group had lower risk-taking on the BART when compared to the non-stressed GD participants. Gambling urges in the stressed GD group did not differ across all three timepoints.

4.1. Acute Stress Reactivity

As expected, an acute psychosocial stress paradigm led to increased TMD and cortisol reactivity across all stressed participants; surprisingly, it also led to decreased α-amylase reactivity. Although a significant increase in stressor-induced change in TMD reactivity was primarily driven by the HC group, a trend towards higher TMD post-

stressor relative to baseline was also seen in the GD group (see Supplementary Materials). Stressor-induced increase in cortisol reactivity, reflecting heightened HPA axis activity, was primarily driven by a marginal increase in cortisol reactivity in the GD group. Similarly, the only other work exploring acute stress reactivity in GD also found a trend towards increased cortisol reactivity in treatment-engaged individuals with GD (Maniaci et al., 2018). Studies using acute stress protocols in substance use disorders also show blunted cortisol responses in treatment-engaged patients relative to healthy participants (Cuttler et al., 2017; Sinha et al., 2011, 2003). Notably, treatment-seeking status or methodological variations may reflect stress reactivity variations across substance and non-substance-based addictions. Although the GD group in the current study included individuals with comorbid conditions, it is representative of the GD population (Dowling et al., 2015). Nevertheless, past psychiatric comorbidities can differentially influence HPA axis reactivity (Van Hedger, Bershad, & de Wit, 2017; Zorn et al., 2017), and SAM system activity given its proposed dysregulation in the neurobiology of substance use addiction (Koob, 1999; Koob & Kreek, 2007).

As expected, the stressed GD group showed dysregulated SAM axis activity when compared to the stressed HC group; however, unexpectedly, the directionality of the change differed as the stressed GD group displayed reduced stressor-induced α-amylase reactivity. This is inconsistent with Sinha and colleague (2003) who find stressor-induced increase in levels of NE in cocaine dependent patients. The difference could be a factor of treatment-seeking status or methodological variations considering Sinha and colleagues (2003) used the Guided Stress Imagery Paradigm, which is reportedly more potent in

inducing negative affect when compared to the TSST (Sinha et al., 1999). Given this is also the first study examining stressor-induced α-amylase reactivity in a GD group, more research is needed to explore SAM reactivity in GD as it may differ from substance use. Maniaci et al., (2018), who used the interbeat interval as a measure of sympathetic nervous system activity, did not find a stressor-induced difference. Finally, stressor-induced α-amylase release was not significantly increased in the stressed HC group, an unexpected finding given previously-reported stressor-induced increases (Pabst et al., 2013), potentially due to decreased power to detect an effect.

Consistent with our findings of lack of a relationship between cortisol and α-amylase reactivities, past work also shows stressor-induced independence in the release of these biomarkers at specific time points (Nater et al., 2006). However, an evaluation of large-scale temporal dynamics reveals positive and negative correlations at several time lags throughout a stress paradigm (Engert et al., 2011). They found α-amylase positively predicted cortisol levels around 14 minutes later, which predicted the inverse release of α-amylase around 14 minutes later. This possible temporal relationship between these two biomarkers may also partly explain our finding of decreased stressor-induced reactivity in α-amylase. It is likely stressor-induced increase in this biomarker may have already occurred 14 minutes into the TSST or it could have been delayed as a factor of the gambling pathology. Interestingly, higher cortisol reactivity post-stressor was associated with a lower change in TMD in the non-stressed GD group (see Supplementary Materials), but not in the stressed GD group, reflecting a potential dissociation between mood and stressor-induced physiological awareness.

In addition, this disengagement could potentially be due to excessive gambling behaviour that alters physiological responses, including increased levels of cortisol in recreational gamblers (Meyer et al., 2000) and of NE in PrG (Meyer et al., 2004). Over time, heightened levels of these biomarkers may lead to HPA and SAM axes changes, altering stress responses, such as altered temporal profiles of heart rate and diastolic blood pressure (Zack et al., 2015) and blunted NE function (Pallanti et al., 2010) in those with GD. Given chronic exposure to a gambling-like reward schedule sensitizes DA pathways in the brain (Zack & Poulos, 2007; Zack et al., 2014) and an amphetamine-induced increase in cardiac responsivity relates to lower gambling severity in those with GD (Zack et al., 2015), the finding of lower gambling severity relating to higher α-amylase reactivity post-task in the stressed GD group is particularly interesting. In light of a positive relationship between gambling severity and DA release those with GD (Boileau, Payer, Chugani, Lobo, Behzadi, et al., 2013), this shows increasing gambling pathology over time may be reflective of a more potent sensitization of the underlying DA pathways, and of dysregulated SAM axis reactivity. For those who present with high gambling severity, gambling with the same frequency may not be as rewarding or mood enhancing particularly under stress, especially in the emotionally-vulnerable subgroup who gambles to escape negative emotions (Blaszczynski & Nower, 2002; Ledgerwood & Petry, 2006). Indeed, a reduced decrease in α-amylase reactivity post stressor is related to a lower change in TMD post tasks, further implying that gambling may still retain mood enhancing effects under stress early on. Based on these findings, it is proposed SAM system dysregulation, potentially driven by NE dysfunction, may underlie gambling

pathophysiology, consistent with the DBSR hypothesis that proposes a broader dysregulation in autonomic control.

4.2. Acute Stress Relationships with Risky Decision-Making

This is the first study exploring stress and risk-taking using the BART in a GD population. Contrary to our prediction, the GD group did not show increased risk-taking relative to the HC group. Surprisingly, the stressed GD group had a significantly lower BART score, reflecting decreased risk-taking, when compared to the non-stressed participants. These behavioural findings suggest decreased reward sensitivity or heighted risk aversion following stress in GD where these individuals bank winnings too soon, and end up earning less money, consistent with findings in substance dependent individuals (Fukunaga et al., 2012). Neuroimaging studies show decreased reward-seeking choices on the BART is related to greater mPFC/ACC downregulation (Bogg et al., 2012); in the current study, diminished risk-taking in the stressed GD group may reflect acute alterations in risk/reward appraisal and performance monitoring. The former may be due to increased hypersensitivity to reward in problem gamblers (Hewig et al., 2010) or decreased loss aversion in GD (Gelskov et al., 2016). Indeed, examination of reward and loss preferences on the IGT revealed group (but not stress) differences when examining the ‘frequency/magnitude of loss’; the GD group preferred decks with high frequency/lower magnitude of losses. In particular, the stressed GD group preferred deck B over decks A and C, but its preference did not differ from D. The nature of the BART confers each pump with risk/reward; as such, combined with the IGT findings, it is hypothesized stress may increase loss aversion in GD. Since decks B and D are associated

with low frequency but high magnitude of punishment, future work should explore whether these stressor-induced effects on loss aversion are an effect of probability or magnitude.

However, there were no main effects of group or the stress condition on IGT scores across the five blocks. Groups did show a within-subjects effect of blocks, whereby scores on block 1 were significantly lower from those on block 3, and from block 5. Inconsitency in learning across blocks may be an effect of group or the stress manipulation. Learning rates may also vary across inidividuals with GD, as is the case with healthy participants (Bull et al., 2015). This could also explain a lack of difference in IGT scores during decision-making under uncertainty (pre-learning) and under risk (post-learning) as transitioning from the former to the latter may be a factor of group or the stress manipulation. In particular, impairments in decision-making on the IGT in GD populations are not always detected (Linnet, Møller, Peterson, Gjedde, & Doudet, 2011) and specific gambling subgroups may underlie this effect (Blaszczynski & Nower, 2002). These may relate to specific profiles of reward responsiveness and panic decision-making style (Franken & Muris, 2005), and other personality traits, such as alexithymia (Aïte et al., 2014) or impulsivity (Upton, Bishara, Ahn, & Stout, 2011) that may be relevant factors to explore in the future. In addition, sex and age may have influenced decision-making and risk-taking. Stressor-induced sex-differences have been observed on the BART; for example, stressed males take more risks, have a faster decision speed, and earn more money relative to stressed females (Lighthall, Mather, & Gorlick, 2009; Lighthall et al., 2012). In addition, age may affect performance on the BART and the

IGT, possibly through its influences on response inhibition as response time increases, and the ability to successfully inhibit one declines, with age (Nielson, Langenecker, & Garavan, 2002).

Overall, the association of the total IGT score with decreased risk-taking on the BART suggests a conservative approach on this task is related to better decision-making on the IGT in the stressed GD group. Further, differential relationships of altered stress reactivity systems with the different phases of the IGT reflect stressor-induced divergence in decision-making strategies in GD. Greater cortisol reactivity post-task related to IGT scores in the pre-learning phase (see Supplementary Materials), suggesting different stressor-induced influences of this hormone on learning and choice behaviour in GD. The HPA axis may be involved in decision-making under uncertainty where implicit learning and exploratory choice behaviour is more relevant. Whereas, the SAM axis (fight or flight responses) may be important for decision-making under risk where explicit goals and risk/reward calculations are necessary. In the stressed GD group, decreased risk-taking may relate to altered SAM axis function, as evidenced by greater α-amylase reactivity post-stressor. This group showed a relationship between post-task α-amylase reactivity and risky decision-making on the IGT during the post-learning phase (i.e. blocks 4 and 5). Specifically, greater changes in α-amylase reactivity post-task were associated with a higher IGT score on the last 2 blocks of trials, reflecting decreased risky decision-making. These findings are consistent with a previous study linking increased α-amylase levels with more advantageous decision-making in GD (Labudda et al., 2007), and together suggest important influences of SAM-axis reactivity in risky decision-making in GD.

Combined with the proposed SAM dysfunction and considering the stressor-induced shift in behavioural control from the PFC to the amygdala, a region that is impaired on the IGT (Bechara et al., 1999), these findings support a broader dysregulation in autonomic control and motivational processes, in line with the DBSR hypothesis.

4.3. Gambling Urges

Contrary to our prediction, based on the additive effects of stressor and cue-induced reactivity (Amlung & Mackillop, 2014a; Stojek et al., 2015), stressed individuals with GD did not report increased gambling urges post-stressor relative to the non-stressed group. This is in spite of past subjective reports of stressful events and negative affect motivating those with GD or with problem gambling (Ledgerwood & Petry, 2006; Tschibelu & Elman, 2010), and in contrast to studies in substance-based addictions reporting increased drug craving in cocaine use disorder patients in response to stress cues (Sinha et al., 1999). Alternatively, this effect could reflect methodological differences in the potency of a stress protocol, or an effect of negative urgency that differentially modulates reactivity to stress induction paradigms (Owens, Amlung, Stojek, & MacKillop, 2018).

Albeit non-significant, the non-stressed GD group reported an increase in gambling urges after the neurocognitive tasks. This could represent a boredom effect consistent with those who identify boredom as a trigger for craving (Cornil et al., 2018), whereby the no-stress control condition (sitting quietly and completing crossword puzzles) may potentiate the arousing effect of the neurocognitive tasks. This could reflect

the ecological validity of these neurocognitive tasks in mimicking real-life gambling situations (Buelow & Blaine, 2015; Buelow & Suhr, 2009; Lejuez et al., 2002), and in increasing gambling urges. Future work should attempt to explore this further with neurocognitive tasks that are longer in length and are separated by repeated measures.

5. Strengths, Limitations and Future Directions

This is the first study to explore the effects of acute stress on multiple indices of stress reactivity, and across two different risky decision-making measures. Although the overall sample is small, significant between-group differences and correlations were observed in the study. In addition, the sample size in the current study contains predominantly males, reflecting the increased prevalence rate of GD in men (Williams et al., 2012). However, it is increasingly relevant to explore sex and age-related influences on decision-making, risk-taking and stress reactivity systems. Furthermore, acute stress could affect the temporal dynamics between the release of cortisol and α-amylase (Engert et al., 2011), potentially influencing the timing of their release as well as its effects on both decision-making and risk-taking.

Future studies could also apply a gambling pathways model which describes three subtypes of gamblers, including behaviourally conditioned, emotionally vulnerable, and antisocial impulsivist, who differ in gambling preferences, motivations and processes (Blaszczynski & Nower, 2002). These gambling subtypes could show different relationships with stress responsivity, reward and punishment sensitivity, and decision-making. For example, the emotionally vulnerable problem gamblers report gambling to avoid and escape; whereas, the antisocial impulsivist display increased propensity

towards risk-taking and decreased sensitivity to rewards (Valleur et al., 2016). Additionally, given the heterogeneity of factors influencing decision-making, future studies can explore the contribution of other components towards impaired IGT performance, such as reversal learning and working memory (Dunn et al., 2006), as well as explore other facets, such as delay discounting and chasing behaviour, and how stress may relate to executive function and cognitive control (Brand et al., 2007; Kräplin et al., 2014). Finally, more neurobiological studies will be important to understand neural substrates mediating the stress response in GD.

6. Conclusion

Acute psychosocial stress induction revealed dysregulated SAM system reactivity and potentially altered HPA axis activity. Further, stressor-induced decrease in risk-taking suggests changes in risk/reward appraisal and performance monitoring, potentially as a result of decreased loss aversion. Overall, the findings of NE dysfunction and atered risk-taking may also be due a dysregulation in autonomic control and motivational processes, in line with the DBSR hypothesis. Future larger psychophysiological studies are needed to examine potential gambling subgroup differences as well as explore other facets of decision-making.

7. Acknowledgements

Dr. Potenza has consulted for Ironwood, Lundbeck, Shire, INSYS, Rivermend Health, Opiant/Lakelight Therapeutics, and Jazz Pharmaceuticals; has received research support (to Yale) from Pfizer, Mohegan Sun Casino and the National Centre for

Responsible Gaming; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for gambling and legal entities on issues related to impulse-control/addictive disorders; provides clinical care in a problem gambling services program; has performed grant reviews for the National Institutes of Health and other agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. The other authors have no disclosures.

Supplementary Materials

1. Participant Clinical Profiles

Participants were administered the SCID. In the GD group, one person reported current Major Depressive Disorder (MDD) and three reported past MDD. Of those with MDD, two reported recurrent episodes, one reported none and another single. Two people with GD reported current alcohol addiction with one of them also reporting current physiological dependence, and one reported current alcohol abuse; and, two people reported past alcohol addiction with one of them also reporting physiological dependence, and one reported past alcohol abuse. Two people with GD reported past sedative-hypnotic anxiolytic addiction and one reported abuse. Three people with GD reported past cannabis addiction, and four reported past abuse. One person with GD reported past opioid addiction with physiological dependence. Four individuals with GD reported past cocaine addiction with full sustained remission, and one reported past abuse with partial sustained remission. One person with GD reported past PCP/Hall abuse. Three people with GD reported current social phobia, subthreshold specific phobia and subthreshold Generalized Anxiety Disorder each. In the HC group, two people reported past MDD with recurrent or single episode each. Two HCs reported past alcohol addiction with one of them also reporting physiological dependence, and one reported past alcohol abuse. One HC reported past cannabis addiction and one reported abuse only. One HC reported past specific phobia.

2. Results

2.1. *POMS*

2.1.1. POMS Absolute TMD Scores

A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task TMD) repeated measures ANOVA was conducted. There was no main effect of group ($p > 0.05$). A main effect of condition ($F_{(2, 122)} = 4.15$, $p < 0.05$) showed significantly higher TMD scores in the stressed condition (95.07 ± 7.56) when compared to the non-stressed condition (74.57 ± 5.91). The test for within-subjects effects showed a significant difference across timepoints ($F_{(2, 122)} = 4.01$, $p < 0.05$, see **Fig.** 1A). TMD and condition displayed a significant interaction ($F_{(2, 122)} = 3.84$, $p < 0.05$). In addition, within-subject contrasts revealed a significant interaction between condition and TMD on the quadratic pattern of the TMD scores ($F_{(1, 61)} = 6.61$, $p < 0.05$). For post-hoc analyses of the different timepoints, HC and GD groups were collapsed across condition. Two paired t-tests in the stressed condition showed TMD scores were significantly different from post-stressor to post-task ($t = -3.15$, $p < 0.03$). Post-task TMD score (32.35 ± 16.99) was significantly lower than the score post-stressor (36.41 ± 18.20). Although the stressed group scored higher post-stressor when compared to the score at baseline (34.53 ± 16.43), this difference was not statistically significant ($p > 0.03$).

In order to explore the effects of the stress condition, two, separate, 2 condition x 3 timepoints repeated measures ANOVAs were conducted in the HC and GD groups. In the GD group, a main effect of condition depicted a trend ($F_{(1, 35)} = 4.\ 00$, $p = 0.053$)

where the stressed participants reported a higher TMD score (103.3 ± 46.8) than the non-stressed ones (76.10 ± 35.8). In the HC group, there was no main effect of condition ($p > 0.05$). Further, test of within-subjects effects revealed a significant difference in TMD across timepoints ($F_{(1.62, 42.1)} = 4.47$, $p < 0.05$), and a significant within-subjects interaction between TMD and condition ($F_{(1.62, 42.1)} = 7.92$, $p < 0.05$). The interaction between TMD and condition was significant ($F_{(1.62, 42.1)} = 7.92$, $p < 0.05$). Two paired t-tests in the stressed HC group showed TMD scores were significantly different from post-stressor to post-task ($t = -2.96$, $p < 0.03$). Post-task TMD score (22.54 ± 10.18) was significantly lower than the score post-stressor (34.38 ± 16.23). Although the stressed group scored higher post-stressor when compared to the score at baseline (27.38 ± 10.71), this difference was not statistically significant ($p > 0.03$).

2.1.2. POMS Subscales

Parametric repeated measures analyses were run on subscale scores that were normally distributed, and non-parametric tests were run to correct for non-normal distribution.

Anger-Hostility A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task TMD) repeated measures ANOVA revealed a between-subjects effect of group ($F_{(1, 61)} = 5.50$, $p < 0.05$), where the GD group (12.1 ± 0.87) reported significantly higher anger overall than the HC group (9.02 ± 1.00). Two follow-up 2x3 repeated measures ANOVA in the stressed and non-stressed conditions revealed a trend towards significantly higher scores in the GD group (13.5 ±

1.32) when compared to the HC group (9.49 ±1.51) across the stressed participants (p = 0.06). In order to explore differences between groups at each timepoint within the stressed condition, three-way ANOVAs, corrected for Bonferroni comparisons, were conducted. No main effect was seen in scores post-stressor and post-task; however, a trend was observed for scores at baseline ($F_{(1, 29)} = 5.29$, $p = 0.053$) which showed participants with GD (14.3 ± 6.75) reported higher anger-hostility when comparted to HCs (9.85 ± 5.40).

Vigour A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task TMD) repeated measures ANOVA revealed a between-subjects effect of group ($F_{(1, 61)} = 8.39$, $p < 0.01$). Two follow-up 2x3 repeated measures ANOVA revealed a between-subjects effect of group in the stressed condition ($F_{(1, 28)} = 5.29$, $p < 0.05$), where the GD group (7.45 ± 1.17) scored significantly higher than the HC group (3.36 ± 1.34); but, not in the non-stressed condition. In order to explore differences between groups at each timepoint within the stressed condition, two one-way ANOVAs were conducted for scores at baseline and at post-task, and a Mann U Whitney test was conducted for score post-stressor. At baseline, the GD group (7.06 ± 5.71) reported significantly higher vigour ($F_{(1, 29)} = 5.35$, $p_{(uncorrected)} < 0.05$) when compared to the HC group (3.00 ± 3.14). Further, the GD group (7.00 ± 6.37) also reported significantly higher vigour post-task (U = 164, $p_{(uncorrected)} < 0.05$) when compared to the HC group (3.62 ± 3.55).

Confusion-Bewilderment Two related-samples Friedman's two-way ANOVAs were conducted in stressed and non-stressed conditions. Post-hoc tests, significant in the

stressed condition (W = 12.93, $p < 0.01$), were driven by a significantly higher score on this scale at time 3 (0.632 ± 0.226) when compared to time 4 (0.531 ± 0.222). Further, four follow-up, Bonferroni-corrected, paired Wilcoxon Signed Ranks tests revealed that these differences were driven by significant differences post-stressor and baseline (W = -2.47, $p < 0.013$), and time post-stressor and post-task (W = -2.67, $p < 0.013$) in the stressed HC group. The stressed HC participants at post-stressor (7.65 ± 6.35) scored significantly higher than baseline (5.56 ± 6.15) and post-task (6.59 ± 6.28).

Tension-Anxiety A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task TMD) repeated measures ANOVA revealed a significant within-subjects interaction of Anxiety and condition ($F_{(2, 122)} = 4.02$, $p < 0.05$). To find out what drove the interaction, two one-way ANOVAs with Anxiety as a within-subject variable in the GD and HC groups were conducted. In the HC group, a within-subjects main effect of Anxiety ($F_{(2, 52)} = 3.86$, $p < 0.05$) was significant. In the GD group, there were no main effects of group, condition or an interaction ($p > 0.05$). However, a quadratic pattern for the Anxiety scores was significant on an interaction between TAs and condition ($F_{(1, 35)} = 6.29$).

Fatigue-Inertia This mixed model revealed a significant within-subjects effect on an interaction between Fatigue and Group ($F_{(2, 122)} = 3.88$, $p < 0.05$). A within-subjects contrast revealed that this interaction was significant for a linear trend of scores on this subscale ($F_{(1, 61)} = 7.22$, $p < 0.01$). A significant, within-subjects interaction between fatigue scores and group in the stressed condition drove this effect ($F_{(2, 56)} = 3.27$, $p < 0.05$).

Friendliness A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task TMD) repeated measures ANOVA did not reveal between or within effects of group, condition or an interaction ($p > 0.05$).

Depression A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task TMD) repeated measures ANOVA did not reveal any main effects of group, condition or an interaction ($p > 0.05$). A within-subjects interaction between depression and the stress condition was significant ($F_{(2, 122)} = 3.25$, $p < 0.05$).

Elation A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task TMD) repeated measures ANOVA did not reveal between or within effects of group, condition or an interaction ($p > 0.05$).

2.2. Physiological Measures

2.2.1. Cortisol

2.2.1.1. *Absolute Levels*

Non-parametric statistical tests were performed to correct for non-normal distribution. Collapsed across groups, two related-samples Friedman's two-way ANOVA conducted on the absolute cortisol values across three timepoints (baseline, post-stressor and post-task) were significant within the stressed ($\chi^2 = 15.70$, $p < 0.03$) and non-stressed conditions ($\chi^2 = 20.19$, $p < 0.03$). Three Bonferroni adjusted post-hoc tests conducted within the stressed condition showed that absolute levels of cortisol differed significantly

between baseline and post-stressor (χ^2 = -0.98, $p < 0.02$), and post-stressor and post-task (χ^2 = 0.78, $p < 0.02$). The stressed participants had significantly higher absolute cortisol values post-stressor (0.63 ± 0.22) when compared to values at baseline (0.47 ± 0.18), and to post-task (0.55 ± 0.23). In the non-stressed groups, three Bonferroni adjusted post-hoc tests showed that absolute levels of cortisol differed significantly between post-stressor and post-task (W = 0.96, $p < 0.02$), and between baseline and post-task (W = 0.89, $p < 0.02$).

In order to see what drove the effect, 8 paired Wilcoxon Signed-Rank tests, corrected for Bonferroni comparisons (0.05/8), were conducted across stressed and non-stressed GD and HC groups (**Fig.** 1B). The absolute cortisol values differed significantly between baseline and post-task in non-stressed GDs (W = -3.40, $p < 0.01$) and in non-stressed HCs (W = -2.89, $p = 0.01$). Across the stressed groups, the HCs scored significantly (W = -2.90, $p = 0.004$) higher post-stressor (0.69 ± 0.21) when compared to baseline (0.52 ± 0.21). The stressed GDs scored significantly (W = -2.34, $p_{(uncorrected)} = 0.019$) higher post-stressor (0.60 ± 0.22) when compared to baseline (0.45 ± 0.16); and significantly higher (W = -2.25, $p_{(uncorrected)} = 0.025$) post-stressor when compared to values post-task (0.50 ± 0.24).

2.2.1.2. *Area Under the Curve*

Area under the curve with respect to the ground (AUC_G) and with respect to increase (AUC_I) was calculated for cortisol samples at baseline, post-stressor and post-task. Two separate multivariate ANOVAs with AUC_G and AUC_I as dependent variables,

and condition and group as independent factors were conducted. A between-subjects effect of condition on AUC_I ($F_{(1, 60)} = 11.83$, $p < 0.03$) showed participants in the stressed condition had a significantly higher mean AUC_I (0.19 ± 0.32) when compared to those in the non-stressed condition (-0.04 ± 0.21). A between-subjects effect of condition on AUC_G ($F_{(1, 60)} = 11.53$, $p < 0.03$) showed the stressed condition had a significantly higher AUC_G (1.15 ± 0.36) when compared to the AUCG in the non-stressed condition (0.89 ± 0.29). There were no main effects of group or an interaction between group and condition ($p > 0.05$).

2.2.2. Alpha-amylase

2.2.2.1. *Absolute Levels*

A 2 group (GD, HC) x 2 condition (stress, non-stress) x 3 Timepoints (baseline, post-stressor, and post-task) repeated measures ANOVA was conducted. There was no main effect of group or condition, or an interaction between the two ($p > 0.05$). The test for within-subjects effects showed a significant difference across timepoints ($F_{(1.68, 122)} = 5.17$, $p < 0.05$, see **Fig.** 1C in paper). In order to explore the effects of the stress condition, two, separate, 2 condition x 3 timepoints repeated measures ANOVAs were conducted in the HC and GD groups. In the GD group, there was no main effect of condition ($p > 0.03$). The test for within-subjects effects showed a significant difference across timepoints ($F_{(1.60, 70.0)} = 3.17$, $p < 0.03$). In the HC group, there was no main effect of condition ($p > 0.05$). A test of within-subjects effects revealed a significant difference across timepoints ($F_{(2, 52)} = 4.60$, $p < 0.03$).

Finally, 4 Bonferroni-corrected, post-hoc paired samples t-tests were conducted across stressed HC and GD groups. In the stressed GD group, post-stressor and baseline ($t = -2.59$, $p_{(uncorrected)} < 0.05$), and post-stressor and post-task ($t = 2.52$, $p_{(uncorrected)} < 0.05$), α-amylase levels differed significantly. Levels of baseline α-amylase (49.05 ± 24.72) was significantly higher than the one post-stressor (38.50 ± 24.88), and post-task α-amylase levels (50.01 ± 27.78) were significantly higher than those post-stressor. In the stressed HC group, post-task levels of α-amylase (35.89 ± 16.72) were significantly higher ($t = 2.64$, $p_{(uncorrected)} < 0.05$) than the ones post-stressor (29.37 ± 11.81).

2.2.2.2. *Area Under the Curve*

To correct for non-normal distributions, non-parametrical statistical tests were performed. Collapsed across groups stressor-induced differences in α-amylase were not significant ($p > 0.05$). In order to explore stress responses by group, two additional Mann-Whitney U tests were conducted across HC and GD groups. In the GD group, stressed participants (-10.06 ± 24.03) had a significantly lower AUC_I ($U = 237$, $p_{(uncorrected)} < 0.05$) when compared to non-stressed ones (7.48 ± 30.37). The stressed and non-stressed HC groups did not differ from each other ($p > 0.05$).

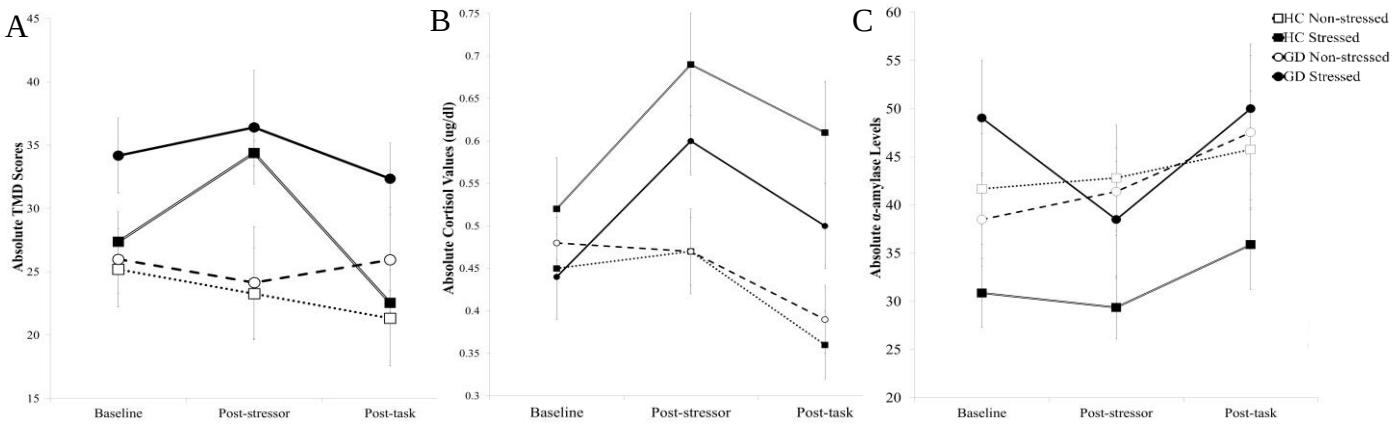

Figure 1 Absolute values of (A) self-reported TMD, (B) cortisol and (C) α-amylase across stressed and non-stressed conditions in HC and GD groups.

2.3. Neurocognitive Tasks

2.3.1. BART Performance

To correct for non-normality, non-parametric tests on the total Money earned were conducted in the HC and GD groups. The Mann-Whitney U tests did not reveal a significant effect of condition on the total Money earned in the HC group ($p > 0.05$). A significant effect of condition in the GD group ($U = 266$, $p < 0.05$) showed stressed participants (744 ± 307) earned less than the non-stressed ones (1023 ± 243) (Fig. 2A).

2.3.2. IGT Performance

The total number of selections made on decks B and D were normally distributed, and those made on decks A and C were non-normally distributed. A 2 group (HC, GD) x 2 condition (stress, non-stress) ANOVA was not significant on decks B and D ($p > 0.05$). Collapsed across stress conditions, two Bonferroni-corrected, Mann-Whitney U tests were conducted on decks A, and C. There was a significant effect of group on the number of choices made from decks C ($U = 298$, $p < 0.02$). To explore this main group effect,

post-hoc tests were run across the stress condition on total deck C selections. The groups did not differ across the non-stressed condition ($p > 0.03$). In the stressed condition, the HC group (30.08 ± 3.75) selected significantly higher cards from deck C (U = 105, $p < 0.03$, see Fig. 5A) when compared to the GD group (19.88 ± 2.24). Overall, the stressed GD group avoided the deck with a lower reward magnitude and a higher frequency of loss.

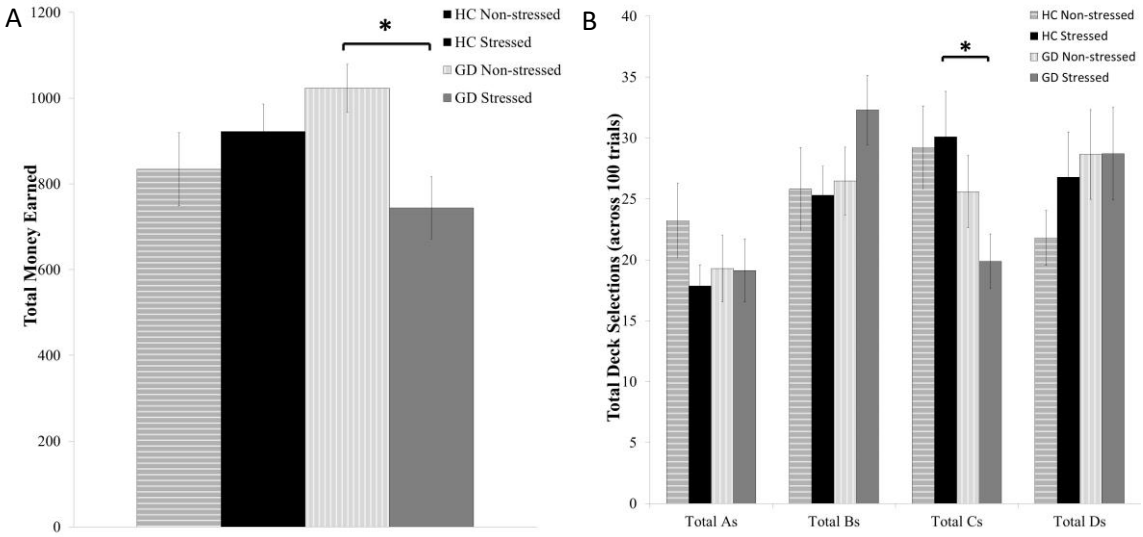

Figure 2 Performance on the BART and IGT. (A) Non-stressed GD group scored significantly higher than the stressed GD group; (B) Stressed HC group made significantly higher selections from deck C when compared to the stressed GD group. $p < 0.05$

2.4. Correlations

2.4.1. Correlations between subjective measures and physiological biomarkers

GD group In non-stressed GD group, a higher $\Delta cortisol_{post\text{-}stressor\%}$ was significantly associated with lower $\Delta TMD_{post\text{-}stressor}$ (r = -0.463, $p < 0.05$, n = 20) and significantly lower $\Delta cortisol_{post\text{-}task\%}$ (r = -0.665, $p < 0.01$, n = 20). In the stressed GD group, a higher

$\Delta\alpha\text{-amylase}_{\text{post-stressor\%}}$ was related to a significantly lower $\Delta\text{TMD}_{\text{post-task}}$ ($\tau b = -.468$, $p < 0.01$, n = 17).

HC group In the stressed HC group, higher $\Delta\alpha\text{-amylase}_{\text{post-stressor\%}}$ was significantly associated with lower $\Delta\alpha\text{-amylase}_{\text{post-task\%}}$ ($\tau b = -.468$, $p < 0.01$, n = 13).

2.4.2. Correlations between stress reactivity and neurocognitive tasks

GD group In the stressed GD group, higher $\Delta\text{cortisol}_{\text{post-task\%}}$ was significantly related to IGT scores in the pre-learning phase ($\tau b = 0.417$, $p < 0.05$, n = 16). In addition, in the stressed (r = 0.552, $p = 0.022$, n = 17) and non-stressed GD (r = 0.674, $p = 0.003$, n = 17) groups, higher IGT scores within the learning phase were significantly associated with higher IGT scores in block 2. Interestingly, in block 3, higher IGT scores were significantly related to high IGT scores within the learning phase in the non-stressed GD group only (r = 0.485, $p = 0.048$, n = 17).

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental Disorders. Text Revision.* (5th ed). American Psychiatric Association.

Aïte, A., Barrault, S., Cassotti, M., Borst, G., Bonnaire, C., Houdé, O., … Moutier, S. (2014). The impact of alexithymia on pathological gamblers' decision making: A preliminary study of gamblers recruited in "sportsbook" casinos. *Cognitive and Behavioral Neurology*, *27*(2), 59–67. https://doi.org/10.1097/WNN.0000000000000027

Alessi, S. M., & Petry, N. M. (2003). Pathological gambling severity is associated with impulsivity in a delay discounting procedure. *Behavioural Processes*, *64*(3), 345–354. https://doi.org/10.1016/S0376-6357(03)00150-5

Amlung, M., & Mackillop, J. (2014a). Clarifying the Relationship between Impulsive Delay Discounting and Nicotine Dependence. *Psychology of Addictive Behaviors*, *28*(3), 761–768. https://doi.org/10.1109/TMI.2012.2196707.Separate

Amlung, M., & Mackillop, J. (2014b). Understanding the effects of stress and alcohol cues on motivation for alcohol via behavioral economics. *Alcoholism: Clinical and Experimental Research*, *38*(6), 1780–1789. https://doi.org/10.1111/acer.12423

Areny Balagueró, M., Vicente, M. J., Molina, A. G., Tormos, J. M., & Roig Rovira, T. (2014). Balloon Analogue Risk Task to assess decision-making in Acquired Brain Injury. *Int.J.Psychol.Res*, *9*(1), 30–39.

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews. Neuroscience*, *10*(6), 410–422. https://doi.org/10.1038/nrn2648

Bagby, R. M., Vachon, D. D., Bulmash, E. L., Toneatto, T., Quilty, L. C., & Costa, P. T. (2007). Pathological gambling and the five-factor model of personality. *Personality and Individual Differences*, *43*(4), 873–880. https://doi.org/10.1016/j.paid.2007.02.011

Balodis, I. M., Wynne-Edwards, K. E., & Olmstead, M. C. (2010). The other side of the curve: Examining the relationship between pre-stressor physiological responses and stress reactivity. *Psychoneuroendocrinology*, *35*(9), 1363–1373. https://doi.org/10.1016/j.psyneuen.2010.03.011

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damageto human prefrontal cortex. *Cognition*, *50*(1–3), 7–15. https://doi.org/10.1016/0010-0277(94)90018-3

Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *19*(13), 5473–5481. https://doi.org/0270-6474/99/19135473-09$05.00/0

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science*, *275*(5304), 1293–1295. https://doi.org/10.1126/science.275.5304.1293

Bechara, A., Damasio, H., Tranel, D., Damasio, A. R., Bushnell, M. C., Matthews, P. M.,

& Rawlins, J. N. P. (1997). Deciding Advantageously Before Knowing the Advantageous Strategy. *Science*, *275*(5304), 1293–1295. https://doi.org/10.1126/science.275.5304.1293

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S. W., & Nathan, P. E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, *39*(4), 376–389. https://doi.org/10.1016/S0028-3932(00)00136-6

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*, *123*(11), 2189–2202. https://doi.org/10.1093/brain/123.11.2189

Black, D. W., Shaw, M., McCormick, B., & Allen, J. (2013). Pathological gambling: Relationship to obesity, self-reported chronic medical conditions, poor lifestyle choices, and impaired quality of life. *Comprehensive Psychiatry*, *54*(2), 97–104. https://doi.org/10.1016/j.comppsych.2012.07.001

Blaszczynski, A., & Nower, L. (2002). A pathways model of problem and pathological gambling. *Addiction*, *97*(5), 487–499. https://doi.org/10.1046/j.1360-0443.2002.00015.x

Bogg, T., Fukunaga, R., Finn, P. R., & Brown, J. W. (2012). Cognitive control links alcohol use, trait disinhibition, and reduced cognitive capacity: Evidence for medial prefrontal cortex dysregulation during reward-seeking behavior. *Drug and Alcohol Dependence*, *122*(1–2), 112–118. https://doi.org/10.1016/j.drugalcdep.2011.09.018

Boileau, I., Payer, D., Chugani, B., Lobo, D., Behzadi, A., Rusjan, P. M., … Zack, M. (2013). The D2/3 dopamine receptor in pathological gambling: A positron emission tomography study with [11C]-(+)-propyl-hexahydro-naphtho-oxazin and [11C]raclopride. *Addiction*, *108*(5), 953–963. https://doi.org/10.1111/add.12066

Boileau, I., Payer, D., Chugani, B., Lobo, D. S. S., Houle, S., Wilson, A. A., … Zack, M. (2013). In vivo evidence for greater amphetamine-induced dopamine release in pathological gambling: a positron emission tomography study with [(11)C]-(+)-PHNO. *Molecular Psychiatry*, *19*(12), 1–9. https://doi.org/10.1038/mp.2013.163

Bowden-Jones, H., McPhillips, M., Rogers, R., Hutton, S., & Joyce, E. (2005). Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(3), 417–420. https://doi.org/10.1176/appi.neuropsych.17.3.417

Brand, M., Labudda, K., & Markowitsch, H. J. (2006). Neuropsychological correlates of decision-making in ambiguous and risky situations. *Neural Networks*, *19*(8), 1266–1276. https://doi.org/10.1016/j.neunet.2006.03.001

Brand, M., Recknor, E. C., Grabenhorst, F., & Bechara, A. (2007). Decisions under ambiguity and decisions under risk: Correlations with executive functions and comparisons of two different gambling tasks with implicit and explicit rules. *Journal of Clinical and Experimental Neuropsychology*, *29*(1), 86–99. https://doi.org/10.1080/13803390500507196

Brevers, D., Cleeremans, A., Goudriaan, A. E., Bechara, A., Kornreich, C., Verbanck, P., & Noël, X. (2012). Decision making under ambiguity but not under risk is related to

problem gambling severity. *Psychiatry Research*, *200*(2–3), 568–574.
Buelow, M. T., & Blaine, A. L. (2015). The Assessment of Risky Decision Making : A Factor Analysis of Performance on the Iowa Gambling Task , Balloon Analogue Risk Task, and Columbia Card Task. *American Psychological Associaton*, *27*(3), 777–785. https://doi.org/10.1037/a0038622
Buelow, M. T., & Suhr, J. A. (2009). Construct validity of the Iowa gambling task. *Neuropsychology Review*, *19*(1), 102–114. https://doi.org/10.1007/s11065-009-9083-4
Bull, P. N., Tippett, L. J., & Addis, D. R. (2015). Decision making in healthy participants on the Iowa Gambling Task: New insights from an operant approach. *Frontiers in Psychology*, *6*, 391. https://doi.org/10.3389/fpsyg.2015.00391
Carroll, D., Ginty, A. T., & Phillips, A. C. (2016). The Behavioral, Cognitive, and Neural Correlates of Deficient Biological Reactions to Acute Psychological Stress. In *Stress: Concepts, Cognition, Emotion, and Behavior* (pp. 187-194).
Cavedini, P., Riboldi, G., Keller, R., D'Annucci, A., & Bellodi, L. (2002). Frontal lobe dysfunction in pathological gambling patients. *Biological Psychiatry*, *51*(4), 334–341. https://doi.org/10.1016/S0006-3223(01)01227-6
Chiba, S., Numakawa, T., Ninomiya, M., Richards, M. C., Wakabayashi, C., & Kunugi, H. (2012). Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *39*(1), 112–119. https://doi.org/10.1016/j.pnpbp.2012.05.018
Clark, L., Li, R., Wright, C. M., Rome, F., Fairchild, G., Dunn, B. D., & Aitken, M. R. F. (2012). Risk-avoidant decision making increased by threat of electric shock. *Psychophysiology*, *49*(10), 1436–1443. https://doi.org/10.1111/j.1469-8986.2012.01454.x
Clark, L., & Manes, F. (2004). Social and emotional decision-making following frontal lobe injury. *Neurocase*, *10*(5), 398–403. https://doi.org/10.1080/13554790490882799
Cornil, A., Lopez-Fernandez, O., Devos, G., De Timary, P., Goudriaan, A. E., & Billieux, J. (2018). Exploring gambling craving through the Elaborated Intrusion Theory of desire: A mixed methods approach. *International Gambling Studies*, *9795*, 1–21. https://doi.org/10.1080/14459795.2017.1368686
Cuttler, C., Spradlin, A., Nusbaum, A. T., Whitney, P., Hinson, J. M., & McLaughlin, R. J. (2017). Blunted stress reactivity in chronic cannabis users. *Psychopharmacology*, *234*(15), 2299–2309. https://doi.org/10.1007/s00213-017-4648-z
Daughters, S. B., Lejuez, C. W., Strong, D. R., Brown, R. A., Breen, R. B., & Lesieur, H. R. (2005). The relationship among negative affect, distress tolerance, and length of gambling abstinence attempt. *Journal of Gambling Studies*, *21*(4), 363–378. https://doi.org/10.1007/s10899-005-5554-6
DeLongis, a, Folkman, S., & Lazarus, R. S. (1988). The impact of daily stress on health and mood: Psychological and social resources as mediators. *Journal of Personality and Social Psychology*, *54*(3), 486–495. https://doi.org/10.1037/0022-3514.54.3.486

Devos, G., Clark, L., Maurage, P., & Billieux, J. (2018). Induced sadness increases persistence in a simulated slot machine task among recreational gamblers. *Psychology of Addictive Behaviors*, *32*(3), 383–388. https://doi.org/10.1037/adb0000364

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, *130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

Dowling, N. A., Cowlishaw, S., Jackson, A. C., Merkouris, S. S., Francis, K. L., & Christensen, D. R. (2015). Prevalence of psychiatric co-morbidity in treatment-seeking problem gamblers: A systematic review and meta-analysis. *Australian and New Zealand Journal of Psychiatry*, *49*(6), 519–539. https://doi.org/10.1177/0004867415575774

Dunn, B. D., Dalgleish, T., & Lawrence, A. D. (2006). The somatic marker hypothesis: A critical evaluation. *Neuroscience and Biobehavioral Reviews*, *30*(2), 239–271. https://doi.org/10.1016/j.neubiorev.2005.07.001

Ehrhart-bornstein, M., & Bornstein, S. R. (2008). Cross-talk between Adrenal Medulla and Adrenal Cortex in Stress. *Annals of the New York Academy of Sciences*, *1148*(1), 112–117. https://doi.org/10.1196/annals.1410.053

El-Guebaly, N., Patten, S. B., Currie, S., Williams, J. V. A., Beck, C. A., Maxwell, C. J., & Wang, J. L. (2006). Epidemiological associations between gambling behavior, substance use & mood and anxiety disorders. *Journal of Gambling Studies*, *22*(3), 275–287. https://doi.org/10.1007/s10899-006-9016-6

Elman, I., Tschibelu, E., & Borsook, D. (2010). Psychosocial stress and its relationship to gambling urges in individuals with pathological gambling. *American Journal on Addictions*, *19*(4), 332–339. https://doi.org/10.1111/j.1521-0391.2010.00055.x

Engert, V., Vogel, S., Efanov, S. I., Duchesne, A., Corbo, V., Ali, N., & Pruessner, J. C. (2011). Investigation into the cross-correlation of salivary cortisol and alpha-amylase responses to psychological stress. *Psychoneuroendocrinology*, *36*(9), 1294–1302. https://doi.org/10.1016/j.psyneuen.2011.02.018

Erickson, K., Drevets, W., & Schulkin, J. (2003). Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neuroscience and Biobehavioral Reviews*, *27*(3), 233–246. https://doi.org/10.1016/S0149-7634(03)00033-2

Franken, I. H. A., & Muris, P. (2005). Individual differences in decision-making. *Personality and Individual Differences*, *39*(5), 991–998. https://doi.org/10.1016/j.paid.2005.04.004

Fukunaga, R., Brown, J. W., & Bogg, T. (2012). Decision making in the Balloon Analogue Risk Task (BART): Anterior cingulate cortex signals loss aversion but not the infrequency of risky choices. *Cognitive, Affective and Behavioral Neuroscience*, *12*(3), 479–490. https://doi.org/10.3758/s13415-012-0102-1

Gelskov, S. V., Madsen, K. H., Ramsøy, T. Z., & Siebner, H. R. (2016). Aberrant neural signatures of decision-making: Pathological gamblers display cortico-striatal hypersensitivity to extreme gambles. *NeuroImage*, *128*, 342–352. https://doi.org/10.1016/j.neuroimage.2016.01.002

Gianferante, D., Thoma, M. V., Hanlin, L., Chen, X., Breines, J. G., Zoccola, P. M., & Rohleder, N. (2014). Post-stress rumination predicts HPA axis responses to repeated acute stress. *Psychoneuroendocrinology*, *49*(1). https://doi.org/10.1016/j.psyneuen.2014.07.021

Ginty, A. T., Phillips, A. C., Higgs, S., Heaney, J. L. J., & Carroll, D. (2012). Disordered eating behaviour is associated with blunted cortisol and cardiovascular reactions to acute psychological stress. *Psychoneuroendocrinology*, *37*(5), 715–724. https://doi.org/10.1016/j.psyneuen.2011.09.004

Goeders, N. E. (2003). The impact of stress on addiction. *European Neuropsychopharmacology*, *13*(6), 435–441. https://doi.org/10.1016/j.euroneuro.2003.08.004

Goldstein, R. Z., & Volkow, N. D. (2002). Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex. *Amer*, *159*(October), 1642–1652. Retrieved from http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.159.10.1642

Goudriaan, A. E., Oosterlaan, J., de Beurs, E., & van den Brink, W. (2006). Psychophysiological determinants and concomitants of deficient decision making in pathological gamblers. *Drug and Alcohol Dependence*, *84*(3), 231–239.

Goudriaan, A. E., Oosterlaan, J., De Beurs, E., & Van Den Brink, W. (2005). Decision making in pathological gambling: A comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. *Cognitive Brain Research*, *23*(1), 137–151. https://doi.org/10.1016/j.cogbrainres.2005.01.017

Grant, J. E., Steinberg, M. A., Kim, S. W., Rounsaville, B. J., & Potenza, M. N. (2004). Preliminary validity and reliability testing of a structured clinical interview for pathological gambling. *Psychiatry Research*, *128*(1), 79–88. https://doi.org/10.1016/j.psychres.2004.05.006

Heaney, J. L. J., Ginty, A. T., Carroll, D., & Phillips, A. C. (2011). Preliminary evidence that exercise dependence is associated with blunted cardiac and cortisol reactions to acute psychological stress. *International Journal of Psychophysiology*, *79*(2), 323–329. https://doi.org/10.1016/j.ijpsycho.2010.11.010

Hewig, J., Kretschmer, N., Trippe, R. H., Hecht, H., Coles, M. G. H., Holroyd, C. B., & Miltner, W. H. R. (2010). Hypersensitivity to Reward in Problem Gamblers. *Biological Psychiatry*, *67*(8), 781–783. https://doi.org/10.1016/j.biopsych.2009.11.009

Hodgins, D. C., & el-Guebaly, N. (2010). The influence of substance dependence and mood disorders on outcome from pathological gambling: Five-Year follow-up. *Journal of Gambling Studies*, *26*(1), 117–127. https://doi.org/10.1007/s10899-009-9137-9

Hodgins, D. C., Shead, N. W., & Makarchuk, K. (2007). Relationship satisfaction and psychological distress among concerned significant others of pathological gamblers. *Journal of Nervous and Mental Disease*, *195*(1), 65–71. https://doi.org/10.1097/01.nmd.0000252382.47434.a6

Jaferi, A., & Bhatnagar, S. (2007). Corticotropin-releasing-hormone Receptors in the Medial Prefrontal Cortex Regulate Hypothalamic-Pituitary-Adrenal Activity and

Anxiety-Related Behaviour Regardsess of Prior Stress Experience. *Brain Research*, *1186*, 212–223. https://doi.org/10.1016/j.immuni.2010.12.017.Two-stage

Kirschbaum, C., Pirke, K.-M., & Hellhammer, D. H. (1993). The "Trier Social Stress Test" - A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology*, *28*, 76–81.

Koob, G. F. (1999). Corticotopin-Releasing Factor, Norephinephrine, and Stress. *Biological Psychiatry*, *46*(9), 1167–1180. https://doi.org/10.1016/j.bbagen.2009.07.018

Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, *24*(2), 97–129. https://doi.org/10.1016/S0893-133X(00)00195-0

Koob, G., & Kreek, M. J. (2007). Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *American Journal of Psychiatry*, *164*(8), 1149–1159. https://doi.org/10.1176/appi.ajp.2007.05030503

Kräplin, A., Dshemuchadse, M., Behrendt, S., Scherbaum, S., Goschke, T., & Bühringer, G. (2014). Dysfunctional decision-making in pathological gambling: Pattern specificity and the role of impulsivity. *Psychiatry Research*, *215*(3), 675–682. https://doi.org/10.1016/j.psychres.2013.12.041

Krueger, T. H. C., Schedlowski, M., & Meyer, G. (2005). Cortisol and Heart Rate Measures during Casino Gambling in Relation to Impulsivity. *Neuropsychobiology*, *52*(4), 206–211. https://doi.org/https://doi.org/10.1159/000089004

Labudda, K., Wolf, O. T., Markowitsch, H. J., & Brand, M. (2007). Decision-making and neuroendocrine responses in pathological gamblers. *Psychiatry Research*, *153*(3), 233–243. https://doi.org/10.1016/j.psychres.2007.02.002

Ledgerwood, D. M., & Petry, N. M. (2006). Psychological experience of gambling and subtypes of pathological gamblers. *Psychiatry Research*, *144*(1), 17–27. https://doi.org/10.1016/j.psychres.2005.08.017

Lejuez, C. W., Aklin, W. M., Jones, H. A., Strong, D. R., Richards, J. B., Kahler, C. W., & Read, J. P. (2003). The Balloon Analogue Risk Task (BART) differentiates smokers and nonsmokers. *Experimental and Clinical Psychopharmacology*, *11*(1), 26–33. https://doi.org/10.1037//1064-1297.11.1.26

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., … Brown, R. a. (2002). Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology. Applied*, *8*(2), 75–84. https://doi.org/10.1037/1076-898X.8.2.75

Lejuez, C. W., Simmons, B. L., Aklin, W. M., Daughters, S. B., & Dvir, S. (2004). Risk-taking propensity and risky sexual behavior of individuals in residential substance use treatment. *Addictive Behaviors*, *29*(8), 1643–1647. https://doi.org/10.1016/j.addbeh.2004.02.035

Lesieur, H. R., & Blume, S. B. (1987). The South Oaks Gambling Screen (SOGS): A new instrument for the identification of pathological gamblers. *American journal of Psychiatry*, *144*(9).

Lighthall, N. R., Mather, M., & Gorlick, M. A. (2009). Acute stress increases sex differences in risk seeking in the Balloon Analogue Risk Task. *PLoS ONE*, *4*(7).

https://doi.org/10.1371/journal.pone.0006002

Lighthall, N. R., Sakaki, M., Vasunilashorn, S., Nga, L., Somayajula, S., Chen, E. Y., … Mather, M. (2012). Gender differences in reward-related decision processing under stress. *Social Cognitive and Affective Neuroscience*, *7*(4), 476–484. https://doi.org/10.1093/scan/nsr026

Linnet, J., Møller, A., Peterson, E., Gjedde, A., & Doudet, D. (2011). Inverse association between dopaminergic neurotransmission and Iowa Gambling Task performance in pathological gamblers and healthy controls. *Scandinavian Journal of Psychology*, *52*(1), 28–34. https://doi.org/10.1111/j.1467-9450.2010.00837.x

Linnet, J., RØjskjÆr, S., Nygaard, Jø., & Maher, B. A. (2006). Episodic chasing in pathological gamblers using the Iowa gambling task. *Scandinavian Journal of Psychology*, *47*(1), 43–49. https://doi.org/10.1111/j.1467-9450.2006.00491.x

Lovallo, W. R. (2004). *Stress and Health: Biological and Psychological Interactions*. SAGE Publications.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Maniaci, G., Goudriaan, A. E., Cannizzaro, C., & van Holst, R. J. (2018). Impulsivity and Stress Response in Pathological Gamblers During the Trier Social Stress Test. *Journal of Gambling Studies*, *34*(1), 147–160. https://doi.org/10.1007/s10899-017-9685-3

McEwen, B. S. (2000). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsychopharmacology*, *22*(2), 108–124. https://doi.org/10.1016/S0893-133X(99)00129-3

McEwen, B. S. (2002). The neurobiology and neuroendocrinology of stress implications for post-traumatic stress disorder from a basic science perspective. *Psychiatric Clinics of North America*, *25*(2), 469–494. https://doi.org/10.1016/S0193-953X(01)00009-0

McEwen, B. S., & Stellar, E. (1993). Stress and the Individual. *Archives of Internal Medicine*, *153*(18), 2093–2101.

McNair, D. M. (1971). *Manual profile of mood states*. Educational & Industrial testing service.

Meyer, G., Hauffa, B. P., Schedlowski, M., Pawlak, C., Stadler, M. A., & Exton, M. S. (2000). Casino gambling increases heart rate and salivary cortisol in regular gamblers. *Biological Psychiatry*, *48*(9), 948–953. https://doi.org/10.1016/S0006-3223(00)00888-X

Meyer, G., Schwertfeger, J., Exton, M. S., Janssen, O. E., Knapp, W., Stadler, M. A., … Krüger, T. H. C. (2004). Neuroendocrine response to casino gambling in problem gamblers. *Psychoneuroendocrinology*, *29*(10), 1272–1280. https://doi.org/10.1016/j.psyneuen.2004.03.005

Morasco, B. J., Pietrzak, R. H., Blanco, C., Grant, B. F., Hasin, D., & Petry, N. M. (2006). Health problems and medical utilization associated with gambling disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med*, *68*(6), 976–984.

https://doi.org/10.1097/01.psy.0000238466.76172.cd

Nater, U. M., La Marca, R., Florin, L., Moses, A., Langhans, W., Koller, M. M., & Ehlert, U. (2006). Stress-induced changes in human salivary alpha-amylase activity - Associations with adrenergic activity. *Psychoneuroendocrinology*, *31*(1), 49–58. https://doi.org/10.1016/j.psyneuen.2005.05.010

Nater, U. M., & Rohleder, N. (2009). Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: Current state of research. *Psychoneuroendocrinology*, *34*(4), 486–496. https://doi.org/10.1016/j.psyneuen.2009.01.014

Nielson, K. A., Langenecker, S. A., & Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. *Psychol Aging*, *17*(1), 56–71. https://doi.org/10.1037//0882-7974.17.1.56

O'Doherty, J. P., Cockburn, J., & Pauli, W. M. (2017). Learning, Reward, and Decision Making. *Annual Review of Psychology*, *68*(1), 73–100. https://doi.org/10.1146/annurev-psych-010416-044216

Owens, M. M., Amlung, M. T., Stojek, M., & MacKillop, J. (2018). Negative urgency moderates reactivity to laboratory stress inductions. *Journal of Abnormal Psychology*, *127*(4), 385–393. https://doi.org/10.1037/abn0000350

Pabst, S., Brand, M., & Wolf, O. T. (2013). Stress effects on framed decisions: there are differences for gains and losses. *Frontiers in Behavioral Neuroscience*, *7*, 142. https://doi.org/10.3389/fnbeh.2013.00142

Paris, J. J., Franco, C., Sodano, R., Frye, C. A., & Wulfert, E. (2010). Gambling Pathology is Associated with Dampened Cortisol Response Among Men and Women. *Physiological Behaviour*, *76*(2), 211–220. https://doi.org/10.1007/s11103-011-9767-z.Plastid

Phelps, E. a, Lempert, K. M., & Sokol-Hessner, P. (2014). Emotion and Decision Making: Multiple Modulatory Neural Circuits. *Annual Review of Neuroscience*, 263–290. https://doi.org/10.1146/annurev-neuro-071013-014119

Porcelli, A. J., Lewis, A. H., & Delgado, M. R. (2012). Acute stress influences neural circuits of reward processing. *Frontiers in Neuroscience*, *6*(NOV), 1–9. https://doi.org/10.3389/fnins.2012.00157

Potenza, M. N., Leung, H.-C., Blumberg, H. P., Peterson, B. S., Fulbright, R. K., Lacadie, C. M., … Gore, J. C. (2003). An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *The American Journal of Psychiatry*, *160*(11), 1990–1994. https://doi.org/10.1176/appi.ajp.160.11.1990

Potenza, M. N., Steinberg, M. A., Skudlarski, P., Fulbright, R. K., Lacadie, C. M., Wilber, M. K., … Wexler, B. E. (2003). Gambling urges in pathological gambling. *Archives of General Psychiatry*, *60*(8), 828–836. https://doi.org/10.1001/archpsyc.60.8.828

Preston, S. D., Buchanan, T. W., Stansfield, R. B., & Bechara, a. (2007). Effects of anticipatory stress on decision making in a gambling task. *Behavioral Neuroscience*, *121*(2), 257–263. https://doi.org/10.1037/0735-7044.121.2.257

Radley, J. J., Arias, C. M., & Sawchenko, P. E. (2006). Regional differentiation of the medial prefrontal cortex in regulating adaptive responses to acute emotional stress.

The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, *26*(50), 12967–12976. https://doi.org/10.1523/JNEUROSCI.4297-06.2006

Raylu, N., & Oei, T. P. S. (2004). The Gambling Urge Scale: Development, Confirmatory Factor Validation, and Psychometric Properties. *Addiction*, *99*(6), 757–769. https://doi.org/10.1111/j.1360-0443.2004.00753.x

Reuter, J., Raedler, T., Rose, M., Hand, I., Gläscher, J., & Büchel, C. (2005). Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience*, *8*(2), 147–148. https://doi.org/10.1038/nn1378

Rohleder, N., Nater, U. M., Wolf, J. M., Ehlert, U., & Kirschbaum, C. (2004). Psychosocial stress-induced activation of salivary alpha-amylase: An indicator of sympathetic activity? *Annals of the New York Academy of Sciences*, *1032*(1), 258–263. https://doi.org/10.1196/annals.1314.033

Schwabe, L., Höffken, O., Tegenthoff, M., & Wolf, O. T. (2013). Stress-induced enhancement of response inhibition depends on mineralocorticoid receptor activation. *Psychoneuroendocrinology*, *38*(10), 2319–2326. https://doi.org/10.1016/j.psyneuen.2013.05.001

Selye, H. (1950). Allergy and the general adaptation syndrome. *British Medical Journal*, *1*(4667), 1383–1392. https://doi.org/10.1159/000227975

Sinha, R. (2008). Chronic Stress, Drug Use, and Vulnerability to Addiction Rajita. *Annals of the New York Academy of Sciences*, *1141*, 105–130. https://doi.org/10.1196/annals.1441.030.Chronic

Sinha, R., Catapano, D., & O'Malley, S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology*, *142*(4), 343–351. https://doi.org/10.1007/s002130050898

Sinha, R., Fox, H. C., Hong, K. A., Bergquist, K., Bhagwagar, Z., & Siedlarz, K. M. (2009). Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. *Neuropsychopharmacology*, *34*(5), 1198–1208. https://doi.org/10.1038/npp.2008.78

Sinha, R., Fox, H. C., Hong, K. I. A., Hansen, J., Tuit, K., & Kreek, M. J. (2011). Effects of adrenal sensitivity, stress- and cue-induced craving,and anxiety on subsequent alcohol relapse and treatment outcomes. *Archives of General Psychiatry*, *68*(9), 942–952. https://doi.org/10.1001/archgenpsychiatry.2011.49

Sinha, R., Talih, M., Malison, R., Cooney, N., Anderson, G. M., & Kreek, M. J. (2003). Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology*, *170*(1), 62–72. https://doi.org/10.1007/s00213-003-1525-8

St. Onge, J. R., & Floresco, S. B. (2010). Prefrontal cortical contribution to risk-based decision making. *Cerebral Cortex*, *20*(8), 1816–1828. https://doi.org/10.1093/cercor/bhp250

Steingroever, H., Wetzels, R., Horstmann, A., Neumann, J., & Wagenmakers, E. J. (2013). Performance of healthy participants on the Iowa Gambling Task. *Psychological Assessment*, *25*(1), 180–193. https://doi.org/10.1037/a0029929

Stojek, M. K., Fischer, S., & MacKillop, J. (2015). Stress, cues, and eating behavior. Using drug addiction paradigms to understand motivation for food. *Appetite*, *92*,

252–260. https://doi.org/10.1016/j.appet.2015.05.027
Thayer, J. F., Hall, M., Sollers, J. J., & Fischer, J. E. (2006). Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. *International Journal of Psychophysiology*, *59*(3), 244–250. https://doi.org/10.1016/j.ijpsycho.2005.10.013
Thoma, M. V., Kirschbaum, C., Wolf, J. M., & Rohleder, N. (2012). Acute stress responses in salivary alpha-amylase predict increases of plasma norepinephrine. *Biological Psychology*, *91*(3), 342–348. https://doi.org/10.1016/j.biopsycho.2012.07.008
Tschibelu, E., & Elman, I. (2010). Gender Differences in Psychosocial Stress and in Its Relationship to Gambling Urges in Individuals with Pathological Gambling. *Journal of Addictive Diseases*, *30*(1), 81–87. https://doi.org/10.1080/10550887.2010.531671
Upton, D. J., Bishara, A. J., Ahn, W. Y., & Stout, J. C. (2011). Propensity for risk taking and trait impulsivity in the Iowa Gambling Task. *Personality and Individual Differences*, *50*(4), 492–495. https://doi.org/10.1016/j.paid.2010.11.013
Valleur, M., Codina, I., Vénisse, J. L., Romo, L., Magalon, D., Fatséas, M., … Challet-Bouju, G. (2016). Towards a validation of the three pathways model of pathological gambling. *Journal of Gambling Studies*, *32*(2), 757–771. https://doi.org/10.1007/s10899-015-9545-y
van den Bos, R., Harteveld, M., & Stoop, H. (2009). Stress and decision-making in humans: Performance is related to cortisol reactivity, albeit differently in men and women. *Psychoneuroendocrinology*, *34*(10), 1449–1458. https://doi.org/10.1016/j.psyneuen.2009.04.016
van Hedger, K., Bershad, A. K., & de Wit, H. (2017). Pharmacological challenge studies with acute psychosocial stress. *Psychoneuroendocrinology*, *85*(August), 123–133. https://doi.org/10.1016/j.psyneuen.2017.08.020
van Honk, J., Schutter, D. J. L. G., Hermans, E. J., & Putman, P. (2003). Low cortisol levels and the balance between punishment sensitivity and reward dependency. *Neuroreport*, *14*(15), 1993–1996. https://doi.org/10.1097/01.wnr.0000091690.72892.ec
Verdejo-Garcia, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Decision-Making and the Iowa Gambling Task: Ecological validity in individuals with substance dependence. *Psychologica Belgica*, *46*(1–2), 55. https://doi.org/10.5334/pb-46-1-2-55
Watt, M. J., Weber, M. A., Davies, S. R., & Forster, G. L. (2017). Impact of juvenile chronic stress on adult cortico-accumbal function: Implications for cognition and addiction. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *79*, 136–154. https://doi.org/10.1016/j.pnpbp.2017.06.015
Williams, R. J., Vohlberg, R. A., & Stevens, R. M. G. (2012). *The Population Prevalence of Problem Gambling: Methodological Influences, Standardized Rates, Jurisdictional Differences, and Worldwide Trends*.
Wise, R. A. (1996). Neurobiology of Addiction. *Neurobiology of Addiction*, *6*, 243–251. https://doi.org/10.1016/B978-0-12-419239-3.X5036-X
Zack, M., Boileau, I., Payer, D., Chugani, B., Lobo, D. S., Houle, S., … Kish, S. J.

(2015). Differential cardiovascular and hypothalamic pituitary response to amphetamine in male pathological gamblers versus healthy controls. *Journal of Psychopharmacology*, *29*(9), 971–982. https://doi.org/10.1177/0269881115592338

Zack, M., Woodford, T. M., Tremblay, A. M., Steinberg, L., Zawertailo, L. A., & Busto, U. E. (2011). Stress and alcohol cues exert conjoint effects on go and stop signal responding in male problem drinkers. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *36*(2), 445–458. https://doi.org/10.1038/npp.2010.177

Zack, M., & Poulos, C. X. (2007). A D2 antagonist enhances the rewarding and priming effects of a gambling episode in pathological gamblers. *Neuropsychopharmacology*, *32*(8), 1678.

Zorn, J. V., Schür, R. R., Boks, M. P., Kahn, R. S., Joëls, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *77*, 25–36. https://doi.org/10.1016/j.psyneuen.2016.11.036