



Cued for risk: Evidence for an incentive sensitization framework to explain the interplay between stress and anxiety, substance abuse, and reward uncertainty in disordered gambling behavior

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Abstract

Gambling disorder is an impairing condition confounded by psychiatric co-morbidity, particularly with substance use and anxiety disorders. Yet, our knowledge of the mechanisms that cause these disorders to coalesce remains limited. The Incentive Sensitization Theory suggests that sensitization of neural “wanting” pathways, which attribute incentive salience to rewards and their cues, is responsible for the excessive desire for drugs and cue-triggered craving. The resulting hyper-reactivity of the “wanting” system is believed to heavily influence compulsive drug use and relapse. Notably, evidence for sensitization of the mesolimbic dopamine pathway has been seen across gambling and substance use, as well as anxiety and stress-related pathology, with stress playing a major role in relapse. Together, this evidence highlights a phenomenon known as cross-sensitization, whereby sensitization to stress, drugs, or gambling behaviors enhance the sensitivity and dopaminergic response to any of those stimuli. Here, we review the literature on how cue attraction and reward uncertainty may underlie gambling pathology, and examine how this framework may advance our understanding of co-morbidity with substance-use disorders (e.g., alcohol, nicotine) and anxiety disorders. We argue that reward uncertainty, as seen in slot machines and games of chance, increases dopaminergic activity in the mesolimbic pathway and enhances the incentive value of reward cues. We propose that incentive sensitization by reward uncertainty may interact with and predispose individuals to drug abuse and stress, creating a mechanism through which co-morbidity of these disorders may emerge.

Keywords Addiction · Gambling · Anxiety · Incentive Sensitization · Nicotine · Alcohol

Introduction

Gambling is a global health concern affecting nearly 1.8 billion individuals worldwide (Shaffer & Hall, 2001). The legalization of gambling across much of the USA has made these activities more readily accessible, from scratch cards in convenience stores to slot machine simulations online and on smartphones (King, Delfabbro, Zwaans, & Kaptsis, 2013; Petry & Blanco, 2013). In the USA, 85% of adults engage in gambling at some point in their lifetime (Cunningham-

Williams et al., 2005; Kessler et al., 2008; Shaffer & Hall, 2001). For most, gambling is a pastime that occurs in various social contexts; however, for a subset of individuals, gambling behavior becomes a debilitating and costly activity (Slutske, Piasecki, Blaszczyński, & Martin, 2010; Slutske, Zhu, Meier, & Martin, 2011). Gambling disorder (GD) is a behavioral addiction characterized by persistent and recurrent gambling behavior that is problematic and impairs quality of life (American Psychiatric Association, 2013; J. E. Grant, Williams, & Kim, 2006). The estimated prevalence of GD parallels that of other major psychiatric disorders like schizophrenia (1.1%), obsessive compulsive disorder (1.0%), and anorexia (0.6%), with an average prevalence rate of approximately 2.3% across countries (Kessler, Chiu, Demler, & Walters, 2005; Kessler et al., 2008). Furthermore, subclinical gambling is estimated to impact approximately 12% of the population (Cunningham-Williams et al., 2005; Kessler et al., 2008), and thus gambling pathology represents a particularly widespread behavioral health concern.

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The prevalence of gambling pathology is particularly alarming considering the significant financial, social, mental, and physical impairments strongly associated with clinical and subthreshold gambling behavior (Potenza, Fiellin, Heninger, Rounsaville, & Mazure, 2002). Substantial financial losses are often accompanied by poor work performance, job loss, and bankruptcy, further increasing the financial burden of gambling on the individual and society (Gerstein, Hoffmann, & Larison, 1999). Individuals with gambling pathology report significantly higher rates of suicidal ideation, suicide attempts, divorce, arrest, spousal abuse, smoking, and physical health concerns, such as cardiac arrest (Petry & Kiluk, 2002; Petry, Stinson, & Grant, 2005; Potenza et al., 2002; Weinberger et al., 2015). Furthermore, gambling disorder frequently co-occurs with substance-use disorders, particularly alcohol and nicotine, as well as mood and anxiety disorders (Conway, Compton, Stinson, & Grant, 2006; B. F. Grant et al., 2004b; Petry et al., 2005; Ronzitti, Kraus, Hoff, & Potenza, 2018). This breadth of impairments has motivated research to better understand the biopsychosocial factors that pose risk for the onset and maintenance of gambling behaviors and co-morbid pathology.

One such body of research has examined how individual differences in the attribution of incentive salience, or “wanting,” to rewards and reward-related cues may contribute to the development and persistence of gambling pathology (M. J. F. Robinson & Berridge, 2015; M. J. F. Robinson, Fischer, Ahuja, Lesser, & Maniates, 2015b; Rømer Thomsen, Fjorback, Møller, & Lou, 2014). The incentive sensitization theory has afforded valuable insight into the neurobiological and behavioral processes that are associated with individual vulnerability to addictive spectrum pathology, such as substance-use disorders (T. E. Robinson & Berridge, 1993) and, more recently, gambling disorder (Linnet, 2014; M. J. F. Robinson, Fischer, Ahuja, Lesser, & Maniates, 2015b; Rømer Thomsen et al., 2014). However, little research has examined the co-morbidity that exists between gambling, substance use, and anxiety or stress-related disorders through this framework. Here, we review the literature on how individual differences in cue-reactivity may confer risk for gambling pathology and interact with causal processes of sensitization and cross-sensitization by reward uncertainty, drugs of abuse, and anxiety through an integrative model of incentive sensitization. We also examine how this conceptualization may advance our understanding of co-morbidity with substance-use disorders (particularly alcohol and nicotine) and anxiety disorders, highlighting potential transdiagnostic neurobiological mechanisms underlying these complex clinical presentations.

Co-morbidity in gambling disorder

Gambling disorder often co-occurs with psychiatric disorders, particularly substance use and anxiety disorders (el-Guebaly

et al., 2006; Kessler et al., 2008; Lorains, Cowlshaw, & Thomas, 2011; Parhami, Mojtabai, Rosenthal, Afifi, & Fong, 2014). The high rates of co-morbidity between these disorders have provided support on a broad level for an overlap in vulnerability and maintenance factors between anxiety, substance use, and gambling disorders.

Prevalent co-morbid conditions

Substance-use disorders

Substance-use disorders are one of the most frequently encountered co-morbid conditions in gambling disorder (K.-L. Chou & Afifi, 2011; Lorains et al., 2011; Walther, Morgenstern, & Hanewinkel, 2012). In particular, alcohol and nicotine are the most often misused substances among individuals with gambling pathology (Petry et al., 2005). A recent meta-analysis including 11 studies conducted between 1998 and 2010 reported an average co-morbidity rate of 28.1% (range: 9.9–73.2%) for alcohol-use disorders and 60.1% (range: 34.9–76.3%) for nicotine dependence in individuals with subthreshold or clinical gambling severity (Lorains et al., 2011; Petry et al., 2005). Of note, there was a considerable range in the reported prevalence of these co-morbidities due to notable differences in sample size, diagnostic assessment method, gambling disorder and problem gambling diagnostic criteria, and geographic location. Though this limitation is important to acknowledge, the evidence suggests that the rates of alcohol- and nicotine-use disorders in individuals with gambling-related pathology largely exceed those reported in the general population (alcohol: 8.5%; nicotine: 12.8%) (Kessler et al., 2005). Similarly, individuals with nicotine- or alcohol-related substance-use disorders are also more likely to meet the diagnostic criteria for GD compared to the general population (Krmopotich et al., 2015; Petry et al., 2005; Rennert et al., 2014). This consistently reported co-morbidity between substance-use disorders and gambling pathology has suggested that these syndromes may emerge from overlapping vulnerability factors, which cause them to often cohere in clinical presentations.

Anxiety disorders

In addition to substance-use disorders, anxiety disorders often present concurrently with gambling pathology. Approximately 37% (range: 14.0–60.3%) of subthreshold and clinical gamblers suffer from an anxiety disorder (Kessler et al., 2008; Lorains et al., 2011; Petry et al., 2005), and approximately 18% of individuals with substance-use disorders meet the past 12-month criteria for an anxiety disorder (B. F. Grant et al., 2004b). In contrast, Grant and colleagues report a 12-month prevalence of 11.10% for any anxiety disorder in the general US population (B. F. Grant et al., 2004b). Additionally, models

adjusted to account for a breadth of sociodemographic vulnerability factors (i.e., age, race/ethnicity, sex, education, income, marital status, geographic region) have demonstrated that individuals with alcohol-use disorders or nicotine dependence are on average at two to three times greater risk for an anxiety disorder in the past 12 months compared to individuals without these conditions (B. F. Grant et al., 2004b; B. F. Grant, Hasin, Chou, Stinson, & Dawson, 2004a; Hasin, Stinson, Ogburn, & Grant, 2007). Taken together, these findings suggest that anxiety disorders may also share vulnerability factors and mechanisms with addictive spectrum disorders. Though not within the scope of the present review, it is noteworthy that these findings extend to mood disorders as well, which are also far more prevalent among individuals with gambling or substance-use disorders than among the general population.

It is important to note that considerable sex differences have been highlighted in the co-morbidity of gambling with anxiety and mood disorders. Mirroring the increased prevalence of anxiety disorders amongst women in the general population (e.g. Generalized Anxiety Disorder: $M = 1.26\%$; $F = 2.79\%$), females with gambling disorder report disproportionately higher rates of anxiety disorders than males ($M = 3.94\%$; $F = 14.53\%$) (Desai & Potenza, 2008; Kessler et al., 1994). Additionally, the lifetime prevalence of anxiety disorders in females with clinical gambling involvement (61.93%) is much greater than that observed for women in the general population (30%) (Blanco, Hasin, Petry, Stinson, & Grant, 2006; J. E. Grant et al., 2006; Kessler et al., 2005). Shared diatheses between anxiety and gambling disorder may thus be particularly pertinent to female presentations.

Stressful events across the lifetime, and particularly in childhood, have been implicated in conferring vulnerability for the onset of anxiety- and stress-related conditions (McLaughlin, Conron, Koenen, & Gilman, 2010). In fact, childhood adversity and trauma exposure (e.g., abuse, neglect) are transdiagnostically associated with the onset of psychopathology for anxiety and substance use (J. G. Green et al., 2010) as well as gambling pathology (Felsher, Derevensky, & Gupta, 2004). Childhood adversity and trauma exposure may thus link these disorders together in co-morbid presentations by triggering or sensitizing shared neurobiological vulnerability factors. Though this pathway has been highlighted as a potential shared diathesis, the complex biopsychosocial mechanisms through which childhood adversity and stressful life events confer risk for these disorders remain largely unknown.

The impact of co-morbidity

Temporal relationships between clinical gambling, substance use, and anxiety

Though the high prevalence of co-morbid gambling, substance use, and anxiety disorders indicates a potential association between these conditions, these cross-sectional findings

fail to provide specific insight into the pathways from which this relationship may emerge. For that reason, several longitudinal studies have examined the temporal onset of these disorders in relation to each other (K.-L. Chou & Afifi, 2011; el-Guebaly et al., 2006; Parhami et al., 2014). Notably, gambling involvement, even at recreational levels, has been shown to predict the onset of anxiety or substance-use disorders 3 years later (Parhami et al., 2014). Furthermore, the more severe the baseline gambling involvement, the more likely the individual was to experience the onset of either an anxiety or a substance-use disorder. For gambling disorder and substance-use disorders, it appears this relationship is bi-directional, as the presence of one of either of these conditions often predicts the onset of the other (Afifi, Nicholson, Martins, & Sareen, 2016; Kessler et al., 2008). These findings not only support the notion that gambling and substance use pathology may have significantly overlapping mechanisms, but also suggest that aspects of repeated gambling or substance use may actively confer risk for one another through biological, behavioral, or environmental pathways.

Anxiety disorders, however, often precede the onset of gambling disorder or substance-use disorders (Blanco et al., 2015; Kausch, Rugle, & Rowland, 2006; Kessler et al., 2008). The high incidence of substance-use disorders in individuals with anxiety and stress-related disorders has been strongly associated with self-medication, suggesting that individuals with stress-related conditions may be more vulnerable to misuse substances to cope with aversive affective states (J. Robinson, Sareen, Cox, & Bolton, 2011). Similarly, individuals with anxiety disorders often report gambling to cope, providing an active pathway through which anxiety may lead to problematic gambling and alcohol use as a maladaptive emotion regulation strategy (Blaszczynski & Nower, 2002; Milosevic & Ledgerwood, 2010). The onset of a co-morbid anxiety or substance-use disorder has been significantly associated with endorsing gambling disorder diagnostic criteria (e.g., “gambling as an escape from negative affect”), supporting the notion that coping may play a significant role in the co-morbidity between anxiety, substance use, and gambling disorders (Lister, Milosevic, & Ledgerwood, 2015; Parhami et al., 2014). However, neural and biological pathways through which anxiety disorders may actively increase risk for addictive spectrum disorders remain largely unknown.

Co-morbidity potentiates clinical severity

In addition to these temporal linkages in the onset of clinical gambling, substance use, co-morbidities, the co-occurrence of these conditions may influence their severity. For example, individuals with alcohol- or nicotine-related substance-use disorders often present with more severe gambling behaviors and involvement (Desai & Potenza, 2008; el-Guebaly et al., 2006; J. E. Grant & Potenza, 2005; Ladd & Petry, 2003; Petry

& Oncken, 2002). Similarly, individuals with gambling disorder demonstrate elevated substance-abuse symptoms compared to those without this condition (K.-L. Chou & Affifi, 2011; el-Guebaly et al., 2006; Parhami et al., 2014; Possemato et al., 2015). Further, the presence of an anxiety disorder has been associated with more severe symptomatology in both gambling and substance use (C. L. Green, Nahhas, Scoglio, & Elman, 2017; Ledgerwood & Petry, 2006; Najavits, Meyer, Johnson, & Korn, 2011; Possemato et al., 2015). In line with these findings, individuals with both anxiety and substance-use disorders are at the highest risk to develop moderate to severe gambling behaviors, compared to those with one or neither of these disorders (el-Guebaly et al., 2006). In accordance with these trends in symptom severity, greater social, financial, and behavioral difficulties have been observed in gamblers who smoke or misuse alcohol, indicating significantly elevated impairments in functioning (McGrath & Barrett, 2009; Moghaddam, Yoon, Campos, & Fong, 2015; Potenza et al., 2004).

Building upon these findings, a “dose-dependent” relationship has been cited between anxiety, substance use, and gambling disorders, whereby the severity of the anxiety symptomatology is positively associated with that of the substance use or gambling disorder (Desai & Potenza, 2008; Giddens, Stefanovics, Pilver, Desai, & Potenza, 2012). These effects do not appear to be merely the result of shared environmental risk factors, as supported by the work of Petry and colleagues, which reported that alcohol-use disorders were significantly related to gambling disorder even after controlling for sociodemographic variables highly associated with the risk for gambling pathology, including ethnicity, age, sex, marital status, and region of origin (Petry et al., 2005). Collectively, these findings suggest that there may be considerable overlap in the factors that confer risk for gambling, substance use, and anxiety disorders, as well as shared causal mechanisms and maintenance factors that cause these disorders to cohere and bi-directionally exacerbate symptom severity.

Overlapping biopsychosocial risks factors

It is important to note that a variety of biological, neural, genetic, and psychological/environmental factors may also constitute risk factors and contribute to the co-morbidity between gambling and substance-abuse disorder (Crockford & el-Guebaly, 1998; Nautiyal, Okuda, Hen, & Blanco, 2017; Wareham & Potenza, 2010). For example, depression, bipolar disorder, and personality disorders are also highly co-morbid with gambling and substance-abuse disorders (Bergamini et al., 2018; Edens & Rosenheck, 2011; Kennedy et al., 2010). In addition, individuals with gambling disorder may have biological or behavioral vulnerability factors that confer an elevated risk for anxiety or substance-use disorders (Ledgerwood & Petry, 2010; Leeman & Potenza, 2012;

Milosevic & Ledgerwood, 2010; Walther et al., 2012). Moreover, studies in support of the classification of gambling disorder as a “behavioral addiction” have produced robust evidence for behavioral, cognitive, and biological similarities between gambling disorder and substance-use disorders (Di Nicola et al., 2015; Leeman & Potenza, 2012, 2013; Potenza, 2008; Slutske, Ellingson, Richmond-Rakerd, Zhu, & Martin, 2013). Here we focus on anxiety disorder and chronic stress since their prevalent co-morbidity and shared risks factors hint at the possible existence of shared neural pathways and neuroadaptations implicated in the confluence of these disorders. A study examining lifetime trauma history amongst pathological gamblers found that 64% of gamblers reported a history of emotional trauma, 40.5%, physical trauma, and 24.3%, sexual trauma, with the majority of these traumatic events occurring in childhood and a history of trauma being associated with greater frequency of drug and alcohol dependence (Kausch et al., 2006). This evidence points to a possible common underlying cause for the coherence of anxiety, gambling, and substance-use disorders; one where the neuroadaptations associated with a history of stress and trauma might predispose certain individuals to the onset of one or more of these disorders and interact with neurobiological vulnerabilities, resulting in complex co-morbid presentations with markedly elevated symptom severity and impairment.

The incentive sensitization theory

Dissociating “wanting” and “liking”

The incentive sensitization theory provides a psychological framework and a common neural currency to explain the development of substance use and gambling disorders. It also indicates how the emergence and persistence of these disorders can be related to stress and anxiety. The incentive sensitization theory (T. E. Robinson & Berridge, 1993, 2008) was initially proposed to distinguish between the different components of reward. It partitioned reward into “liking,” “wanting,” and learning, with an important focus on the distinction between “liking” and “wanting.” Whereas “liking” accounts for the objective hedonic and pleasurable response to rewards, the primary focus is placed on “wanting.” “Wanting” represents the visceral motivation and attraction attributed to a reward and reward-related cues. Often referred to as incentive salience, it is the psychological process by which rewards and the cues associated with them become imbued with subconscious motivational value and are transformed into objects of desire (M. J. F. Robinson, Robinson, & Berridge, 2013; T. E. Robinson & Berridge, 1993, 2008). The attribution of incentive salience is a psychological process mediated by mesocorticolimbic systems in the brain that help direct behavior towards naturally sought-after rewards, such as food,

water, and sex. It heightens perception and focuses attention towards the particular sights, sounds, and smells associated with these rewards in a way that adaptively promotes well-being and survival (Hickey & Peelen, 2015).

“Wanting” and “liking” typically fluctuate in unison, where “liking” a particular reward renders it commensurately “wanted.” However, under particular circumstances such as drug addiction, “liking” and “wanting” can be dissociated, where “wanting” may even occur despite the fact that the user might not subjectively enjoy the reward itself (Berridge & Robinson, 2003; Berridge, Robinson, & Aldridge, 2009). In fact, certain highly addictive drugs such as nicotine are exceedingly “wanted” despite producing little to no feelings of pleasure or euphoria (Benowitz, 1996; Isomura, Suzuki, & Murai, 2014; West, 2009), and drug self-administration can be maintained in the absence of any subjective pleasure (Fischman & Foltin, 1992). This evidence supports the view that subjective pleasure does not play a necessary causal role in drug-taking behavior. In particular, following repeated exposure to drugs of abuse, which progressively increases “wanting” and desire for more drug (Vezina, 2004; Vezina, Lorrain, Arnold, Austin, & Suto, 2002), individuals tend to escalate their consumption by increasing both the frequency with which drug is taken and the quantity consumed during each drug-taking episode. This increased urge for the drug is due to a sensitization of the neural pathways responsible for “wanting” (Ferrario & Robinson, 2007; Ferrario et al., 2005). This process, known as incentive sensitization, renders individuals hyper-responsive to drugs and their cues. It sensitizes the incentive value attributed to drugs, but also particularly to the cues that have been associated with the drug. In turn these cues can become motivational magnets that attract attention and trigger intense bouts of craving and desire to seek and take their associated drug reward (M. J. F. Robinson et al., 2013; M. J. F. Robinson, Fischer, Ahuja, Lesser, & Maniates, 2015b). However, repeated drug intake does not appear to produce a sensitization of “liking” (Bartlett, Hallin, Chapman, & Angrist, 1997). Instead, the pleasure that is often derived from taking a particular drug becomes dissociated from the amount to which it is “wanted.” While in some cases repeated drug use results in no change in drug “liking,” it can also undergo tolerance, where the hedonic response to drug tends to gradually decrease with repeated use. Similar findings suggesting blunted euphoria and response in opioid systems thought to be involved in “liking” has been reported in individuals with gambling problems (Mick et al., 2016). This dissociation between “liking” and “wanting” supports the existence of two distinct neural pathways that can independently undergo separate forms of plasticity.

A common neural currency for “wanting”

Natural rewards such as food, water, and sex all share a common neural substrate. The same is believed to be true for a

wide range of addictive substances including alcohol, nicotine, caffeine, barbiturates, benzodiazepines, cannabis, and phencyclidine (Di Chiara & Imperato, 1988; Wise & Bozarth, 1987). While these rewards typically all generate pleasure, a vast body of evidence, in both rodents and humans, suggests that the mesolimbic system is preferentially active during exposure to rewards, with the primary consequence being the release of the neurotransmitter dopamine (Balfour, 2015a; Berridge & Robinson, 1998; Corrigall, Coen, & Adamson, 1994; Di Chiara & Imperato, 1988). Although it was long believed that dopamine was the neurotransmitter responsible for pleasure, this has since been disproved, and a large body of evidence suggests that it instead modulates “wanting” (Berridge & Valenstein, 1991; Peciña, Cagniard, Berridge, Aldridge, & Zhuang, 2003; Tindell, Berridge, Zhang, Peciña, & Aldridge, 2005; Wyvell & Berridge, 2000). In humans, studies show that dopamine levels are more highly correlated with subjective ratings of “wanting” a reward than with pleasure ratings of that same reward (Leyton et al., 2002; Volkow et al., 2002). The mesolimbic dopamine system is thought to be responsible for generating “wanting” and assigning incentive salience to rewards and their cues. This system is comprised of dopaminergic fibers that project from the ventral tegmental area in the midbrain, to limbic and cortical structures such as the nucleus accumbens, ventral pallidum, amygdala, and prefrontal cortex (Di Chiara & Imperato, 1988; T. E. Robinson & Berridge, 1993).

Beyond mesolimbic dopamine’s role in natural rewards and the self-administration of a wide range of addictive substances, recent evidence also suggests that gambling results in increases in mesolimbic and striatal dopamine release (Joutsa et al., 2012; Linnet et al., 2012; Linnet, Møller, Peterson, Gjedde, & Doudet, 2011; Zack & Poulos, 2009). Together this evidence suggests that dopamine may act as a common neural currency for both gambling and substance-use disorder, that may be triggered when exposed to their respective cues, leading to sudden peaks in craving, and ultimately to long-lasting neural changes associated with addiction and relapse.

Cue sensitivity and the sensitization of “wanting”

Drugs of abuse, like gambling, acquire different degrees of control over thoughts and actions based not only on the effects of drugs themselves or an individual’s gambling-related earnings, but also on predispositions of the individual. While alcohol, nicotine, gambling, and other abused substances are rewarding for many individuals, only a subset of users compulsively seek out and engage in these activities. In particular, specific individuals may be more vulnerable to addictive spectrum disorders due to a naturally heightened sensitivity to reward cues (T. E. Robinson, Yager, Cogan, & Saunders, 2014b; Yager & Robinson, 2013). These cues can trigger surges in dopamine release that promote intense craving.

Similarly, repeated exposure to drugs of abuse and gambling can produce intense spikes of mesolimbic dopamine release. Together these repeated peaks of mesolimbic dopamine release lead to brain neuroadaptations, in particular, sensitization of these dopamine-related systems (T. E. Robinson & Becker, 1986; T. E. Robinson, Jurson, Bennett, & Bentgen, 1988). Sensitization of mesolimbic dopamine function results in the amplification of the neural mechanisms for incentive salience that transform ordinary levels of cue-triggered “wanting” into excessive levels of urges to take drugs and gamble, and a persistent vulnerability to relapse (Boileau et al., 2014; W. Y. Kim, Cho, Kwak, & Kim, 2017; Leyton, 2007). This incentive sensitization also produces hyper-reactivity of the mesolimbic dopaminergic system in response to reward-related cues, resulting in heightened, intense bouts of cue-induced craving. For example, in animal studies, sensitization increases neuronal firing in VTA–accumbens–pallidal pathways that code incentive salience as well as the behavioral ability of reward cues to trigger frenzied bursts of effort to obtain the reward (Peciña & Berridge, 2013; Tindell et al., 2005; Wyvell & Berridge, 2001). Sensitization can also be seen as a greater behavioral response to the drug or enhanced acquisition and escalation of drug self-administration, which accompany brain neural adaptations that underlie amplified “wanting” for the reward (Ferrario et al., 2005; Ferrario & Robinson, 2007; Vezina, 2004; Vezina et al., 2002). Yet, sensitization does not increase “liking” reactions that reflect the hedonic impact of the reward when it actually arrives (Bartlett et al., 1997).

Cue sensitivity and sensitization in substance abuse

In humans, studies show that individuals who abuse cocaine or alcohol show abnormally high dopaminergic activity in the ventral striatum and elevated self-reported craving in response to drug-related cues (Heinz et al., 2014; Miedl, Büchel, & Peters, 2014; Volkow et al., 2006). In smokers, the presentation of smoking-related cues produces enhanced attentional bias towards those cues (Littel, Franken, & Van Strien, 2009). In fact, greater attentional bias to drug-related cues is not only greater in individuals suffering from substance use, but can actually predict rates of relapse after treatment for numerous drugs, including for nicotine (Jane Powell, Dawkins, West, Powell, & Pickering, 2010; Waters et al., 2003) and alcohol (W. M. Cox, Hogan, Kristian, & Race, 2002; W. M. Cox, Pothos, & Hosier, 2007), suggesting that cue reactivity correlates with drug “wanting.” More recently, these behavioral indices of greater attentional bias and incentive salience attributed to drug cues have also been shown to possess several neural correlates that also predict relapse (Janes et al., 2010; Marhe, Luijten, van de Wetering, Smits, & Franken, 2013). In fact, Franken and colleagues showed that even after 12 months of treatment individuals recovering

from a substance-use disorder still displayed heightened cue reactivity, and that exposure to drug cues increased feelings of craving and depression (Franken, de Haan, van der Meer, Haffmans, & Hendriks, 1999).

Similarly in animals, cue attraction predicts cue-induced reinstatement of nicotine self-administration, while conversely, nicotine administration enhances cue-induced approach behavior (Palmatier, Kellicut, Brianna Sheppard, Brown, & Robinson, 2014; Versaggi, King, & Meyer, 2016), an effect that is disrupted by dopamine antagonists (Palmatier et al., 2014). The same is true of alcohol, whereby alcohol-paired cues also trigger cue approach and alcohol-seeking behavior (Krank, 2003; Krank, O'Neill, Squarey, & Jacob, 2008; Srey, Maddux, & Chaudhri, 2015; Tomie & Sharma, 2013). In particular, adolescent alcohol exposure amplifies the incentive value and attraction of reward-predictive cues (Hellberg, Levit, & Robinson, 2018; Madayag, Stringfield, Reissner, Boettiger, & Robinson, 2017), and does so through potentiation of dopamine signaling (Spoelder, Tsutsui, Lesscher, Vanderschuren, & Clark, 2015).

Sensitization caused by repeated drug use has been observed with many drugs of abuse, including alcohol and nicotine (Benwell & Balfour, 1992; Cadoni & Di Chiara, 2000; Govind, Vezina, & Green, 2009; Laviolette & van der Kooy, 2004). In humans, several reports have provided evidence of sensitization in psychostimulant drug users leading to enhanced drug-seeking, despite showing tolerance to the drug's euphoric effects (Bartlett et al., 1997; Reed et al., 2009; Small et al., 2009). In animals, recent findings have shown that repeated alcohol consumption leading to sensitization results in increased dopaminergic reactivity to alcohol (Didone, Masson, Quoilin, Seutin, & Quertemont, 2014), and greater behavioral responsivity (Hoshaw & Lewis, 2001). Similarly, in humans a dissociation has been found between “liking” and “wanting” for alcohol where small doses of alcohol cause spikes in “wanting” yet leave “liking” unaffected (Hobbs, Remington, & Glautier, 2005; Ostafin, Marlatt, & Troop-Gordon, 2010), and heavy drinkers show higher sensitivity to alcohol's stimulating and rewarding effects (A. C. King, Hasin, O'Connor, McNamara, & Cao, 2016).

For nicotine, animal studies have shown that repeated intermittent injections of nicotine typically cause sensitization or enhancement of the drug's locomotor activating effects (L. K. Baker et al., 2013; Benwell & Balfour, 1992; Clarke & Kumar, 1983; Vezina, McGehee, & Green, 2007). For example, adolescent nicotine treatment predisposes adult rats to develop increased behavioral sensitivity to chronic nicotine treatment and to be more sensitive to the initial effects of nicotine (Bracken, Chambers, Berg, Rodd, & McBride, 2011). Exposure to nicotine also increases its subsequent self-administration, which is further enhanced by nicotine-paired cues (Neugebauer, Cortright, Sampedro, & Vezina, 2014). Furthermore, drugs such as nicotine produce increases

in dopamine transmission but fail to produce any reported “liking” or euphoria in humans, suggesting the absence of any clear relationship between “liking” and the excessive “wanting” that leads to addiction (Balfour, 2015b; Caggiula et al., 2009; Rose, Behm, Westman, & Johnson, 2000).

Cue sensitivity and sensitization in gambling

Gambling environments are robustly full of cues, such as flashing lights and sounds (Griffiths, 1993; Noseworthy & Finlay, 2009; Parke & Griffiths, 2006), and gamblers have been shown to display greater attentional bias and fixate their gaze for longer on gambling-related cues (Hudson, Olatunji, Gough, Yi, & Stewart, 2016; McGrath, Meitner, & Sears, 2018). The cues in the gambling environment in and of themselves have demonstrated the ability to elicit craving and induce urges to gamble (Kushner et al., 2008; Park et al., 2015; Potenza et al., 2003; Wulfert, Maxson, & Jardin, 2009). For example, individuals playing blackjack in a gambling-like environment reported greater urges to gamble than those in a neutral context (Kushner et al., 2008; McGrath, Dorbeck, & Barrett, 2013). Interestingly, the effects of cue-induced craving extend beyond the physical casino environment and into the virtual gambling environment. One study analyzed reports of craving in virtual casino environments and found gambling cues to increase subjective reports of craving in recreational gamblers (Park et al., 2015).

Various studies support the notion that cue reactivity is heightened amongst individuals with problematic gambling and gambling behavior (Hønsi, Mentzoni, Molde, & Pallesen, 2012; Thalemann, Wölfling, & Grüsser, 2007; Wulfert et al., 2009). For example, individuals with gambling pathology show elevated craving, urges to gamble, and physiological and neurological reactivity to cues associated with gambling (Goudriaan, Yucel, & van Holst, 2014; van Holst et al., 2012; Wulfert et al., 2009). In particular, problem gamblers appear more sensitive to bias attention towards gambling-related cues and to experience craving after exposure to gambling cues than healthy controls (Goudriaan et al., 2014; van Holst et al., 2012). Similarly, an fMRI study found increased attraction to cues in the gambling setting that required disordered gambling men and healthy controls to view a video of a neutral or gambling scenario. Men with gambling disorder who viewed the gambling scenario showed increased activation in regions previously shown to be involved in emotional and motivational responses (Potenza et al., 2003).

Research has also found that problem gamblers have a sensitized dopaminergic response to gambling-related cues. Studies have correlated striatal dopamine release in problem gamblers with severity of problem gambling (Joutsa et al., 2012) and with self-reported levels of excitement during a gambling task (Linnet et al., 2011). This sensitized “wanting” that is present in problem gamblers might explain their

willingness to persist in gambling despite the negative consequences, such as significant financial losses. A study by Linnet and colleagues found that problem gamblers exhibited increased dopamine release in their ventral striatum compared to healthy controls when they lost money in a gambling task, implying that loss has come to generate motivation in problem gamblers (Linnet, Peterson, Doudet, Gjedde, & Møller, 2010). Additionally, a study by Clark and colleagues found that near-misses (or almost winning) in a slot machine gambling task recruited areas of the brain that respond to wins. Participants in this study reported that near-misses were significantly less pleasant than full misses, but triggered their urge to play more (L. Clark, Lawrence, Astley-Jones, & Gray, 2009), illustrating that although problem gamblers do not enjoy losses, they do find losses highly motivating. This provides further evidence for the neural and psychological dissociation of “liking” and “wanting” and an exacerbation of “wanting” in problem gambling.

It is worth mentioning that certain studies instead report a blunted striatal dopamine response to cues in pathological gamblers (Balodis et al., 2012; Miedl, Peters, & Büchel, 2012). However, it has been suggested that such contradictory reports can be explained by the absence of familiar or relevant gambling cues during laboratory testing (Leyton & Vezina, 2012), which when present instead produce an exaggerated striatal dopamine response (T. D. L. Steeves et al., 2009). This finding implies that while gambling-related cues take on increased incentive salience, other non-related or unfamiliar cues may become less important or even inhibit motivation (Leyton, 2007, 2014; Leyton & Vezina, 2012, 2014). What is it then in gambling that enhances the attraction of gambling cues and sensitizes the dopaminergic response?

The role of uncertainty in cue sensitivity and sensitization in gambling

One of the hallmarks of gambling, and indeed of most games, is the presence of uncertainty (Costikyan, 2013). It is thought that reward uncertainty, like drugs of abuse, may also sensitize neural systems to rewards and reward-related cues (Anselme & Robinson, 2013; Anselme, Robinson, & Berridge, 2013; Berridge, 2007; Mascia et al., 2018; M. J. F. Robinson, Anselme, Fischer, & Berridge, 2014a; Rømer Thomsen et al., 2014). For example, studies in rats suggest that uncertainty pertaining to the probability and magnitude of the reward outcome can cause attribution of additional incentive salience to reward-related cues. Exposure to an uncertain rather than a certain reward schedule (where both the chances of receiving a reward and the magnitude of this reward vary) significantly increases the attention and attraction directed to the reward cue, making uncertain reward-related cues appear more “wanted” (Anselme et al., 2013). Exposure to reward uncertainty even increases the proportion of individuals that

ascribe incentive value to cues, and further narrows their focus on cues (Hellberg et al., 2018; M. J. F. Robinson, Anselme, Suchomel, & Berridge, 2015a). The role of uncertainty in attributing excessive incentive value can also be seen in humans. A series of studies by Brevers and colleagues indicate that problem gamblers exhibit attentional bias toward uncertain gambling-related cues as compared to healthy controls, suggesting that these stimuli also take on increased salience in human gamblers and may possess “motivational magnet” properties (Brevers et al., 2014a; Brevers, Koritzky, Bechara, & Noël, 2014b).

These findings regarding uncertainty are paradoxical since they contradict the idea that the motivational value of a cue should be monotonically related to its predictive value. Under reward uncertainty, when the cue only predicts the reward 50% of the time, the predictive value of the cue is degraded, yet these findings suggest that it is more attractive and “wanted” more. These results are consistent with the incentive salience theory, however, and highlight the dissociation that can occur between the predictive value of a cue, driven by cue learning (cue-reward association), and the attribution of cue “wanting” (T. E. Robinson & Flagel, 2009; Zhang, Berridge, Tindell, Smith, & Aldridge, 2009). Furthermore, cues that predict reward with a large degree of uncertainty are also more likely to acquire incentive salience. For example, distal cues that are on the periphery of our attention are typically ignored under certain and predictable reward conditions, but when reward conditions are unpredictable, these cues attract more attention (M. J. F. Robinson et al., 2014a). The effects of uncertainty also parallel those robustly observed during amphetamine sensitization, suggesting that uncertainty may sensitize craving and reward-seeking comparable to drugs of abuse (M. J. F. Robinson, Anselme, Suchomel, & Berridge, 2015a). This is likely due to the fact that cues that predict an uncertain reward (50% probability) produce a greater dopamine signal, originating from the ventral midbrain, during the anticipation of the uncertain outcome (Anselme, 2013; Fiorillo, Tobler, & Schultz, 2003), and that this dopaminergic signal appears to promote risk-seeking behavior, as evidenced in gambling (Fiorillo, 2011).

One approach for examining the role of uncertainty on risk preference is the rodent gambling task (rGT), adapted from the Iowa Gambling Task (Bechara, Damasio, Tranel, & Damasio, 1997; Rivalan, Ahmed, & Dellu-Hagedorn, 2009; Zeeb, Robbins, & Winstanley, 2009). It presents animals with the choice of four options (two safe and two risky), each associated with different magnitude and probability of reward, and durations of punishing time-outs. While the majority of animals learn to choose the safe and advantageous options, a small proportion tend to be more risk-preferring, and these risk-preferring animals make more drug-seeking responses and show greater cue-induced incubation of craving after cocaine self-administration (Ferland & Winstanley, 2016).

Crucially, it appears that repeated exposure to reward uncertainty subsequently increases risk preference on the rGT (Zeeb, Li, Fisher, Zack, & Fletcher, 2017). Similarly, the introduction of salient cues to winning trials, to what is termed the cued rGT, results in riskier and more disadvantageous choice behavior than when exposed to the uncued task (Barrus & Winstanley, 2016). Along with evidence that in humans win-associated cues, such as jingles varying in length and size in function of win size, both increase arousal and lead subjects to overestimate their frequency of winning (Dixon et al., 2014), this evidence suggests a strong connection between reward uncertainty, gambling propensity, substance abuse, and cue sensitivity.

In all, research suggests that cues can become powerful instigators of gambling behavior. Therefore, games that are governed by reward uncertainty and contain a large number of cues or a high prevalence of flashing lights and sounds, such as electronic gambling machines, might be particularly capable of eliciting motivated play and sensitizing “wanting” pathways in a manner that promotes excessive attentional bias and risky decision-making. In turn, attentional bias towards gambling cues has been suggested to play a critical role in the transition from recreational to problem gambling (L. D. Grant & Bowling, 2015; van Holst et al., 2012).

Cue sensitivity and sensitization by stress

In the human literature, substantial research has supported the notion that individual differences in the sensitivity to cues may also confer risk for anxiety disorders (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Heeren, Peschard, & Philippot, 2011; Mogg & Bradley, 2018; Shackman et al., 2016; Van Bockstaele et al., 2014). However, the majority of this work has examined abnormalities in neural, cognitive, and behavioral reactivity towards threat cues versus neutral cues, or compared to healthy control populations (e.g., Dieterich, Endrass, & Kathmann, 2017). Within this line of work, uncertainty has emerged as an important moderator of this observed individual difference in sensitivity to threat cues, with individuals with anxiety disorders demonstrating enhanced reactivity to uncertain compared to certain threat cues (Bradford, Kaye, & Curtin, 2014a; Bradford, Magruder, Korhumel, & Curtin, 2014b; Grupe & Nitschke, 2013). Intolerance to uncertainty is a transdiagnostic factor strongly implicated in the maintenance of anxiety disorders, and is associated with greater physiological reactivity, attentional biases, and neural activation to uncertainty and uncertain threat cues (Carleton, 2012; Krain et al., 2006; Mahoney & McEvoy, 2012; Nelson & Shankman, 2011; Simmons, Matthews, Paulus, & Stein, 2008). Notably, individuals with high intolerance to uncertainty display greater neural activity of the insula and amygdala in response to uncertainty (Tanovic, Gee, & Joormann, 2018). Studies also suggest that

individuals with high intolerance for uncertainty are susceptible to alcohol use as a form of stress reduction in response to uncertainty, suggesting a possible pathway through which individuals suffering or predisposed to generalized anxiety disorder and exposed to high levels of uncertainty through gambling might be inclined to abuse alcohol as a form of self-medication (Bradford, Shapiro, & Curtin, 2013; Hefner, Moberg, Hachiya, & Curtin, 2013).

However, to date, very few studies have directly examined the distinction and overlap of this neurobiological sensitivity to cues and uncertainty in intense positive and negative valence events. The studies that have examined both reward and threat cue processing do suggest highly overlapping neurobiological and psychological processing abnormalities in anxiety disorders that may generally encompass the attribution of value and recruitment of attention to valenced cues, rather than just threat cues (Gorka, Nelson, Phan, & Shankman, 2016; Tanovic et al., 2018). In particular, one human study demonstrated that uncertain rewards, similar to threats, result in increased insula responsivity (Gorka et al., 2016). Interestingly, although there are dopaminergic neurons that encode for just positive or negative motivational events, there are more numerous dopaminergic neurons that excite similarly to both threatening and rewarding events (Matsumoto & Hikosaka, 2009). One animal study has supported this model, with high anxiety animals demonstrating particular vulnerability to attend to reward-related uncertain cues (Hellberg et al., 2018).

Given the uncertainty inherent to games of chance, it follows that individuals at risk for anxiety disorders, due to high levels of intolerance of uncertainty, may be particularly vulnerable to over-attend to uncertainty-related cues and subsequently becoming more motivated and intensely focused on gambling behaviors through incentive sensitization. Both positive and negative valenced cues in gambling, such as those associated with wins and losses, may particularly sensitize reactivity to gambling-related cues in individuals with anxiety disorders.

Furthermore, there is evidence that stress cues similarly elicit craving by inducing anxiety (Coffey, Stasiewicz, Hughes, & Brimo, 2006; Fox, Bergquist, Hong, & Sinha, 2007; Sinha & Li, 2007; Sinha et al., 2009; 2003). Specifically, stress cues significantly increased both alcohol craving and reported anxiety levels in abstinent alcohol-dependent individuals (Fox et al., 2007), and this pattern of reactivity was associated with enhanced activation in regions linked to mesolimbic reward processing, including the medial prefrontal, anterior and posterior cingulate, and striatal and posterior insula cortex (Sinha & Li, 2007). These responses to stress cues were on the whole comparable to those induced by alcohol-associated cues (Fox et al., 2007; Sinha et al., 2009; Sinha & Li, 2007), and support the evidence that the physiological reactivity elicited by stress cues may serve as a

powerful catalyst for craving and subsequent relapse (Sinha et al., 2011). In anxiety disorders, such as panic disorder (PD) or post-traumatic stress disorder, interoceptive and physiological sensations serve as particularly potent stress cues, and are known to elicit negative affective states, such as anxiety and even panic attacks. This seems notable, given the relationship between anxiety disorders, such as PD, and the strikingly high rates of co-morbidity and prospective onset of alcohol and tobacco use disorders among these individuals (Zimmermann et al., 2003; Zvolensky, Bernstein, Marshall, & Feldner, 2006). Interestingly, individuals with PD specifically have been shown to have particularly difficult experiences with withdrawal and high rates of relapse, due to the syndromic sensitivity to these interoceptive arousal cues that characterize withdrawal from tobacco or other substances of abuse (Zvolensky & Bernstein, 2005; Zvolensky, Stewart, Vujanovic, Gavric, & Steeves, 2009). These effects have been less well examined within substance use and gambling; however, the mechanism by which somatic cues elicit persistent engagement with nicotine and relapse among these individuals naturally extends to other substance and behavioral addictions.

Stress, similar to drugs of abuse, may also induce neurological changes that enhance dopaminergic activity and the attribution of incentive value to rewards and their cues (Berridge, 2012; T. E. Robinson, Angus, & Becker, 1985; Yap et al., 2015). Exposure to acute and chronic stressors often results in initial sensitization of the hypothalamic-pituitary-adrenal (HPA) axis, which may then produce hypersensitivity to other stressors. Sensitization can also affect other physiological systems (i.e., plasma catecholamines, brain monoamines), which appears to be long lasting, a finding that may explain the long-term consequences of early-life adversity and traumatic stressors (Belda, Fuentes, Daviu, Nadal, & Armario, 2015). In particular, there may be critical periods, such as during childhood, in which neural systems are particularly vulnerable to sensitization by stress (Rodrigues, Leão, Carvalho, Almeida, & Sousa, 2011). There is substantial evidence to support to notion that stressful experiences during early development may sensitize mesolimbic dopamine signaling in neural regions, inducing permanent changes in the neural programming of dopaminergic activity (Rodrigues et al., 2011). These findings align well with the stress-sensitization hypothesis of the role of early life adversity in the onset of anxiety disorders, substance use, and gambling disorder (McLaughlin et al., 2010). There is also evidence to suggest that the physiological response to stress, involving elevated corticotropin-releasing factor (CRF), a hormone highly implicated in the stress response, recruits activity in dopaminergic pathways and elevates dopaminergic activity (Berridge, 2010; Cuadra, Zurita, Lacerra, & Molina, 1999; Dallman, 2010; Peciña, Schulkin, & Berridge, 2006). In turn, administration of CRF has been shown to elevate the value of

Pavlovian-associated reward cues (Peciña et al., 2006). Chronic and acute stress may therefore produce similar neural adaptations in the mesolimbic dopamine circuit that are responsible for increased “wanting” of rewards and enhanced cue reactivity. In this vein, stress has been shown to elicit similar neuroadaptations to alcohol and nicotine, increasing the excitatory strength of dopamine neurons in midbrain (e.g., VTA, NAc) in animals (Saal, Dong, Bonci, & Malenka, 2003). Traumatic events or chronic distressed states, typical of anxiety disorders, may therefore leave individuals more susceptible to the rewarding effects of drugs and gambling and predispose individuals to over-attribute value to drugs and gambling cues. Through these neuroadaptations in the mesolimbic dopamine pathway, dysfunctions in the stress response may heighten the risk for substance use and gambling disorder, and contribute to the high prevalence of comorbidity between anxiety, gambling, and substance-use disorders (Fig. 1).

Cross-sensitization as a framework for co-morbidity

Cross-sensitization: definition

When experienced together, substances such as nicotine and alcohol, and stress and reward uncertainty might exert a cumulative effect on the mesolimbic reward system, a phenomenon known as cross-sensitization. Cross-sensitization occurs when sensitization to one reward results in an amplified response to another related reward. In the context of drug use, cross-sensitization refers to when sensitization to one drug will produce a sensitized response to other drugs (such as between heroin and cocaine) (Antelman, Eichler, Black, & Kocan, 1980; Cunningham & Kelley, 1992; Horger, Giles, & Schenk, 1992; Piazza, Deminiere, le Moal, & Simon, 1990; T. E. Robinson et al., 1985). In cases of cross-sensitization of “wanting,” an individual, as a result of excessively consuming one drug, is rendered hyper-responsive to the motivational effects of other drugs, including ones that may have never been previously consumed. A study by Horger et al. found that rats given nine daily injections of amphetamine or nicotine acquired cocaine self-administration much quicker than control animals (Casey, Benkelfat, Young, & Leyton, 2006; Horger et al., 1992; Munafò, Mannie, Cowen, Harmer, & McTavish, 2007), whereas Cortright et al. found that nicotine pretreatment enhances acquisition of amphetamine self-administration, particularly in the presence of nicotine-associated cues (Cortright, Sampedro, Neugebauer, & Vezina, 2012). Similarly, a study by Cunningham et al. found that rats who were given intra-accumbens treatment of certain opiates (such as morphine) later proved to be sensitized to the behavioral effects of amphetamine (Cunningham & Kelley, 1992). Together these studies demonstrate that repeated exposure to one drug can render

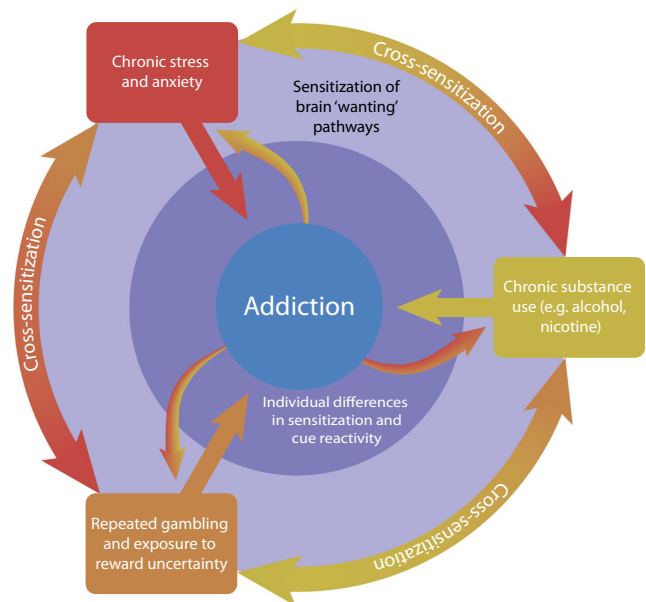


Fig. 1 Anxiety, gambling, and substance use have all been associated with the sensitization of neural pathways involved in motivation and reward (light blue outer ring). These factors may act independently and interact with each other through a process of cross-sensitization (outer ring), conferring significant risk for the development of an addictive spectrum disorder like gambling disorder (center). In turn, the development of an addictive spectrum disorder, whether to a substance or gambling behavior, may increase the risk of developing and subsequent severity of an anxiety, substance use or gambling disorder (outward facing arrows). In addition, beyond chronic exposure, acute encounters with either stress, drugs or gambling and their associated cues may be able to trigger intense bouts of craving and potentially relapse. Finally, individual differences in the propensity to attribute value to reward cues may confound with these factors and put specific individuals at high risk for addiction (dark blue inner ring)

individuals more susceptible to the reinforcing effects of another, and highlight the importance played by contextual cues.

However, cross-sensitization does not only occur between drugs of abuse. Cross-sensitization and the resulting hyper-responsivity of dopaminergic systems also occurs between drugs of abuse and natural rewards (Avena & Hoebel, 2003) and drugs of abuse and stress (at both behavioral and physiological levels) (Cruz, Marin, Leão, & Planeta, 2011; Garcia-Keller et al., 2013; Piazza et al., 1990). There is also evidence for cross-sensitization between drugs of abuse and gambling (Boileau et al., 2014; Mascia et al., 2018; Singer, Scott-Railton, & Vezina, 2012; Zack, Featherstone, Mathewson, & Fletcher, 2014; Zeeb et al., 2017), and between gambling and stress (C. L. Green et al., 2017).

Cross-sensitization between drugs and gambling

The most compelling evidence for neural sensitization of dopamine release and resulting cross-sensitization with gambling comes from Parkinson patients who develop dopamine dysregulation syndrome (DDS). DDS occurs in a small proportion of

Parkinson's patients being treated with dopamine agonist medication (Dodd et al., 2005; Evans, Lawrence, Cresswell, Katzenschlager, & Lees, 2010; Evans et al., 2006). It typically leads to compulsive use of their dopaminergic drug medications, with increased reports of drug "wanting" but not drug "liking." It is also accompanied by increased dopamine release in the ventral striatum especially in the combined presence of cues and the dopamine-stimulating drug. Crucially, it is frequently accompanied by the development of pathological gambling, hypersexuality, food bingeing, and punding (a form of complex behavioral stereotypy), suggesting that incentive sensitization of their dopamine-stimulating medication produces cross-sensitization to several other rewards including gambling. Interestingly, in many of these patients, discontinuation of their dopaminergic medication resolved their pathological gambling (Dodd et al., 2005).

There is also direct evidence for cross-sensitization of the dopaminergic system under gambling-like conditions in animals (Mascia et al., 2018; Singer et al., 2012; Zack et al., 2014; Zeeb et al., 2017). Uncertainty causes cross-sensitization of the dopaminergic system, as seen by increased reactivity to a single dose of amphetamine, in the same way that repeated exposure to drugs of abuse sensitizes this system. Zack and colleagues found that rats exposed to maximally uncertain conditions showed the greatest locomotor response to an amphetamine challenge (Zack et al., 2014). In a similar study, Singer and his collaborators found that rats trained to press a lever for reward on a variable schedule showed a greater locomotor response to amphetamine than those who were rewarded on a fixed schedule (Singer et al., 2012). Using a similar approach, Mascia and her colleagues found that repeated exposure to uncertainty resulted in self-administration of more amphetamine and a greater dopaminergic response to amphetamine (Mascia et al., 2018).

Cross-sensitization of dopaminergic systems from gambling has also been observed in humans. Boileau and colleagues found that problem gamblers have increased dopamine release in their dorsal striatum in response to amphetamine in comparison with healthy controls (Boileau et al., 2014). Conversely, a study by Barrett and colleagues examined the effect of co-administration of alcohol and nicotine in regular video lottery terminal gamblers. Their results showed that while administration of alcohol increased cigarette craving and "wanting" to consume more alcohol, it also increased the urge to gamble, whereas nicotine increased average wagers. This suggests that both alcohol and nicotine increased the incentive value and propensity to gamble but through separate processes (Barrett, Collins, & Stewart, 2015).

Together these results suggest that exposure to reward uncertainty and gambling can increase sensitivity to drugs of abuse, which in turn can increase the incentive value associated to gambling and its cues, and possibly promote the transition from casual recreational gambling to compulsive gambling.

Cross-sensitization between drugs and stress

There is a long history of evidence suggesting that prior exposure to chronic or acute stress predisposes individuals to substance use and abuse. In particular, evidence suggests that final maturation of behavior, dopamine systems, and HPA axis occurs during adolescence, suggesting that individuals experiencing stressful events during early life and adolescence are particularly prone to develop cross-sensitization to drugs of abuse (Burke & Miczek, 2014; Rodrigues et al., 2011). For example, in one study, chronically stressed animals displayed a sensitized response to the effects of acute cocaine administration, increased self-administration of cocaine, and demonstrated increased dopamine release in the nucleus accumbens (Holly, Shimamoto, DeBold, & Miczek, 2012). A study by Zago and colleagues demonstrated that the co-occurrence of repeated stress alongside chronic nicotine administration resulted in behavioral sensitization, particularly in adolescent animals (Zago et al., 2012). Some studies have reported sex differences in cross-sensitization, where early life stress enhanced nicotine sensitization in female rats, yet rendered males more sensitive to further stress (McCormick, Robarts, Gleason, & Kelsey, 2004). Repeated stress during adolescence has also been shown to increase the incentive value and attraction to contexts previously paired with either nicotine or alcohol, even at lower doses (Briellmaier, McDonald, & Smith, 2012; Song et al., 2007). In mice, chronic stress during adolescence has also been shown to increase alcohol preference and overall alcohol consumption in adulthood (Chester, Barrenha, Hughes, & Keuneke, 2008; Lopez, Doremus-Fitzwater, & Becker, 2011). Similar findings have also been reported in humans, where adverse childhood experiences were associated with increased likelihood of alcohol use during adolescence and of alcohol abuse as an adult (Dube, Anda, Felitti, Edwards, & Croft, 2002; Dube et al., 2006; Enoch, 2011). Together these findings strongly suggest a role for stress, particularly during early life and adolescence, in sensitizing reward systems responsible for the attribution of drug and cue "wanting," thus placing individuals at greater risk for substance-use disorders, such as commonly observed in alcohol and nicotine dependence. However, the relationship between drugs and stress is not unidirectional. Recent human studies have shown that exposure to only three doses of amphetamine can cause cross-sensitization to stress, resulting in an increased cortisol response to stress and greater striatal dopamine release (Booij et al., 2016). Such findings are problematic when one considers that beyond the impact of stress on the initial response and consumption to drugs of abuse, stressful life events can also act as powerful triggers of drug cravings and relapse. For example, many human and animal studies have shown that exposure to acute and chronic stress following abstinence increases the likelihood of relapse to both alcohol and nicotine (Breese et al., 2005; Buczek, Lê,

Wang, Stewart, & Shaham, 1999; Lê et al., 1998; Mantsch, Baker, Funk, Lê, & Shaham, 2016; Matheny & Weatherman, 1998; Perkins & Grobe, 1992). Taken together these findings suggest the potential existence of a vicious cycle whereby acute or chronic stress enhances “wanting” for drugs and their cues. This in turn may serve to increase stress through financial, social, and other impairments caused by escalating drug use. In addition, attempts at abstinence may precipitate withdrawal, which can promote further anxiety, resulting in enhanced dopaminergic reactivity to drugs and their cues, therefore placing individuals at greater risk for stress-induced relapse (Fig. 1).

Cross-sensitization between gambling and stress

Similar to drugs of abuse, there is evidence suggesting that stress may render individuals more vulnerable to gambling behavior and associated reward cues (Biback & Zack, 2015). A recent study by Green and colleagues investigated the relationship between post-traumatic stress symptoms and gambling problems. Their findings suggest that pathological gamblers displayed greater post-traumatic stress symptoms, specifically they demonstrated enhanced severity of associated physiological arousal. The degree of post-traumatic stress symptomatology correlated with greater gambling severity, suggesting a strong relationship between experience of stressful events and gambling problems (C. L. Green et al., 2017) and highlighting enhanced physiological reactivity as a potential contributing factor to this association. In a pilot study, Elman and colleagues attempted to examine whether pathological gamblers were more sensitive to stress by injecting them with yohimbine, an alpha-2 adrenoceptor antagonist that elicits stress-like physiological and psychological effects in both humans and in laboratory animals. They found that in pathological gamblers, yohimbine produced greater reactivity in the left amygdala and tended to elicit greater subjective stress ratings than in healthy controls (Elman et al., 2012). Additional studies by the same group also found that psychosocial stress strongly correlated with gambling urges, particularly in women (Elman, Tschibelu, & Borsook, 2010; Tschibelu & Elman, 2011). In contrast, a recent study examining risky decision-making more broadly, found that cortisol led to a striking increase in risk-taking in men, whereas it had no effect on risk-taking behavior in women (Kluen, Agorastos, Wiedemann, & Schwabe, 2017). In animals, studies using the rodent Gambling Task demonstrated that injections of corticosterone prevented animals from improving their decision-making and avoiding disadvantageous options (Koot, Baars, Hesselting, van den Bos, & Joëls, 2013). Taken together these results highlight a link between gambling propensity and stress; however, further studies are needed to examine whether acute stress produces greater dopaminergic responses in individuals suffering from gambling disorder.

In addition, while evidence appears to suggest that stress might be a direct constituent of the response to uncertainty, chronic stress also appears to place individuals at greater risk of gambling pathology. The direction of the relationship between gambling and stress may therefore be bi-directional, but further research is needed for it to be fully elucidated.

Long-lasting neuroadaptations

Possibly the most concerning finding regarding the impact of incentive sensitization and cross-sensitization on co-morbidity between stress, drugs of abuse, and gambling is that the neural changes that underlie sensitization, and thus cross-sensitization, appear to be long-lasting. This would explain why sensitization to stress during early life and adolescence can still have an impact on reward sensitivity to drugs of abuse like nicotine and alcohol and gambling during adulthood. A study by Paulson and colleagues showed that when rats were pretreated with amphetamine, they exhibited sensitization an entire year after the pretreatment was discontinued (Paulson, Camp, & Robinson, 1991). Likewise, other studies have reported that mice demonstrate behavioral or psychomotor sensitization, in the form of increased locomotor activity, up to 3 months after cocaine exposure (Shuster, Yu, & Bates, 1977) and up to 8 months after morphine exposure (Shuster, Webster, & Yu, 1975), while monkeys still display a sensitized response to amphetamine even 2 years post-treatment (Castner & Goldman-Rakic, 1999). In humans, evidence suggests that exposure to only four doses of amphetamine produced a sensitized dopaminergic response when tested up to 1 year later (Boileau et al., 2006). These results might explain why recent evidence suggests that exposure to early life adversity in rats increases reward and cue “wanting,” and potentiates the expression of addiction-related traits in adulthood (Hynes et al., 2017). Studies like these confirm that the neuroadaptations seen in the brain that underlie incentive and dopaminergic sensitization are long-lasting. In fact, these neuroadaptations are believed to persist even long after an individual has undergone recovery from substance use or gambling disorder. This pervasive sensitization of the mesolimbic dopamine system would explain why bouts of craving can occur even years later and why stress remains such a potent trigger of relapse.

Susceptibility to sensitization

It is important to note that incentive sensitization does not affect everyone equally. Sensitization is a complex phenomenon that is influenced by the quantity, timing, and spacing with which a reward or stress is encountered, along with the context in which it is experienced. These factors interact with individual features of the person, including genes, sex, hormonal status, etc. The phenomenon of sensitization displays a

tremendous amount of individual variation, with some individuals developing rapid and robust sensitization in contrast to others who sensitize very little, if at all. Some of this can be explained by the fact that individuals differ in their patterns of drug-taking (Allain, Minogianis, Roberts, & Samaha, 2015). To date, it has been shown in animals that there are genetic differences in the propensity of individual brains to undergo sensitization, and in the functioning of the mesolimbic dopamine system (Dietz, Tapocik, Gaval-Cruz, & Kabbaj, 2005; Phillips, 1997). There is also evidence suggesting that the genetic variation in acute responsiveness to drugs is different to that responsible for differences in sensitization (Eisener-Dorman, Grabowski-Boase, & Tarantino, 2011; Phillips, Huson, & McKinnon, 1998; Phillips, Huson, Gwiazdon, Kasch, & Shen, 1995). Nonetheless, most animals and likely humans do show some degree of psychomotor sensitization, although few may still reach the levels sufficient to trigger compulsive drug-seeking and taking. However, for those who do become sensitized, mesolimbic interactions with corticolimbic circuitry focus excessive desire specifically on that target of addiction, resulting in surges of enhanced “wanting” of the addictive target upon encountering related cues or vivid imagery. This heightened “wanting” in response to cues in turn leads to sudden and almost uncontrollable bouts of cue-triggered craving and excessive control of behavior by reward-related cues.

Concluding remarks

In a gambling setting, cues associated with gambling machines, cigarette smoking, and alcohol use may work synergistically to drive motivation, and the cross-sensitization of reward pathways caused by these factors might accelerate and worsen the pathology of gambling disorder. Here, we reviewed the literature suggesting a mechanistic interplay between stress/anxiety, alcohol and nicotine use, and gambling disorder, and provided a framework to suggest that comorbidity and cue reactivity may powerfully moderate one’s vulnerability as it pertains to disordered gambling behavior.

To date, a few of the most common options for gambling disorder treatment include group psychotherapy, conjoint marital therapy, psychoanalysis, brief therapy, behavioral counseling, cognitive restructuring, hypnotherapy, and pharmacological and physiological treatments. Of these options, the cognitive and behavioral treatments, which include problem solving, social skills training, and relapse prevention, seem to provide the most promise (Petry & Armentano, 1999). However, there is no standard intervention for gambling disorder, and long-term rates of abstinence are alarmingly low. In fact, an analysis of various treatment outcomes revealed that 50% of individuals remain abstinent at 6 months post-gambling involvement, approximately 29% remain

abstinent after 1 year, and only 15% are abstinent after 2 years (Stinchfield & Winters, 2001). Gamblers Anonymous, the most popular form of intervention, has an alarmingly low abstinence rate, with only 8% of patients remaining abstinent after 1 year of treatment (Petry & Armentano, 1999). Studies of epidemiology and co-morbidity demonstrate a large degree of variation within the disordered gambling population, and gambling disorder treatments fail to successfully address comorbidity, cultural influences, and socio-demographic differences within the gambling population.

To better understand the mechanisms that contribute to disordered gambling behavior, future studies will need to address all the factors that contribute to the development and maintenance of gambling behavior and how they interact. This includes co-morbidity across substance-use disorders, particularly alcohol and nicotine use, and anxiety disorders. Crucially, further research is needed to better understand the phenomenon of cross-sensitization between these different disorders in a hope to develop treatments that regulate its effects on cue reactivity and possibly reverse some of the neural adaptations that underlie its development. Studying the combined effects of gambling disorder, substance abuse, and anxiety diagnoses is a crucial next step in understanding the underpinnings of gambling disorder and developing effective treatments.

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