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REVIEW

Gambling disorder: an integrative review of animal and human studies

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Gambling disorder (GD), previously called pathological gambling and classified as an impulse control disorder in DSM-III and DSM-IV, has recently been reclassified as an addictive disorder in the DSM-5. It is widely recognized as an important public health problem associated with substantial personal and social costs, high rates of psychiatric comorbidity, poor physical health, and elevated suicide rates. A number of risk factors have been identified, including some genetic polymorphisms. Animal models have been developed in order to study the underlying neural basis of GD. Here, we discuss recent advances in our understanding of the risk factors, disease course, and pathophysiology. A focus on a phenotype-based dissection of the disorder is included in which known neural correlates from animal and human studies are reviewed. Finally, current treatment approaches are discussed, as well as future directions for GD research.

Keywords: gambling disorder; animal models; impulsivity; pathological gambling

Introduction

Behavioral addictions are increasingly being recognized as psychiatric disorders and garnering the interest of the scientific community. Gambling disorder (GD) is often considered the prototypical example of a behavioral addiction and is currently the only one included in DSM-5. Although still understudied, GD is now widely recognized as an important public health problem associated with substantial personal and social costs, high psychiatric comorbidity, poor physical health, and elevated suicide rates.[1] As gambling activities are present in almost every culture, gambling problems are also ubiquitous: worldwide, around 0.2–5.3% of the adult population develops a GD at some point in their lives.[2] In view of evidence demonstrating that GD and substance use disorders (SUDs) share similar clinical risk factors and high rates of comorbidity and clinical expression, DSM-5 now includes GD as a "Substance-Related and Addictive Disorder."[3,4]

Gambling-related disorders have received a variety of names, with the same term sometimes used to define two or more different constructs. Before the DSM-5, pathological gambling was considered an impulse-control disorder not elsewhere classified, and generally used to include individuals who met five or more DSM-IV diagnostic criteria, with problem gambling often referring to individuals meeting 3–4 criteria. Disordered gambling was often used to encompass both problem and pathological gambling. Because problem and pathological gambling are often seen as a continuum,[5] the present review draws on data from studies that include problem gambling, pathological gambling, disordered gambling, and DSM-5–defined GD. This review uses the term GD to denote all of these terms and is not circumscribed to GD as defined in DSM-5. Because there are several recent comprehensive reviews of GD,[6–11] the aim of this review is

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to integrate key relevant findings from human and animal studies focused on the identification of the biological basis of phenotypes that are central to GD. Specifically, we synthesize selected neuroimaging and treatment studies that include individuals with GD and also individuals participating in gambling tasks and attempt to integrate this information with studies from animal models that offer insights into the pathophysiology of GD. Our focus on key phenotypes found in patients with GD is to aid in bridging the translation gap in GD research. We highlight studies that use parallel tasks to study these phenotypes in animals and humans, as we believe these hold potential for elucidating the mechanisms by which treatments may lead to improved clinical outcomes. Last, we discuss directions for future research that may help advance the field of GD.

Risk factors

Prevalence rates across the world report past 12-month rates of GD ranging from 0.2% (Norway) to 5.3% (Hong Kong).[2,12,13] In the United States, the largest national epidemiological survey reported a 0.4% lifetime prevalence of GD.[14] The lifetime prevalences for men and women were 0.64% and 0.23%, respectively.

A large number of studies have documented a broad range of risk factors for GD, including sociodemographic characteristics, such as male gender, younger age, neighborhood disadvantage, and low socioeconomic status.[15–17] Early exposure and initiation of gambling activities;[18] gambling availability;[19] psychiatric comorbidity, including SUDs;[20,21] adverse childhood events;[22] and a family history of GD or SUD[23] have also been identified as risk factors for the development of GD. There has been less work directed at examining how these different risk factors relate to each other or the role of those relationships in the etiology of GD. One of the earliest approaches to integration, the pathways model,[24,25] proposed the existence of three progressively more severe subgroups of individuals with GD: behaviorally conditioned, emotionally vulnerable, and antisocial impulsivist. Behaviorally conditioned disordered gamblers are distinguished by the absence of specific premorbid features of psychopathology and gamble primarily as a result of the effects of conditioning, distorted cognitions surrounding the probability of winning, and poor decision making rather than because of impaired control. Emotionally vulnerable disordered gamblers have the characteristics of the behaviorally conditioned subtype, but also have mood disorders that precede GD, a history of poor coping and problem-solving skills, problematic family background experiences, and major traumatic life events; they gamble primarily to modulate affective states or meet specific psychological needs. Antisocial impulsivists possess psychosocial and biologically based vulnerabilities similar to those in emotionally vulnerable subtype but are primarily distinguished by features of impulsivity, antisocial personality traits and behaviors, and attention deficits, manifesting in severe multiple maladaptive behaviors, including comorbid addictions. More recently, taking a developmental perspective and on the basis studies suggesting that the etiology of most psychiatric disorders is largely multifactorial,[26] one study used the largest epidemiologic survey in the United States to describe a conceptual model for GD.[27] The study found that a broad range of childhood, adolescence, and adulthood variables increased the likelihood of lifetime GD when examined individually. However, only social deviance in early adolescence, the number of comorbid personality disorders, past history of GD, and past-year nicotine dependence predicted GD after adjusting for the effect of covariates. Interestingly, the study did not find significant gender interactions in the model.

Certain cultural groups appear more vulnerable to early gambling initiation and the development of GD.[28] In the United States, Native Americans, Asians, and blacks show a greater prevalence of GD compared with whites.[29] These findings are similar to those found in aboriginal groups in other countries, including Canada, Greenland, and Australia.[19] Risk factors for GD, such as socioeconomic disadvantage and a higher prevalence of psychiatric disorders, including SUDs, are more prominent in certain ethnic and racial groups. Beliefs, values, gambling availability, and cultural acceptability toward gambling also vary in different parts of the world.[28] For some ethnic and racial groups, difficulties during immigration include unemployment, language barriers, and social exclusion, which may lead to increased gambling participation. Finally, the high levels of stigma toward seeking help may play a role in the perpetuation of GD in some cultures.[30]

Course and prognosis

The course of GD is variable, with some individuals having an episodic condition and others having a more chronic course.[31] It has been suggested that the gender gap for the prevalence of GD is closing and that, although GD in women may start later in life, the time elapsed between the age of regular involvement in the primary gambling activity and the age at onset of the disorder (latency of GD onset) may be a shorter, a course described as the *telescoping phenomenon*.[32,33] Although the lifetime prevalence for GD is higher in men than in women, when the prevalence of GD is examined within the sample of individuals who gamble (five or more times in at least 1 year of their life), 1.92% of men and 1.05% of women meet criteria for pathological gambling and 20.43% of men and 15.09% of women meet criteria for problem gambling.[32] Thus, it is possible that other factors, including increased exposure to gambling, social norms opposing gambling in women, or treatment-related issues, may partially account for some of the prevalence differences. Gender differences have been observed in gambling. While men with GD are more likely to engage in strategic or "face-to- face" forms of gambling (e.g., poker), commit illegal acts, and have SUDs, women with GD are more likely to report problems with nonstrategic, less interpersonally interactive forms of gambling (e.g., slot machines) and to use gambling to escape problems.[34–36] Individuals with earlier-onset GD (before age 25) are more likely male, less likely to have a mood disorder, and more likely to belong to younger cohorts.[37] One study suggested that the latency of GD onset is shorter for slot machine gamblers.[38] The study did not find an effect of gender or comorbid disorders on the latency of GD onset, leading to the hypothesis that the shorter latency could be related to the social, environmental, and stimulus features of machine gambling.

Compared with the general population, individuals with GD are at increased risk for suicide.[39] Studies in Austria, Germany, and the United States have reported rates of suicidal ideation and suicide attempts among individuals with GD ranging from 17% to 80% and 4% to 23%, respectively.[40] In treatment-seeking populations, other studies have reported that 32% of individuals with GD have experienced suicidal ideation and 17% have made at least one suicide attempt.[41] The largest epidemiologic survey in the United States reported that 49% of individuals with GD had a lifetime history of suicidal ideation, and 18% had made a suicide attempt.[39] Despite findings on decreased quality of life in GD, increased medical and psychiatric comorbidity, and often chronic course, only 10% of individuals with GD ever seek treatment for GD, although treatment-seeking rates appear higher for those with greater disorder severity.[31] Commonly reported barriers to GD treatment include individuals' wishes to handle the problem on their own, shame/stigma, difficulties acknowledging the problem, and treatment-related issues (availability of effective treatments, cost, and time concerns).[42]

Animal models of GD

As with other psychiatric disorders, the use of animal models has been critical to a better understanding of the pathophysiology of GD. A number of rodent models of gambling with good face validity have been developed. These are mostly based on the human Iowa gambling task (IGT), in which subjects make a series of card choices from four decks that result in winning or losing hypothetical money. Unbeknown to the subjects, two decks are "risky" (associated with large wins but larger losses) and lead to debt. The other two decks are "safe," yielding smaller wins but negligible losses. While healthy subjects develop a preference for the safe decks over 100 trials, individuals with GD maintain a preference for the risky decks, accumulating debt.[43–45]

Many of the first paradigms developed to model gambling behavior in animals were designed based on the human IGT.[46–48] One of the first of these was the rat gambling task (rGT), which uses a classic operant box with four nose-poke holes given as choice options with each assigned a "win" value (number of sugar pellets ranging from 1 to 4), a "loss" value (length of time-out from 5 to 40 s), and a risk value (probabilities of receiving reward ranging from 0.4 to 0.9), similar to the four decks in the IGT.[46] Instead of money, the rodent task uses a primary reinforcer as a reward—the sugar pellets are palatable for rodents and are further rewarding because the rats are generally maintained under mild food restriction. During a learning period, rats are required to sample each option. The task is designed to have advantageous options in a given session length, and rats successfully learn to choose the most advantageous option with the maximal

long-term payout. That is, they can accurately assess probability over many trials, and it is clear that the magnitude of wins and losses is salient. Once the task is learned, the effect of pharmacological manipulations on choice can help provide a better understanding of the neural circuitry of gambling.

Other gambling paradigms use intracranial self-stimulation (ICSS) as a reward instead of food.[49,50] While more invasive (surgically) and used less frequently, ICSS has some advantages by eliminating potential feeding-related confounds. Specifically, in food-restricted subjects, the value of the rewards can diminish over the course of a session, since subjects become increasingly sated with the delivery of more food rewards, while the ICSS rewards maintain the same value throughout the session. Additionally, manipulations that affect performance in the rGT may have effects *via* feeding-specific circuits rather than having direct relevance to gambling.

Paradigms for use in mice have also been developed, which are important because they allow the use of the many genetic, viral, optogenetic, and *in vivo* imaging tools available in mice. The mouse version of the Iowa gambling task (mIGT) uses the same paradigm as the rGT.[51,52] Additionally, nonoperant-based tasks have been developed and used in rats and mice, which measure choice behavior with a multiarm maze.[48] In one version of this paradigm called the mouse gambling task, each arm of the maze offers an immediate smaller reward (one or two sugar pellets) and then a subsequent larger reward (three to five sugar pellets) or an equivalent "nonreward," which was nonpalatable quinine pellets, with probabilities ranging from 0.05 to 0.9.[53]

This latter mouse paradigm is interesting because it includes the receipt of nonpalatable pellets instead of the absence of the reward plus a time-out, which is given in the rGT and mIGT. However, in some cases, rats are excluded if they consume the nonpalatable quinine pellets, limiting the benefit of this additional nonreward.[54] Overall, the representation of loss seems to be one of the most difficult aspects of gambling to model. In the rGT and mIGT, losses are modeled as time-outs from the task, in which the rats are unable to "play the slots" for a period of time. This modeling of loss is not the opposite of a reward, but rather a time period in which wins cannot be achieved. Other tasks model losses in the form of foot shock, which seems to be a representation of punishment rather than loss.[55] The nonpalatable pellets may most closely mimic the negative context associated with loss.

These rodent gambling assays have been used in conjunction with pharmacologic and lesion methods to investigate the neural basis of gambling behavior. The studies provide a complex story of how globally or locally altering neurotransmission affects this multifaceted behavior, which includes aspects of behavioral inhibition, risk taking, probabilistic discounting, temporal discounting, timing distortions, working memory, incentive salience, hedonic value, motivation, and satiety.

Pathophysiology

Although the pathophysiology of GD is not fully understood, there appears to be broad consensus that a number of core phenotypes are involved, including increased impulsive behavior, risky decision making, increased sensation seeking, the presence of cognitive distortions, increased compulsivity, and altered reward sensitivity.[56–60] Importantly, all of these phenotypes can be readily modeled in rodent paradigms with good construct and face validity.[46–49,54,61–65] In the following sections, we summarize human and animal studies examining these different GD phenotypes.

Decision making

Individuals with GD have deficits in decision making, as measured in the IGT.[58,66] Additionally, poor performance on the IGT is predictive of problem gambling.[67] These deficits are seen even in cases where there are explicit descriptions of probabilities and outcomes, suggesting that the assessment of probabilities is not the underlying issue, but rather making decisions on the basis of the probabilities.[68] In addition to the rodent gambling tasks, gambling-related decision making has also been modeled in rodents using probabilistic discounting tasks. These tasks measure the impact of risk on reward valuation, and the operant task generally consists of two options (levers or nose-poke holes) that give a small and reliable reward or a large risky reward but have equivalent expected values. This paradigm has also been referred to as the rodent betting task (rBT).[69]

Overall, many monoaminergic systems have been linked to decision making in these rodent gambling tasks, and, in particular, there has been a lot of focus on dopamine (DA). For example, amphetamine has

been reported to increase choice for the risky lever in rats, which is modulated through DA signaling at the D_1 and D_2 receptors.[70] On the other hand, activation of D_3 receptors has the reverse effect and causes decreases in selection of the risky option. However, in other tasks, such as the rGT, and when punishment with a foot shock replaced the absence of reward in the risky trials, amphetamine actually decreased the risky choice, highlighting the importance of drug doses and paradigm differences.[46,55,71] In mice, knockdown of the gene encoding the DA transporter, which causes increased extracellular DA levels, results in riskier choices in the mIGT.[52] This may be due to developmental effects on DA signaling, because increasing DA transmission alone with pharmacological blockade of the transporter in the adult rat caused no effect on choice behavior in the rGT.[72] In electrophysiological experiments, probability of reward correlates with phasic DA activation.[73] This may be in part due to inhibitory tone on DA neurons. In mice, genetic deletion of the β3 subunit of $GABA_A$ receptors on DA cells, which attenuates inhibitory tone on DA neurons, causes increased risk-taking behavior in a probabilistic selection task.[74]

Interestingly, blockade of norepinephrine (NE) or 5-HT signaling alone did not have an effect on performance in the rGT, but the combined increase in DA and NE or DA and 5-HT did impair performance.[75,76] This suggests that the interaction of transmitter systems is important for this complex paradigm modeling gambling-like behavior. Although increase in serotonin signaling with selective serotonin reuptake inhibitors (SSRIs) alone does not have large effects on gambling-like behavior in the rat, activation of $5\text{-}HT_{1A}$ receptor signaling specifically with 8-OH-DPAT impairs performance on the rGT, causing rats to increase their choice of the suboptimal option.[46] The effect of the agonist was eliminated when the time-out durations were equalized between the options, suggesting that $5\text{-}HT_{1A}$ activation possibly increases aversion to the longer time-outs.[46] This converges with results from a human positron emission tomography (PET) imaging study showing a correlation between $5\text{-}HT_{1A}$ binding in the hippocampus and greater sensitivity to probability of winning.[77] Additionally, blockade of $5\text{-}HT_{2A}$ with ketanserin in humans caused participants to be more risk averse, which was mediated by changes in ventral striatum (VS) activity as measured by functional magnetic resonance imaging (fMRI).[78] Surprisingly, there is a paucity of parallel research from rodent models linking $5\text{-}HT_{2A}$ to risky decision making.[79]

Cortical mechanisms of action of risk-based decision making have also been studied in rodent models of gambling. For example, inactivation of the orbitofrontal cortex (OFC) increased risk-taking behavior in the most risk-averse rats on the spectrum of variation of behavior in the rBT.[69] This is consistent with other reports of inactivation of the OFC increasing risk in probabilistic discounting tasks.[80] Additionally, reduced inhibition of the medial prefrontal cortex (mPFC) in rats (through local injection of a GABA antagonist) reduced risk-taking behavior.[81] Lesions of the agranular insula and OFC also impaired performance on the rGT. However, OFC lesions that were made after the rules of the task had been learned did not affect performance, suggesting that OFC lesion effects may be, in part, due to deficits learning the task rules rather than influencing risk-based decision making, which was impaired with agranular insula lesions.[82,83] Rats also increased their choice of disadvantageous options following inactivation of either infralimbic or prelimbic cortical regions.[84]

In general, the animal studies are consistent with the evidence linking the prefrontal cortex (PFC) to risk-based decision making in humans. Neuropsychological studies of GD individuals have reported that they have deficits in risky decision making that resemble deficits seen in individuals with lesions in the ventromedial prefrontal cortex (vmPFC) as measured with the IGT.[85] In fMRI studies of GD patients, there is altered activation of the OFC and vmPFC during risky decisions.[86–88] Additionally, lesions of the OFC result in impaired performance on the IGT, with patients preferring riskier, less advantageous long-term strategies.[85,89] Also, application of transcranial direct current stimulation to the OFC results in more advantageous decision making in the IGT.[90] Some studies suggest that the difficulties in decision making in individuals with OFC lesions may be due to a disrupted reversal learning (as seen by a failure to rapidly learn from negative feedback), and that the OFC is critically involved in representing the relative value of stimuli and plays a role in reinforcement learning and value-based judgment.[91,92]

Impulsivity

Increasing evidence supports the dissociation of multiple components of impulsive behavior.[93–96] Two of the most commonly referenced components are impulsive action and impulsive choice. While the latter concerns the ability to delay gratification, the former is characterized as the ability to withhold responses. Individuals with GD have impairments in both of these dimensions of impulsive behavior and consistently score high on measures of trait impulsivity (e.g., high scores on the Eysenck Impulsivity Scale).[8,45,97,98]

Impulsive action is measured in tests of premature responding and behavioral inhibition. In humans, go/no-go and stop signal tasks (SST) are used, and GD individuals show deficits in performance on these neurocognitive tests.[99,100] In rodents, impulsive action is commonly tested in operant behavior paradigms, including differential reinforcement of low-rate responding (DRL), go/no-go, and 5-choice serial reaction time task (5-CSRTT), which closely follow behavioral tests used in humans and assess the ability of rodents to delay or withhold responses that are associated with a reward.[97,101–103] DA signaling has been strongly implicated in the modulation of this type of impulsive behavior.[104,105] Administration of amphetamine increases premature responding in rats,[94,106,107] as does specific inhibition of DA reuptake.[108] However, amphetamine generally improves behavioral inhibition in humans, which adds to the complexity of the translational interpretation.[109,110] However, one study found that amphetamine increased self-reported motivation for gambling in individuals with GD and that the severity of their GD predicted positive subjective effects of the drug and motivation to gamble when taking it.[111] Interestingly, in rats, exposure to gambling-like reward delivery was sufficient to result in increased sensitization to amphetamine.[112] Another study in individuals with GD found that the dopaminergic response to amphetamine was positively associated with D_3 receptor levels in the substantia nigra and that it was related to GD severity.[113]

The reports on correlations between impulsive behavior and DA receptor function are mixed. In one case, rats selected for high impulsive behavior in the 5-CSRTT had higher levels of D_2 mRNA in the mesolimbic pathway compared with rats that showed less impulsive behavior.[114] Other studies show decreased D_2/D_3 receptor levels in highly impulsive rats.[115] Although these receptor levels were independent of DA levels, another study showed that DA release was inversely correlated with impulsivity.[116] Pharmacological studies in rats suggest that D_1 is also involved, as antagonists reduce premature responding.[117] These effects of DA are mediated, at least in part, through signaling in the shell of the nucleus accumbens (NAc),[118] converging with human neuroimaging studies that consistently link changes in activity of the NAc with impulsivity and severity of gambling.[119,120]

NE is also involved in the regulation of impulsive action. The NE reuptake inhibitor atomoxetine, which is used as a treatment for attention deficit/hyperactivity disorder (ADHD), reduces premature responding in rodents in the 5-CSRTT.[94,121] In healthy volunteers as well as in Parkinson's patients, atomoxetine has also been shown to reduce impulsive action as measured in the SST.[122,123] It has shown promise in treating some disorders in which impulsive action is a key symptom, such as binge eating disorder.[124] However, this and other NE-acting drugs have showed minimal efficacy in treating SUDs,[125–127] and to our knowledge have not yet been systematically studied as a treatment for patients with GD.

Finally, serotoninergic signaling also has large effects on impulsive action.[72,128,129] Brain-wide serotonin signaling has been implicated in the modulation of the neural circuits underlying impulsive action in animal models. In rats, global depletion of serotonin induces increases in impulsive action, and SSRI administration decreases impulsivity in the 5-CSRTT.[72,130] Additionally, optogenetic activation of serotonin raphe neurons in mice results in an increased ability to wait for rewards.[131,132] There is less evidence supporting effects of serotonin on response inhibition in humans,[122,133,134] except in the context of Parkinson's disease, where the SSRI citalopram reduced impulsivity as measured by the SST.[135]

Serotonin signaling through the 5-HT_{1B} receptor has been implicated in the regulation of impulsive action.[93,136] Specifically, genetic ablation of the receptor in adult mice increases premature responding and induces deficits in behavioral inhibition in DRL and go/no-go paradigms.[137,138] In a human PET imaging study, 5-HT_{1B} receptor binding in the VS, putamen, and anterior cingulate predicted

severity of gambling.[139] Additionally, the 5-HT_{2A} and 5-HT_{2c} receptors have also been implicated in response inhibition.[140] In rodents, stimulation of 5-HT_{2C} reduces premature responding and other impulsive action behaviors; the antagonist increases these behaviors.[141–143] Interestingly, the 5-HT_{2A} receptor seems to work in opposition to 5-HT_{2C} signaling. Stimulation of 5-HT_{2A} receptors increases premature responding, with antagonism decreasing this type of impulsivity.[143,144] Additionally, density of 5-HT_{2A} receptor binding is correlated with increased premature responding, and levels of receptor expression are also increased in the brains of rats that show high levels of impulsive behavior in the rGT.[145,146] Finally, the 5-HT_{2B} receptor is also implicated in the regulation of impulsivity in both humans and mouse models, with reduced expression associated with increased impulsivity in a number of domains of impulsive behavior.[147]

Impulsive choice, another facet of impulsive behavior, refers to the ability to delay gratification. Individuals with GD consistently discount delayed rewards at a higher rate than normal controls, preferring small immediate rewards over large delayed ones.[97,101] In rodents, impulsive choice is measured in operant tasks that are similar to neurocognitive tests used in humans. These tasks provide rodents with a choice between a smaller, immediate reward or a larger delayed reward. Alterations in DA signaling alter this choice; however, the effects of amphetamine on impulsive choice are complex and vary with sex, strain, and paradigm.[148–151] D_1 antagonists, as well as dopaminergic lesions to the dorsolateral striatum or the nucleus accumbens core, increase impulsive choice in delay-discounting tasks in rodents, resulting in choice of the smaller nondelayed reward more often.[152–154] In humans, there is also an extensive and complex literature linking DA to neural circuitry underlying "now versus later" decisions, which are dysregulated in addiction and GD.[155]

Serotonin is also implicated in the neural basis of impulsive choice. In humans, low serotonin levels are associated with increased impulsivity in delay-discounting tasks.[156] While in rodents, 5,7-DHT-induced serotonin lesions alone have no effect on impulsive choice, they do attenuate the increased impulsivity resulting from D-amphetamine administration.[157] One purported locus for this serotonin–DA interaction is within the NAc, since the effects of systemic 8-OH-DPAT are blocked by intra-accumbal DA lesions.[158]

Noradrenergic signaling is also implicated in impulsive choice, and, similar to impulsive action, atomoxetine reduces impulsivity in a rodent delay-discounting task.[159] There are also long-term effects of chronic atomoxetine administration to rats during adolescence, which causes decreased impulsive choice during adulthood.[160] This suggests a role for noradrenergic signaling in the maturation of the neural circuits controlling impulsive choice and may have implications for adolescents undergoing treatment for ADHD. Furthermore, modafinil, a DA–NE reuptake inhibitor, significantly reduced the mean bet size in individuals with GD, although it had bidirectional effects on subjective motivation to gamble in individuals with low versus high impulsivity.[161] Thus, some of these differences may be related to the heterogeneity of individuals with GD.

Compulsivity

A shift from impulsivity to compulsivity, described as a response perseveration and action with diminished relationship to goals or reward, has also been described in GD.[162] Slower contingency learning and response perseveration have been described in individuals with GD.[163,164] For instance, compared with healthy controls, one study showed that individuals with GD exhibited greater response perseveration on a card playing task where the optimal strategy involves deciding to play less frequently.[58] Using a measure of cognitive flexibility, the Wisconsin Card Sorting Task, one study found that, compared with healthy controls, individuals with GD made significantly more perseverative errors.[165]

Top-down cortical control mechanisms drive many regulatory behavioral mechanisms, including compulsive behavior, and dysregulations in corticostriatal circuits have been implicated in the neural basis of compulsivity in both human and animal studies. Most of the studies on compulsive behavior in humans have relied on obsessive compulsive disorder patients and report a hyperactive OFC–striatum circuit and reductions in the volume of the OFC.[166–168] Animal models of compulsive behavior have focused on repetitive behaviors in models of obsessive compulsive behavior. These studies have found a role for corticostriatal projections in the modulation of perseverative behavior, as measured in grooming behavior. For example,

repeated optogenetic stimulation of excitatory projections from the OFC to the ventral medial striatum resulted in increased grooming behavior in mice, potentially mimicking the hyperactive circuit found in human patients.[169] However, in another study using a genetic mouse model that lacks a synaptic scaffolding gene, Sapap3, and shows increased baseline grooming, stimulation of a lateral OFC-to-striatum projection reduced this repetitive grooming behavior.[170]

Additional animal models, which are arguably more relevant to the compulsive deficits found in GD, use the persistence of motivation to obtain a reward despite negative consequences as a measure of compulsivity. In one mouse model of chronic ethanol intake, dysregulated cortical glutamatergic signaling was associated with punished responding for ethanol.[171] Specifically, GluN1 and GluN2A subunits of NMDA receptors located in the medial orbitofrontal cortex (mOFC) were upregulated in mice that were less sensitive to the punishment (i.e., the mice that continued to seek ethanol despite the footshock punishment). As might be expected, these studies addressing continued motivation for rewards despite negative consequences have also revealed underlying neural mechanisms that are linked to reward circuits. Specifically, in a paradigm in which rats were overfed a high-fat palatable diet for extended periods, the animals developed an addiction-like phenotype in which rats persisted to seek the palatable diet despite having to cross a shock floor to receive it.[172] Reduced expression of D_2 receptors in the striatum resulted in increased vulnerability and faster onset of this compulsive behavior.

Cognitive distortions

Several cognitive distortions have been identified in GD. These include gamblers' interpretations of their chances of winning, their subjective feeling of control over outcomes, their attributions for failure, their justifications for continuing to gamble, and their estimations of their skills.[43,173] For instance, "chasing losses" refers to the belief that financial losses can be recovered by continuing to gamble, and people reliably make riskier decisions immediately following a loss compared with a win.[174] While cognitive distortions are also found in infrequent gamblers, several studies have demonstrated that these distortions are exacerbated in individuals with GD and frequent gamblers.[174,175] In healthy controls, activity in the vmPFC and dorsal anterior cingulate cortex were associated with choosing to chase losses.[176] In another study, frequent gamblers, compared with nongambling controls, had reduced activity in frontal cortical regions, including the dorsal anterior cingulate cortex, following losses, suggesting a possible decreased regulation of decision making in these loss-chasing conditions. [174] Rodent paradigms have been developed to model the cognitive distortions found in humans; for example, chasing losses has been modeled in rats by allowing rats to make a risky decision to attempt to fast-forward through a time-out period, at the cost of potentially doubling the time-out period.[177] 8-OH-DPAT reduces chasing or "doubling-down" behavior, and instead rats chose the safer option more often,[177] implicating serotonergic signaling in the neural basis of this cognitive distortion.

Near misses are another salient cognitive distortion in GD. Individuals with GD often interpret near misses (e.g., cases in which the reels of the slot machine land adjacent to a win) as evidence that they are mastering the game, fostering an illusion of control and a belief that they are not constantly losing but rather constantly nearly winning.[178] In a study using a slot machine task that delivered occasional jackpot wins, near misses were associated with a higher self-reported motivation to gamble compared with nonwins.[179] In particular, these near-loss outcomes cause increased activation of the VS and anterior insula.[179,180] While these neural patterns in response to near misses are also present in recreational or occasional gamblers, in a sample of regular gamblers, the severity of gambling measured by the SOGS (South Oaks Gambling Screen) was predictive of increases in these neural patterns.[180]

A rodent slot machine task (rSMT) was designed to measure near miss–related behavior. It presents 0–3 flashing lights, and rats are rewarded if they choose to "cash out" by pressing a lever only when three of the lights are flashing.[181,182] A near miss would include a trial in which two of the three lights are flashing. D_2 and D_4 receptor agonists affected the reward expectancies in the rSMT measured by increases in cash out responses during near-miss trials.[182,183] The effects of the D_4 agonist are modulated, at least in part, through signaling in the anterior cingulate cortex.[184] In humans, mesolimbic circuits have also been implicated in this type of

cognitive distortion, with heightened activity seen in cortical mesolimbic regions during near-miss events in fMRI studies.[179,180,185] Furthermore, these increases are greater in GD individuals compared with controls.[186] These imaging studies also reported stronger striatal–insula connections when gamblers had higher illusions of control.[187] Finally, the insula has also been strongly implicated in the processing of near-miss events. In rats, inactivation of the agranular insula impaired performance in the rSMT by increasing reward expectancies when one or two lights are illuminated.[187] However, humans with lesions in the insula are less motivated by near-miss trials.[188]

Sensation seeking

Individuals with sensation seeking or novelty traits tend to pursue varied, novel, complex, and intense situations and experiences and are willing to take physical, social, and financial risks for the sake of these experiences.[189] Sensation seeking and novelty seeking have been consistently associated with problem behaviors in humans, including substance use and risky sexual behaviors.[189] Although there are some differing reports based on the scales used and the populations studied, there is strong evidence supporting increased sensation seeking in patients with GD compared with healthy volunteers.[190]

Novelty seeking and sensation seeking have also been modeled in well-validated rodent paradigms. In some tests, the time spent exploring a novel object or novel environment is measured.[191] In operant tasks, rats will increase disadvantageous choices when rewards are paired with audiovisual cues modeling the flashing lights and sounds of a winning slot machine, suggesting that these cues are rewarding or attractive.[181] Furthermore, rodents will readily press levers to obtain animated multisensory stimuli as the sole reward.[192–194] Studies have examined the neural basis of the incentive value of novel visual stimuli.[195] Similar to operant responding for drugs, dopaminergic signaling is implicated in operant sensation seeking. DA antagonists increase responding for sensory stimuli, and genetic ablation of D_1 receptors prevents the acquisition of lever pressing for sensory stimuli.[194] Other studies have shown that mGluR5, a receptor shown to be important for drug self-administration, is also critical for rodent sensation seeking.[90] Furthermore, ablation of mGluR5 on D_1-expressing neurons prevents responding for sensory stimuli.[196] While there is not much evidence linking D_1 and sensation seeking in humans, DA transmission is strongly implicated in the neural basis of sensation seeking. PET studies have shown that individuals with higher sensation-seeking traits tend to have higher endogenous DA levels and greater DA responses to anticipation of reward, as well as a lower density of D_2/D_3 receptors.[197,198] Additionally, haloperidol, a D_2 antagonist, reduces the drive for sensation seeking in humans,[199] and, in a study including individuals with GD, it was found to modify reward-related responses (e.g., relationship between payoff and bet size on consecutive trials over the course of a slot machine game).[200]

Reward and punishment sensitivity

Several studies have suggested altered punishment and reward sensitivity in GD, as seen in the Sensitivity to Punishment and Sensitivity to Reward Questionnaire.[201] While only studied in SUDs, a variant of the IGT in which the advantageous decks result in high immediate punishment but also in an even higher delayed reward might offer valuable information regarding punishment and reward sensitivity in GD. In this variant, the disadvantageous decks result in low immediate punishment but in even lower delayed reward. Thus, abnormal performance on this task would suggest hypersensitivity to reward (choosing the disadvantageous decks, since they are more rewarding in the start, relative to the advantageous decks), as well as hypersensitivity to punishment (by avoiding to choose from the advantageous decks, which render high immediate punishment).

One aspect of reward sensitivity that can be assayed in rodents is the ability to store and retrieve the value of an outcome and choose an appropriate behavioral response on the basis of that representation, particularly when the reward is not directly observable. This allows an investigation into the evaluation of a positive or negative outcome and the ability to modify or update that representation. In both human and animal studies, the ventral PFC has been strongly implicated in reward sensitivity. Specifically, it seems to be necessary for storing and revising the representations of the reward outcome and furthermore in choosing between outcomes on the basis of that information.[202] In humans, using a probabilistic reversal-learning task in which subjects could win and lose money, individuals with

GD, compared with healthy controls, have shown decreased responsiveness of the ventrolateral PFC and hypoactivation of the ventral PFC in response to monetary gains and losses.[164] Additionally, the ability to devalue a stimulus that was previously rewarding (essentially to update a previous representation of a reward) correlates significantly with fMRI activity in the human ventral PFC, specifically within the mOFC.[203] In rats, lesions to the mOFC resulted in an inability to use or retrieve outcome value information to guide behavior.[204] Consistent with this, in mice, activation of the mOFC using designer receptors exclusively activated by designer drugs (DREADDS) increased the sensitivity to reward value.[205] Interestingly, the projections of these stimulated neurons were to the medial dorsal striatum, a projection similar to the circuitry implicated in compulsive behavior, described above.

As one would expect, DA reward circuits are also implicated in dysregulated reward sensitivity. In a translational report using both human and mouse subjects, increasing overall DA signaling through DA reuptake blockade resulted in increased sensitivity to high-reward outcomes.[206] This effect may be mediated through D_2 receptor signaling, given an elegant behavioral dissection that showed that overexpression of the D_2 receptor specifically in the striatum of mice resulted in a deficit in cost/benefit calculation and reduced sensitivity to valuation of future rewards.[207]

Genetics of gambling

Familial and twin studies have reported a higher prevalence of GD in family members of individuals diagnosed with GD, suggesting that familial transmission plays a role in the etiology of GD. Studies conducted in clinical samples have reported a lifetime prevalence of GD of up to 20% among first-degree relatives of individuals with GD.[208] Three twin studies have also provided evidence of the role of genetic factors in the development of GD.[23,209,210] One of these studies also found overlapping genetic risk factors that suggest an association in the risk for GD and alcohol-abuse disorders (AUDs) in both men and women.[210] A secondary case–control analysis from one of these twin cohorts, using a genome-wide association study (GWAS), showed that two single-nucleotide polymorphisms (SNPs) on chromosomes 9 and 12 had significant associations with the lifetime diagnosis of GD.[211]

In gene-association studies, polymorphisms in a number of genes, including *MAOA, SLC6A4 (5-HTTLPR), DRD3, DRD4, HTR2A*, and *COMT,* have been linked to GD.[20,145,212–215] One interesting translational report linked *DRD3* to GD in humans as well as in a rodent model.[145] First, addiction-related SNPs were genotyped in GD patients, which revealed that *DRD3* and *CAMK2D* were significantly associated with GD compared with controls. The expression of these genes was then measured in the brains of rats that had been tested in the rGT. *DRD3* expression levels within regions of the VS correlated with performance in the rGT.

The development of humanized mice, transgenic mice that contain a human genetic variant, could prove useful animal models to study genetic risk factors of GD. In some cases, these models have been developed already, such as in the case of the *COMTVal158Met* allele, but have not yet been studied in the context of gambling.[216] In other cases, genetic knockout (KO) mice have been developed and assessed in tests of gambling-like behavior; however, these global KOs might not accurately model the effect of the polymorphism. One example of this is the *DRD4*-KO mouse, which does not show the expected deficits in novelty seeking or impulsive behavior.[217] The development of a mouse model of the polymorphism in the 48-bp repeat of the third cytoplasmic loop of the D_4 receptor may produce subtle changes in signaling that result in effects on gambling-like behavior that are not captured in the full KO.

Comorbidities

A significant percentage of individuals with GD meet criteria for another psychiatric disorder at some point of their lives.[14] Using DSM-IV criteria, the largest epidemiologic survey conducted in the United States found that, among individuals with GD, 50% had a lifetime mood disorder, 41% had an anxiety disorder, and 61% had a personality disorder. With reference to SUDs, 73% of individuals with GD had a lifetime AUD, 38% had any drug use disorder, and 60% had a diagnosis of nicotine dependence.[14]

Several studies have proposed different GD subgroups on the basis of patterns of psychiatric comorbidity and clustering of risk factors and biological vulnerabilities that ultimately result in impaired control over gambling behavior.[24,25] Per-

haps the best known example of this approach is the "pathways model" described above.

Testing gambling-like behavior in rodent models of addiction and depression could help determine if the disorders are predisposing for the development of GD and/or have shared etiologies. There are both genetic and behavioral paradigms that exploit the known pathophysiology and predispositions of SUDs and major depressive disorder (MDD), which have been used extensively to investigate the underlying neural circuitry for these psychiatric disorders. One such approach has generated genetic KO mouse models of disorder-relevant genes identified from the GWAS or candidate gene-association studies: for example, the μ-opioid receptor (OPRM1) and the Val allele of the COMT gene for SUD and serotonin-related genes like the serotonin transporter-linked polymorphic region (5-HTTLPR) for MDD. Additionally, nongenetic models are also commonly used to induce a state of depression or addiction. For the former, chronic stress models induced by prolonged exposure to stressors or stress hormones induce depressive-like states in rodents. Likewise, repeated exposure to some drugs of abuse, like cocaine, results in an addiction-like drug-seeking state. It would be useful to test gambling-like behavior in these genetic and behavioral models of these disorders that are comorbid with GD to gain a better understanding of potential causal and/or common factors that contribute to the etiology of these disorders.

Approaches to treatment

Psychotherapy

Cognitive–behavioral therapy (CBT) is currently the best-supported treatment for GD. Even though there are variations within CBT modalities, altogether, CBT has demonstrated reduced gambling symptom severity, decreased financial loss, and less frequent gambling at posttreatment in several randomized control trials (RCTs).[1] One CBT modality is focused on identifying and modifying poor coping responses, focusing on training in new skills to manage high-risk situations.[218] An RCT comparing this CBT modality plus a Gambler's Anonymous (GA) referral versus GA alone found that the acquisition of coping skills mediated the reduction in gambling behaviors regardless of the treatment that individuals had received.[218] The learning strategies to identify and manage triggers related to craving may be mediated by an increased prefrontal cortical control over motivational drives involving subcortical brain regions.[219,220]

Another CBT modality focuses primarily on correcting the cognitive distortions and biased information processing found in GD.[173] This process may involve balancing activity of brain circuits coding conflicting motivational states (e.g., increased activation of dorsal anterior cingulate, insula, and PFC relative to reward/motivational systems).[219] However, a study comparing different GD psychotherapies (i.e., cognitive, behavioral, motivational, and minimal intervention) revealed that addressing cognitive distortions did not yield superior outcomes compared with psychotherapies that did not explicitly target them.[221] Thus, there may be several pathways to therapeutic change that do not necessarily require the modification of this core GD phenotype.

Motivational interviewing (MI) has also been shown to decrease gambling frequency and financial loss in GD as either a stand-alone treatment or in combination with CBT.[222–224] MI is a client-centered approach that works under the assumption that a primary obstacle to change is ambivalence.[224] It uses specific techniques to elicit "change talk" in order to help patients change their behaviors. A meta-analysis of GD psychotherapies indicated a large effect size of 2.01 at the end of treatment and an effect size of 1.59 upon follow-up (average of 17 months), suggesting favorable short- and long-term improvements.[225] However, dropout rates in psychotherapy studies are often high, posing a validity threat to these findings and suggesting the need to find better strategies to engage and retain patients.

One study demonstrated the potential of using brain imaging to explore the relationship between the fMRI correlates of cognitive control and treatment outcomes in GD. The study used fMRI Stroop measures before treatment onset in individuals with GD and was able to link Stroop-related brain activations before treatment onset to treatment outcome in individuals with GD receiving CBT incorporating aspects of imaginal desensitization and MI. Changes in symptomatology correlated positively with activation in the vmPFC, including in the OFC and medial frontal gyrus, and in the right VS, including the nucleus accumbens. Activity in additional brain regions, including the amygdala, hippocampus, parahippocampus, inferior temporal gyrus, and occipital cortex, also correlated with changes in symptomatology.[219]

Other than CBT and MI, there are no current psychotherapies addressing core phenotypes in GD.[226,227] In contingency management (CM), patients receive tangible rewards to reinforce positive behaviors, such as abstinence. For instance, in *voucher-based reinforcement,* which has been shown to be effective in several RCTs for SUD, patients receive a voucher for every drug-free urine sample provided. The voucher values are low at first, but increase as the number of consecutive drug-free urine samples increases; positive urine samples reset the value of the vouchers to the initial low value. Another type of CM uses *prize incentives* with chances to win cash prizes instead of vouchers.[228] Typically, program participants supplying drug-negative urine draw from a bowl for the chance to win prizes. RCTs of this sort have not been shown to promote gambling behavior in SUD populations.[228] On the basis of these principles, there is currently one research group enrolling patients in an open label trial using CM for GD (https://clinicaltrials.gov/ct2/show/study/NCT02613754).

Pharmacotherapy

To date, there are no medications approved by the U.S. Food and Drug Administration (FDA) for GD. Different classes of agents have been tested in RCTs, including antidepressants, mood stabilizers (lithium and topiramate), antipsychotics (olanzapine), and opioid antagonists.[229] Interestingly, to date, these pharmacological targets have little overlap with the pharmacology work seen in most of the animal studies that model gambling-like behavior or phenotypes found in GD. Conversely, existing work on animal models of gambling has not generally guided treatment development for GD.

A hypothesized hypoactive serotoninergic system has provided the rationale for testing several SSRIs. These trials are complicated by high noncompletion rates. Large placebo effects have been noted in RCTs testing fluvoxamine, sertraline, and paroxetine.[230,231] Bupropion was also tested in a 12-week RCT.[232] The study found a few differences between the group receiving bupropion and the one receiving placebo on primary and secondary outcome measures, with subjects in both groups experiencing significant improvement. A meta-analysis that included the six RCTs examining the effects of antidepressants (fluvoxamine, paroxetine, sertraline, and bupropion) versus placebo failed to find a statistically significant benefit of antidepressants compared with placebo.[230] Other antidepressants, including clomipramine, fluoxetine, citalopram, and nefazodone, showed some positive outcomes in open-label studies. Altogether, studies have been limited by their design, small size, high dropout rates, high placebo rates, and short follow-up periods.

An RCT suggested possible benefits with lithium in patients with GD and bipolar spectrum disorders (largely bipolar II disorder).[233] Compared with placebo, individuals showed a statistically significant decrease in GD symptoms as well as decreased affective instability. This sample was used to examine differences between 21 individuals with GD and bipolar spectrum disorders and 21 controls using PET.[234] The study found that GD with bipolar spectrum disorders had lower regional glucose metabolic rates in subcortical regions, including the ventral VS, and that lithium treatment was associated with increasing the regional glucose metabolic rate in the VS. These findings should be interpreted with caution given the characteristics of this subgroup of patients.

Topiramate, an anticonvulsant medication with antiglutamatergic and pro–GABA and α-amine-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist properties, was not superior to placebo in a 12-week RCT.[235] Another RCT comparing four sessions of CBT plus either topiramate or placebo found that individuals in both groups exhibited significant improvement over time.[236] Olanzapine, a DA and serotonin antagonist with high affinity for D_2 and 5-HT_{2A} receptors, was examined in two RCTs. Both studies found no significant differences from placebo.[230]

Opioid antagonists have been the most promising in GD. Opioid receptors are widely distributed in the mesolimbic system and are related to the hedonic aspects of reward processing.[237] Opiate antagonists that decrease DA release attenuate reward-related responses in the VS and enhance punishment sensitivity in the mPFC in a gambling activity.[238] Naltrexone and nalmefene, two prototypical nonspecific opioid antagonists that have been shown to reduce drinking in patients with AUD, have been examined in five RCTs for GD.[230] In a fixed-effects meta-analysis, opioid antagonists demonstrated a small (effect size Cohen's $d = 0.22$), but significant benefit compared with placebo.[230] Similar to other

Table 1. Gambling disorder phenotypes

Phenotype	Clinical manifestation	Assessment in humans	Neural basis in humans	Assessment in rodents	Neural basis in rodents
Decision making	Continuous gambling despite negative expected value ("the house always wins")	Measured by IGT, Cambridge Gambling Task, and Game of Dice Task[11,68,241]	Dysregulated OFC, vmPFC, and ventral striatum activity[88,242]	Rodent gambling tasks,[46,48,50,53] rodent betting task,[69] and probabilistic discounting/selection tasks[74,93]	Increasing dopamine signaling and inactivation of the OFC increase risky choices;[52,69,70,81] lesions to the agranular insula, infralimbic, or prelimbic cortex increase risky decision making[84,169]
Impulsivity	Inability to control gambling urges, diminished regard for future negative consequences, lacking forethought	Measure Eysenck Impulsivity Scale, go/no-go, and stop signal tasks[58]	Reduced dorsomedial PFC activity; dysregulated dopamine signaling; and impulsivity is inversely correlated with serotonin levels[242–244]	Go/no-go,[104,137] 5-choice serial reaction time task,[10] differential reinforcement of low-rate responding,[137] and delayed discounting[93,245]	Activation of serotonin neurons decreases waiting impulsivity;[132] 5-HT_{1B}, 5-HT2B, and 5-HT_{2C} blockade/absence increase impulsive action[137,141,147] and 5-HT_{2A} blockade decreases it;[106] D1 antagonists and striatal DA lesions increase impulsive choice;[117,118] and NE reuptake reduces impulsivity[94,121]
Compulsivity	Persistent and recurrent gambling despite jeopardizing or losing a significant relationship, job, or educational or career opportunity	Measured with Wisconsin Card Sorting Task, set-shifting, and reversal learning tasks[58,162]	Hyperactive corticostriatal circuit[162,166]	Perseverative behavior (e.g., time spent grooming),[170] habit formation,[246] and persistence of reward seeking despite negative consequences (e.g., shock)[171]	Hyperactive corticostriatal activity is associated with compulsivity;[169] reduced striatal D_2 receptors increase compulsivity[172]
Cognitive distortions	Control over outcomes, estimation of skill, attribution for failure all dysregulated	Loss-chasing behavior, sensitivity to near misses, and using the Gambling Related Cognitions Scale (GRCS)[247]	Lesions to the insula decrease near-miss effects,[188] elevated activity in the anterior cingulate cortex (in healthy controls participating in gambling tasks)[179]	Rodent model of loss chasing[177] and rodent slot machine task[182]	5-HT_{1A} agonists reduce chasing-like behavior;[177] inactivation of agranular insula increases chasing[184]
Sensation seeking	Gambling as a way to seek excitement or in response to boredom, experiencing a "rush"	Sensation-seeking scale[248]	Increased endogenous dopamine levels; D_2 receptor antagonists reduce sensation seeking[198]	Exploration in a novel environment;[191] operant tasks with multisensory stimuli[181,192]	D1 receptor antagonists increase responding for sensory stimuli[194,196]
Reward and punishment sensitivity	Inaccurate perception or representation of the value of outcomes: rewards or losses	Sensitivity to Punishment and Sensitivity to Reward Questionnaire, Card Guessing Task, and Probabilistic Reversal Task[11]	Decreased activity in the VLPFC found in GD, which also correlates with deficits in devaluing previous rewards[119,185]	Devaluation and reversal learning tasks[64,204,205]	Decreased ventral PFC (mOFC) to striatum activity[204,205] and increased DA (D_2) signaling[206 207] result in diminished reward sensitivity

medication and psychotherapy trials, dropout rates have been high (45.8–66%). Some data suggest that these medications appear particularly helpful in individuals with a family history of AUD.[239]

Overall, it may be useful to begin testing medications, perhaps already approved for the treatment of other conditions, which target neurobiology that has been implicated in GD phenotypes from mouse studies. For example, FDA-approved drugs that target individual serotonin receptors (rather than increasing serotonin globally) could be tested for their ability to reduce impulsivity found in GD patients.

Conclusions

As this review highlights, there is a large amount of human- and animal-based research focused on the phenotypes found in GD. However, in many cases, the translation from mouse to human and back has been limited. Novel evidence-based interventions are needed for the treatment of GD. The development of these interventions could rely on animal models in which targeted manipulations can be tested in the absence of many confounds. The identification of the neural circuits that subserve phenotypes found in GD is an important avenue to pursue. In humans, we do not yet have ways to identify neural system—or phenotype-specific dysfunction at the individual patient level, which could potentially lead to specific treatment recommendations. Ongoing work on the various brain mechanisms associated with the symptoms of GD in individuals is likely to be the basis for novel, personalized therapeutic alternatives. Using a phenotype-based approach in parallel in humans and animal models may aid in bridging the translational gap between basic science and clinical research by making the integration of the translational results more straightforward. It can also help lend clarity to the issues relating to underlying phenotypes shared by GD and SUD. The inclusion of GD in the DSM-5 among the substance-related and addictive disorders should encourage this phenotypic approach to better understanding the shared and distinct behavioral, neural, and genetic phenotypes. Additionally, the deconstruction of GD into distinct phenotypes allows for the development of better animal models with good construct validity and can make determining the neural basis more tractable as well, since there are likely multiple dysregulated neural circuits that contribute to GD. With better information about the biological basis of these phenotypes, the heterogeneity of GD patients can be addressed with more theory-based personalized treatment.

This integration of animal and human studies offers an overview of the course, genetics, pathophysiology, and treatment of GD (Table 1). Given the complex pathways and genetics involved in the development of GD, we encourage further integrative translational strategies to advance GD research. Using a phenotype-based approach may aid in bridging the translational gap between basic science and clinical research. Breaking GD down into components can make determining the neural basis of this complex disorder more tractable, especially in animal models. Because there are likely multiple dysregulated neural circuits to which GD can be attributed, this approach may be better suited than seeking a unique neural basis of GD. To improve translation to human research, the development of animal paradigms can benefit from ongoing dialogue with clinicians, and additional available tools should be used to dissect the neural circuits that subserve phenotypes that are seen as dysregulated in GD. At the same time, clinical trials could be designed to enroll patients with phenotype specificity, and interventions could be chosen on the basis of phenotype-specific neurobiology. Additionally, the use of behavioral measures of these phenotypes should be included in clinical trials to assess behavioral effects that might not be seen in global end point measures of gambling severity.

Finally, from a treatment perspective, even though a substantial proportion of patients respond to CBT, most individuals with GD do not seek treatment. Some pharmacological agents have been tested in animal studies and show some promise in GD but still need to be tested in humans. With better information about the biological basis of these phenotypes taken from animal models, the heterogeneity of GD patients may be made clear on the basis of phenotype-specific diagnoses, which can be addressed with more theory-based personalized treatment. In relation to psychotherapy, treatment availability and dissemination remain key issues. Evidence-based interventions that use newer technologies may be the key to increase dissemination of GD treatments.[240] Interventions of this sort may offer an alternative that could address the shortage

of providers properly trained to provide evidence-based treatments for GD.

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Competing interests

The authors declare no competing interests.

References

1. Cowlishaw, S., S. Merkouris, N. Dowling, *et al.* 2012. Psychological therapies for pathological and problem gambling. *The Cochrane Database Syst. Rev.* **11:** CD008937.
2. Hodgins, D.C., J.N. Stea & J.E. Grant. 2011. Gambling disorders. *Lancet* **378:** 1874–1884.
3. American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders DSM-5* (5th ed.). Washington, DC. American Psychiatric Association.
4. Petry, N.M., C. Blanco, C. Jin, *et al.* 2014. Concordance between gambling disorder diagnoses in the DSM-IV and DSM-5: results from the National Epidemiological Survey of Alcohol and Related Disorders. *Psychol. Addict. Behav.* **28:** 586–591.
5. Strong, D.R. & C.W. Kahler. 2007. Evaluation of the continuum of gambling problems using the DSM-IV. *Addiction* **102:** 713–721.
6. Ashley, L.L. & K.K. Boehlke. 2012. Pathological gambling: a general overview. *J. Psychoactive Drugs* **44:** 27–37.
7. Conversano, C., D. Marazziti, C. Carmassi, *et al.* 2012. Pathological gambling: a systematic review of biochemical, neuroimaging, and neuropsychological findings. *Harv. Rev. Psychiatry* **20:** 130–148.
8. Grant, J.E., B.L. Odlaug & S.R. Chamberlain. 2016. Neural and psychological underpinnings of gambling disorder: a review. *Prog. Neuro-psychopharmacol. Biol. Psychiatry* **65:** 188–193.
9. Raylu, N. & T.P. Oei. 2002. Pathological gambling. A comprehensive review. *Clin. Psychol. Rev.* **22:** 1009–1061.
10. Potenza, M.N. 2008. Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **363:** 3181–3189.
11. Fauth-Buhler, M., K. Mann & M.N. Potenza. 2016. Pathological gambling: a review of the neurobiological evidence relevant for its classification as an addictive disorder. *Addict. Biol.* doi: 10.1111/adb.12378.
12. Bland, R.C., S.C. Newman, H. Orn, *et al.* 1993. Epidemiology of pathological gambling in Edmonton. *Can. J. Psychiatry* **38:** 108–112.
13. Cunningham-Williams, R.M., L.B. Cottler, W.M. Compton, 3rd, *et al.* 1998. Taking chances: problem gamblers and mental health disorders—results from the St. Louis Epidemiologic Catchment Area Study. *Am. J. Public Health* **88:** 1093–1096.
14. Petry, N.M., F.S. Stinson & B.F. Grant. 2005. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J. Clin. Psychiatry* **66:** 564–574.
15. Martins, S.S., C.L. Storr, G.P. Lee, *et al.* 2013. Environmental influences associated with gambling in young adulthood. *J. Urban Health* **90:** 130–140.
16. Volberg, R.A. 1994. The prevalence and demographics of pathological gamblers: implications for public health. *Am. J. Public Health* **84:** 237–241.
17. Welte, J.W., G.M. Barnes, W.F. Wieczorek, *et al.* 2004. Risk factors for pathological gambling. *Addict. Behav.* **29:** 323–335.
18. Browne, B.A. & D.J. Brown. 1994. Predictors of lottery gambling among American college students. *J. Soc. Psychol.* **134:** 339–347.
19. Okuda, M., W. Liu, J.A. Cisewski, *et al.* 2016. Gambling disorder and minority populations: prevalence and risk factors. *Curr. Addict. Rep.* **3:** 280–292.
20. Ibanez, A., I. Perez de Castro, J. Fernandez-Piqueras, *et al.* 2000. Pathological gambling and DNA polymorphic markers at MAO-A and MAO-B genes. *Mol. Psychiatry* **5:** 105–109.
21. Slutske, W.S., S. Eisen, H. Xian, *et al.* 2001. A twin study of the association between pathological gambling and antisocial personality disorder. *J. Abnorm. Psychol.* **110:** 297–308.
22. Petry, N.M., K.L. Steinberg & C. Women's Problem Gambling Research. 2005. Childhood maltreatment in male and female treatment-seeking pathological gamblers. *Psychol. Addict. Behav.* **19:** 226–229.
23. Blanco, C., J. Myers & K.S. Kendler. 2012. Gambling, disordered gambling and their association with major depression and substance use: a web-based cohort and twin-sibling study. *Psychol. Med.* **42:** 497–508.
24. Blaszczynski, A. & L. Nower. 2002. A pathways model of problem and pathological gambling. *Addiction* **97:** 487–499.
25. Nower, L., S.S. Martins, K.-H. Lin, *et al.* 2013. Subtypes of disordered gamblers: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction* **108:** 789–798.
26. Kendler, K.S., C.O. Gardner & C.A. Prescott. 2002. Toward a comprehensive developmental model for major depression in women. *Am. J. Psychiatry* **159:** 1133–1145.
27. Blanco, C., J. Hanania, N.M. Petry, *et al.* 2015. Towards a comprehensive developmental model of pathological gambling. *Addiction* **110:** 1340–1351.
28. Raylu, N. & T.P. Oei. 2004. Role of culture in gambling and problem gambling. *Clin. Psychol. Rev.* **23:** 1087–1114.
29. Alegria, A.A., N.M. Petry, D.S. Hasin, *et al.* 2009. Disordered gambling among racial and ethnic groups in the US:

results from the National Epidemiologic Survey on Alcohol and Related Conditions. *CNS Spectr.* **14:** 132–142.
30. Okuda, M., I. Balan, N.M. Petry, *et al.* 2009. Cognitive–behavioral therapy for pathological gambling: cultural considerations. *Am. J. Psychiatry* **166:** 1325–1330.
31. Slutske, W.S. 2006. Natural recovery and treatment-seeking in pathological gambling: results of two U.S. national surveys. *Am. J. Psychiatry* **163:** 297–302.
32. Blanco, C., D.S. Hasin, N. Petry, *et al.* 2006. Sex differences in subclinical and DSM-IV pathological gambling: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol. Med.* **36:** 943–953.
33. Ibanez, A., C. Blanco, I. Perez de Castro, *et al.* 2003. Genetics of pathological gambling. *J. Gambl. Stud.* **19:** 11–22.
34. Potenza, M.N., M.A. Steinberg, S.D. McLaughlin, *et al.* 2001. Gender-related differences in the characteristics of problem gamblers using a gambling helpline. *Am. J. Psychiatry* **158:** 1500–1505.
35. Odlaug, B.L., P.J. Marsh, S.W. Kim, *et al.* 2011. Strategic vs nonstrategic gambling: characteristics of pathological gamblers based on gambling preference. *Ann. Clin. Psychiatry* **23:** 105–112.
36. Ledgerwood, D.M. & N.M. Petry. 2006. Psychological experience of gambling and subtypes of pathological gamblers. *Psychiatry Res.* **144:** 17–27.
37. Verdura Vizcaino, E.J., P. Fernandez-Navarro, N. Petry, *et al.* 2014. Differences between early-onset pathological gambling and later-onset pathological gambling: data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Addiction* **109:** 807–813.
38. Breen, R.B. & M. Zimmerman. 2002. Rapid onset of pathological gambling in machine gamblers. *J. Gambl. Stud.* **18:** 31–43.
39. Moghaddam, J.F., G. Yoon, D.L. Dickerson, *et al.* 2015. Suicidal ideation and suicide attempts in five groups with different severities of gambling: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Am. J. Addict.* **24:** 292–298.
40. Maccallum, F. & A. Blaszczynski. 2003. Pathological gambling and suicidality: an analysis of severity and lethality. *Suicide Life Threat. Behav.* **33:** 88–98.
41. Petry, N.M. & B.D. Kiluk. 2002. Suicidal ideation and suicide attempts in treatment-seeking pathological gamblers. *J. Nerv. Ment. Dis.* **190:** 462–469.
42. Suurvali, H., J. Cordingley, D.C. Hodgins, *et al.* 2009. Barriers to seeking help for gambling problems: a review of the empirical literature. *J. Gambl. Stud.* **25:** 407–424.
43. Clark, L. 2010. Decision-making during gambling: an integration of cognitive and psychobiological approaches. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **365:** 319–330.
44. Goudriaan, A.E., J. Oosterlaan, E. de Beurs, *et al.* 2006. Neurocognitive functions in pathological gambling: a comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction* **101:** 534–547.
45. Petry, N.M. 2001. Pathological gamblers, with and without substance use disorders, discount delayed rewards at high rates. *J. Abnorm. Psychol.* **110:** 482–487.
46. Zeeb, F.D., T.W. Robbins & C.A. Winstanley. 2009. Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology* **34:** 2329–2343.
47. Rivalan, M., S.H. Ahmed & F. Dellu-Hagedorn. 2009. Risk-prone individuals prefer the wrong options on a rat version of the Iowa gambling task. *Biol. Psychiatry* **66:** 743–749.
48. van den Bos, R., W. Lasthuis, E. den Heijer, *et al.* 2006. Toward a rodent model of the Iowa gambling task. *Behav. Res. Methods* **38:** 470–478.
49. Rokosik, S.L. & T.C. Napier. 2011. Intracranial self-stimulation as a positive reinforcer to study impulsivity in a probability discounting paradigm. *J. Neurosci. Methods* **198:** 260–269.
50. Tedford, S.E., N.A. Holtz, A.L. Persons, *et al.* 2014. A new approach to assess gambling-like behavior in laboratory rats: using intracranial self-stimulation as a positive reinforcer. *Front. Behav. Neurosci.* **8:** 215.
51. Pena-Oliver, Y., S. Sanchez-Roige, D.N. Stephens, *et al.* 2014. Alpha-synuclein deletion decreases motor impulsivity but does not affect risky decision making in a mouse gambling task. *Psychopharmacology* **231:** 2493–2506.
52. Young, J.W., J. van Enkhuizen, C.A. Winstanley, *et al.* 2011. Increased risk-taking behavior in dopamine transporter knockdown mice: further support for a mouse model of mania. *J. Psychopharmacol.* **25:** 934–943.
53. Pittaras, E., J. Callebert, M. Chennaoui, *et al.* 2016. Individual behavioral and neurochemical markers of unadapted decision-making processes in healthy inbred mice. *Brain Struct. Funct.* **221:** 4615–4629.
54. de Visser, L., J.R. Homberg, M. Mitsogiannis, *et al.* 2011. Rodent versions of the Iowa gambling task: opportunities and challenges for the understanding of decision-making. *Front. Neurosci.* **5:** 109.
55. Simon, N.W., R.J. Gilbert, J.D. Mayse, *et al.* 2009. Balancing risk and reward: a rat model of risky decision making. *Neuropsychopharmacology* **34:** 2208–2217.
56. Blaszczynski, A. 1999. Pathological gambling and obsessive–compulsive spectrum disorders. *Psychol. Rep.* **84:** 107–113.
57. Frost, R.O., B.M. Meagher & J.H. Riskind. 2001. Obsessive–compulsive features in pathological lottery and scratch-ticket gamblers. *J. Gambl. Stud.* **17:** 5–19.
58. Goudriaan, A.E., J. Oosterlaan, E. de Beurs, *et al.* 2005. Decision making in pathological gambling: a comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. *Brain Res. Cogn. Brain Res.* **23:** 137–151.
59. Odlaug, B.L., S.R. Chamberlain, S.W. Kim, *et al.* 2011. A neurocognitive comparison of cognitive flexibility and response inhibition in gamblers with varying degrees of clinical severity. *Psychol. Med.* **41:** 2111–2119.
60. van Holst, R.J., W. van den Brink, D.J. Veltman, *et al.* 2010. Brain imaging studies in pathological gambling. *Curr. Psychiatry Rep.* **12:** 418–425.
61. Cocker, P.J., K. Dinelle, R. Kornelson, *et al.* 2012. Irrational choice under uncertainty correlates with lower striatal D(2/3) receptor binding in rats. *J. Neurosci.* **32:** 15450–15457.
62. Rokosik, S.L. & T.C. Napier. 2012. Pramipexole-induced increased probabilistic discounting: comparison between

a rodent model of Parkinson's disease and controls. *Neuropsychopharmacology* **37:** 1397–1408.
63. Winstanley, C.A. 2011. Gambling rats: insight into impulsive and addictive behavior. *Neuropsychopharmacology* **36:** 359.
64. Zeeb, F.D. & C.A. Winstanley. 2013. Functional disconnection of the orbitofrontal cortex and basolateral amygdala impairs acquisition of a rat gambling task and disrupts animals' ability to alter decision-making behavior after reinforcer devaluation. *J. Neurosci.* **33:** 6434–6443.
65. Zeeb, F.D., A.C. Wong & C.A. Winstanley. 2013. Differential effects of environmental enrichment, social-housing, and isolation-rearing on a rat gambling task: dissociations between impulsive action and risky decision-making. *Psychopharmacology* **225:** 381–395.
66. Brevers, D., A. Bechara, A. Cleeremans, *et al.* 2013. Iowa gambling task (IGT): twenty years after—gambling disorder and IGT. *Front. Psychol.* **4:** 665.
67. Ciccarelli, M., M.D. Griffiths, G. Nigro, *et al.* 2017. Decision making, cognitive distortions and emotional distress: a comparison between pathological gamblers and healthy controls. *J. Behav. Ther. Exp. Psychiatry* **54:** 204–210.
68. Brand, M., E. Kalbe, K. Labudda, *et al.* 2005. Decision-making impairments in patients with pathological gambling. *Psychiatry Res.* **133:** 91–99.
69. Barrus, M.M., J.G. Hosking, P.J. Cocker, *et al.* 2016. Inactivation of the orbitofrontal cortex reduces irrational choice on a rodent Betting Task. *Neuroscience* **345:** 38–48.
70. St Onge, J.R. & S.B. Floresco. 2009. Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology* **34:** 681–697.
71. Simon, N.W., K.S. Montgomery, B.S. Beas, *et al.* 2011. Dopaminergic modulation of risky decision-making. *J. Neurosci.* **31:** 17460–17470.
72. Baarendse, P.J. & L.J. Vanderschuren. 2012. Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. *Psychopharmacology* **219:** 313–326.
73. Fiorillo, C.D., P.N. Tobler & W. Schultz. 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* **299:** 1898–1902.
74. Parker, J.G., M.J. Wanat, M.E. Soden, *et al.* 2011. Attenuating GABA(A) receptor signaling in dopamine neurons selectively enhances reward learning and alters risk preference in mice. *J. Neurosci.* **31:** 17103–17112.
75. Baarendse, P.J., C.A. Winstanley & L.J. Vanderschuren. 2013. Simultaneous blockade of dopamine and noradrenaline reuptake promotes disadvantageous decision making in a rat gambling task. *Psychopharmacology* **225:** 719–731.
76. Silveira, M.M., W.S. Murch, L. Clark, *et al.* 2016. Chronic atomoxetine treatment during adolescence does not influence decision-making on a rodent gambling task, but does modulate amphetamine's effect on impulsive action in adulthood. *Behav. Pharmacol.* **27:** 350–363.
77. Faulkner, P., S. Selvaraj, A. Pine, *et al.* 2014. The relationship between reward and punishment processing and the 5-HT1A receptor as shown by PET. *Psychopharmacology* **231:** 2579–2586.
78. Macoveanu, J., J.B. Rowe, B. Hornboll, *et al.* 2013. Serotonin 2A receptors contribute to the regulation of risk-averse decisions. *Neuroimage* **83:** 35–44.
79. Amodeo, D.A., J.H. Jones, J.A. Sweeney, *et al.* 2014. Risperidone and the 5-HT2A receptor antagonist M100907 improve probabilistic reversal learning in BTBR T + tf/J mice. *Autism Res.* **7:** 555–567.
80. Stopper, C.M., E.B. Green & S.B. Floresco. 2014. Selective involvement by the medial orbitofrontal cortex in biasing risky, but not impulsive, choice. *Cereb. Cortex* **24:** 154–162.
81. Piantadosi, P.T., S. Khayambashi, M.G. Schluter, *et al.* 2016. Perturbations in reward-related decision-making induced by reduced prefrontal cortical GABA transmission: relevance for psychiatric disorders. *Neuropharmacology* **101:** 279–290.
82. Pushparaj, A., A.S. Kim, M. Musiol, *et al.* 2015. Differential involvement of the agranular vs granular insular cortex in the acquisition and performance of choice behavior in a rodent gambling task. *Neuropsychopharmacology* **40:** 2832–2842.
83. Zeeb, F.D. & C.A. Winstanley. 2011. Lesions of the basolateral amygdala and orbitofrontal cortex differentially affect acquisition and performance of a rodent gambling task. *J. Neurosci.* **31:** 2197–2204.
84. Zeeb, F.D., P.J. Baarendse, L.J. Vanderschuren, *et al.* 2015. Inactivation of the prelimbic or infralimbic cortex impairs decision-making in the rat gambling task. *Psychopharmacology* **232:** 4481–4491.
85. Bechara, A., A.R. Damasio, H. Damasio, *et al.* 1994. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50:** 7–15.
86. Northoff, G., S. Grimm, H. Boeker, *et al.* 2006. Affective judgment and beneficial decision making: ventromedial prefrontal activity correlates with performance in the Iowa gambling task. *Hum. Brain Mapp.* **27:** 572–587.
87. Power, Y., B. Goodyear & D. Crockford. 2012. Neural correlates of pathological gamblers preference for immediate rewards during the Iowa gambling task: an fMRI study. *J. Gambl. Stud.* **28:** 623–636.
88. Tanabe, J., L. Thompson, E. Claus, *et al.* 2007. Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. *Hum. Brain Mapp.* **28:** 1276–1286.
89. Bechara, A., H. Damasio, A.R. Damasio, *et al.* 1999. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J. Neurosci.* **19:** 5473–5481.
90. Ouellet, J., A. McGirr, F. Van den Eynde, *et al.* 2015. Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): a randomized and sham-controlled exploratory study. *J. Psychiatr. Res.* **69:** 27–34.
91. Fellows, L.K. 2007. The role of orbitofrontal cortex in decision making: a component process account. *Ann. N.Y. Acad. Sci.* **1121:** 421–430.
92. Fellows, L.K. & M.J. Farah. 2005. Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cereb. Cortex* **15:** 58–63.

93. Nautiyal, K.M., M.M. Wall, S. Wang, *et al.* 2017. Genetic and modeling approaches reveal distinct components of impulsive behavior. *Neuropsychopharmacology* **42:** 1182–1191.
94. Broos, N., L. Schmaal, J. Wiskerke, *et al.* 2012. The relationship between impulsive choice and impulsive action: a cross-species translational study. *PLoS One* **7:** e36781.
95. Berg, J.M., R.D. Latzman, N.G. Bliwise, *et al.* 2015. Parsing the heterogeneity of impulsivity: a meta-analytic review of the behavioral implications of the UPPS for psychopathology. *Psychol. Assess.* **27:** 1129–1146.
96. Winstanley, C.A., J.W. Dalley, D.E. Theobald, *et al.* 2004. Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. *Neuropsychopharmacology* **29:** 1331–1343.
97. Brevers, D., A. Cleeremans, F. Verbruggen, *et al.* 2012. Impulsive action but not impulsive choice determines problem gambling severity. *PLoS One* **7:** e50647.
98. Hodgins, D.C. & A. Holub. 2015. Components of impulsivity in gambling disorder. *Int. J. Ment. Health Addict.* **13:** 699–711.
99. Dannon, P.N., N. Shoenfeld, O. Rosenberg, *et al.* 2010. Pathological gambling: an impulse control disorder? Measurement of impulsivity using neurocognitive tests. *Isr. Med. Assoc. J.* **12:** 243–248.
100. Kertzman, S., K. Lowengrub, A. Aizer, *et al.* 2008. Go-no-go performance in pathological gamblers. *Psychiatry Res.* **161:** 1–10.
101. Albein-Urios, N., J.M. Martinez-Gonzalez, O. Lozano, *et al.* 2012. Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: implications for cocaine-induced neurotoxicity. *Drug Alcohol Depend.* **126:** 1–6.
102. Roca, M., T. Torralva, P. Lopez, *et al.* 2008. Executive functions in pathologic gamblers selected in an ecologic setting. *Cogn. Behav. Neurol.* **21:** 1–4.
103. Rodriguez-Jimenez, R., C. Avila, M.A. Jimenez-Arriero, *et al.* 2006. Impulsivity and sustained attention in pathological gamblers: influence of childhood ADHD history. *J. Gambl. Stud.* **22:** 451–461.
104. Bari, A. & T.W. Robbins. 2013. Inhibition and impulsivity: behavioral and neural basis of response control. *Prog. Neurobiol.* **108:** 44–79.
105. Simon, N.W., B.S. Beas, K.S. Montgomery, *et al.* 2013. Prefrontal cortical–striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. *Eur. J. Neurosci.* **37:** 1779–1788.
106. Fletcher, P.J., Z. Rizos, K. Noble, *et al.* 2011. Impulsive action induced by amphetamine, cocaine and MK801 is reduced by 5-HT(2C) receptor stimulation and 5-HT(2A) receptor blockade. *Neuropharmacology* **61:** 468–477.
107. Tremblay, M. & C.A. Winstanley. 2016. Anticonvulsant medications attenuate amphetamine-induced deficits in behavioral inhibition but not decision making under risk on a rat gambling task. *Behav. Brain Res.* **314:** 143–151.
108. van Enkhuizen, J., M.A. Geyer & J.W. Young. 2013. Differential effects of dopamine transporter inhibitors in the rodent Iowa gambling task: relevance to mania. *Psychopharmacology* **225:** 661–674.
109. de Wit, H., J. Crean & J.B. Richards. 2000. Effects of D-amphetamine and ethanol on a measure of behavioral inhibition in humans. *Behav. Neurosci.* **114:** 830–837.
110. de Wit, H., J.L. Enggasser & J.B. Richards. 2002. Acute administration of D-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology* **27:** 813–825.
111. Zack, M. & C.X. Poulos. 2004. Amphetamine primes motivation to gamble and gambling-related semantic networks in problem gamblers. *Neuropsychopharmacology* **29:** 195–207.
112. Zack, M., R.E. Featherstone, S. Mathewson, *et al.* 2014. Chronic exposure to a gambling-like schedule of reward predictive stimuli can promote sensitization to amphetamine in rats. *Front. Behav. Neurosci.* **8:** 36.
113. Boileau, I., D. Payer, B. Chugani, *et al.* 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:** 1305–1313.
114. Besson, M., Y. Pelloux, R. Dilleen, *et al.* 2013. Cocaine modulation of frontostriatal expression of Zif268, D2, and 5-HT2c receptors in high and low impulsive rats. *Neuropsychopharmacology* **38:** 1963–1973.
115. Dalley, J.W., T.D. Fryer, L. Brichard, *et al.* 2007. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* **315:** 1267–1270.
116. Zeeb, F.D., A.D. Soko, X. Ji, *et al.* 2016. Low impulsive action, but not impulsive choice, predicts greater conditioned reinforcer salience and augmented nucleus accumbens dopamine release. *Neuropsychopharmacology* **41:** 2091–2100.
117. van Gaalen, M.M., R.J. Brueggeman, P.F. Bronius, *et al.* 2006. Behavioral disinhibition requires dopamine receptor activation. *Psychopharmacology* **187:** 73–85.
118. Economidou, D., D.E. Theobald, T.W. Robbins, *et al.* 2012. Norepinephrine and dopamine modulate impulsivity on the five-choice serial reaction time task through opponent actions in the shell and core sub-regions of the nucleus accumbens. *Neuropsychopharmacology* **37:** 2057–2066.
119. Balodis, I.M., H. Kober, P.D. Worhunsky, *et al.* 2012. Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. *Biol. Psychiatry* **71:** 749–757.
120. Miedl, S.F., J. Peters & C. Buchel. 2012. Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. *Arch. Gen. Psychiatry* **69:** 177–186.
121. Paterson, N.E., C. Wetzler, A. Hackett, *et al.* 2012. Impulsive action and impulsive choice are mediated by distinct neuropharmacological substrates in rat. *Int. J. Neuropsychopharmacol.* **15:** 1473–1487.
122. Chamberlain, S.R., U. Muller, A.D. Blackwell, *et al.* 2006. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* **311:** 861–863.
123. Kehagia, A.A., C.R. Housden, R. Regenthal, *et al.* 2014. Targeting impulsivity in Parkinson's disease using atomoxetine. *Brain* **137:** 1986–1997.
124. McElroy, S.L., A. Guerdjikova, R. Kotwal, *et al.* 2007. Atomoxetine in the treatment of binge-eating disorder: a ran-

domized placebo-controlled trial. *J. Clin. Psychiatry* **68:** 390–398.
125. Levin, F.R., J.J. Mariani, A. Secora, *et al.* 2009. Atomoxetine treatment for cocaine abuse and adult attention-deficit hyperactivity disorder (ADHD): a preliminary open trial. *J. Dual Diagn.* **5:** 41–56.
126. Raby, W.N., E.A. Rubin, F. Garawi, *et al.* 2014. A randomized, double-blind, placebo-controlled trial of venlafaxine for the treatment of depressed cocaine-dependent patients. *Am. J. Addict.* **23:** 68–75.
127. Tirado, C.F., M. Goldman, K. Lynch, *et al.* 2008. Atomoxetine for treatment of marijuana dependence: a report on the efficacy and high incidence of gastrointestinal adverse events in a pilot study. *Drug Alcohol Depend.* **94:** 254–257.
128. Isherwood, S.N., A. Pekcec, J.R. Nicholson, *et al.* 2015. Dissociable effects of mGluR5 allosteric modulation on distinct forms of impulsivity in rats: interaction with NMDA receptor antagonism. *Psychopharmacology* **232:** 3327–3344.
129. Winstanley, C.A., J.W. Dalley, D.E.H. Theobald, *et al.* 2004. Fractionating impulsivity: contrasting effects of central 5-HT depletion on different measures of impulsive behavior. *Neuropsychopharmacology* **29:** 1331–1343.
130. Harrison, A.A., B.J. Everitt & T.W. Robbins. 1997. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology* **133:** 329–342.
131. Miyazaki, K.W., K. Miyazaki & K. Doya. 2012. Activation of dorsal raphe serotonin neurons is necessary for waiting for delayed rewards. *J. Neurosci.* **32:** 10451–10457.
132. Miyazaki, K.W., K. Miyazaki, K.F. Tanaka, *et al.* 2014. Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards. *Curr. Biol.* **24:** 2033–2040.
133. Drueke, B., M. Boecker, S. Schlaegel, *et al.* 2010. Serotonergic modulation of response inhibition and re-engagement? Results of a study in healthy human volunteers. *Hum. Psychopharmacol.* **25:** 472–480.
134. Nandam, L.S., R. Hester, J. Wagner, *et al.* 2011. Methylphenidate but not atomoxetine or citalopram modulates inhibitory control and response time variability. *Biol. Psychiatry* **69:** 902–904.
135. Ye, Z., E. Altena, C. Nombela, *et al.* 2014. Selective serotonin reuptake inhibition modulates response inhibition in Parkinson's disease. *Brain* **137:** 1145–1155.
136. Clark, M.S. & J.F. Neumaier. 2001. The 5-HT1B receptor: behavioral implications. *Psychopharmacol. Bull.* **35:** 170–185.
137. Nautiyal, K.M., K.F. Tanaka, M.M. Barr, *et al.* 2015. Distinct circuits underlie the effects of 5-HT1B receptors on aggression and impulsivity. *Neuron* **86:** 813–826.
138. Pattij, T., L.M. Broersen, J. van der Linde, *et al.* 2003. Operant learning and differential-reinforcement-of-low-rate 36-s responding in 5-HT1A and 5-HT1B receptor knockout mice. *Behav. Brain Res.* **141:** 137–145.
139. Potenza, M.N., E. Walderhaug, S. Henry, *et al.* 2013. Serotonin 1B receptor imaging in pathological gambling. *World J. Biol. Psychiatry* **14:** 139–145.
140. Winstanley, C.A., D.E. Theobald, J.W. Dalley, *et al.* 2004. 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: interactions with global 5-HT depletion. *Psychopharmacology* **176:** 376–385.
141. Fletcher, P.J., A.D. Soko & G.A. Higgins. 2013. Impulsive action in the 5-choice serial reaction time test in 5-HT(2)c receptor null mutant mice. *Psychopharmacology* **226:** 561–570.
142. Humby, T., J.B. Eddy, M.A. Good, *et al.* 2013. A novel translational assay of response inhibition and impulsivity: effects of prefrontal cortex lesions, drugs used in ADHD, and serotonin 2C receptor antagonism. *Neuropsychopharmacology* **38:** 2150–2159.
143. Fletcher, P.J., M. Tampakeras, J. Sinyard, *et al.* 2007. Opposing effects of 5-HT(2A) and 5-HT(2C) receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test. *Psychopharmacology* **195:** 223–234.
144. Higgins, G.A., M. Enderlin, M. Haman, *et al.* 2003. The 5-HT2A receptor antagonist M100,907 attenuates motor and 'impulsive-type' behaviours produced by NMDA receptor antagonism. *Psychopharmacology* **170:** 309–319.
145. Lobo, D.S., L. Aleksandrova, J. Knight, *et al.* 2015. Addiction-related genes in gambling disorders: new insights from parallel human and pre-clinical models. *Mol. Psychiatry* **20:** 1002–1010.
146. Fink, L.H., N.C. Anastasio, R.G. Fox, *et al.* 2015. Individual differences in impulsive action reflect variation in the cortical serotonin 5-HT2A receptor system. *Neuropsychopharmacology* **40:** 1957–1968.
147. Bevilacqua, L., S. Doly, J. Kaprio, *et al.* 2010. A population-specific HTR2B stop codon predisposes to severe impulsivity. *Nature* **468:** 1061–1066.
148. Eubig, P.A., T.E. Noe, S.B. Floresco, *et al.* 2014. Sex differences in response to amphetamine in adult Long–Evans rats performing a delay-discounting task. *Pharmacol. Biochem. Behav.* **118:** 1–9.
149. Huskinson, S.L., C.A. Krebs & K.G. Anderson. 2012. Strain differences in delay discounting between Lewis and Fischer 344 rats at baseline and following acute and chronic administration of D-amphetamine. *Pharmacol. Biochem. Behav.* **101:** 403–416.
150. Krebs, C.A. & K.G. Anderson. 2012. Preference reversals and effects of D-amphetamine on delay discounting in rats. *Behav. Pharmacol.* **23:** 228–240.
151. Tanno, T., D.R. Maguire, C. Henson, *et al.* 2014. Effects of amphetamine and methylphenidate on delay discounting in rats: interactions with order of delay presentation. *Psychopharmacology* **231:** 85–95.
152. Cardinal, R.N., D.R. Pennicott, C.L. Sugathapala, *et al.* 2001. Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* **292:** 2499–2501.
153. Koffarnus, M.N., A.H. Newman, P. Grundt, *et al.* 2011. Effects of selective dopaminergic compounds on a delay-discounting task. *Behav. Pharmacol.* **22:** 300–311.
154. Tedford, S.E., A.L. Persons & T.C. Napier. 2015. Dopaminergic lesions of the dorsolateral striatum in rats increase

delay discounting in an impulsive choice task. *PLoS One* **10:** e0122063.
155. Volkow, N.D. & R.D. Baler. 2015. NOW vs LATER brain circuits: implications for obesity and addiction. *Trends Neurosci.* **38:** 345–352.
156. Schweighofer, N., M. Bertin, K. Shishida, *et al.* 2008. Low-serotonin levels increase delayed reward discounting in humans. *J. Neurosci.* **28:** 4528–4532.
157. Winstanley, C.A., J.W. Dalley, D.E.H. Theobald, *et al.* 2003. Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology* **170:** 320–331.
158. Winstanley, C.A., D.E.H. Theobald, J.W. Dalley, *et al.* 2005. Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulse control disorders. *Neuropsychopharmacology* **30:** 669–682.
159. Smethells, J.R., N.L. Swalve, L.E. Eberly, *et al.* 2016. Sex differences in the reduction of impulsive choice (delay discounting) for cocaine in rats with atomoxetine and progesterone. *Psychopharmacology* **233:** 2999–3008.
160. Sun, H., P.J. Cocker, F.D. Zeeb, *et al.* 2012. Chronic atomoxetine treatment during adolescence decreases impulsive choice, but not impulsive action, in adult rats and alters markers of synaptic plasticity in the orbitofrontal cortex. *Psychopharmacology* **219:** 285–301.
161. Zack, M. & C.X. Poulos. 2009. Effects of the atypical stimulant modafinil on a brief gambling episode in pathological gamblers with high vs. low impulsivity. *J. Psychopharmacol.* **23:** 660–671.
162. Leeman, R.F. & M.N. Potenza. 2012. Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity. *Psychopharmacology* **219:** 469–490.
163. Vanes, L.D., R.J. van Holst, J.M. Jansen, *et al.* 2014. Contingency learning in alcohol dependence and pathological gambling: learning and unlearning reward contingencies. *Alcohol Clin. Exp. Res.* **38:** 1602–1610.
164. de Ruiter, M.B., D.J. Veltman, A.E. Goudriaan, *et al.* 2009. Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. *Neuropsychopharmacology* **34:** 1027–1038.
165. Marazziti, D., M. Catena Dell'osso, C. Conversano, *et al.* 2008. Executive function abnormalities in pathological gamblers. *Clin. Pract. Epidemiol. Ment. Health* **4:** 7.
166. Lagemann, T., J. Rentzsch, C. Montag, *et al.* 2012. Early orbitofrontal hyperactivation in obsessive–compulsive disorder. *Psychiatry Res.* **202:** 257–263.
167. Rotge, J.Y., D. Guehl, B. Dilharreguy, *et al.* 2009. Meta-analysis of brain volume changes in obsessive–compulsive disorder. *Biol. Psychiatry* **65:** 75–83.
168. Zhu, Y., Q. Fan, H. Zhang, *et al.* 2016. Altered intrinsic insular activity predicts symptom severity in unmedicated obsessive–compulsive disorder patients: a resting state functional magnetic resonance imaging study. *BMC Psychiatry* **16:** 104.
169. Ahmari, S.E., T. Spellman, N.L. Douglass, *et al.* 2013. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. *Science* **340:** 1234–1239.
170. Burguiere, E., P. Monteiro, G. Feng, *et al.* 2013. Optogenetic stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors. *Science* **340:** 1243–1246.
171. Radke, A.K., N.J. Jury, A. Kocharian, *et al.* 2015. Chronic EtOH effects on putative measures of compulsive behavior in mice. *Addict. Biol.* **22:** 423–434.
172. Johnson, P.M. & P.J. Kenny. 2010. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat. Neurosci.* **13:** 635–641.
173. Ladouceur, R., C. Sylvain, C. Boutin, *et al.* 2001. Cognitive treatment of pathological gambling. *J. Nerv. Ment. Dis.* **189:** 774–780.
174. Brevers, D., Q. He, G. Xue, *et al.* 2017. Neural correlates of the impact of prior outcomes on subsequent monetary decision-making in frequent poker players. *Biol. Psychol.* **124:** 30–38.
175. Joukhador, J., F. Maccallum & A. Blaszczynski. 2003. Differences in cognitive distortions between problem and social gamblers. *Psychol. Rep.* **92:** 1203–1214.
176. Campbell-Meiklejohn, D.K., M.W. Woolrich, R.E. Passingham, *et al.* 2008. Knowing when to stop: the brain mechanisms of chasing losses. *Biol. Psychiatry* **63:** 293–300.
177. Rogers, R.D., A. Wong, C. McKinnon, *et al.* 2013. Systemic administration of 8-OH-DPAT and eticlopride, but not SCH23390, alters loss-chasing behavior in the rat. *Neuropsychopharmacology* **38:** 1094–1104.
178. Griffiths, M. 1991. Psychobiology of the near-miss in fruit machine gambling. *J. Psychol.* **125:** 347–357.
179. Clark, L., A.J. Lawrence, F. Astley-Jones, *et al.* 2009. Gambling near-misses enhance motivation to gamble and recruit win-related brain circuitry. *Neuron* **61:** 481–490.
180. Chase, H.W. & L. Clark. 2010. Gambling severity predicts midbrain response to near-miss outcomes. *J. Neurosci.* **30:** 6180–6187.
181. Barrus, M.M. & C.A. Winstanley. 2016. Dopamine D3 receptors modulate the ability of win-paired cues to increase risky choice in a rat gambling task. *J. Neurosci.* **36:** 785–794.
182. Winstanley, C.A., P.J. Cocker & R.D. Rogers. 2011. Dopamine modulates reward expectancy during performance of a slot machine task in rats: evidence for a 'near-miss' effect. *Neuropsychopharmacology* **36:** 913–925.
183. Cocker, P.J., B. Le Foll, R.D. Rogers, *et al.* 2014. A selective role for dopamine D_4 receptors in modulating reward expectancy in a rodent slot machine task. *Biol. Psychiatry* **75:** 817–824.
184. Cocker, P.J., J.G. Hosking, W.S. Murch, *et al.* 2016. Activation of dopamine D4 receptors within the anterior cingulate cortex enhances the erroneous expectation of reward on a rat slot machine task. *Neuropharmacology* **105:** 186–195.
185. Worhunsky, P.D., R.T. Malison, R.D. Rogers, *et al.* 2014. Altered neural correlates of reward and loss processing during simulated slot-machine fMRI in pathological gambling and cocaine dependence. *Drug Alcohol Depend.* **145:** 77–86.
186. Sescousse, G., L.K. Janssen, M.M. Hashemi, *et al.* 2016. Amplified striatal responses to near-miss outcomes in pathological gamblers. *Neuropsychopharmacology* **41:** 2614–2623.

187. Cocker, P.J., M.Y. Lin, M.M. Barrus, *et al.* 2016. The agranular and granular insula differentially contribute to gambling-like behavior on a rat slot machine task: effects of inactivation and local infusion of a dopamine D4 agonist on reward expectancy. *Psychopharmacology* **233:** 3135–3147.
188. Clark, L., B. Studer, J. Bruss, *et al.* 2014. Damage to insula abolishes cognitive distortions during simulated gambling. *Proc. Natl. Acad. Sci. U.S.A.* **111:** 6098–6103.
189. Martins, S.S., M.M. Wall, R. Eisenberg, *et al.* 2015. Trajectories of sensation seeking among Puerto Rican children and youth. *J. Am. Acad. Child. Adolesc. Psychiatry* **54:** 1042–1050.
190. Nower, L., J.L. Derevensky & R. Gupta. 2004. The relationship of impulsivity, sensation seeking, coping, and substance use in youth gamblers. *Psychol. Addict. Behav.* **18:** 49–55.
191. Cuenya, L., M. Sabariego, R. Donaire, *et al.* 2016. Exploration of a novel object in late adolescence predicts novelty-seeking behavior in adulthood: associations among behavioral responses in four novelty-seeking tests. *Behav. Processes* **125:** 34–42.
192. Blatter, K. & W. Schultz. 2006. Rewarding properties of visual stimuli. *Exp. Brain Res.* **168:** 541–546.
193. Olsen, C.M., D.S. Childs, G.D. Stanwood, *et al.* 2010. Operant sensation seeking requires metabotropic glutamate receptor 5 (mGluR5). *PLoS One* **5:** e15085.
194. Olsen, C.M. & D.G. Winder. 2009. Operant sensation seeking engages similar neural substrates to operant drug seeking in C57 mice. *Neuropsychopharmacology* **34:** 1685–1694.
195. Cain, M.E., T.A. Green & M.T. Bardo. 2006. Environmental enrichment decreases responding for visual novelty. *Behav. Processes* **73:** 360–366.
196. Parkitna, J.R., M. Sikora, S. Golda, *et al.* 2013. Novelty-seeking behaviors and the escalation of alcohol drinking after abstinence in mice are controlled by metabotropic glutamate receptor 5 on neurons expressing dopamine d1 receptors. *Biol. Psychiatry* **73:** 263–270.
197. Gjedde, A., Y. Kumakura, P. Cumming, *et al.* 2010. Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking. *Proc. Natl. Acad. Sci. U.S.A.* **107:** 3870–3875.
198. Norbury, A. & M. Husain. 2015. Sensation-seeking: dopaminergic modulation and risk for psychopathology. *Behav. Brain Res.* **288:** 79–93.
199. Norbury, A., Z. Kurth-Nelson, J.S. Winston, *et al.* 2015. Dopamine regulates approach-avoidance in human sensation-seeking. *Int. J. Neuropsychopharmacol.* **18**: pyv041.
200. Tremblay, A.M., R.C. Desmond, C.X. Poulos, *et al.* 2011. Haloperidol modifies instrumental aspects of slot machine gambling in pathological gamblers and healthy controls. *Addict. Biol.* **16:** 467–484.
201. Goudriaan, A.E., J. Oosterlaan, E. de Beurs, *et al.* 2004. Pathological gambling: a comprehensive review of biobehavioral findings. *Neurosci. Biobehav. Rev.* **28:** 123–141.
202. Wallis, J.D. 2011. Cross-species studies of orbitofrontal cortex and value-based decision-making. *Nat. Neurosci.* **15:** 13–19.
203. Valentin, V.V., A. Dickinson & J.P. O'Doherty. 2007. Determining the neural substrates of goal-directed learning in the human brain. *J. Neurosci.* **27:** 4019–4026.
204. Bradfield, L.A., A. Dezfouli, M. van Holstein, *et al.* 2015. Medial orbitofrontal cortex mediates outcome retrieval in partially observable task situations. *Neuron* **88:** 1268–1280.
205. Gourley, S.L., K.S. Zimmermann, A.G. Allen, *et al.* 2016. The medial orbitofrontal cortex regulates sensitivity to outcome value. *J. Neurosci.* **36:** 4600–4613.
206. van Enkhuizen, J., B.L. Henry, A. Minassian, *et al.* 2014. Reduced dopamine transporter functioning induces high-reward risk-preference consistent with bipolar disorder. *Neuropsychopharmacology* **39:** 3112–3122.
207. Ward, R.D., E.H. Simpson, V.L. Richards, *et al.* 2012. Dissociation of hedonic reaction to reward and incentive motivation in an animal model of the negative symptoms of schizophrenia. *Neuropsychopharmacology* **37:** 1699–1707.
208. Walters, G.D. 2001. Behavior genetic research on gambling and problem gambling: a preliminary meta-analysis of available data. *J. Gambl. Stud.* **17:** 255–271.
209. Eisen, S.A., W.S. Slutske, M.J. Lyons, *et al.* 2001. The genetics of pathological gambling. *Semin. Clin. Neuropsychiatry* **6:** 195–204.
210. Slutske, W.S., J.M. Ellingson, L.S. Richmond-Rakerd, *et al.* 2013. Shared genetic vulnerability for disordered gambling and alcohol use disorder in men and women: evidence from a national community-based Australian Twin Study. *Twin Res. Hum. Genet.* **16:** 525–534.
211. Lind, P.A., G. Zhu, G.W. Montgomery, *et al.* 2013. Genome-wide association study of a quantitative disordered gambling trait. *Addict. Biol.* **18:** 511–522.
212. Comings, D.E., N. Gonzalez, S. Wu, *et al.* 1999. Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. *Am. J. Med. Genet.* **88:** 358–368.
213. Grant, J.E., E.W. Leppink, S.A. Redden, *et al.* 2015. COMT genotype, gambling activity, and cognition. *J. Psychiatr. Res.* **68:** 371–376.
214. Perez de Castro, I., A. Ibanez, J. Saiz-Ruiz, *et al.* 2002. Concurrent positive association between pathological gambling and functional DNA polymorphisms at the MAO-A and the 5-HT transporter genes. *Mol. Psychiatry* **7:** 927–928.
215. Wilson, D., D.S. da Silva Lobo, H. Tavares, *et al.* 2013. Family-based association analysis of serotonin genes in pathological gambling disorder: evidence of vulnerability risk in the 5HT-2A receptor gene. *J. Mol. Neurosci.* **49:** 550–553.
216. Risbrough, V., B. Ji, R. Hauger, *et al.* 2014. Generation and characterization of humanized mice carrying COMT158 Met/Val alleles. *Neuropsychopharmacology* **39:** 1823–1832.
217. Helms, C.M., N.R. Gubner, C.J. Wilhelm, *et al.* 2008. D4 receptor deficiency in mice has limited effects on impulsivity and novelty seeking. *Pharmacol. Biochem. Behav.* **90:** 387–393.
218. Petry, N.M., M.D. Litt, R. Kadden, *et al.* 2007. Do coping skills mediate the relationship between cognitive–behavioral therapy and reductions in gambling in pathological gamblers? *Addiction* **102:** 1280–1291.

219. Potenza, M.N., I.M. Balodis, C.A. Franco, *et al.* 2013. Neurobiological considerations in understanding behavioral treatments for pathological gambling. *Psychol. Addict. Behav.* **27:** 380–392.
220. Potenza, M.N., M. Sofuoglu, K.M. Carroll, *et al.* 2011. Neuroscience of behavioral and pharmacological treatments for addictions. *Neuron* **69:** 695–712.
221. Toneatto, T. & M. Gunaratne. 2009. Does the treatment of cognitive distortions improve clinical outcomes for problem gambling? *J. Contemp. Psychother.* **39:** 221–229.
222. Carlbring, P., J. Jonsson, H. Josephson, *et al.* 2010. Motivational interviewing versus cognitive behavioral group therapy in the treatment of problem and pathological gambling: a randomized controlled trial. *Cogn. Behav. Ther.* **39:** 92–103.
223. Diskin, K.M. & D.C. Hodgins. 2009. A randomized controlled trial of a single session motivational intervention for concerned gamblers. *Behav. Res. Ther.* **47:** 382–388.
224. Petry, N.M., J. Weinstock, B.J. Morasco, *et al.* 2009. Brief motivational interventions for college student problem gamblers. *Addiction* **104:** 1569–1578.
225. Pallesen, S., M. Mitsem, G. Kvale, *et al.* 2005. Outcome of psychological treatments of pathological gambling: a review and meta-analysis. *Addiction* **100:** 1412–1422.
226. Bickel, W.K., B.A. Jones, R.D. Landes, *et al.* 2010. Hypothetical intertemporal choice and real economic behavior: delay discounting predicts voucher redemptions during contingency-management procedures. *Exp. Clin. Psychopharmacol.* **18:** 546–552.
227. Prendergast, M., D. Podus, J. Finney, *et al.* 2006. Contingency management for treatment of substance use disorders: a meta-analysis. *Addiction* **101:** 1546–1560.
228. Petry, N.M., K.B. Kolodner, R. Li, *et al.* 2006. Prize-based contingency management does not increase gambling. *Drug Alcohol Depend.* **83:** 269–273.
229. Grant, J.E. & S.W. Kim. 2006. Medication management of pathological gambling. *Minn. Med.* **89:** 44–48.
230. Bartley, C.A. & M.H. Bloch. 2013. Meta-analysis: pharmacological treatment of pathological gambling. *Expert Rev. Neurother.* **13:** 887–894.
231. Grant, J.E., B.L. Odlaug & L.R. Schreiber. 2014. Pharmacological treatments in pathological gambling. *Br. J. Clin. Pharmacol.* **77:** 375–381.
232. Black, D.W., R.B. Goldstein, R. Noyes, Jr., *et al.* 1994. Compulsive behaviors and obsessive–compulsive disorder (OCD): lack of a relationship between OCD, eating disorders, and gambling. *Compr. Psychiatry* **35:** 145–148.
233. Hollander, E., S. Pallanti, A. Allen, *et al.* 2005. Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? *Am. J. Psychiatry* **162:** 137–145.
234. Pallanti, S., M.M. Haznedar, E. Hollander, *et al.* 2010. Basal Ganglia activity in pathological gambling: a fluorodeoxyglucose-positron emission tomography study. *Neuropsychobiology* **62:** 132–138.
235. Berlin, H.A., A. Braun, D. Simeon, *et al.* 2013. A double-blind, placebo-controlled trial of topiramate for pathological gambling. *World J. Biol. Psychiatry* **14:** 121–128.
236. de Brito, A.M., M.G. de Almeida Pinto, G. Bronstein, *et al.* 2016. Topiramate combined with cognitive restructuring for the treatment of gambling disorder: a two-center, randomized, double-blind clinical trial. *J. Gambl. Stud.* **33:** 249–263.
237. Barbano, M.F. & M. Cador. 2007. Opioids for hedonic experience and dopamine to get ready for it. *Psychopharmacology* **191:** 497–506.
238. Petrovic, P., B. Pleger, B. Seymour, *et al.* 2008. Blocking central opiate function modulates hedonic impact and anterior cingulate response to rewards and losses. *J. Neurosci.* **28:** 10509–10516.
239. Grant, J.E., S.W. Kim, E. Hollander, *et al.* 2008. Predicting response to opiate antagonists and placebo in the treatment of pathological gambling. *Psychopharmacology* **200:** 521–527.
240. Rosa, C., A.N. Campbell, G.M. Miele, *et al.* 2015. Using e-technologies in clinical trials. *Contemp. Clin. Trials* **45:** 41–54.
241. Zois, E., N. Kortlang, S. Vollstadt-Klein, *et al.* 2014. Decision-making deficits in patients diagnosed with disordered gambling using the Cambridge Gambling task: the effects of substance use disorder comorbidity. *Brain Behav.* **4:** 484–494.
242. Potenza, M.N. 2014. The neural bases of cognitive processes in gambling disorder. *Trends Cogn. Sci.* **18:** 429–438.
243. Potenza, M.N., H.C. Leung, H.P. Blumberg, *et al.* 2003. An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *Am. J. Psychiatry* **160:** 1990–1994.
244. de Ruiter, M.B., J. Oosterlaan, D.J. Veltman, *et al.* 2012. Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug Alcohol Depend.* **121:** 81–89.
245. Mar, A.C. & T.W. Robbins. 2007. Delay discounting and impulsive choice in the rat. *Curr. Protoc. Neurosci.* Chapter 8: Unit 8.22.
246. Smith, K.S. & A.M. Graybiel. 2016. Habit formation coincides with shifts in reinforcement representations in the sensorimotor striatum. *J. Neurophysiol.* **115:** 1487–1498.
247. Raylu, N. & T.P. Oei. 2004. The Gambling Related Cognitions Scale (GRCS): development, confirmatory factor validation and psychometric properties. *Addiction* **99:** 757–769.
248. Petry, N.M. 2001. Substance abuse, pathological gambling, and impulsiveness. *Drug Alcohol Depend.* **63:** 29–38.