Dopaminergic signalling of uncertainty and the aetiology of gambling addiction

Martin Zack [a, b] Ross St. George [c] Luke Clark [d]

a. Centre for Addiction and Mental Health, 33 Russell St, Toronto, ON Canada M5S 2S1 E-mail: martin.zack@camh.ca Phone: (416) 799-0584 (**Corresponding Author**)
b. Department of Pharmacology & Toxicology, University of Toronto, 1 King's College Circle, Toronto, ON Canada M5S 1A8
c. Department of Psychology, University of British Columbia, Okanagan Campus, 3333 University Way, Kelowna, BC Canada V1V 1V7 E-mail: r.stgeorge@alumni.ubc.ca
d. Centre for Gambling Research at UBC, Department of Psychology, University of British Columbia, Vancouver Campus, 6398 University Blvd, Vancouver, BC Canada V6T 1Z4 E-mail: luke.clark@psych.ubc.ca

Contributions: Martin Zack, Ross St. George, and Luke Clark each wrote sections of the manuscript, and each author reviewed and revised the full manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Disclosures:

Martin Zack	Declarations of Interest: None.
Ross St. George	Declarations of Interest: None.

Luke Clark is the Director of the Centre for Gambling Research at UBC, which is supported by funding from the Province of British Columbia and the British Columbia Lottery Corporation (BCLC), a Canadian Crown Corporation. The BCLC and BC Government impose no constraints on publishing. LC has received speaking/travel reimbursements from the National Association for Gambling Studies (Australia) and National Center for Responsible Gaming (US), and fees for academic services from the National Center for Responsible Gaming (US) and Gambling Research Exchange Ontario (Canada). He has not received any further direct or indirect payments from the gambling industry or groups substantially funded by gambling. He has received royalties from Cambridge Cognition Ltd. relating to neurocognitive testing.

Funding: MZ holds a grant from the National Center for Responsible Gaming (US)

LC is supported by the Centre for Gambling Research at UBC, which was funded by the Province of British Columbia and the British Columbia Lottery Corporation (BCLC). LC holds a Discovery Award from the Natural Sciences and Engineering Research Council (Canada) and a project grant from the BC Ministry of Finance.

These bodies had no involvement in the preparation of this paper and impose no constraints on publishing.

Key Words: Gambling, uncertainty, dopamine, sensitization, electronic gaming machine

Word Count: 8, 467 **Tables:** 0 **Figures:** 1

Abstract

Although there is increasing clinical recognition of behavioral addictions, of which gambling disorder is the prototype example, there is a limited understanding of the psychological properties of (non-substance-related) behaviors that enable them to become 'addictive' in a way that is comparable to drugs of abuse. According to an influential application of reinforcement learning to substance addictions, the direct effects of drugs to release dopamine can create a perpetual escalation of incentive salience. This article focusses on reward uncertainty, which is proposed to be the core feature of gambling that creates the capacity for addiction. We describe the neuro-dynamics of the dopamine response to uncertainty that may allow a similar escalation of incentive salience, and its relevance to behavioral addictions. We review translational evidence from both preclinical animal models and human clinical research, including studies in people with gambling disorder. Further, we describe the evidence for 1) the effects of the omission of expected reward as a stressor and to promote sensitization, 2) the effect of the resolution of reward uncertainty as a source of value, 3) structural characteristics of modern Electronic Gaming Machines (EGMs) in leveraging these mechanisms, 4) analogies to the aberrant salience hypothesis of psychosis for creating and maintaining gambling-related cognitive distortions. This neurobiologically-inspired model has implications for harm profiling of other putative behavioral addictions, as well as offering avenues for enhancing neurological, pharmacological and psychological treatments for gambling disorder, and harm reduction strategies for EGM design.

Words: 239

1. Introduction

The 'brain disease model' of addiction asserts that the symptoms of addiction are caused by chronic exposure to drugs, and that enduring drug-induced changes in neural circuitry mediate these effects (Leshner, 1997; Volkow et al., 2016). Although multiple systems are implicated in this process, the common ability of addictive drugs to activate dopamine (DA) has been cited as critical to their pathogenic effects. By inducing supra-physiological DA activation, drugs are thought to 'hijack' the neurocircuitry responsible for motivating survival-based behaviors (e.g., eating, sex) (Dackis and O'Brien, 2005), so that a bias develops to pursue drugs at the expense of natural reinforcers despite their severe negative consequences.

In recent decades, a set of disorders has emerged whose symptoms correspond closely to those of drug addiction, but whose object is an activity rather than a drug. These 'behavioral addictions' – of which Gambling Disorder (GD) is the prototype and focus of this article – seem to contradict the special status of drugs as agents of addiction (Robbins and Clark, 2015). Instead, these emerging conditions raise the possibility that certain behaviors can engage DA in ways that are functionally similar to drugs, even though no chemical agent enters the brain to instantiate the hijacking process.

Psychological theories that accommodate behaviors as addictive reinforcers have identified key commonalities shared with drugs. The Syndrome Model (Shaffer et al., 2004) emphasizes the shared psychosocial and neurobiological causes and sequelae of substance and behavioral addictions and proposes that any reinforcer capable of reliably modulating subjective state could become addictive. The Components Model (Griffiths, 2005) identifies criteria to be met for a

behavior to be considered addictive, including mood modification, tolerance, and withdrawal. Although these models identify symptom-related similarities of substance and behavioral addictions, they do not specify the psychological variables that allow behaviors to reliably modify mood and reconfigure motivational neurocircuitry, paving the way for addiction. Such understanding is critical for differentiating between behaviors increasingly regarded as potentially addictive (gambling, video gaming) from rewarding behaviors that are presumably unable to induce addiction (a warm bath?).

2. Operant and Pavlovian influences in slot machine gambling

This article seeks to characterize the psychological and neurobiological sequelae of reward uncertainty, which we posit to be the defining feature of gambling (Clark, 2014; Clark et al., 2019; Ferster and Skinner, 1957). We consider these influences primarily in the context of electronic gaming machines (EGMs), a type of gambling that includes slot machines and video lottery terminals, and is widely regarded as among the most harmful forms of gambling (Binde et al., 2017; Markham et al., 2016), although we note that these principles should apply similarly to all modes of gambling. For example, GD subjects exhibit delayed electrophysiological responses to negative outcomes (i.e. impaired negative feedback processing) following risky decisions in a game of blackjack, a form of gambling that, unlike EGMs, is partly skill-based and technologically simple (Kreussel et al., 2013). At a behavioral level, EGM gambling can be considered as an instance of a standard operant learning paradigm, comprising three events. First, a Discriminative Stimulus (i.e. the slot machine) signals reward availability if the operant response is performed. At this time, the gambler may configure his or her betting options (e.g., selecting the bet size). Second, the Operant Response is made (i.e. pressing the spin button). This

initiates a few seconds of anticipation, when the reels spin. Third, the reels stop to reveal whether or not the player has won (the Rewarding Outcome). Importantly, there is no contingency between the response and the occurrence of winning outcomes, which is determined by a random number generator at the moment the response is made.

Pavlovian conditioning, in which a neutral stimulus comes to be associated with an appetitive or aversive stimulus, also plays a clear role in gambling and GD, congruent with its broader role in addictive disorders (Bickel and Kelly, 2019; Everitt et al., 1999). This conditioning ranges from situational effects such as the thrill of entering a casino (Schüll, 2014), attentional biases to gambling-related stimuli (Hønsi et al., 2013), and game-level effects such as the response to win-paired audiovisual feedback on EGMs (e.g., Cherkasova et al., 2018). Pavlovian conditioning facilitates timely responding to stimuli needed for survival. In this way, scarce resources can be rapidly acquired based on their smell or appearance, or rapidly avoided in the case of threats. Other things being equal, the more salient a stimulus (the more readily it captures attention), the greater the likelihood of survival. Stimulus detection is necessary but not sufficient for adaptive responding; the organism must also respond behaviorally. Activation of DA is critical to the behavioral response, by energizing approach and avoidance of salient stimuli (Berridge, 2007). Thus, adaptive responding entails a two-step process – the formation of an association between an initially meaningless object or event (the conditioned stimulus; CS) and an inherently meaningful one (the unconditioned stimulus; US). Pavlovian conditioning denotes the forging of this association such that the CS becomes a signal for the US, a process mediated by the neurotransmitter glutamate (Laroche et al., 1987; Roberts and Glanzman, 2003). The second step, whereby a salient stimulus triggers an overt response is referred to as Pavlovian approach

(or avoidance). DA is posited to be crucial in this process, transforming CS signals for important opportunities or resources into motivational 'magnets' capable of eliciting approach (Parkinson et al., 2002). Such a CS is said to have incentive salience (Berridge, 2007).

3. Dopamine escalation during reward anticipation and relevance to behavioral addictions

Building on extensive research on reinforcement learning, Redish (2004) proposed that the ability of drugs to pharmacologically activate DA enables drug stimuli (including the physical drug itself) to continuously gain incentive salience with each use through temporal difference learning (TDL; Redish, 2004). In the seminal electrophysiological research by Schultz, non-drug reinforcers (e.g., fruit juice) cease to generate a phasic DA spike once their delivery is fully predicted by a Pavlovian cue (Schultz, 1998; Schultz et al., 1997). The key difference with drug-related learning, according to Redish, is that drugs' pharmacological actions enable them to activate DA (directly or indirectly) despite extensive use, and even though their arrival may be fully predicted by conditioned stimuli (e.g., drug paraphernalia). As a result, the incentive salience of drug stimuli may escalate, perhaps indefinitely. By pharmacologically activating DA, drugs create the equivalent of a reward prediction error (RPE) on each administration, leading to a positive feedback loop. This not only reinforces drug taking but also promotes an escalating bias to approach drugs through increased incentive salience attribution (See Figure 1).

[Insert Figure 1 about here]

Redish's formulation is congruent with the influential incentive sensitization theory of addictions (Robinson and Berridge, 1993; Robinson and Berridge, 2001). Accounts that only consider TDL or RPEs do not entirely explain how RPE teaching signals induce approach. Incentive

sensitization asserts a central role for DA in mediating the attribution of incentive salience to CSs for drug rewards, and the expression of this attribution in the form of 'wanting' or learned approach responding. Through their ability to strongly and reliably activate DA, drug consumption then further induces neuroplasticity in underlying brain networks (Robinson and Berridge, 2001). To the extent that this activation exceeds that of alternative rewards in degree or consistency, an addictive US should become preferred relative to alternative rewards, and this bias should in turn extend to the CS for these addictive reinforcers.

The mesolimbic DA pathway projects from the ventral tegmental area (VTA; cell body region) in the midbrain to the nucleus accumbens (NAcc; terminal region). The other two main DA pathways – mesocortical and nigrostriatal – project from the VTA to the prefrontal cortex (PFC) (Hauser et al., 2017), and from the substantia nigra pars compacta (SN; cell bodies) to the caudate-putamen (CPu; terminal region), respectively. The neuroplasticity induced by addictive drugs may also establish new connections among the three pathways; for example, drug use may transition from a flexible, goal-directed behavior (that is sensitive to positive or negative outcomes) to an inflexible, habit-based behavior (that is insensitive to such outcomes)(Everitt and Robbins, 2005). Robinson and Berridge (2001) outlined a range of further neuroplastic changes associated with stimulant drugs (e.g., amphetamine, cocaine), including: increased DA overflow from NAcc synapses; increased sensitivity of post-synaptic D1 receptors; decreased sensitivity of glutamate receptors; and proliferation and lengthening of medium spiny neurons in striatum and PFC, which together enhance functional coupling of regions in the reward circuit.

Based on Redish's account, behaviors with addictive potential, like gambling, should also be capable of promoting escalating TDL, analogous to the pattern described for drugs. In this article, we isolate key aspects of gambling that we expect to engage DA, and describe the neuro-dynamic processes in the DA system that are likely to occur during gambling. We describe how chronic exposure to gambling could modify DA transmission in ways that promote transition to addiction. Based on evidence from humans, including individuals with GD, as well as studies in animals chronically exposed to gambling-like schedules of unpredictable reward, we propose that GD represents a sensitization-like syndrome, similar to that produced by chronic exposure to drugs, especially psychostimulants. We argue that the ultimate pattern of DA response to gambling in a particular individual reflects the influence of three interactive factors: State (e.g., appetite/homeostatic deficit, cues, outcomes) x Trait (e.g., genes, developmental history) x Dose (degree of acute and chronic exposure), much as it does in drug addiction.

In sum, we posit that gambling has addictive potential due to its ability to perpetually engage DA pathways and processes that promote incentive salience of gambling-related stimuli relative to non-addictive reinforcers.

4. Moderators of Incentive Sensitization in Gambling

In the case of gambling, it has long been acknowledged that intermittent schedules of reinforcement create persistent, ingrained patterns of responding (Ferster and Skinner, 1957). By obscuring the prediction of reward by its antecedents (both Pavlovian cues and operant responses), uncertainty ensures that reward delivery during gambling is always a surprise, and therefore capable of evoking an RPE (see Clark et al., 2019; Redish, 2004). Reward uncertainty

has profound effects on DA transmission, as discussed in the next section. But it is worth noting that the uncertainty of trial-to-trial reward (i.e. *whether* the reward is delivered) is not the only means by which an escalating mechanism could operate to promote behavioral addiction. A complementary mechanism allows the *magnitude* of the (uncertain) reinforcement to also vary, and gambling games harness this by typically offering a range of win sizes (e.g., for different symbol combinations on an EGM). It is implemented more pointedly in video game design, in which players work to achieve more points and higher levels, as principles of 'gamification' (c.f. Dicheva et al., 2015; Shen and Hsee, 2017). A second possibility is to offer an unlimited range of versions of the rewarding stimulus, so that each distinct version evokes an RPE and concomitant spike in phasic DA (c.f. Takahashi et al., 2017). Uncertainty in the timing of reward delivery can also modulate RPE signalling, particularly in the context of dual uncertainty over whether the reward itself will be delivered (Starkweather et al., 2017). These cases highlight the opportunities for games (gambling or video games) to layer multiple sources of uncertainty to generate RPEs that will persist over time.

At the same time, much of day-to-day life entails some degree of uncertainty, but most daily activities are not addictive. Berridge noted that state factors powerfully influence the attribution and expression of incentive salience (Berridge, 2012). A CS for food will have high incentive salience when an animal is hungry but the same CS may be considered irrelevant or even noxious when the animal is sated. This underscores the principle that DA does not encode an inherent association between CS and US, because this relationship is dynamic based upon motivational state. Other things being equal, the greater the need state for a specific reward, the greater the incentive salience of a CS for that reward and corresponding DA activation.

In the absence of a strong appetite/need state, a highly salient reward may still evoke reward seeking. This may partly explain the impact of early Big Wins on development of gambling problems (Turner et al., 2008), by creating inflated reward expectancies that are hard to fulfill. Conversely, genuine deficits in reward (e.g., large debts) should promote persistent pursuit of large (but not normative) payoffs in people with GD, much as an individual addicted to drugs may seek high doses and experience increased appetites (priming) from modest doses that might satiate a recreational drug user. Coupled with state differences in 'appetite' are differences in the passive, coping-based effects of gambling for GD vs. non-GD gamblers. That is, the incentive value of gambling for people with GD may also derive from the ability of gambling, and EGMs specifically, to create an immersive state to temporarily escape conscious concerns (sometimes referred to as 'dark flow') (Dixon et al., 2018; Murch et al., 2017)

In sum, the incentive value of gambling to a person with GD will vary with his/her financial state and tolerability of his/her current cognitive-emotional state.

5. Neuro-dynamics of reward uncertainty

In a seminal study linking DA signalling with reward uncertainty, Fiorillo et al recorded the activity of midbrain DA neurons during an appetitive Pavlovian task in monkeys (Fiorillo et al., 2003). The task involved multiple discrete visual CSs that predicted fruit juice US, and the critical manipulation was the relationship between CS and US, varying from impossible (0%) to certain reward (100%) in 25% steps. In the two best-known conditions (Schultz, 1998), DA neurons in the 0% condition fired phasically to the receipt of the (unexpected) juice US, whereas

in the 100% condition, DA neurons fired to the predictive CS and not the US. The novel finding pertained to the intermediate probabilities: during the CS-US interval, DA neurons displayed a gradual escalation in tonic firing intensity from CS onset to the expected time of reward delivery. This DA activity was maximal in the 50% condition, when the CS-US relationship was maximally uncertain, but could also be discerned at the 25% and 75% conditions, which is important given the range of probabilities that occur in real-world gambling (see Lidstone et al., 2010; Zald et al., 2004). Subsequent findings suggest that concomitant signaling of reward *proximity* (time until delivery) by the CS, rather than reward *uncertainty* alone, may be critical for this effect (Howe et al., 2013; Mikhael et al., 2019). As a further nuance relevant to gambling and other behavioral addictions, DA activity was greatest when the size of the reward was also most variable (Fiorillo et al., 2003, Figure 4); which illustrates the layering of uncertainty outlined earlier. Fiorillo et al posited that the additional DA activity in the CS-US interval, corresponding to the reel spin on an EGM, could reinforce gambling behavior, operating over and above the phasic spikes to intermittent wins. It is conceivable that these sustained DA signals could also be subjectively reinforcing, corresponding to 'hope'. Notably, Fiorillo et al reported that the monkeys' anticipatory licking of the spout that delivered juice reward increased directly with the probability of reward delivery but did not differ between rewarded and unrewarded trials (confirming trial-to-trial uncertainty of reward delivery). That is, appetitive behavior appeared to reflect relative confidence in reward delivery in response to the different CSs.

Subsequent studies with rats have demonstrated the impact of reward uncertainty on incentive and behavioral (i.e. locomotor) sensitization. Psychostimulants are noted for their reliable ability to induce such sensitization (Kuczenski and Segal, 1988). *Intermittent* dosing of stimulants leads

to particularly robust sensitization (Kawa et al., 2016), and intermittency may even determine whether or not sensitization will emerge (Calipari et al., 2013). Robinson et al. manipulated the consistency of CS-US mapping, size of the US, and location of the CS/operandum (lever) such that each association was highly uncertain (MJF Robinson et al., 2014). Compared to animals trained under conditions of certainty, animals trained under high uncertainty developed a pronounced bias to approach and interact with the CS/operandum. This behavior escalated from looking to approaching to sniffing to biting of the lever, as animals experienced increasing uncertainty exposure. This illustrates the progressive escalation in appetitive behavior predicted by Incentive Sensitization Theory, and the putative pattern expected of a gambler becoming increaingly obsessed with the game. No such pattern was evident in animals trained under certainty. The behavior exhibited by the uncertainty-trained animals is referred to as 'sign-tracking,' and is characterized by preferential attention and motivated interaction with the CS rather than US (e.g., food)(Blaha et al., 1997). Although trait factors can strongly influence sign-tracking (Flagel et al., 2007), because the animals were randomly assigned to each reward condition, selective development of sign-tracking in the uncertain condition indicates that the behavioral profile was induced by uncertainty exposure.

Whereas sign-tracking may reflect a trait bias, 'autoshaping' refers to experimental induction of sign-tracking, such that a CS that is noncontingently paired with reward acquires the ability to elicit approach and behavioral interaction. Uncertainty-induced autoshaping is hypothesized as a model of the compulsive reward-seeking ('chasing') exhibited by people with GD (Anselme and Güntürkün, 2019). Accordingly, animals that underwent uncertainty training in MJF Robinson et al.'s (2014) studies displayed an increase in risky (i.e. gambling-like) behavior, approaching a

lever in an open (risky) vs. closed (safe) arm of a training box more than animals trained under conditions of certain/consistent reward delivery.

Other research using a rat gambling task (rGT) has shown that exposure to uncertainty in an instrumental paradigm can also produce risky behavior, even in the absence of a reward-related CS. Using a procedure previously found to promote increased locomotor response to amphetamine (Singer et al., 2012), Zeeb et al. trained animals to nose poke for saccharin reward delivered under a fixed (FR) or variable (VR) ratio schedule, in the absence of cues or operanda, and found that the animals that had undergone unpredictable reward delivery (VR) later displayed significantly more risky decision making on the rGT than FR/certainty-trained animals (Zeeb et al., 2017). The uncertainty-trained animals also displayed increased locomotor response to a challenge dose of amphetamine, a common behavioral proxy for DA sensitization. Thus, it appears that uncertainty-induced DA sensitization and gambling-like behavior can emerge in the absence of Pavlovian cues for unpredictable reward.

More recently, Mascia et al. (2019) found that the same VR training regimen that led to increased locomotor response to amphetamine and risky decision-making on the rGT (Singer et al., 2012; Zeeb et al., 2017) also increased DA release in the NAcc in response to an amphetamine challenge, strongly indicating that the prior behavioral expressions of sensitization were indeed due to increased striatal DA release. VR/uncertainty-exposed animals also displayed increased amphetamine self-administration in a drug-seeking test, relative to FR/certainty-trained animals (Mascia et al., 2019).

Translating these preclinical phenomena to humans, and establishing the pathophysiological relevance to GD is not straightforward. Although it is possible to manipulate DA transmission in humans using pharmacological challenge designs (e.g. placebo-controlled administration of amphetamine) and to quantify DA release using PET imaging with DA radiotracers like [11C]raclopride, neither methodology offers temporal resolution at an event level to characterize DA responses. These constraints notwithstanding, a landmark study by Zald et al. used raclopride PET to quantify DA release to a simple operant task in healthy volunteers, testing an FR condition, in which the subject won on every fourth trial and a VR condition in which the same rewards were delivered unpredictably on 1 in 4 trials (loosely akin to the 25% Pavlovian condition of Fiorillo et al., 2003)(Zald et al., 2004). Relative to visuomotor baseline, the VR condition elicited significant striatal DA release, whereas the FR condition did not (Zald et al., 2004). Related work has tested the placebo effect to levodopa medication in patients with Parkinson's Disease, using the [11C]raclopride PET ligand. An initial study found that Parkinson's patients displayed significant DA release to a placebo that substituted for a dopaminergic medication (De la Fuente-Fernández et al., 2001; Lidstone et al., 2010). A follow-up study tested different probabilities of receiving the medication (25%, 50%, 75%, and 100%, manipulated by verbal instruction) in a four-group design, and DA release was only reliable in the 75% condition

To examine DA sensitization in GD, Boileau et al. measured displacement of the DA D3-receptor preferring radiotracer, [(11)C]-(+)-PHNO during an amphetamine challenge (Boileau et al., 2014). They observed a greater reduction in striatal PHNO binding potential in the GD group relative to healthy volunteers, indicating heightened DA release in GD. This finding resembles

the increased amphetamine-induced striatal DA release seen in animals exposed to chronic reward uncertainty via a VR schedule of saccharin reinforcement (Mascia et al., 2019).

In the Boileau et al (2014) study, amphetamine-induced DA release correlated with more rapid (i.e. partially automatized) betting responses in the GD subjects during an off-line episode of EGM play. Likewise, rats that underwent chronic VR training similar to the regimen used by Mascia et al. subsequently displayed indiscriminate decision-making on the rGT, whereas control rats displayed consistently advantageous rGT responding (Zeeb et al., 2017). Collectively, these findings provide empirical support for the possibility that GD is a sensitization-like syndrome, caused in part by chronic exposure to intermittent, unpredictable reward and mediated by sustained hyper-reactivity of brain DA pathways.

The functional role of sustained (or tonic) DA activity in these effects remains less clear. Hernandez et al. recorded NAcc dialysate to predictable vs unpredictable intra-cranial brain stimulation, and observed no differences in DA overflow (Hernandez et al., 2008). More recent work has examined sustained DA activity using fast-scan cyclic voltammetry. In an experiment where rats navigated a maze that took between 5 and 10 seconds to reach their food goal (Howe et al., 2013), DA activity escalated progressively as the distance to the goal decreased, but this effect did not change as a function of learned performance. This was interpreted as evidence that uncertainty was not the mediating mechanism. However, a subsequent paper using the same procedure did find evidence for dissociable sustained and phasic components of DA release from NAcc, with the sustained component scaling with reward variance (i.e. uncertainty) and stable over learning (Hart et al., 2015).

Separating phasic and tonic DA activity in humans is particularly challenging. An early study by Dreher et al. used an fMRI design in which different slot machines were paired with 50%- or 25%-win probabilities, with a lengthy (14-s) delay between the cue and reward (Dreher et al., 2005). Comparing delay-related activity between the 50% and 25% cues revealed activity in the midbrain and ventral striatum, whereas midbrain and prefrontal cortex showed a cue-related (i.e. phasic) response to reward expectation. More recently, Rigoli et al. used a rewarded visual search task in which 'baseline' monetary reward varied on a block-to-block basis, and further trial-by-trial rewards were available for correct responses (Rigoli et al., 2016). Critically, by revealing the baseline reward one block in advance, Rigoli et al. could separate the (phasic) RPE to discovering that the future block will be better or worse than average, from the tonic signal to the current level of reward. Under these conditions, a tonic response coding the average reward level was detected in the fMRI signal in the dopaminergic midbrain, and this signal further correlated with response vigor, coded as key press force. Thus, tonic DA does appear to register aggregate reward over the course of decision trials in humans, and this effect coincides with psychomotor activation. These human models have yet to be tested in people with GD.

In the case of addiction, Grace proposed that sensitization entails an increase in tonic DA activity that preferentially stimulates high-affinity dopamine D2 auto-receptors, which in turn act to oppose phasic stimulus-induced DA release. He used this model to explain tolerance to the rewarding effects of addictive drugs (Grace, 2000). Increased tonic DA firing could also reduce detection at high affinity D2 receptors of the DA pauses to expected reward omission (discussed in detail below). If sensitization were to enhance tonic DA firing, these effects and the

accompanying increase in D2 receptor stimulation could disrupt calibration of approach and avoidance responding and compromise extinction learning. Accordingly, Evers et al. reported that methylphenidate, a drug that acts primarily to increase tonic DA levels, systematically reduced striatal fMRI responses to gains and losses in a gambling task (Evers et al., 2017). Such effects may also contribute to chasing in people with GD. In a study of healthy volunteers, a low dose of the D2 antagonist, haloperidol increased approach responses to CSs for reward ("Go" stimuli) by removing negative feedback, increasing DA release, and enhancing phasic D1 stimulation to RPEs (Frank and O'Reilly, 2006). In contrast, stimulation of D2 auto-receptors with a low (auto-receptor-preferring) dose of the D2 agonist, cabergoline impaired conditioned approach responding.

To investigate these effects in GD, Tremblay et al. administered a sub-clinical dose of haloperidol (3-mg) in a 2 x 2 design (GD vs healthy controls, placebo-controlled) (Tremblay et al., 2011). Following dosing, subjects played an authentic slot machine, where the analysis tested the coupling between credits won on a given trial and bet size on the following trial. Under placebo, controls showed a modest but reliable positive correlation between wins and bet size, which was not consistently found in the GD group. Haloperidol restored the win-bet coupling in the GD group, inducing a behavioral profile similar to the placebo pattern in healthy controls. Importantly, the prospective correlation between reward and bet size on consecutive trials in Tremblay et al.'s study emerged despite the lack of contingency between the two events, indicating that random outcomes can reinforce gambling behavior by exploiting the same circuitry that guides adaptive reward-seeking behavior.

In sum, evidence from healthy humans and individuals with GD aligns with data from animal models of uncertain reward exposure to indicate that gambling schedules can alter neurocircuitry in a manner similar to addictive drugs, and raising the possibility that sensitization-related elevations in tonic DA signaling at D2 receptors may drive disruptions in outcome processing that could contribute to chasing behavior in GD.

6. Omission of expected reward as a stressor

The flipside of uncertain reward delivery on VR schedules is the omission of expected reward (OER). In an episode of commercial slot machine gambling, the player will experience reward delivery and omission with roughly equal frequency (i.e. akin to the 50% maximally uncertain condition of Fiorillo et al (2003) (Tremblay et al., 2011). DA neurons also register OERs as negative RPEs, seen as a phasic pause ('dip') in firing rate (Schultz et al., 1997). In fact, chronic OER is a reliable stressor in animal studies, and repeated episodes of OER sensitize the DA system to subsequent stressors, such that DA response is potentiated and DA D1 receptor mRNA is reduced relative to unstressed animals (Burokas et al., 2012; Papini and Dudley, 1997; Vindas et al., 2014). In humans, frustration is a logical subjective correlate of OER (Gipson et al., 2012). Based on fMRI data from healthy humans, Abler et al posited two neural responses to OER: an allocentric response to the environmental violation (expressed as decreased ventral striatum activity, analogous to the pause in DA firing) and an egocentric response denoting the subject's evaluation of his/her state in light of the negative outcome, and centring on emotional frustration. The latter was expressed as increased right insula and ventral PFC activity (Abler et al., 2005). Thus, over repeated episodes of EGM gambling, recurrent activation of stress neurocircuitry by OER may amplify the effects of intermittent reward on DA sensitization (Biback and Zack,

2015; see Bjork et al., 2008; Lavezzi and Zahm, 2011). Such events could promote seeking of a Big Win to alleviate the stress of accumulated losses and unfulfilled expectancies, and also decrease the ability of reward omission to extinguish further gambling.

As discussed earlier, state influences moderate DA responsivity, and stress states may be one such influence, operating via hypothalamic pituitary adrenal (HPA) stress axis interactions with mesolimbic circuitry (Berridge, 2012). As evidence for these mechanisms, sign-trackers release more corticosterone (rodent analogue to cortisol in humans) as well as DA in response to reward cues, and this pattern is amplified by microinjection of CRF into the NAcc shell (Flagel et al., 2009; Peciña et al., 2006; Tomie et al., 2004). Furthermore, the same GD subjects who exhibited increased amphetamine-induced DA release in the PHNO-PET scan also displayed significant deficits in pre-drug cortisol levels, and these deficits were reversed by amphetamine (Zack et al., 2015).

Other emerging evidence identifies a midbrain structure proximal to the VTA called the habenula, and particularly the lateral habenula (LHb), as relevant to OER. This structure has been characterized as a critical node in the brain's "anti-reward system" (Mathis and Kenny, 2018). The LHb exerts an inhibitory effect over midbrain DA neurons. Lesions of this structure reinstate DA responses to reward omission even though DA responses to aversive stimuli themselves remain unchanged (Tian and Uchida, 2015). Thus, the LHb appears to be especially important for registering and effecting responses critical to extinction. Importantly, LHb lesions also impair the ability of DA neurons to reliably signal *graded* positive RPEs without fully inhibiting DA signalling (Tian and Uchida, 2015). That is, the LHb appears to be important for

maintaining the fidelity of DA response to complex and subtle variations in reward and loss signaling. Chronic cocaine exposure leads to a parallel reduction in the fidelity of these inputs, to size, timing and overall value (Takahashi et al., 2019), suggesting that impaired LHb functioning may mirror some aspects of psychostimulant sensitization. Studies using optogenetics reveal that selectively silencing the hypothalamus-to-habenula pathway disrupts avoidance learning (Trusel et al., 2019), further suggesting involvement of the HPA stress axis in the behavioral influence of the habenula. In healthy humans undergoing fMRI, positive and negative deflections in habenula activity tracked CS exposure to aversive vs. rewarding outcomes, and also predicted behavioral invigoration (Lawson et al., 2014). Thus, impairment of the habenula appears to *disinhibit* (i.e., invigorate) DA responses in a manner that resembles the increase in progressive ratio responding seen in animals chronically exposed to reward uncertainty (MJF Robinson et al., 2019, Exp. 2).

Regardless of the outcome (win or lose) on any given trial, continued gambling is *prima facie* evidence of an expectation of reward. This is corroborated by self-reports of people with GD who chase losses (Gainsbury et al., 2014). In this situation, CSs for monetary reward can serve as reminders of this expectancy and amplify its intensity (i.e. increase wanting). In this context, OERs signal an increase in the need state of the gambler that may be expressed instrumentally as chasing. Chasing losses in people with GD indicates a failure to use feedback about negative outcomes over trials to change response strategy, e.g., by stopping gambling. The habenula has extensive connections to the striatum, amygdala and PFC, permitting a wide range of modulatory effects (Graziane et al., 2018). Chronic OER also induces neuroplasticity in this circuitry, such that the medial habenula assumes greater influence than the LHb (Batalla et al., 2017). This plasticity appears to coincide with a shift in motivational focus from reward seeking to "misery

fleeing" (Batalla et al., 2017), and by analogy, chasing in GD may entail a transition to negative reinforcement or relief-seeking (c.f. Campbell-Meiklejohn et al., 2011) that is exacerbated by ongoing reward omission.

In sum, OER may contribute to the induction of incentive sensitization arising from reward uncertainty, and these effects may be mediated by stress, impairment of the habenula and linked circuitry that is critical for feedback processing, updating of behavior, and negative reinforcement, potentially establishing a mechanism for loss chasing in people with GD.

7. Resolution of reward uncertainty as a source of value

The discussion so far has blended research findings using operant tasks (e.g., Howe et al., 2013; Zald et al., 2004) and appetitive Pavlovian conditioning (Fiorillo et al., 2003), acknowledging that both influences are present in gambling. Indeed, it may be argued that Pavlovian (CS-US) and operant (R-S_R) learning are functionally equivalent, inasmuch as each process trains an *expectancy* (Bolles, 1972). This framework emphasizes the cognitive nature of reinforcement as a mental representation of the contingency. In this regard, an important distinction should be made between reward prediction and reward expectation. The former implies a specific outcome probability that can be confirmed or refuted (RPE) on each trial; the latter denotes a more pervasive process (akin to 'hope' or 'desperation') that may not be readily refuted or extinguished (see Anselme and Güntürkün, 2019; Collins et al., 2016; Koob, 2017), and may persist as long as the gambler has resources to play (c.f. Abler et al., 2009).

In conditions of uncertainty, actions taken to obtain reward (gambling) may be construed as hypothesis testing of reward expectancies. In an active inference framework, phasic and tonic DA establish expectancies by means of bottom-up and top-down processing, respectively (Friston et al., 2012): phasic DA encodes *Bayesian surprise* (probabilistic reward delivery) while tonic DA encodes *epistemic value* – motivation for an even better, but uncertain reward. Adaptive behavior involves a trade-off between these pragmatic and epistemic goals, which corresponds to the exploit-explore distinction in behavioral ecology (Addicott et al., 2017). Exploit decisions capitalize on current opportunity, whereas explore decisions forego current opportunities in order to discover new resources. Tonic DA transmission has been posited to reflect the shift from exploit (low) to explore (high) responses (Beeler et al., 2012), and high tonic DA can also render the decision-maker insensitive to valuable currently available options (Beeler et al., 2010).

In this framework, it is not uncertainty *per se* that provides 'value' for decision-making. Rather, the reduction in, or resolution of, uncertainty offers value by supporting future goal-directed behavior (Pezzulo and Friston, 2019). Shen et al. compared motivated behavior in healthy humans under conditions where each response (e.g., running a lap around a track) was incentivized either by a certain or uncertain reward. Subjects were more likely to repeat these behaviors when the reward was uncertain, even when the certain reward was more valuable (e.g. 5 points for certain, vs. 3 or 5 points uncertain) (Shen et al., 2018). Critically, this effect was observed in 'continuous' tasks and only when the uncertainty was resolved immediately upon completion of each round. Thus, uncertainty is attractive when its resolution confers information

about ongoing performance, and this is an important distinction from other phenomena in behavioral economics where unknown options are typically avoided (c.f. ambiguity aversion).

The relevance of uncertainty resolution to gambling is perhaps obvious, especially in continuous forms of gambling like EGMs where the operant response can be repeated immediately. The occurrence of a win not only signals a focal reward, but also informs the gambler's decision-making strategy by resolving a deficit in 'epistemic value': *You got what you expected, so your strategy is sound*. Based on evidence of impaired processing of moderate win and loss outcomes in GD (de Ruiter et al., 2009), it is possible that only highly salient outcomes can confer sufficient information to resolve these individuals' deficit in epistemic value, whereas normal feedback signals (modest wins) fail to 'satiate' this excessive appetite (e.g., a sense that one is 'due' for a Big Win). This explanation aligns with research in healthy volunteers who exhibit riskier choices and blunted phasic responses to unexpected wins in basal ganglia and midbrain after an acute dose of the D2/3 agonist pramipexole (a medication linked with *de novo* GD in patients with Parkinson's disease)(Riba et al., 2008). Thus, pharmacological increases in D2/3 signaling – similar to the putative increase in D2 signaling by tonic DA during sensitization (Grace, 2000) – can induce a state that is functionally similar to GD. The precise mechanisms that mediate this effect in GD, and their subjective-motivational correlates are important issues for future investigation.

In sum, uncertainty may motivate reward seeking by creating a state that demands resolution. In this regard it is similar to the effects of hunger, thirst and libido which motivate behaviors that

resolve their respective appetites. In gambling, uncertainty may thus reflect a kind of cognitive appetite.

9. Structural characteristics of modern Electronic Gaming Machines (EGMs)

Modern EGMs contain an array of psychological ingredients, termed structural characteristics that are thought to account for why gamblers choose, and persist in gambling on, certain games over others. While there is no universally accepted classification of these structural characteristics – partly due to their ongoing evolution via new technologies – several variables are widely recognized as appealing to individuals with GD, and relevant to regulation of gambling products (Griffiths, 1993; Meyer et al., 2011).

9.1 *Illusory Control.* Uncertainty is intimately related to the capacity for agency and control: resolution of uncertainty can only benefit ongoing behavior if the animal has some control of its environment. Many gambling games offer opportunities for choice or instrumental action (e.g. pressing a button, throwing a ball) that do not objectively alter the likelihood of winning, therefore representing instances of illusory control (Langer, 1975; Stefan and David, 2013). Despite their simple operanda (the spin button), these features are nevertheless present in EGMs; for example, the ability to change the number of lines or size of the bet. A more direct example on some EGMs is the 'stop button', a device that enables the gambler to brake the reels during the spin. This feature has been associated with faulty cognitive beliefs about the game (Ladouceur and Sevigny, 2005) and also permits a faster speed of play (see Event Frequency, below) (Chu et al., 2018), and stop buttons are prohibited in some jurisdictions. By extrapolation to everyday operant devices (e.g., vending machines), the stop button becomes a discriminative

stimulus and the button press an apparent cause. Employed in this way, stop buttons exploit a process known as 'intentional binding' whereby contiguity between action and outcome creates an erroneous belief in agency (see Tobias-Webb et al., 2017 for demonstration of the link between gambling-related illusory control and intentional binding). Dopaminergic agents can also modulate intentional binding (Moore et al., 2010), and elevated DA availability has been implicated in increased sense of agency regarding coincidental outcomes (Render and Jansen, 2019). Similarly, DA activation during EGM play could promote a sense of agency, with associated effects on reward expectations and seeking behavior, and a sensitized DA system may make GD players especially prone to such effects. Accordingly, GD induced by DA agonist medication in patients with Parkinson's disease is characterized by erroneous (high) intentional binding (Ricciardi et al., 2017).

9.2 *Event frequency*. A critical determinant of gambling-related harm is event frequency. EGMs are a form of gambling with one of the highest event frequencies. Using a modern, authentic slot machine that was studied in a laboratory environment, experienced gamblers were found to play 10.5 to 16.6 spins per minute (Chu et al., 2018). This equates to a spin every 3.6 – 5.7 seconds, affording 300 – 500 events within just a 30-minute period of play. EGM features like stop buttons contribute to this accelerated play (Chu et al., 2018). Regular gamblers prefer EGMs that offer faster speed of play, and people with GD tend to play more quickly (Harris and Griffiths, 2017; Linnet et al., 2013). Because each gamble holds a negative (objective) reward expectancy (i.e. credits lost > credits won), higher event frequencies result in greater financial losses within a fixed session length. From the standpoint of neuro-plasticity, the high addictive potential of EGMs can be partly attributed to the brute effects of repetition on

learning. But in addition, the assumed compression of positive and negative RPEs within such a session may correspond to the intensity of sensitization induced by intermittent dosing with psychostimulants (Calipari et al., 2013; Kawa et al., 2016).

9.3 *Near Miss Events.* In decision-making research, choice outcomes are typically considered in binary terms: win or lose. Gambling, as well as other real-world examples like competitions, involves events that blur this distinction. A near-miss is an outcome that is objectively a loss but is somehow perceptually close to a win (thus technically, these events may be more accurately labelled 'near-wins'). Although near-misses occur across all forms of games, the potential to engineer an elevated rate of near-misses in EGMs, coupled with evidence that disordered gamblers show amplified striatal responses to near-misses (Chase and Clark, 2010; Sescousse et al., 2016), creates a need for careful regulation (Harrigan, 2007). With regard to the DA neuro-dynamics outlined above, near-misses may fuel DA sensitization in several ways. First, near-misses may be interpreted as evidence of skill acquisition, operating to enhance the illusory control described above. In support of this, Clark et al. observed that the subjective and neural effects of slot machine near-misses were primarily observed when the subject could configure their gamble (by choosing a 'play icon') and not when such agency was lacking (Clark et al., 2009). It should also be noted that near-misses are not instantaneous events. There is a temporal unfolding that entails both reward expectancy and uncertainty resolution. For example, on a traditional slot machine, the reels stop in a sequence, so that when the second reel matches the first reel, a reward expectancy is triggered. On many commercial EGMs this is accompanied by audiovisual cues that compound the expectancy. This is shortly followed by a non-match on the third reel. Delivery of this OER at an acute moment of reward expectation could amplify the

subjective experience of frustration in ways similar to those described by Abler et al (2005), although the details remain to be determined empirically. As evidence for the role of the initial expectancy, Wu et al. masked the spinner on a wheel of fortune task during the anticipatory period, and found that the response to near-miss outcomes (both near-wins and near-losses) was markedly blunted (Wu et al., 2017, Exp. 2).

9.4 *Losses Disguised as Wins*. The multi-line nature of EGMs enables several bets to be placed on a single spin, setting up the possibility of a "Loss Disguised as a Win" (LDW) in which that spin's payoff (e.g., 25 credits) does not cover the bet (e.g., 50 credits). LDWs generate psychophysiological responses that are qualitatively similar to full wins, and also promote over-estimation of the perceived frequency of wins tested after the game (Jensen et al., 2013). The distortion also relies on the selective pairing of reinforcement with audiovisual feedback (bells, lights) and can be corrected by presenting discriminatory feedback to LDWs and wins (Dixon et al., 2015). These features of payoffs on EGMs increase the salience of reward delivery without correcting for less obvious net losses. As a result, it is possible that, over the course of a gambling episode tonic DA may convey an inflated estimate of long-run reward (c.f. Daw and Touretzky, 2002).

In sum, structural characteristics of EGMs – whether by coincidence or design – seem to harness the neuro-dynamic processes that recruit mesolimbic DA and incentive salience mechanisms. Regulation of the specific features that promote this process may reduce the addictive potential of these games, especially in GD individuals who may be sensitized to their effects.

10. The 'aberrant salience' hypothesis of psychosis and gambling-related cognitive distortions

Distinctive, intense, appetitive, or aversive stimuli are all salient and attention-grabbing because they promote survival. Conversely, physically unremarkable stimuli like money can also come to capture attention via acquisition of incentive salience (Berridge, 2007), and is thought to be a primary mechanism in addictions. But under conditions where tonic DA is elevated, salience may also be accorded to stimuli that are *not* objectively important, perhaps through a resemblance to stimuli with intrinsic survival value. For example, irregular shapes (a bush in a dark forest) may be misperceived as threatening. The concept of *aberrant salience* was introduced to explain extreme manifestations of this process: hallucinations and delusions - objectively false perceptions and beliefs imbued with meaning – in people with schizophrenia (Kapur, 2003). Hyper-sensitivity of D2 receptors is a hallmark of schizophrenia (Seeman, 2013), and selective D2 blockade with antipsychotic drugs may be an effective treatment by reducing aberrant salience (Howes et al., 2009). By implication, people *without* schizophrenia who have increased D2 expression/sensitivity or elevated tonic DA activity could fall prey to similar misattributions. Such a process may help to explain how in GD, random numerical patterns, sensory cues, or behavioral sequences become signals for reward, capable of promoting continued betting, when the objective long-run expectancy of reward is negative.

Associations between disordered gambling and psychosis are evident from the clinical literature, but mechanistic research is scant (Pullman et al., 2018). Individuals with psychotic disorders are at a fourfold higher risk of problem gambling than the general population (Haydock et al., 2015) and the presence of psychosis is associated with increased gambling severity (Cassetta et al.,

2018). The antipsychotic aripiprazole has also been linked to emergence of problematic gambling, in a comparable manner to the medication syndrome in Parkinson's Disease, where DA D2/3 agonists (e.g., pramipexole) can induce disordered gambling and other reward-driven behaviors (e.g., hypersexuality, compulsive shopping) as a side-effect (Weintraub et al., 2006). In the case of aripiprazole, induction of GD may arise from its action as a D2/3 partial agonist (Smith et al., 2011). In linking these effects to aberrant salience, a large PET study in healthy volunteers (n = 58), found that individual differences in presynaptic striatal DA correlated *negatively* with RPE signals in the PFC and ventral striatum (Boehme et al., 2015). This may be surprising given that RPEs are salient events registered by prefrontal and ventral striatal phasic DA (Corlett et al., 2004; D'Ardenne et al., 2008). Using a Salience Attribution Test (SAT) that measured the ability to rapidly discriminate cues linked with high vs. low reward, subjects with high basal DA levels not only registered weaker RPEs, but also failed to discriminate behaviorally between cues for high vs. low reward. Boehme et al invoked the concept of aberrant salience to explain this impaired discrimination learning. A similar pattern was found in Parkinson's patients who received DA D2/3 agonist medication for 12 weeks before testing on the same salience paradigm (Nagy et al., 2012). Thus, pharmacologically augmenting basal DA at D2 receptors can *induce* a state of aberrant salience.

Aberrant salience can also apply to OER: when tonic DA is elevated (e.g., in later stages of a gambling episode), the registration of phasic pauses in DA firing may be impaired, so that OER does not lead to avoidance / extinction. Illustrating such a mechanism, unmedicated patients with schizophrenia performing a monetary incentive delay task did not display the typical pattern of neural differentiation between trials where losses were successfully avoided versus trials where

they failed to avoid the loss (Schlagenhauf et al., 2009), and delusion severity further predicted this impaired discrimination. Disturbed negative feedback processing similar to the pattern seen in people with schizophrenia may also disinhibit reward seeking in people with GD by impeding registration of events that would otherwise promote extinction via LHb activation (Stopper and Floresco, 2014). Starkweather et al. noted that the "medial prefrontal cortex shapes dopamine reward prediction errors under state uncertainty" (p. 616) by drawing inferences about 'hidden states,' when signals are ambiguous (Starkweather et al., 2018). Perseverative errors have been linked with PFC hypoactivation to both rewards and punishments in GD (de Ruiter et al., 2009), consistent with impaired integration of LHb-PFC circuitry (Baker et al., 2016). Such mechanisms could be usefully tested in the context of chasing in GD.

Lastly, as alluded to above, aberrant salience in GD is a ***state*** that varies with exposure to the game. By activating DA, EGMs could transform otherwise latent beliefs about gambling into immediate, vivid, and hard-to-ignore convictions that drive persistent gambling behavior. This aligns with the presumed role of DA in aberrant salience in psychotic experience (Kapur, 2003), where DA is posited to act as the "wind in the psychotic fire" (Laruelle and Abi-Dargham, 1999). Similarly, misattributions in people with GD may derive from *temporary* hyper-activation of D2 receptors as tonic DA levels escalate over the course of a game.

In sum, elevated DA signalling arising from incentive sensitization in GD could promote cognitive distortions via an analogous mechanism to that posited for psychosis. This state could further disturb negative feedback processing and promote perseverative responding.

11. Conclusions, Limitations, and Future Directions

This article has proposed that bouts of intermittent DA activation and quiescence, together with repeated episodes of uncertainty during gambling can fool the DA system into perceiving contingencies that do not exist, or believing that a future reward is more likely than it actually is. At the 'state' level, acute activation of DA by such cues could promote approach and discourage avoidance or cessation of gambling during an episode of EGM play by augmenting incentive salience. We surmise that, over time, exposure to this constellation of events can disturb the finely-tuned neurocircuitry that guides adaptive behavior, leading to drug-like sensitization and misperception of apparent signals for reward.

This account has several limitations. First, our arguments were largely based on indirect evidence. Second, multiple neurotransmitters apart from DA appear to influence reward- and loss-processing including serotonin, glutamate, GABA, and endogenous opioids (Leeman and Potenza, 2012). More research is required to fully delineate these processes and leverage this knowledge into medications for GD. Third, individual differences will profoundly influence how EGM play will impact brain DA function. Given that only a minority of gamblers develop GD, investigation of genetic and epigenetic interactions is an important avenue of future research. Accordingly, researchers should beware a one-size-fits-all explanation of GD symptoms or EGM gambling.

The main goal of this analysis was to inform the development of interventions for GD (cognitive therapy, brain stimulation, medication), and identify features of EGMs that could be targeted to most effectively reduce their harmful effects. In line with its benefits in other addictive disorders,

a harm reduction approach could be fruitfully applied to GD (Langham et al., 2015; Wardle et al., 2019). In terms of acute exposure to EGMs, built-in time outs could temper the escalation of tonic DA that we suggest partly mediates chasing (Auer and Griffiths, 2015; c.f. Blaszczynski et al., 2016). These 'intermissions' could also provide an opportunity for casino staff to check in with players to gauge their current risk (e.g., accumulated debt) or for players themselves to implement disengagement strategies like CBT. To minimize design-related erroneous cognitions, interventions should explicitly identify the discrete events that occur during an EGM trial; emphasize that they are arbitrary, and explain how contiguity can create the illusion of causality by exploiting the brain's built-in perceptual processes (e.g., Broussard and Wulfert, 2019). Given the pivotal role of experience-dependent plasticity in GD, treatments that can target and reverse this process (e.g., non-invasive brain stimulation) may be especially valuable (Dickler et al., 2018). Such treatments can be applied alone or combined with medications that promote plasticity (e.g., glutamatergic agents). More generally, treatments that help to restore the regional balance of phasic and tonic DA signaling may be a promising means to alleviate sensitization-related neural perturbations in people with GD (Creed, 2017).

References

Abler, B., Hahlbrock, R., Unrath, A., Grön, G., Kassubek, J., 2009. At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists. Brain 132(9), 2396-2402.
Abler, B., Walter, H., Erk, S., 2005. Neural correlates of frustration. Neuroreport 16(7), 669-672.
Addicott, M.A., Pearson, J.M., Sweitzer, M.M., Barack, D.L., Platt, M.L., 2017. A Primer on Foraging and the Explore/Exploit Trade-Off for Psychiatry Research. Neuropsychopharmacology 42(10), 1931-1939.
Anselme, P., Güntürkün, O., 2019. How foraging works: Uncertainty magnifies food-seeking motivation. Behav. Brain Sci. 42.
Auer, M.M., Griffiths, M.D., 2015. The use of personalized behavioral feedback for online gamblers: an empirical study. Frontiers in psychology 6, 1406.
Baker, P.M., Jhou, T., Li, B., Matsumoto, M., Mizumori, S.J., Stephenson-Jones, M., Vicentic, A., 2016. The lateral habenula circuitry: reward processing and cognitive control. J. Neurosci. 36(45), 11482-11488.
Batalla, A., Homberg, J.R., Lipina, T.V., Sescousse, G., Luijten, M., Ivanova, S.A., Schellekens, A.F., Loonen, A.J., 2017. The role of the habenula in the transition from reward to misery in substance use and mood disorders. Neurosci. Biobehav. Rev. 80, 276-285.
Beeler, J.A., Daw, N.D., Frazier, C.R., Zhuang, X., 2010. Tonic dopamine modulates exploitation of reward learning. Frontiers in behavioral neuroscience 4, 170.
Beeler, J.A., Frazier, C.R., Zhuang, X., 2012. Putting desire on a budget: dopamine and energy expenditure, reconciling reward and resources. Front Integr Neurosci 6, 49.
Berridge, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl). 191(3), 391-431.
Berridge, K.C., 2012. From prediction error to incentive salience: mesolimbic computation of reward motivation. Eur. J. Neurosci. 35(7), 1124-1143.
Biback, C., Zack, M., 2015. The relationship between stress and motivation in pathological gambling: A focused review and analysis. Current Addiction Reports 2(3), 230-239.
Bickel, W.K., Kelly, T.H., 2019. Stimulus Control of Drug Self-Administration. Environment And Behavior, 116.
Binde, P., Romild, U., Volberg, R.A., 2017. Forms of gambling, gambling involvement and problem gambling: evidence from a Swedish population survey. International Gambling Studies 17(3), 490-507.
Bjork, J.M., Smith, A.R., Hommer, D.W., 2008. Striatal sensitivity to reward deliveries and omissions in substance dependent patients. NeuroImage 42(4), 1609-1621.
Blaha, C.D., Yang, C.R., Floresco, S.B., Barr, A.M., Phillips, A.G., 1997. Stimulation of the ventral subiculum of the hippocampus evokes glutamate receptor-mediated changes in dopamine efflux in the rat nucleus accumbens. Eur. J. Neurosci. 9(5), 902-911.
Blaszczynski, A., Cowley, E., Anthony, C., Hinsley, K., 2016. Breaks in play: Do they achieve intended aims? Journal of Gambling Studies 32(2), 789-800.
Boehme, R., Deserno, L., Gleich, T., Katthagen, T., Pankow, A., Behr, J., Buchert, R., Roiser, J.P., Heinz, A., Schlagenhauf, F., 2015. Aberrant salience is related to reduced reinforcement learning signals and elevated dopamine synthesis capacity in healthy adults. J. Neurosci. 35(28), 10103-10111.

Boileau, I., Payer, D., Chugani, B., Lobo, D.S., Houle, S., Wilson, A.A., Warsh, J., Kish, S.J., Zack, M., 2014. In vivo evidence for greater amphetamine-induced dopamine release in pathological gambling: a positron emission tomography study with [(11)C]-(+)-PHNO. Mol. Psychiatry 19(12), 1305-1313.
Bolles, R.C., 1972. Reinforcement, expectancy, and learning. PsychologR 79(5), 394-409.
Broussard, J.D., Wulfert, E., 2019. Debiasing Strategies for Problem Gambling: Using Decision Science to Inform Clinical Interventions. Current Addiction Reports 6(3), 175-182.
Burokas, A., Gutiérrez-Cuesta, J., Martín-García, E., Maldonado, R., 2012. Operant model of frustrated expected reward in mice. Addict. Biol. 17(4), 770-782.
Calipari, E.S., Ferris, M.J., Zimmer, B.A., Roberts, D.C., Jones, S.R., 2013. Temporal pattern of cocaine intake determines tolerance vs sensitization of cocaine effects at the dopamine transporter. Neuropsychopharmacology 38(12), 2385.
Campbell-Meiklejohn, D., Wakeley, J., Herbert, V., Cook, J., Scollo, P., Ray, M.K., Selvaraj, S., Passingham, R.E., Cowen, P., Rogers, R.D., 2011. Serotonin and dopamine play complementary roles in gambling to recover losses. Neuropsychopharmacology 36(2), 402-410.
Cassetta, B., Kim, H., Hodgins, D., McGrath, D., Tomfohr-Madsen, L., Tavares, H., 2018. Disordered gambling and psychosis: Prevalence and clinical correlates. Schizophr. Res. 192, 463.
Chase, H.W., Clark, L., 2010. Gambling severity predicts midbrain response to near-miss outcomes. J Neurosci 30(18), 6180-6187.
Cherkasova, M.V., Clark, L., Barton, J.J., Schulzer, M., Shafiee, M., Kingstone, A., Stoessl, A.J., Winstanley, C.A., 2018. Win-concurrent sensory cues can promote riskier choice. J. Neurosci. 38(48), 10362-10370.
Chu, S., Limbrick-Oldfield, E.H., Murch, W.S., Clark, L., 2018. Why do slot machine gamblers use stopping devices? Findings from a 'Casino Lab'experiment. International Gambling Studies 18(2), 310-326.
Clark, L., 2014. Disordered gambling: the evolving concept of behavioral addiction. Ann N Y Acad Sci 1327, 46-61.
Clark, L., Boileau, I., Zack, M., 2019. Neuroimaging of reward mechanisms in Gambling disorder: an integrative review. Mol. Psychiatry 24(5), 674-693.
Clark, L., Lawrence, A.J., Astley-Jones, F., Gray, N., 2009. Gambling near-misses enhance motivation to gamble and recruit win-related brain circuitry. Neuron 61(3), 481-490.
Collins, A.L., Greenfield, V.Y., Bye, J.K., Linker, K.E., Wang, A.S., Wassum, K.M., 2016. Dynamic mesolimbic dopamine signaling during action sequence learning and expectation violation. Scientific reports 6, 20231.
Corlett, P.R., Aitken, M.R., Dickinson, A., Shanks, D.R., Honey, G.D., Honey, R.A., Robbins, T.W., Bullmore, E.T., Fletcher, P.C., 2004. Prediction error during retrospective revaluation of causal associations in humans: fMRI evidence in favor of an associative model of learning. Neuron 44(5), 877-888.
Creed, M.C., 2017. Toward a targeted treatment for addiction. Sci 357(6350), 464-465.
D'Ardenne, K., McClure, S.M., Nystrom, L.E., Cohen, J.D., 2008. BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. Sci 319(5867), 1264-1267.
Dackis, C., O'Brien, C., 2005. Neurobiology of addiction: treatment and public policy ramifications. Nat. Neurosci. 8(11), 1431.
Daw, N.D., Touretzky, D.S., 2002. Long-term reward prediction in TD models of the dopamine system. NeCom 14(11), 2567-2583.

De la Fuente-Fernández, R., Ruth, T.J., Sossi, V., Schulzer, M., Calne, D.B., Stoessl, A.J., 2001. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Sci 293(5532), 1164-1166.
de Ruiter, M.B., Veltman, D.J., Goudriaan, A.E., Oosterlaan, J., Sjoerds, Z., van den Brink, W., 2009. Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. Neuropsychopharmacology 34(4), 1027-1038.
Dicheva, D., Dichev, C., Agre, G., Angelova, G., 2015. Gamification in education: A systematic mapping study. Educational Technology & Society 18(3), 75-88.
Dickler, M., Lenglos, C., Renauld, E., Ferland, F., Edden, R.A., Leblond, J., Fecteau, S., 2018. Online effects of transcranial direct current stimulation on prefrontal metabolites in gambling disorder. Neuropharmacology 131, 51-57.
Dixon, M.J., Collins, K., Harrigan, K.A., Graydon, C., Fugelsang, J.A., 2015. Using sound to unmask losses disguised as wins in multiline slot machines. Journal of Gambling Studies 31(1), 183-196.
Dixon, M.J., Stange, M., Larche, C.J., Graydon, C., Fugelsang, J.A., Harrigan, K.A., 2018. Dark flow, depression and multiline slot machine play. Journal of Gambling Studies 34(1), 73-84.
Dreher, J.-C., Kohn, P., Berman, K.F., 2005. Neural coding of distinct statistical properties of reward information in humans. Cereb. Cortex 16(4), 561-573.
Everitt, B.J., Parkinson, J.A., Olmstead, M.C., Arroyo, M., Robledo, P., Robbins, T.W., 1999. Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. Ann N Y Acad Sci 877, 412-438.
Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8(11), 1481-1489.
Evers, E., Stiers, P., Ramaekers, J., 2017. High reward expectancy during methylphenidate depresses the dopaminergic response to gain and loss. Social cognitive and affective neuroscience 12(2), 311-318.
Ferster, C.B., Skinner, B.F., 1957. Schedules of reinforcement.
Fiorillo, C.D., Tobler, P.N., Schultz, W., 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. Sci 299(5614), 1898-1902.
Flagel, S.B., Akil, H., Robinson, T.E., 2009. Individual differences in the attribution of incentive salience to reward-related cues: Implications for addiction. Neuropharmacology 56, 139-148.
Flagel, S.B., Watson, S.J., Robinson, T.E., Akil, H., 2007. Individual differences in the propensity to approach signals vs goals promote different adaptations in the dopamine system of rats. Psychopharmacology 191(3), 599-607.
Frank, M.J., O'Reilly, R.C., 2006. A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav Neurosci 120(3), 497-517.
Friston, K.J., Shiner, T., FitzGerald, T., Galea, J.M., Adams, R., Brown, H., Dolan, R.J., Moran, R., Stephan, K.E., Bestmann, S., 2012. Dopamine, affordance and active inference. PLoS Comp. Biol. 8(1), e1002327.
Gainsbury, S.M., Suhonen, N., Saastamoinen, J., 2014. Chasing losses in online poker and casino games: Characteristics and game play of Internet gamblers at risk of disordered gambling. Psychiatry Res. 217(3), 220-225.
Gipson, C.D., Beckmann, J.S., Adams, Z.W., Marusich, J.A., Nesland, T.O., Yates, J.R., Kelly, T.H., Bardo, M.T., 2012. A translational behavioral model of mood-based impulsivity: Implications for substance abuse. Drug Alcohol Depend. 122(1-2), 93-99.

Grace, A.A., 2000. The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. Addiction 95 Suppl 2, S119-128.
Graziane, N.M., Neumann, P.A., Dong, Y., 2018. A focus on reward prediction and the lateral habenula: functional alterations and the behavioral outcomes induced by drugs of abuse. Frontiers in synaptic neuroscience 10, 12.
Griffiths, M., 1993. Fruit machine gambling: The importance of structural characteristics. Journal of gambling studies 9(2), 101-120.
Griffiths, M., 2005. A 'components' model of addiction within a biopsychosocial framework. J. Subst. Use 10(4), 191-197.
Harrigan, K.A., 2007. Slot machine structural characteristics: Distorted player views of payback percentages. Journal of Gambling Issues 20, 215-234.
Harris, A., Griffiths, M.D., 2017. A critical review of the harm-minimisation tools available for electronic gambling. Journal of Gambling Studies 33(1), 187-221.
Hart, A.S., Clark, J.J., Phillips, P.E., 2015. Dynamic shaping of dopamine signals during probabilistic Pavlovian conditioning. Neurobiol. Learn. Mem. 117, 84-92.
Hauser, T.U., Eldar, E., Dolan, R.J., 2017. Separate mesocortical and mesolimbic pathways encode effort and reward learning signals. Proceedings of the National Academy of Sciences 114(35), E7395-E7404.
Haydock, M., Cowlishaw, S., Harvey, C., Castle, D., 2015. Prevalence and correlates of problem gambling in people with psychotic disorders. Compr. Psychiatry 58, 122-129.
Hernandez, G., Rajabi, H., Stewart, J., Arvanitogiannis, A., Shizgal, P., 2008. Dopamine tone increases similarly during predictable and unpredictable administration of rewarding brain stimulation at short inter-train intervals. Behav. Brain Res. 188(1), 227-232.
Hønsi, A., Mentzoni, R.A., Molde, H., Pallesen, S., 2013. Attentional bias in problem gambling: a systematic review. Journal of Gambling Studies 29(3), 359-375.
Howe, M.W., Tierney, P.L., Sandberg, S.G., Phillips, P.E., Graybiel, A.M., 2013. Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. Nature 500(7464), 575.
Howes, O., Egerton, A., Allan, V., McGuire, P., Stokes, P., Kapur, S., 2009. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. Curr. Pharm. Des. 15(22), 2550-2559.
Jensen, C., Dixon, M.J., Harrigan, K.A., Sheepy, E., Fugelsang, J.A., Jarick, M., 2013. Misinterpreting 'winning'in multiline slot machine games. International Gambling Studies 13(1), 112-126.
Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am. J. Psychiatry 160(1), 13-23.
Kawa, A.B., Bentzley, B.S., Robinson, T.E., 2016. Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. Psychopharmacology 233(19-20), 3587-3602.
Koob, G.F., 2017. Antireward, compulsivity, and addiction: seminal contributions of Dr. Athina Markou to motivational dysregulation in addiction. Psychopharmacology 234(9-10), 1315-1332.
Kreussel, L., Hewig, J., Kretschmer, N., Hecht, H., Coles, M.G., Miltner, W.H., 2013. How bad was it? Differences in the time course of sensitivity to the magnitude of loss in problem gamblers and controls. Behav. Brain Res. 247, 140-145.
Kuczenski, R., Segal, D.S., 1988. Psychomotor stimulant-induced sensitization: behavioral and neurochemical correlates. Sensitization in the nervous system, 175-205.

Ladouceur, R., Sevigny, S., 2005. Structural characteristics of video lotteries: effects of a stopping device on illusion of control and gambling persistence. J Gambl Stud 21(2), 117-131.
Langer, E.J., 1975. The illusion of control. JPSP 32(2), 311.
Langham, E., Thorne, H., Browne, M., Donaldson, P., Rose, J., Rockloff, M., 2015. Understanding gambling related harm: A proposed definition, conceptual framework, and taxonomy of harms. BMC Public Health 16(1), 80.
Laroche, S., Errington, M., Lynch, M., Bliss, T., 1987. Increase in [3H] glutamate release from slices of dentate gyrus and hippocampus following classical conditioning in the rat. Behav. Brain Res. 25(1), 23-29.
Laruelle, M., Abi-Dargham, A., 1999. Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. J. Psychopharm. 13(4), 358-371.
Lavezzi, H.N., Zahm, D.S., 2011. The mesopontine rostromedial tegmental nucleus: an integrative modulator of the reward system. Basal ganglia 1(4), 191-200.
Lawson, R.P., Seymour, B., Loh, E., Lutti, A., Dolan, R.J., Dayan, P., Weiskopf, N., Roiser, J.P., 2014. The habenula encodes negative motivational value associated with primary punishment in humans. Proceedings of the National Academy of Sciences 111(32), 11858-11863.
Leeman, R.F., Potenza, M.N., 2012. Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity. Psychopharmacology (Berl). 219(2), 469-490.
Leshner, A.I., 1997. Addiction is a brain disease, and it matters. Sci 278(5335), 45-47.
Lidstone, S.C., Schulzer, M., Dinelle, K., Mak, E., Sossi, V., Ruth, T.J., de la Fuente-Fernández, R., Phillips, A.G., Stoessl, A.J., 2010. Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch. Gen. Psychiatry 67(8), 857-865.
Linnet, J., Thomsen, K.R., Møller, A., Callesen, M.B., 2013. Slot machine response frequency predicts pathological gambling. International Journal of Psychological Studies 5(1), 121-127.
Markham, F., Young, M., Doran, B., 2016. The relationship between player losses and gambling-related harm: evidence from nationally representative cross-sectional surveys in four countries. Addiction 111(2), 320-330.
Mascia, P., Neugebauer, N.M., Brown, J., Bubula, N., Nesbitt, K.M., Kennedy, R.T., Vezina, P., 2019. Exposure to conditions of uncertainty promotes the pursuit of amphetamine. Neuropsychopharmacology 44(2), 274.
Mathis, V., Kenny, P.J., 2018. From controlled to compulsive drug-taking: The role of the habenula in addiction. Neurosci. Biobehav. Rev.
Meyer, G., Fiebig, M., Häfeli, J., Mörsen, C., 2011. Development of an assessment tool to evaluate the risk potential of different gambling types. International Gambling Studies 11(2), 221-236.
Mikhael, J.G., Kim, H.R., Uchida, N., Gershman, S.J., 2019. Ramping and State Uncertainty in the Dopamine Signal. bioRxiv, 805366.
Moore, J.W., Schneider, S.A., Schwingenschuh, P., Moretto, G., Bhatia, K.P., Haggard, P., 2010. Dopaminergic medication boosts action–effect binding in Parkinson's disease. Neuropsychologia 48(4), 1125-1132.
Murch, W.S., Chu, S.W., Clark, L., 2017. Measuring the slot machine zone with attentional dual tasks and respiratory sinus arrhythmia. Psychology of Addictive Behaviors 31(3), 375.
Nagy, H., Levy-Gigi, E., Somlai, Z., Takáts, A., Bereczki, D., Kéri, S., 2012. The effect of dopamine agonists on adaptive and aberrant salience in Parkinson's disease. Neuropsychopharmacology 37(4), 950.

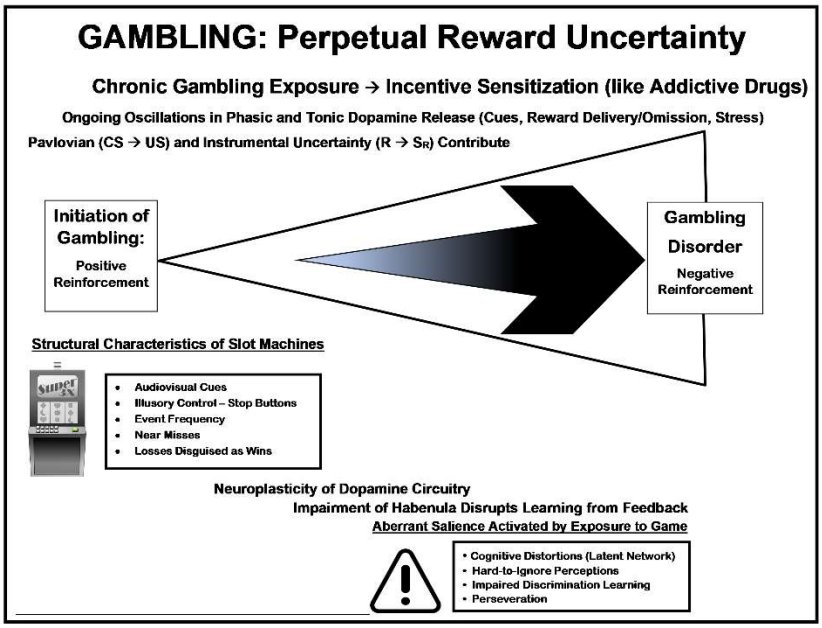
Papini, M.R., Dudley, R.T., 1997. Consequences of surprising reward omissions. Review of General Psychology 1(2), 175-197.
Parkinson, J., Dalley, J., Cardinal, R., Bamford, A., Fehnert, B., Lachenal, G., Rudarakanchana, N., Halkerston, K., Robbins, T., Everitt, B., 2002. Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. Behav. Brain Res. 137(1-2), 149-163.
Peciña, S., Schulkin, J., Berridge, K.C., 2006. Nucleus accumbens corticotropin-releasing factor increases cue-triggered motivation for sucrose reward: paradoxical positive incentive effects in stress? BMC Biol. 4(1), 8.
Pezzulo, G., Friston, K.J., 2019. The value of uncertainty: An active inference perspective. Behav. Brain Sci. 42, e47.
Pullman, R.E., Potenza, M.N., Kraus, S.W., 2018. Recommendations for increasing research on co-occurring serious mental illness and gambling problems: Commentary on: Disordered gambling and psychosis: Prevalence and clinical correlates (Cassetta et al., 2018). Journal of behavioral addictions 7(4), 897-899.
Redish, A.D., 2004. Addiction as a computational process gone awry. Sci 306(5703), 1944-1947.
Render, A., Jansen, P., 2019. Dopamine and sense of agency: Determinants in personality and substance use. PLoS ONE 14(3), e0214069.
Riba, J., Kramer, U.M., Heldmann, M., Richter, S., Munte, T.F., 2008. Dopamine agonist increases risk taking but blunts reward-related brain activity. PLoS ONE 3(6), e2479.
Ricciardi, L., Haggard, P., de Boer, L., Sorbera, C., Stenner, M.-P., Morgante, F., Edwards, M.J., 2017. Acting without being in control: Exploring volition in Parkinson's disease with impulsive compulsive behaviours. Parkinsonism & related disorders 40, 51-57.
Rigoli, F., Chew, B., Dayan, P., Dolan, R.J., 2016. The dopaminergic midbrain mediates an effect of average reward on Pavlovian vigor. J. Cognit. Neurosci. 28(9), 1303-1317.
Robbins, T.W., Clark, L., 2015. Behavioral addictions. Curr. Opin. Neurobiol. 30, 66-72.
Roberts, A.C., Glanzman, D.L., 2003. Learning in Aplysia: looking at synaptic plasticity from both sides. Trends Neurosci. 26(12), 662-670.
Robinson, M.J., Anselme, P., Fischer, A.M., Berridge, K.C., 2014. Initial uncertainty in Pavlovian reward prediction persistently elevates incentive salience and extends sign-tracking to normally unattractive cues. Behav. Brain Res. 266, 119-130.
Robinson, M.J., Clibanoff, C., Freeland, C.M., Knes, A.S., Cote, J.R., Russell, T.I., 2019. Distinguishing between predictive and incentive value of uncertain gambling-like cues in a Pavlovian autoshaping task. Behav. Brain Res. 371, 111971.
Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Rev. 18(3), 247-291.
Robinson, T.E., Berridge, K.C., 2001. Incentive-sensitization and addiction. Addiction 96(1), 103-114.
Schlagenhauf, F., Sterzer, P., Schmack, K., Ballmaier, M., Rapp, M., Wrase, J., Juckel, G., Gallinat, J., Heinz, A., 2009. Reward feedback alterations in unmedicated schizophrenia patients: relevance for delusions. Biol. Psychiatry 65(12), 1032-1039.
Schüll, N.D., 2014. Addiction by design: Machine gambling in Las Vegas. Princeton University Press.
Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80(1), 1-27.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Sci 275(5306), 1593-1599.

Seeman, P., 2013. Schizophrenia and dopamine receptors. Eur. Neuropsychopharmacol. 23(9), 999-1009.
Sescousse, G., Janssen, L.K., Hashemi, M.M., Timmer, M.H., Geurts, D.E., Ter Huurne, N.P., Clark, L., Cools, R., 2016. Amplified Striatal Responses to Near-Miss Outcomes in Pathological Gamblers. Neuropsychopharmacology 41(10), 2614-2623.
Shaffer, H.J., LaPlante, D.A., LaBrie, R.A., Kidman, R.C., Donato, A.N., Stanton, M.V., 2004. Toward a syndrome model of addiction: Multiple expressions, common etiology. Harv. Rev. Psychiatry 12(6), 367-374.
Shen, L., Hsee, C.K., 2017. Numerical nudging: Using an accelerating score to enhance performance. Psychological science 28(8), 1077-1086.
Shen, L., Hsee, C.K., Talloen, J.H., 2018. The Fun and Function of Uncertainty: Uncertain Incentives Reinforce Repetition Decisions. J. Cons. Res. 46(1), 69-81.
Singer, B.F., Scott-Railton, J., Vezina, P., 2012. Unpredictable saccharin reinforcement enhances locomotor responding to amphetamine. Behav Brain Res 226(1), 340-344.
Smith, N., Kitchenham, N., Bowden-Jones, H., 2011. Pathological gambling and the treatment of psychosis with aripiprazole. The British Journal of Psychiatry 199(2), 158-159.
Starkweather, C.K., Babayan, B.M., Uchida, N., Gershman, S.J., 2017. Dopamine reward prediction errors reflect hidden-state inference across time. Nat. Neurosci. 20(4), 581.
Starkweather, C.K., Gershman, S.J., Uchida, N., 2018. The medial prefrontal cortex shapes dopamine reward prediction errors under state uncertainty. Neuron 98(3), 616-629. e616.
Stefan, S., David, D., 2013. Recent developments in the experimental investigation of the illusion of control. A meta-analytic review. Journal of Applied Social Psychology 43(2), 377-386.
Stopper, C.M., Floresco, S.B., 2014. Dopaminergic circuitry and risk/reward decision making: implications for schizophrenia. Schizophr. Bull. 41(1), 9-14.
Takahashi, Y.K., Batchelor, H.M., Liu, B., Khanna, A., Morales, M., Schoenbaum, G., 2017. Dopamine neurons respond to errors in the prediction of sensory features of expected rewards. Neuron 95(6), 1395-1405. e1393.
Takahashi, Y.K., Stalnaker, T.A., Marrero-Garcia, Y., Rada, R.M., Schoenbaum, G., 2019. Expectancy-Related Changes in Dopaminergic Error Signals Are Impaired by Cocaine Self-Administration. Neuron 101(2), 294-306. e293.
Tian, J., Uchida, N., 2015. Habenula lesions reveal that multiple mechanisms underlie dopamine prediction errors. Neuron 87(6), 1304-1316.
Tobias-Webb, J., Limbrick-Oldfield, E.H., Gillan, C.M., Moore, J.W., Aitken, M.R., Clark, L., 2017. Let me take the wheel: Illusory control and sense of agency. The Quarterly Journal of Experimental Psychology 70(8), 1732-1746.
Tomie, A., Tirado, A.D., Yu, L., Pohorecky, L.A., 2004. Pavlovian autoshaping procedures increase plasma corticosterone and levels of norepinephrine and serotonin in prefrontal cortex in rats. Behav. Brain Res. 153(1), 97-105.
Tremblay, A.M., Desmond, R.C., Poulos, C.X., Zack, M., 2011. Haloperidol modifies instrumental aspects of slot machine gambling in pathological gamblers and healthy controls. Addict. Biol. 16, 467-484.
Trusel, M., Nuno-Perez, A., Lecca, S., Harada, H., Lalive, A.L., Congiu, M., Takemoto, K., Takahashi, T., Ferraguti, F., Mameli, M., 2019. Punishment-predictive cues guide avoidance through potentiation of hypothalamus-to-habenula synapses. Neuron 102(1), 120-127. e124.

Turner, N.E., Jain, U., Spence, W., Zangeneh, M., 2008. Pathways to pathological gambling: Component analysis of variables related to pathological gambling. International Gambling Studies 8(3), 281-298.
Vindas, M.A., Sørensen, C., Johansen, I.B., Folkedal, O., Höglund, E., Khan, U.W., Stien, L.H., Kristiansen, T.S., Braastad, B.O., Øverli, Ø., 2014. Coping with unpredictability: dopaminergic and neurotrophic responses to omission of expected reward in Atlantic salmon (Salmo salar L.). PLoS ONE 9(1), e85543.
Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic Advances from the Brain Disease Model of Addiction. N. Engl. J. Med. 374(4), 363-371.
Wardle, H., Reith, G., Langham, E., Rogers, R.D., 2019. Gambling and public health: we need policy action to prevent harm. BMJ 365, l1807.
Weintraub, D., Siderowf, A.D., Potenza, M.N., Goveas, J., Morales, K.H., Duda, J.E., Moberg, P.J., Stern, M.B., 2006. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch. Neurol. 63(7), 969-973.
Wu, Y., van Dijk, E., Li, H., Aitken, M., Clark, L., 2017. On the Counterfactual Nature of Gambling Near-misses: An Experimental Study. J Behav Decis Mak 30(4), 855-868.
Zack, M., Boileau, I., Payer, D., Chugani, B., Lobo, D.S., Houle, S., Wilson, A.A., Warsh, J.J., Kish, S.J., 2015. Differential cardiovascular and hypothalamic pituitary response to amphetamine in male pathological gamblers versus healthy controls. J Psychopharmacol 29(9), 971-982.
Zald, D.H., Boileau, I., El-Dearedy, W., Gunn, R., McGlone, F., Dichter, G.S., Dagher, A., 2004. Dopamine transmission in the human striatum during monetary reward tasks. J. Neurosci. 24(17), 4105-4112.
Zeeb, F.D., Li, Z., Fisher, D.C., Zack, M.H., Fletcher, P.J., 2017. Uncertainty exposure causes behavioural sensitization and increases risky decision-making in male rats: toward modelling gambling disorder. J. Psychiatry Neurosci. 42(6), 404-413.

Figure Caption

Figure 1. Schematic showing the proposed processes that contribute to the transition from initial participation in gambling to Gambling Disorder (GD). Chronic exposure to uncertain reward induces a sensitization-like syndrome mediated by phasic dopamine (DA) firing when reward is randomly delivered (Pleasant Surprise: reward prediction error; RPE) or withheld (Unpleasant Surprise: omission of expected reward; OER). Conditioned cues for reward (bells, lights) and instrumental actions (betting/initiating a spin) acquire increased ability to motivate 'wanting' (conditioned approach) to gamble through incentive sensitization. Neural sensitization leads to increased tonic DA activity that preferentially stimulates inhibitory D2 auto-receptors, impeding detection of phasic RPEs and OERs that guide adaptive decision-making (e.g., extinction). Long-run net losses lead to increased need or appetite for money, along with stress from repeated failures to win enough money to offset losses. Structural characteristics of electronic gaming machines (EGMs) further promote the perceived likelihood of winning (with corresponding escalation in tonic DA) and a perceived contingency between gambling and reward. Acute exposure to EGMs can activate cognitive distortions that are difficult to ignore (I am ‘due’ for a Big Win) and perseverative betting despite mounting losses (‘chasing’ or relief-seeking) in GD players who are sensitized to these effects. (We thank Spencer Murch for the graphic of the EGM).


GAMBLING: Perpetual Reward Uncertainty
Chronic Gambling Exposure → Incentive Sensitization (like Addictive Drugs)
Ongoing Oscillations in Phasic and Tonic Dopamine Release (Cues, Reward Delivery/Omission, Stress)
Pavlovian (CS → US) and Instrumental Uncertainty (R → S_R) Contribute
Initiation of Gambling:
Positive Reinforcement
Gambling Disorder
Negative Reinforcement
Structural Characteristics of Slot Machines
Audiovisual Cues
Illusory Control – Stop Buttons
Event Frequency
Near Misses
Losses Disguised as Wins
Neuroplasticity of Dopamine Circuitry
Impairment of Habenula Disrupts Learning from Feedback
Aberrant Salience Activated by Exposure to Game
Cognitive Distortions (Latent Network)
Hard-to-Ignore Perceptions
Impaired Discrimination Learning
Perseveration