Gambling disorder

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Abstract | Gambling disorder is characterized by a persistent, recurrent pattern of gambling that is associated with substantial distress or impairment. The prevalence of gambling disorder has been estimated at 0.5% of the adult population in the United States, with comparable or slightly higher estimates in other countries. The aetiology of gambling disorder is complex, with implicated genetic and environmental factors. Neurobiological studies have implicated cortico-striato-limbic structures and circuits in the pathophysiology of this disorder. Individuals with gambling disorder often go unrecognized and untreated, including within clinical settings. Gambling disorder frequently co-occurs with other conditions, particularly other psychiatric disorders. Behavioural interventions, particularly cognitive-behavioural therapy but also motivational interviewing and Gamblers Anonymous, are supported in the treatment of gambling disorder. No pharmacological therapy has a formal indication for the treatment of gambling disorder, although placebo-controlled trials suggest that some medications, such as opioid-receptor antagonists, may be helpful. Given the associations with poor quality of life and suicide, improved identification, prevention, policy and treatment efforts are needed to help people with gambling disorder.

It is with significant sadness that we note the passing of Dr Nancy M. Petry on 17 July 2018. Dr Petry made many important contributions to the field of gambling research and addiction research more generally. We will miss her and her important contributions in the areas of treatment development, nomenclature and mentorship, among others.

Gambling is defined as an activity that involves placing something of value at risk in the hopes of gaining something of greater value[1]. Popular forms of gambling include casino gambling (including table-based forms, such as blackjack, and electronic-based forms, such as slot machines), lotteries (including instant lotteries or 'scratch' cards) and Internet gambling (including poker or sports gambling). Other behaviours, for example, buying stocks, are considered forms of gambling by some[2], with the public perception of gambling arguably linked to the relative amount of risk and reward associated with the behaviour (for example, buying on margin or day-trading isolated stocks could be seen more as gambling than buying mutual funds, yet in all cases money is being risked to obtain more money). Debates exist regarding the extent to which specific activities (such as daily fantasy sports[3,4] or loot boxes or loot crates in video games[5,6] (BOX 1)) constitute gambling.

Gambling environments have changed over time owing to the availability of new gambling modalities and changes in legislation. For example, Internet-based gambling has grown in popularity and might continue to do so owing to the increased numbers and use of portable digital devices such as smartphones[7]. In addition, specific states in the United States have recently legalized sports gambling[8]. The majority of adults gamble, and most do so without developing problems[1]. However, for some individuals, gambling can lead to substantial impairment in multiple areas, including health, social or relational, occupational and financial domains.

Gambling disorder (GD) is the term used in the fifth edition of the *Diagnostic and Statistical Manual* (DSM-5) to define a persistent, recurrent pattern of gambling that is associated with substantial distress or impairment[9] (BOX 2). The term 'pathological gambling' was used in the third and fourth editions of the DSM (DSM-III and DSM-IV) and the 10th edition of the International Classification of Diseases (ICD-10)[10]. Throughout this Primer, GD refers to a condition intended to relate to a DSM-5 diagnosis, whereas 'pathological gambling' refers to those with DSM-III or DSM-IV diagnoses and 'problem gambling' refers to individuals in studies that did not use formal diagnostic criteria and/or included individuals with a range of severity of gambling-related problems (such as subsyndromal problems). Individuals with subsyndromal gambling problems (who meet some criteria but not enough to make a formal diagnosis of GD) have negative health correlates similar to those

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with mild substance-use disorders (SUDs[11]), perhaps because a more stringent threshold is used for making a diagnosis of GD as compared with SUDs[9].

GD was reclassified as an addictive disorder in the DSM-5 rather than an impulse-control disorder, becoming the first and only formal behavioural addiction in the manual[9]. Part of the reasoning for this reclassification was that pathological gambling was found to share more similarities with SUDs than with impulse-control disorders or obsessive-compulsive disorder[12,13]. Consistent with this reclassification, GD has inclusionary criteria for tolerance (gambling more over time to achieve the desired effect) and withdrawal (becoming irritable when immediately trying to cease gambling). Similarly, the WHO has reclassified GD as an addictive disorder in the ICD-11 (REF.[14]; BOX 2). Although 'cycle of addiction' models of GD have been proposed, many have been based theoretically on clinical samples and have not received empirical support for the proposed progression[15]. As with SUDs, many people seem to recover naturally from GD without formal intervention; however, they can experience substantial harms by the time they do[16].

Forms of gambling warrant consideration with respect to GD. Some forms of gambling are conducted by large proportions of the population (such as daily lotteries) and may have lower propensities to lead to GD[17]. Conversely, some researchers have suggested that some forms of gambling (such as electronic gambling machines or 'slots') could have a more addictive potential, although this notion has been debated[18]. For some vulnerable individuals (such as those with schizophrenia), gambling low monetary values could have considerable negative effects[19]. Among such vulnerable groups and in general individuals with problem gambling or GD, multiple forms of gambling are frequently reported, indicating the importance of considering 'poly-gambling' behaviours[20,21].

This Primer describes the epidemiology, comorbidity, genetics, neurobiology, diagnosis, screening, prevention and treatment of GD, and discusses the quality of life of individuals with this disorder. Future directions will also be considered for this disorder, a disorder that is associated with substantial negative health measures and that often goes undiagnosed and untreated[16,22].

Epidemiology

Prevalence and co-occurring disorders

The prevalence of lifetime pathological gambling (as defined in the DSM-IV[10]) ranges from 0.4% to 0.6%[23,24] in large-scale epidemiological studies of the general population in the United States, with higher estimates obtained in studies using screening instruments[25]. Indeed, the use of screening instruments in prevalence studies can lead to false positives and inflated estimates (see Diagnosis, screening and prevention, below). Comparable or slightly higher prevalence estimates have been reported in the United Kingdom (0.6–0.9%)[26], Germany (0.2–0.6%)[27], Australia (0.5–2.0%)[28] and Hong Kong (1.8%)[29]. One systematic review demonstrated differences in problem gambling prevalence estimates between countries (between 0.12% and 5.8%), but these differences were difficult to interpret given the variation in study design and other factors[30].

Given the differences in the diagnostic criteria for pathological gambling and GD (as defined in DSM-5 (REFS[9,31])), it is possible that future studies could yield slightly higher prevalence rates (as a GD diagnosis requires one less diagnostic criterion than pathological gambling)[9]. However, findings from studies that included both diagnostic criteria demonstrated slightly higher, albeit relatively equivalent, prevalence estimates[32,33]. Although early studies suggested that prevalence estimates might be increasing owing to greater gambling availability and social acceptability[34], more recent studies have indicated largely stable prevalence estimates over the past four decades[35,36]. In addition, sequential prevalence-estimate studies have indicated that forms of gambling that were not previously available in a location can be introduced without increasing prevalence estimates for GD and could, perhaps, even decrease rates, with the introduction of appropriate responsible gambling measures (such as with the introduction of integrated resort casinos in Singapore)[37].

High prevalence estimates for pathological gambling have been reported in specific clinical populations. For example, prevalence estimates of 6.9% and 4.3% have been reported in psychiatric inpatients and in individuals receiving treatment for substance use, respectively[38,39]. These estimates are consistent with data that indicate frequent co-occurrence between pathological gambling and SUDs[38,40], mood disorders[38,40], impulse-control disorders[25,41] and medical and neurological conditions, including Parkinson disease[42]. Estimates of the prevalence of pathological gambling in patients with Parkinson disease are high (2.2–7%)[42,43].

In individuals with pathological gambling, 96% have been estimated to have one or more psychiatric disorder and 64% have been estimated to have three or more psychiatric disorders[24]. Indeed, SUDs, impulse-control disorders, mood disorders and anxiety disorders were particularly prevalent among individuals with pathological gambling in the US National Comorbidity Survey Replication[36] (FIG. 1). Similar results were obtained in the National Epidemiologic Survey on Alcohol and Related Conditions, with the additional increased likelihood of personality disorders[35]. Some disorders, such as attention-deficit/hyperactivity disorder, do not have

significantly elevated odds ratios in association with pathological gambling in the general population, but have been linked to the onset and persistence of pathological gambling in both community[36] and clinical[40] samples. Other putative behavioural addictions (such as gaming disorder, compulsive sexual behaviour disorder or shopping or buying disorder) have largely been omitted from large-scale epidemiological studies that have included measures of pathological gambling. Similarly, pathological gambling and eating disorders have typically not been concurrently assessed in large epidemiological studies. Although elevated body-mass indices have been observed in association with gambling problems[44,45], some clinical studies have not found elevated rates of pathological gambling in individuals with eating disorders (such as those with binge-eating disorder[46]). Gender-related differences have been observed in pathological gambling, with women more likely than men to experience comorbid mood and anxiety disorders[47]. The frequent co-occurrence of pathological gambling and SUDs in the general population could indicate common vulnerability mechanisms across substance and behavioural addictions, consistent with recent genetic and functional and structural neuroimaging findings[48–50].

Box 1 | **Key terms**

Cognitive appraisal
Subjective interpretations of environmental stimuli.

Disordered gambling
Patterns of betting or wagering that interfere in major life areas of functioning and persist despite adverse consequences. Typically used synonymously with *Diagnostic and Statistical Manual* (DSM)-defined or International Classification of Diseases (ICD)-defined diagnoses.

Gambler's fallacy
The belief that likelihoods of outcomes of statistically independent events are altered based on prior outcomes.

Gambling disorder
DSM fifth edition and ICD 11th edition terminology for recurrent gambling behaviours that are problematic and associated with impairment.

Gambling-related cognitive distortions
Erroneous beliefs that one can control or predict outcomes of chance events.

Imaginal desensitization
An exposure- and relaxation-based technique that seeks to decouple cues from behaviours.

Interoception
The central perception of bodily states.

Loot boxes
Virtual items or rewards unlocked in crates during the playing of video games.

Losses disguised as wins
When individuals 'win' back money that is less than what they have wagered.

Near-miss effect
Where a loss is perceived as close to a win.

Pathological gambling
DSM third and fourth edition and ICD 10th edition terminology for recurrent gambling behaviours that are problematic and associated with impairment.

Probabilistic learning
The acquisition of information that is based on the likelihoods of prior events that have been paired with likelihoods of specific outcomes, often as reflected in subsequent behavioural choices.

Problem gambling
Recurrent and interfering patterns of gambling of a range of severities, typically including individuals with subdiagnostic problems and possibly those meeting criteria for a gambling disorder diagnosis.

Skin gambling
Using virtual items, often those with cosmetic appeal in video games, as the currency of wagering in video games, including professional matches.

Vulnerability and risk factors

Certain groups may have an elevated risk for pathological gambling; for example, adolescents and young-to-middle-aged adults; black individuals; people with low educational status, trauma histories, psychopathology and high impulsivity; and those who live in disadvantaged neighbourhoods may be at elevated risk, whereas parental supervision and religious attendance seem to be protective[51–54]. Although the precise reasons for these differences are not known, models have been proposed in some cases, for example, to explain adolescent propensities for gambling problems and other addictive behaviours[55,56]. Historically, males have been more likely than females to experience pathological gambling, with an ~2:1 ratio, although this sex difference might be narrowing[47,57].

Similar to individuals with alcohol-use disorders, individuals with pathological gambling have been proposed to segregate into different subgroups. A 'pathways model' has been proposed, with emotionally vulnerable, antisocial or impulsive and behaviourally conditioned groups proposed as being vulnerable to developing and experiencing pathological gambling; this set of subgroups has received subsequent empirical support[58]. Other data-driven models support important roles for co-occurring disorders and relational factors (peer and parental) in the aetiology of pathological gambling[53,59]. Irrational gambling-related cognitions have also been proposed as contributing to pathological gambling, although these are also found in gamblers without pathological gambling[60].

Sociodemographic factors

Women are more likely to report engaging in non-strategic gambling (for example, on electronic gambling machines), negative-reinforcement motivations (for example, gambling to relieve depression) and 'telescoping' (more rapid progression of gambling problems) than men[57,61,62]. Gender-related considerations are relevant to treatment outcome, as male gender and low depression scores are the most consistent predictors of successful treatment outcomes[53], although in an Australian sample, women were more likely to seek treatment for and recover from pathological gambling than men[22]. Pathological gambling may manifest differently in children and adolescents, in part given limited financial resources, lack of employment and age restrictions for many forms of gambling. Consistently, school problems may be an important 'warning sign' of pathological gambling in adolescents, whereas more substantial financial problems and relationship discord with spousal partners could be more prominently linked in adults.

Box 2 | **Diagnostic criteria for gambling disorder**

DSM-5 Gambling Disorder (312.31; F63.0)

The diagnostic criteria in the fifth edition of the *Diagnostic and Statistical Manual* (DSM-5)[9] for gambling disorder include nine inclusionary criteria and one exclusionary criterion, namely that "the gambling behaviour is not better explained by a manic episode". The central element is "persistent and recurrent maladaptive gambling behaviour leading to clinically significant impairment or distress", as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

- Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
- Is restless or irritable when attempting to cut down or stop gambling.
- Has made repeated unsuccessful attempts to control, cut back or stop gambling.
- Is often preoccupied with gambling (for example, having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
- Often gambles when feeling distressed (for example, helpless, guilty, anxious, depressed).
- After losing money, often returns another day to get even ('chasing' one's losses).
- Lies to conceal the extent of involvement with gambling.
- Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
- Relies on others to provide money to relieve a desperate financial situation caused by gambling.

Specifiers for the diagnosis are as follows:

- Episodic: meeting diagnostic criteria at more than one point, with symptoms subsiding between periods of gambling disorder for at least several months.
- Persistent: experiencing continuous symptoms, to meet diagnostic criteria for multiple years.
- In early remission: after full criteria for gambling disorder were previously met, none of the criteria for gambling disorder has been met for at least 3 months but for less than 12 months.
- In sustained remission: after full criteria for gambling disorder were previously met, none of the criteria for gambling disorder has been met for a period of 12 months or longer.

Specifiers for the severity are as follows:

- Mild: four or five criteria met.
- Moderate: six or seven criteria met.
- Severe: eight or nine criteria met.

ICD-11 Gambling Disorder (6C50)

According to the International Classification of Diseases 11th Revision (ICD-11; REF.[14]), gambling disorder is characterized by a pattern of persistent or recurrent gambling behaviour, which may be online (that is, over the Internet) or offline, manifested by: impaired control over gambling (for example, onset, frequency, intensity, duration, termination and context); increasing priority given to gambling to the extent that gambling takes precedence over other life interests and daily activities; and continuation or escalation of gambling despite the occurrence of negative consequences.

The behaviour pattern is of sufficient severity to result in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. The pattern of gambling behaviour may be continuous or episodic and recurrent. The gambling behaviour and other features are normally evident over a period of at least 12 months in order for a diagnosis to be assigned, although the required duration may be shortened if all diagnostic requirements are met and symptoms are severe. May include predominantly offline (6C50.0), predominantly online (6C50.1) or unspecified (6C50.Z) behaviours.

Inclusions for the diagnosis are as follows:

- Compulsive gambling.

Exclusions for the diagnosis are as follows:

- Bipolar type I disorder (6A60).
- Bipolar type II disorder (6A61).
- Hazardous gambling or betting (QE21).

Mechanisms/pathophysiology

Aetiological models

Multiple aetiological models for pathological gambling have been proposed, with a change in focus from cognitive-behavioural frameworks[63] to biopsychosocial formulations[64,65] over the past decade. One prominent model, the pathways model, suggests that three distinct groups of individuals with pathological gambling might exist: behaviourally conditioned, emotionally vulnerable and antisocial impulsivist[65]. This model is supported by latent class analysis[66]. Gambling-related motivations can differ across these groups; for example, individuals in the emotionally vulnerable group gamble for negative-reinforcement motivations (for example, to escape from negative mood states) and individuals in the antisocial impulsivist group gamble for positive-reinforcement motivations (such as sensation-seeking).

In addition, pathological gambling may be associated with specific psychological factors, such as gambling-related cognitive distortions. These cognitive distortions might relate to erroneous beliefs about independent effects in gambling (gambler's fallacy), the processing of near misses as wins (BOX 1) or feelings that one may be able to control events over which one does not have control (illusion of control)[60]. As these irrational cognitions could represent a target for treatment interventions[67], they warrant consideration in clinical settings. Further, these cognitions could link to specific neural circuits involving the insula[68], which has been implicated in craving in GD and has been proposed as a neurobiological target for interventions[69].

Genetics

Population-based studies suggest that risk for GD is related to both environmental and genetic factors. Findings from molecular genetic studies of GD should largely be considered preliminary, but these results support the hypothesis of genetic involvement in specific, clinically relevant features of GD. Genome-wide association studies (GWAS) using larger sample sizes are needed.

Heritability. Heritability estimates for GD in twin studies have primarily been derived from two large registries: the Vietnam Era Twin Registry (VET-R), comprising >7,000 male twins[70]; and the Australian Twin Study of Gambling, comprising >4,500 men and women[22].

Estimates derived from the VET-R have indicated that inherited factors account for 35–54% of the liability for meeting features of DSM-III pathological gambling[71]. Moreover, bivariate biometric modelling has indicated that 66% of the variance in pathological gambling is due to genetic factors, whereas 34% is due to unique environmental factors[72]. Studies using VET-R data have also indicated that the co-occurrence of GD and other psychiatric disorders or features is due to shared genetic factors for major depression[72], generalized anxiety disorder[73], stimulant-use disorders[50] and obsessive-compulsive features[74], and due to shared genetic and environmental factors for alcohol-use disorders[75], panic disorder[73], nicotine dependence[50] and cannabis-use disorders[50].

Largely consistent with VET-R findings, heritability estimates of 40% for DSM-IV pathological gambling

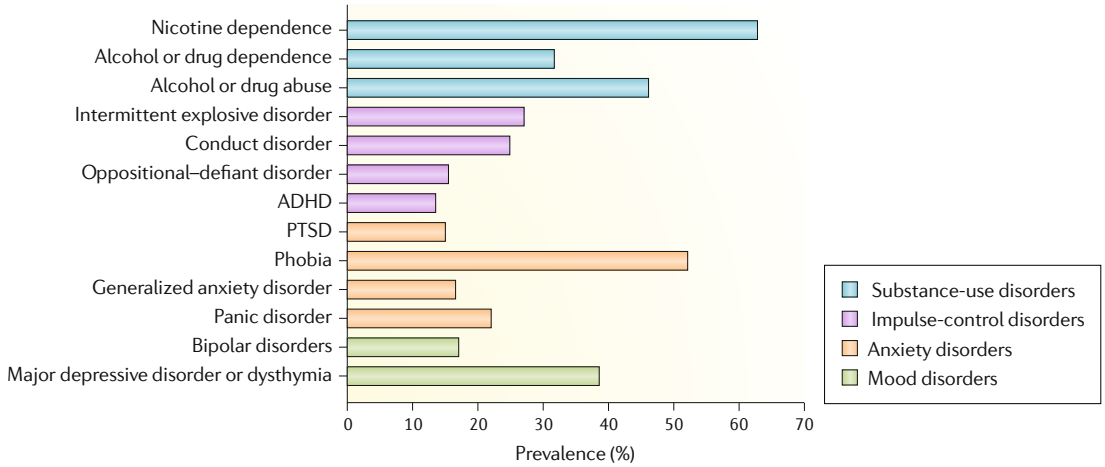

Fig. 1 | **Psychiatric comorbidities with gambling disorder.** Many disorders co-occur with gambling disorder, including substance-use, impulse-control, mood and anxiety disorders. Data derived from the National Comorbidity Survey Replication[24]. ADHD, attention-deficit/hyperactivity disorder; PTSD, post-traumatic stress disorder.

were derived from the Australian Twin Registry, with estimates ranging from 50% to 58% reported for problem-gambling groups meeting fewer criteria; importantly, findings were similar among both men and women[76]. However, data from the Australian Twin Registry have also indicated sex-related differences in the genetic contribution to gambling behaviours. For example, genetic factors contribute predominantly to the age of gambling onset in men, but shared environmental factors contribute to the age of gambling onset in women[77].

Genetic contributions to individual variations in personality features accounted for >40% of the genetic risk for features of DSM-IV pathological gambling, with a larger contribution in women relative to men[78]. Low self-control was associated with genetic risk for features of pathological gambling only in women[78]. In addition, gene–environment interactions have been demonstrated in GD and related constructs of disordered gambling, including an association between genetic factors and local area characteristics (such as local area disadvantage), whereby local area disadvantage can increase the genetic risk for disordered gambling (that is, the genetic risk for GD may make individuals more susceptible to the negative effects of disadvantage)[79]. Further work is needed to identify putative epigenetic factors (relating to gene–environment interactions) linked to pathological gambling. In preliminary studies, the epigenetic modulation of *DRD2* was associated with GD treatment outcome, particularly among individuals with impulsivity[80,81]. As GD probably will relate to small contributions from multiple genes and genomic regions interacting with complex environmental events, a more complete understanding may involve large studies with detailed assessments spanning multiple domains.

Molecular genetics

Molecular genetic studies have suggested the possible involvement of dopaminergic (such as *DRD1*, *DRD2* and *DRD4*) and serotonergic (such as *SLC6A4*, *MAOA* and *MAOB*) genes in conferring vulnerability for GD[82–84]. However, these findings should be interpreted cautiously owing to methodological limitations including those related to sample size and phenotypic characterization[83].

In the first GWAS for disordered gambling, no single-nucleotide polymorphism was associated with disordered gambling after genome-wide statistical correction; however, six variants in *MT1X*, *ATXN1* and *VLDLR* were identified using a less-stringent threshold[85]. These genes encode metallothionein 1X, ataxin 1 and very-low-density lipoprotein receptor, respectively, and were not previously hypothesized to be involved in GD, although some studies have linked variants in these genes to SUDs and other psychiatric disorders[85]. These variants have small effect sizes, and the clinical significance of these findings warrants further investigation. In addition, a second GWAS failed to identify genome-wide significant regions for pathological gambling[86], and *MT1X*, *ATXN1* and *VLDLR* were not identified using a less-stringent threshold. However, this study did demonstrate an association between a polygenic risk score for alcoholism and severity of problem gambling, again supporting a link between alcohol use and GD.

In addition to GWAS, a complementary line of genetic enquiry is the assessment of variants with known functional correlates, such as treatment outcomes and functional brain imaging measures. In a proof-of-concept study, treatment response to tolcapone, a catechol-*O*-methyltransferase (COMT) inhibitor that could be effective for the treatment of GD, was associated with *COMT* Val-158-Met status, such that individuals with the Val allele had the greatest symptom improvement[87]. In the same study, symptom improvement following tolcapone treatment was positively associated with increased frontoparietal activity during performance of an executive-function task[87]. A separate study found that a functional variant of *DBH* (encoding dopamine β-hydroxylase) was associated with subjective and brain responses to sad stimuli in individuals with or without GD, consistent with the notion of a mechanism underlying emotional responsiveness across diagnostic boundaries[88]. Given the exploratory nature

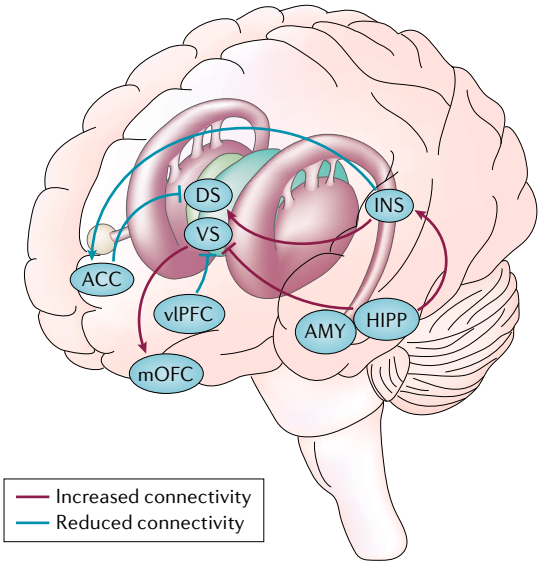

Fig. 2 | **Theoretical model for neural differences in gambling disorder.** The proposed model suggests patterns of regional connectivity that might be altered in individuals with gambling disorder compared with individuals without gambling disorder. This model is intended to serve as a basis for hypothesis-testing, particularly as larger databases accrue and as newer methodologies for systematically examining connectivity are used. ACC, anterior cingulate cortex; AMY, amygdala; DS, dorsal striatum; HIPP, hippocampus; INS, insula; mOFC, medial orbitofrontal cortex; vlPFC, ventrolateral prefrontal cortex; VS, ventral striatum.

of these studies, further research is needed to confirm these data. However, the studies suggest moving towards more personalized interventions in the future.

In general, further work to elucidate specific genetic factors in relation to GD vulnerability is needed. For example, although features associated with GD (such as impulsivity) are heritable[89], the extent to which the genetic contributions to GD overlap with those for specific forms of impulsivity has not been investigated directly.

Neurobiology

GD has been linked to differences in frontostriatal and limbic regions of the brain, including the striatum, orbitofrontal cortex, anterior cingulate cortex, insula, hippocampus and amygdala (FIGS 2,3). These regions are associated with clinical characteristics of GD, including those related to reward or excitement sensitivity, loss-chasing behaviour, stress dysregulation and social-emotional problems.

Striatum and the dopaminergic system. Most neuroimaging studies of GD have implicated alterations in the striatum and prefrontal cortex (PFC) and how these changes could contribute to maladaptive decision-making[90]. The striatum has been implicated in reward processing and related functions; indeed, the ventral striatum has been implicated in learning stimulus–outcome associations, such as the link between gambling cues and monetary gains, in experimental gambling tasks, whereas the dorsal striatum (that is, the dorsal caudate and the putamen) has been implicated in learning stimulus–action associations, such as the link between gambling cues and approach-oriented behaviours[91].

One meta-analysis of reward-processing studies showed relatively diminished activation of the ventral striatum during reward anticipation in individuals with gambling and SUDs[92]. In addition, preliminary studies have demonstrated greater ventral striatum volumes[93] and increased functional connectivity of the ventral striatum[94] in individuals with GD compared with healthy individuals. Other preliminary studies have demonstrated associations between availability of dopamine receptor in the striatum and mood-related impulsivity (such as making impulsive choices under stress) and between availability of dopamine receptor in the ventral striatum and behavioural disinhibition (such as overspending) in people with GD compared with healthy comparison individuals[95,96]. Collectively, these findings suggest that abnormalities in the ventral striatum could contribute to impulsive behaviours in those with GD.

Increased dopamine transmission in the dorsal striatum has been linked to severity of problem gambling[97]. Moreover, increased dopamine-receptor binding and gambling-evoked activation of the substantia nigra (which projects to the dorsal striatum) have been positively associated with the severity of problem gambling[98,99]. These findings suggest that increased sensitivity of the dopamine response within the dorsal striatum may contribute to individual variation in the severity of GD. However, given the preliminary nature of many of these studies (owing to small sample sizes and lack of replication), the central role of dopamine in GD has been questioned[100,101], as it has been for SUDs[102].

A possible mechanistic role has been proposed for dopamine in the development of problem gambling with dopamine replacement therapies in patients with Parkinson disease[42,103,104]. However, multiple factors have been associated with GD and impulse-control behaviours or disorders in patients with Parkinson disease[42,105], suggesting a complex aetiology that involves multiple components. Interestingly, dopaminergic abnormalities in individuals with pathological gambling and Parkinson disease have not been observed in individuals with pathological gambling without Parkinson disease[101]. Among individuals with Parkinson disease, those with pathological gambling as compared with those without have been reported to display greater dopamine release during a gambling task[104]. Among individuals without Parkinson disease, some PET studies have shown increased dopamine release in the striatum following an amphetamine challenge related to pathological gambling[97], whereas other studies have reported conflicting data[95,106]. Although differences in striatal availability of dopamine receptor have been associated with pathological gambling among individuals with Parkinson disease[104], similar levels of striatal dopamine receptors have been reported among individuals with and without pathological gambling and without Parkinson disease[95]. These findings contrast with those for cocaine dependence, in which differences in both striatal and midbrain availability of D2-like dopamine receptors have been observed[107]. Nonetheless, several small PET studies have suggested possible links between availability of

dopamine receptor and impulsivity and measures of severity of problem gambling in people without Parkinson disease[95,97,106]. PET findings in individuals with GD diverge from the reduced striatal dopamine receptors reported in those with SUDs[108,109], suggesting that the latter could represent the neurotoxic effects of substances, rather than be a mechanism of addiction. In addition, other factors (such as age, marital status and geographical location), which are seemingly unrelated to dopamine, have been independently associated with GD and other impulse-control-related conditions in individuals with Parkinson disease[42,110]. For these reasons, other neural systems have been recently examined, with blunted amphetamine-related opioid release in the putamen having been observed in individuals with GD as compared with individuals without GD[110].

Frontostriatal circuits. The striatum projects to regions of the PFC, particularly the medial PFC, that are relevant for reward-based decisions. Blunted activity in frontostriatal regions has been observed in SUDs[111]. Neuroimaging studies in GD have demonstrated relatively decreased activity in frontostriatal regions during cue exposure[112], simulated gambling[113], inhibitory control[114,115] and reward anticipation[116]. In addition, reduced connectivity between the striatum and the medial PFC has been implicated in cue-induced craving in GD[69]. The medial orbitofrontal cortex (involved in the subjective value of choices) and the anterior cingulate cortex (involved in encoding choice predictions and prediction errors) might contribute to GD[117,118]. The medial orbitofrontal cortex and the anterior cingulate cortex showed increased activation in response to gambling cues in individuals with pathological gambling, and these regions and the striatum showed reduced activation in response to gambling-related gains[119]. These data suggest that regions involved in reward valuation may be more sensitive to external cues that indicate the availability of gambling than to the actual value that is won or lost during gambling in individuals with GD.

In addition, the striatum interacts with other prefrontal regions that are involved in tracking losses and switching action patterns once they have proved unsuccessful[120], such as the ventrolateral PFC (or lateral orbitofrontal cortex). This region shows reduced activation in people with gambling problems when attempting to switch perseverative action patterns[115,121], which might hinder the ability of individuals with GD to stop gambling when losses grow. Moreover, individuals with GD have greater engagement of a medial prefrontal cortical circuit in decision-making related to ceasing of loss-chasing behaviours compared with individuals with cocaine dependence or with neither disorder[122].

The severity of problem gambling has been linked to reduced functional connectivity between the striatum and the dorsal anterior cingulate cortex, which might be involved in computing gaps between anticipated or predicted rewards and actual receipt or notification thereof[123]. Moreover, attenuated frontostriatal signalling has been linked to severity of problem gambling; indeed, reduced ventromedial PFC and ventral striatal activities negatively correlate with South Oaks Gambling Screen (SOGS) scores during simulated gambling[113], near-miss processing[98] and delay-discounting[124]. Similarly, hypoactivation of the ventral PFC, particularly the ventrolateral PFC, correlates with severity of problem gambling during inhibitory control or reversal learning, which shows anatomical overlap with findings from nicotine-dependent and cocaine-dependent populations[115], suggesting common neural alterations across substance-based and behavioural addictions. Similarly, impulsivity scores reported by individuals with GD inversely relate to anticipatory ventral striatal activity[116], which is similar to findings from individuals with alcohol-use disorders[125] and those at risk for addiction[126]. Problem-gambling severity is associated with a weaker connection between the ventral striatum and the anterior cingulate cortex, an area implicated in error-monitoring[123].

The insula. The insula has been implicated in interoception[127] (BOX 1); ventral-anterior regions are involved in the perception of bodily feedback and emotional experiences, whereas dorsal-anterior regions are implicated in higher-order cognition[128]. During experimental gambling tasks, the insula could be involved in tracking changes in bodily feedback (such as heartbeat

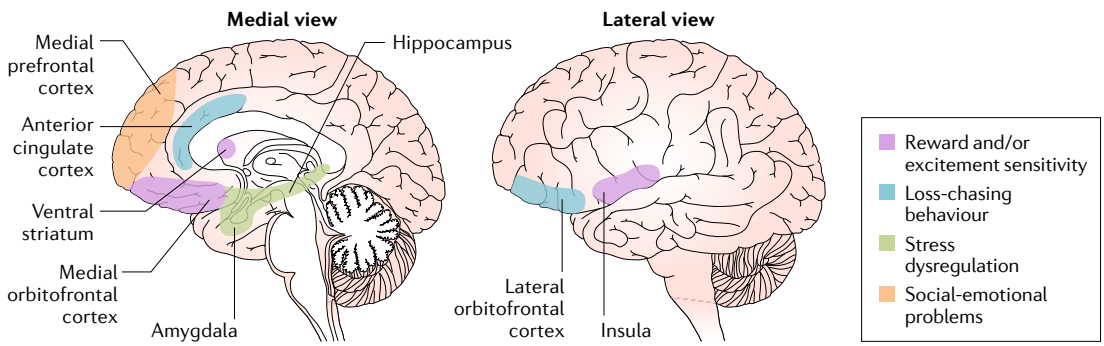

Fig. 3 | **Neurobiology of gambling disorder.** Studies over the past two decades have implicated multiple brain regions in gambling disorder. Implicated regions include the ventral prefrontal cortices (including the medial and lateral orbitofrontal cortices), medial prefrontal cortex and adjacent anterior cingulate cortex, striatum, amygdala, hippocampus and insula. Based on existing data, dysfunction in these brain regions has been proposed to be associated with disruptions to or differences in several processes and functions, such as sensitivity to reward and excitement, loss-chasing behaviour, stress dysregulation and social-emotional problems.

sensations) and encode this information in terms of risk or excitement[129,130]. In addition, the insula has been implicated in the cognitive appraisal (BOX 1) of this feedback, as specific lesions in the insula can abolish gambling-related cognitive distortions such as the gambler's fallacy (BOX 1) and the near-miss effect[60,68]. Individuals with GD have greater insula activation during cue-induced craving[69] compared with healthy individuals, which might be particularly relevant to gambling urges in women with GD given gender-related differences observed during a neuroimaging study of gambling urges[131]. In addition, individuals with gambling problems might have increased insula and striatal activation when making risk-related decisions and experiencing losses or near misses, and may demonstrate increased connectivity between the insula and the amygdala during these types of processes[132–134]. Thus, the insula might abnormally interact with regions involved in reward and punishment learning in GD, which could lead to experiencing bodily feedback (such as increased heartbeat sensations preceding gambling) as reward, excitement or stress signals[135].

Hippocampus and amygdala. The hippocampus and the amygdala have been implicated in emotional learning and stress regulation[136]. During experimental gambling tasks, the hippocampus has been implicated in the probabilistic learning (BOX 1) of stimulus–outcome contingencies (for example, predicting when gambling cues indicate rewards versus punishments) and the amygdala has been implicated in cost–benefit analyses oriented towards loss aversion[137,138]. In real-life gambling, probabilistic learning can be challenged by intermittent reward schedules of gambling devices such as electronic gambling machines, suggesting that engaging in some forms of gambling may influence decision-making tendencies. Individuals with pathological gambling have smaller amygdala and hippocampus volumes, with smaller hippocampal volumes associated with lower tendencies to avoid punishment[139]. Furthermore, individuals with pathological gambling can have enhanced amygdalar responses to the stress-enhancing drug yohimbine[140], but show less recruitment of a striatal–amygdalar network during processing of decisions that leads to cessation of loss-chasing behaviour[122].

In addition, other cognitive components have been associated with GD-related alterations in the neural correlates of processing subjective value[124], monetary reward anticipation[116,141], non-monetary rewards[142] and resting-state connectivity[143]. These studies suggest more nuanced findings, moving beyond a hypo-functioning or hyper-functioning model of reward neurocircuitry revealing both shared and unique alterations in GD and other addictions. Distinctive GD-related features such as the 'near-miss' phenomenon recruit the reward neurocircuitry and might increase gambling motivations[48,133]. Individuals with GD or cocaine dependence have increased anticipatory responding in the reward neurocircuitry[48] to a near-miss outcome compared with healthy individuals, suggesting a possible mechanism of how this type of loss could promote persistent gambling and foster cognitive distortions. Indeed, illusions of control predict stronger connections between ventral striatal and insula areas[123], consistent with the latter's role in representing bodily awareness and craving states[144].

Structural differences. Several neuroimaging studies have not demonstrated structural differences between individuals with and without GD, whereas other studies have demonstrated differences that are not as robust as those in individuals with SUDs[145,146]. One study found that levels of grey matter density in people with GD were similar to those in healthy individuals, whereas decreased volumes in the left superior frontal cortex, left precentral cortex, right insula, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex were observed in people with alcohol-use disorders relative to individuals with GD or neither disorder[147]. Another study demonstrated reduced frontal grey matter volumes in the superior medial and orbitofrontal cortices in individuals with GD compared with those without, with additional grey matter reductions in cortical regions in individuals with GD and alcohol-use comorbidities[148]. In addition, one study demonstrated relatively diminished hippocampal and amygdalar volumes that were linked to behavioural inhibition in individuals with GD[139]. More recently, a volumetric study demonstrated reduced medial prefrontal cortical volumes in individuals with cocaine dependence compared with individuals with GD or neither disorder, with impulsivity across groups linked to lower volumes in the amygdala, hippocampus and insula[145]. These findings are consistent with the neurotoxic effects of cocaine and provide support for both diagnostic and *trans*-diagnostic approaches to understanding the pathophysiology related to GD. Currently, whether the differences in findings between substance and gambling addictions are due to substance exposure is speculative and warrants direct examination in longitudinal studies, especially as reduced frontal cortical volumes have been linked to Internet gaming disorder in a meta-analysis[149].

Diagnosis, screening and prevention

In the DSM-5 (REF.[9]), the most recent version, GD refers to a persistent maladaptive behaviour pattern associated with excessive gambling that disrupts personal, family or vocational pursuits (BOX 2). The DSM-5 includes nine criteria, of which four must be met for a diagnosis. Problematic gambling that occurs primarily during a manic episode is an exclusionary criterion for diagnosis: that is, although bipolar disorder and GD can co-occur, the problematic gambling must not occur exclusively during manic episodes for a GD diagnosis to be permitted. However, the ICD-11 has taken a different approach when considering GD exclusionary criteria (see BOX 2). Although the DSM criteria for GD have remained similar to those used for the past 20 years[10], the DSM-5 instituted three notable changes to its diagnosis[150] (BOX 3).

Screening tools

Although the DSM-5 criteria remain the current gold standard for diagnosing GD, multiple screening and assessment instruments have been developed[151]. Many screening instruments have not undergone rigorous

Box 3 | **Changes to diagnostic criteria in the DSM-5**

The *Diagnostic and Statistical Manual* fifth edition (DSM-5) diagnosis for gambling disorder (GD) eliminated one criterion from the fourth edition (DSM-IV) (that is, 'commits illegal acts to support gambling'). This criterion was removed because it was rarely endorsed unless multiple other criteria were also present, thereby adding little to the diagnosis[31,33]. Nonetheless, the removal of this criterion could have implications for how legal decisions regarding individuals with GD are considered (such as with respect to criminal responsibility and sentencing[2,319]). In addition, the DSM-5 decreased the threshold for diagnosis from five of ten criteria in the DSM-IV to four of nine in the DSM-5. This threshold more accurately classifies a greater proportion of persons with clinically meaningful problems related to gambling[32,320], and it only modestly increases prevalence rates in epidemiological studies[31,33]. Moreover, the DSM-5 moved GD from the 'Impulse-Control Disorders Not Elsewhere Classified' section of the DSM-IV into the 'Substance-Related and Addictive Disorders' section, based on epidemiological, biological, genetic and treatment studies that demonstrated similarities between substance-use and gambling disorders. Other changes include the addition of severity indices (mild, moderate and severe) in the DSM-5 that are linked to the number of inclusionary criteria met, although further research is needed to examine whether this is the most appropriate measure of severity. As described above, the DSM-5 also changed the name from pathological gambling to GD.

psychometric evaluation, but they have nevertheless been used in many prevalence studies internationally, often with modified criteria and changes in wording to make them culturally appropriate.

Two early and widely used screening instruments are the Gamblers Anonymous 20 questions (GA20) developed by the Gamblers Anonymous organization (accordingly, little is known about the development, origin, reliability, validity and classification accuracy of this instrument) and the SOGS[152], which was based on the DSM-III[151] and DSM-III-Revised[153] diagnostic criteria. Although the SOGS was originally developed for use within clinical settings, it has been used as a survey instrument internationally in epidemiological studies. Other more recent and widely used instruments include the Massachusetts Gambling Screen (MAGS)[154], the Diagnostic Interview for Gambling Schedule (DIGS)[155], the National Opinion Research Center DSM-IV Screen for Gambling Problems (NODS)[17], the Canadian Problem Gambling Index (CPGI)[156] and the Victorian Gambling Screen (VGS)[157]. Although these screening instruments vary in their conceptualization of problematic or disordered gambling, they have considerable overlap in the items and types of questions included. In several large and well-designed epidemiological studies, instruments designed to assess DSM criteria (such as the Alcohol Use Disorder and Associated Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders, fourth edition, version (AUDADIS-IV[35,158]) or the WHO Composite International Diagnostic Interview (CIDI[36,159])) have been used. Most clinicians have relied on the use of the DSM criteria for diagnosing GD, whereas the CPGI has been frequently used as a screening instrument in research studies.

Briefer screening instruments were important after some governmental agencies, public health officials and researchers began to incorporate gambling-related items into large-scale surveys. Some brief instruments were also designed for use by physicians to screen for problematic gambling. Such instruments include the Lie–Bet scale (two items)[160], the National Opinion Research Center Diagnostic Screen for Gambling Disorders, Loss of Control, Lying and Preoccupation Screen (NODS-CLiP; three items)[161], the National Opinion Research Center Diagnostic Screen for Gambling Disorders, Preoccupation, Escape, Risked Relationships and Chasing Screen (NPODS-PERC; four items)[162], the Brief Biosocial Gambling Screen (BBGS; three items)[163] and the short SOGS (five items)[164]. Although each of these scales tends to use items derived from the DSM-IV diagnostic criteria[10], they select different items for inclusion, often without much justification, leading to concerns regarding predictive accuracy[165]. Although these instruments may be used in clinical or other high-risk settings, most have generally been used in prevalence studies.

Adolescents are a high-risk group for disordered gambling[52]. Most screening instruments to identify gambling problems in adolescents are adaptations of adult screening instruments, in which items have been changed to be more appropriate for younger populations, the timeframes associated with excessive gambling have been modified and the criterion levels and number of items necessary to reach clinical criteria have been reduced. Adolescent screening instruments include the South Oaks Gambling Screen — Revised for Adolescents (SOGS-RA)[166], the DSM-IV-J[167] and its revision the DSM-IV-MR-J[168], the MAGS[154] and the Canadian Adolescent Gambling Inventory (CAGI)[169]. Within clinical settings, most treatment providers use adaptations of the DSM-5 criteria for identifying gambling problems in adolescents. One study that used the DSM-IV-J, the SOGS-RA and the GA20 reported reasonably good concordance rates in identifying adolescents with problem gambling and noted the overlap and similarities of items[170]. Similar to other screening instruments, the reliability and validity of these instruments need to be evaluated further, particularly in light of recent changes in types of gambling opportunities (for example, on the Internet). Screening instruments for other high-risk groups have been developed, including the Early Identification Gambling Health Test (EIGHT) developed for use by general practitioners[171] and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease (QUIP) developed for screening for GD and other impulse-control behaviours in patients with Parkinson disease[172].

Prevention

Given both the short-term and long-term negative harms associated with problem gambling, multiple prevention initiatives aimed at harm minimization or reduction have been developed. The application of these prevention strategies often stems from prevention initiatives that were initially developed for SUDs. Besides governmental age restrictions and prohibitions for regulated forms of gambling, these prevention efforts have traditionally focused upon issues of personal responsibility, controlled use and healthy choices[173]. Countries with strict efforts to prevent problem gambling have reported low (and seemingly decreasing) prevalence estimates for disordered gambling. For example, in Singapore, citizens are charged more money than tourists are to enter resort casinos[37]. One widely available prevention approach, including in many less restrictive

jurisdictions, includes voluntary self-exclusion from casinos. However, although many individuals with GD have reported benefits from self-exclusion programmes, these programmes seem to be under-utilized[174]. Another prevention strategy is to increase the age of legal gambling; indeed, raising the age for legalized gambling from 15 to 18 years of age was associated with fewer gambling problems in adolescents and young adults in Finland[175]. These and other prevention strategies warrant additional investigation.

Assuming a harm-minimization strategy, the ultimate goal of prevention is to reduce, minimize or eliminate the potential harmful consequences that are concomitant with gambling in general, and problem or disordered gambling in particular. As such, harm-reduction strategies have been proposed. Such strategies are consistent with preliminary data suggesting that most people who recover from GD continue to gamble at non-problematic levels[176]. However, the concept of gambling while in recovery is not consistent with abstinence-based approaches (such as Gamblers Anonymous), and given data from other addictive disorders regarding priming effects (whereby, for example, a sip of alcohol leads to craving and biological changes that predispose to more drinking and relapse behaviours[177,178]), continued or controlled gambling during recovery should be considered cautiously.

Harm-minimization strategies have taken multiple forms and have incorporated either more generalized risk strategies or those specific for particular forms of gambling. These strategies are based on structural characteristics (such as the rate of outcomes being displayed on electronic gambling machines), modes of delivery (such as online gambling or land-based operations) or environments or venues in which gambling occurs (such as poker rooms, bars, betting shops or casinos, often referred to as situational characteristics). Such examples, in line with guidelines generated in Reno (and, therefore, termed the Reno model[179]), include time or monetary pre-commitments[180], voluntary self-exclusion from casinos[181,182] and approaches such as GameSense[183] that provide information to consumers regarding how to gamble responsibly. These approaches incorporate a diverse range of interventions and strategies to promote consumer protection, community and consumer awareness, and education[179]. However, they have often lacked empirical testing. Indeed, further study in five specific areas has been suggested: voluntary self-exclusion; using information about gambling behaviour to develop interventions; limit-setting; responsible-gambling features in gambling machine features; and training of employees[184]. Research is also needed to understand how the types and extents of inducements may affect gambling[185].

Structural and situational factors and potential determinants of cognitive-belief structures that could contribute to the development and maintenance of GD include the stake or bet size, event frequency, near misses, losses disguised as wins (BOX 1), speed of gambling, jackpot size and sound and lighting effects[186,187]. Accordingly, factors that have been suggested for the prevention of GD have included the use of a clock for players to monitor their time, the displaying of money versus credits, the regulation of note or bill acceptors in machines, establishing pre-set time and monetary loss limits, self-exclusion policies for land-based and online venues, automatic cash-outs, the removal of easy access to automated-teller machines, forced breaks in gambling, pop-up messaging with player feedback, the use of personalized normative feedback messaging, and mandatory closing and shut-down periods. The potential effects of gambling promotion and advertising on vulnerable populations, particularly children and adolescents, also warrant consideration[188,189]. As the use of social casino games and micro-transactions (such as paying to continue to play) within Internet-based games have been linked to gambling and features of gambling problems in youths[190,191], these also warrant further study. Similarly, the inclusion of other gambling elements (such as loot boxes or crates that can contain gaming items of differing value when opened) within games has been considered gambling within some jurisdictions and linked to problem gambling, leading to increased regulation[192]. Internet gambling may attract individuals with specific vulnerabilities (such as those who gamble in non-peer or solitary fashions[193]), and data from ecological momentary assessment suggest that solitary gambling mediates the relationship between anxiety sensitivity and excessive gambling in young adults[194].

Although research on the efficacy of the inclusion of many specific gambling product features and approaches as prevention strategies remains inconclusive, there is consensus calling for the early detection and prevention of gambling problems[195]. This call has resulted in the development of school-based prevention programmes[196,197]; the need for greater parental[198], teacher[199] and provider[200] awareness of the early risk signs for gambling problems; and calls for enhanced mandatory education of staff and employees of gambling venues[195].

Despite little systematic research on the overall effect and effectiveness of specific strategies to reduce the incidence of problem gambling, prevalence estimates for GD over the past three decades have not risen dramatically or consistently across studies, despite substantial expansion of gambling opportunities, leading to proposals of adaptation models[201]. Putting aside the multiple possible aetiological causes and pathways associated with GD[65], gambling features and the availability and accessibility of specific forms of gambling could contribute importantly to our understanding of GD.

Management

Epidemiological studies have suggested that ~10% of people with pathological gambling seek professional treatment or attend self-help groups like Gamblers Anonymous[16]. Data from gambling helplines similarly report low rates of treatment-seeking (2.6%), with men typically gambling for longer periods of time before calling for help than women (~10 years versus 7 years) and seeking help at younger ages (38 years versus 45 years of age)[57]. In an Australian study, women were more likely than men to seek treatment for GD (32% versus 13%) and were more likely to recover (56% versus 36%[22]), although in this study recovery might have involved persistent gambling[176]. Motivations for seeking treatment vary and

may include financial, relational, legal and other problems, and obtaining information from collateral sources (such as family members) might be very informative. At times, family members may enquire about treatment options on behalf of family members, and treatment or support groups for family members might also be helpful (such as Gam-Anon).

How best to assess the outcomes of GD treatment has been debated. Although consensus guidelines suggest using measures of gambling behaviour, gambling-related problems, quality of life and mechanisms of change[202], one systematic review demonstrated that 63 different outcome measures have been used across multiple domains, suggesting a multidimensional conceptualization of recovery[203]. Management of patients with GD requires consideration of multiple factors, including the presence or absence of co-occurring psychiatric disorders, in addition to whether the patient wishes to engage in treatment. Treatments typically include psychotherapy and/or pharmacotherapy, although no medication has been approved in any country by a regulatory board for the expressed treatment of GD.

Psychosocial interventions

Gamblers Anonymous. Gamblers Anonymous, with groups throughout the world, is the most common intervention for GD. However, despite the widespread availability of Gamblers Anonymous, it may not resonate equally with all cultures globally. Gamblers Anonymous was modelled after Alcoholics Anonymous, and consists of a 12-step fellowship programme that involves regular attendance at group meetings and obtaining a sponsor. In addition, some groups provide peer assistance with managing financial problems that are related to gambling. The underlying theory of Gamblers Anonymous is that gambling is a disease, requiring total abstinence. Little is known about the effectiveness of Gamblers Anonymous, in part because of the anonymity that is central to this programme. However, in one longitudinal evaluation of 232 consecutive Gamblers Anonymous attendees[204], only 8% of attendees remained engaged for 1 year and maintained gambling abstinence throughout the year. Nevertheless, patients who attend Gamblers Anonymous while receiving professional care are more likely to achieve gambling abstinence than those who do not participate in Gamblers Anonymous[205,206].

Cognitive therapies. Some interventions try to alter cognitive distortions, termed cognitive therapies. Cognitive therapies, as compared with cognitive-behavioural therapies (CBTs), do not incorporate a focus on behavioural aspects (such as identifying external triggers, practising alternative responses to triggers and promoting gambling alternatives) as a main focus[207]. Although cognitive therapy focusing on correcting irrational thoughts is associated with a reduction in indices of gambling-related urges and problems, there is no evidence suggesting long-term benefits associated with cognitive therapy or that it improves outcomes better than other treatments[208,209]. An early review and meta-analysis reported large effect sizes for psychotherapies broadly defined (including a range of cognitive and behavioural therapies) for shorter-term and longer-term outcomes[210]. A more recent systematic review of psychosocial treatments for gambling problems demonstrated a short-term benefit in most studies, but a long-term benefit in only a few[211]. The authors of this study concluded that although individuals with less severe gambling problems may benefit from brief interventions, those with more severe problems may require therapist contact using cognitive-behavioural approaches[211].

Cognitive-behavioural therapy. CBT has been reported to be the most commonly used treatment approach for helping individuals with gambling problems[212]. Integrated CBT addresses the cognitive components of gambling (such as cognitive distortions, emotions that can lead to or stem from gambling and cravings or urges) along with behavioural aspects, as described above[207]. Although CBT has demonstrated medium to large short-term effects (0–3 months following treatment), less evidence supports longer-term effects (for example, at 9–12 months[213]).

In one study, 8-week Internet-delivered CBT with telephone call and e-mail contact led to a significant reduction in an index of gambling-related problems during the study period, compared with waitlist controls, with treatment effects sustained up to 36 months[214]. In another study, CBT (either delivered using a workbook containing CBT exercises or delivered by a therapist in weekly sessions) and attendance at Gamblers Anonymous were associated with a significantly greater reduction in days gambling and gambling-related problems as assessed by standardized questionnaires compared with attendance at Gamblers Anonymous alone, and some benefits of CBT were maintained throughout 12-month follow-up[215]. In this latter study, therapist-delivered CBT outperformed workbook-delivered CBT with respect to some outcomes, particularly in terms of reducing the amounts gambled, which related to enhanced engagement with the therapist-delivered format.

Motivational interventions. Interventions that seek to understand and address barriers to change include motivational interviewing, which is goal-oriented, focused on the individual in counselling and oriented towards understanding ambivalence regarding treatment[216]. Elements of motivational interviewing involve assessing the patient's readiness for change; assuming a non-judgmental, non-confrontational and non-adversarial position; and using interventions that involve open-ended questions, affirmations, reflective listening and brief summarizations[216]. Motivational interviewing attempts to enhance engagement, and may, therefore, be particularly relevant for GD, as up to two-thirds of patients who seek treatment do not become actively engaged in or complete it[211].

In one study, patients who received motivational interviewing and CBT demonstrated greater reductions in gambling (assessed using a questionnaire that enquired about gambling-related cognitions and behaviours) than those who attended Gamblers Anonymous alone[217]. In addition, in another study, use of a CBT self-help workbook combined with motivational interviewing telephone calls significantly decreased the gambling

frequency and amount in individuals with problem gambling compared with use of a CBT self-help workbook alone or waitlist controls[218]. In this study, use of the CBT self-help workbook alone did not improve gambling problems compared with waitlist controls. Motivational interviewing in conjunction with the workbook maintained treatment improvement at follow-up to 12 months, particularly in those with less-severe gambling problems[218]. Additionally, motivational interviewing in conjunction with a self-help workbook versus a workbook alone demonstrated better outcomes (greater abstinence, less money gambled, fewer days gambled and lower problem-gambling severity) at 24-month follow-up[219]. Subsequent studies demonstrated that booster motivational interviewing telephone calls[220] or additional mailings of relapse-prevention booklet materials[221] failed to yield any longer-term benefits than the CBT workbook alone. In two randomized trials involving individuals with gambling problems, motivational interviewing alone resulted in improvements on some outcomes (number of days gambling, amount of money spent on gambling) compared with waitlist controls[222,223].

The participants in the studies mentioned above were seeking treatment, but some studies have also applied motivational interviewing to individuals with gambling problems who were not explicitly seeking treatment. In one study of college students, a single motivational interviewing session was equally efficacious to 4–6 weeks of CBT compared with an assessment-only control condition[224]. In addition, in another study of college students with gambling problems, students who received 10 min of brief advice, a single motivational interviewing session or a single motivational interviewing session plus three CBT sessions had decreased frequencies and amounts spent on gambling compared with individuals who received no intervention, although only motivational interviewing alone increased the likelihood of a clinically significant reduction in gambling (dollars wagered) at 9-month follow-up[225].

Patients with co-occurring gambling problems may also benefit from brief motivational interviewing. In one study of individuals in substance-abuse-treatment clinics or inner-city medical clinics who screened positive for gambling problems, 10 min of brief advice reduced the amounts spent on gambling compared with assessment-only in the short term, and was associated with a clinically significant reduction in gambling 9 months later[226]. In this study, a single motivational interviewing session or a single motivational interviewing session plus three CBT sessions had effects on some, but not all, outcomes[226]. In a subsequent study, patients in treatment for substance abuse who screened positive for gambling problems were randomized to a single brief psychoeducation gambling intervention, a single brief advice intervention or four 50-min sessions of motivational interviewing and CBT[227]. Overall, participants reduced their gambling days, amounts and problems markedly in the first 5 months, and brief advice significantly reduced days of gambling during this timeframe compared with psychoeducation. Motivational interviewing and CBT did not improve the number of days gambled beyond those obtained with brief advice, but it resulted in more precipitous declines in dollars gambled and problems experienced in the initial 5 months, and yielded greater clinically significant improvements in gambling in the short term and the long term, compared with the brief interventions.

To summarize, psychosocial interventions such as Gamblers Anonymous, CBT and motivational interviewing can reduce gambling problems. Providing four to eight sessions of CBT more consistently decreases gambling[211], and attending Gamblers Anonymous in conjunction with CBT can further enhance abstinence relative to each intervention alone in those with severe GD[205,206]. Motivational interviewing and CBT may also be useful, although benefits might be limited to the short term[218,219], and motivational interviewing is no more effective than CBT or other treatments[228,229]. Furthermore, as a standalone intervention, motivational interviewing is usually provided to individuals with less-severe gambling problems. Delivering interventions over the Internet or in a workbook may expand treatment access and minimize costs, but these formats generally result in relatively low engagement[211,214]. Other interventions including mindfulness-based approaches[230,231], cognitive remediation[232], Internet-based approaches[233] and neuromodulation to influence cognitive processes[232,234] have been proposed and examined in preliminary studies and warrant additional testing. As the field matures, it will be important to move beyond waitlist-control study designs and evaluate long-term efficacy of psychotherapies alone or in combination, as well as with pharmacotherapies.

Pharmacological treatment

In one review and meta-analysis, antidepressants, opioid-receptor antagonists and mood stabilizers were associated with an improvement in GD relative to placebo or no treatment with an overall effect size of 0.78 (REF.[235]). Several medications have been investigated based on the available neurochemical, neurocognitive or neuroimaging evidence for the pathophysiology of GD, including serotonergic antidepressants, lithium, glutamatergic agents, COMT inhibitors, neuroleptics, dopamine-1-receptor and dopamine-2-receptor antagonists and opioid-receptor antagonists. Although multiple open-label studies have shown promise, results from double-blind, placebo-controlled trials have often demonstrated mixed efficacy[236], in part given high placebo responses in GD. Thus, no pharmacological agents have been approved with an expressed indication for the treatment of GD. Although the systematic study of pharmacotherapy treatment efficacy and tolerability for GD is in the early stages, specific drug therapies do have promise for treatment. Although issues regarding medication selection and duration cannot be sufficiently addressed with the available data, an updated proposed treatment algorithm (revised from a pharmacotherapy algorithm[237] and focusing on existing data with greater empirical support) is presented (FIG. 4).

Opioid-receptor antagonists. The class of medications that has arguably received the greatest attention for GD treatment is opioid-receptor antagonists, such as naltrexone or nalmefene[238]. These drugs may indirectly

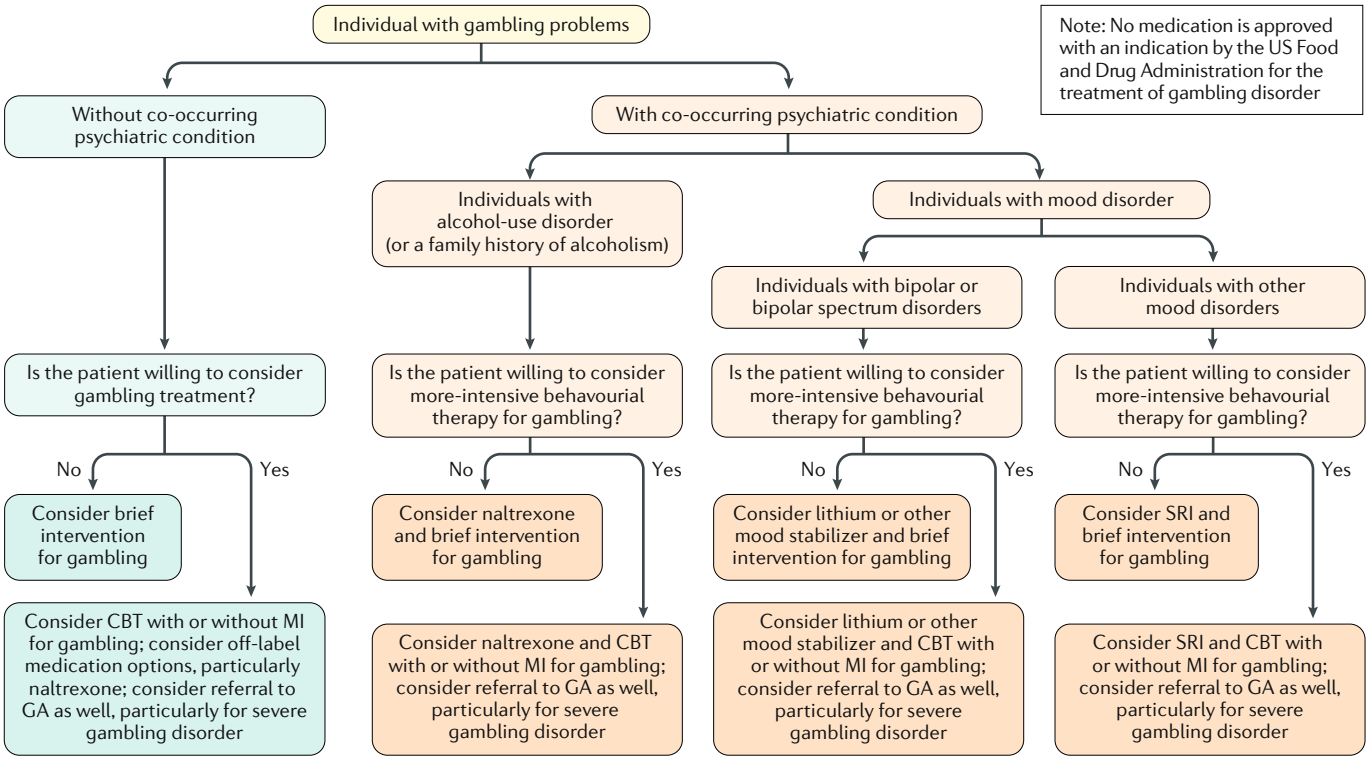

Fig. 4 | **Proposed treatment algorithm for gambling disorder.** The proposed treatment model is based on existing data from clinical trials of behavioural and pharmacological therapies and clinical experience. The presence of comorbid psychiatric disorders and whether the patient is willing to consider treatment are considered. Given the existing gaps in knowledge (including with respect to the combination of behavioural and pharmacological interventions), this algorithm can be refined over time to accommodate additional data. This algorithm focuses on treating the component of the presentation related to gambling disorder, and how best to treat the co-occurring disorders (for example, simultaneously versus sequentially) often involves clinical judgement. CBT, cognitive-behavioural therapy; GA, Gamblers Anonymous; MI, motivational interviewing; SRI, serotonin-reuptake inhibitor.

influence dopaminergic neurons in the mesolimbic pathway, although their precise mechanism of action in GD is currently speculative[239].

Four double-blind, placebo-controlled studies have supported the efficacy of opioid-receptor antagonists to varying degrees. A 12-week, double-blind, placebo-controlled trial of naltrexone demonstrated a reduction in gambling urges and behaviour in 45 individuals with GD compared with placebo[240]. These results were confirmed in a second study of 77 individuals over an 18-week period[241]. In addition, two multicentre, placebo-controlled studies have demonstrated the efficacy of nalmefene (which has less potential for hepatotoxicity than naltrexone) for the treatment of GD. In the first study of 207 individuals, 59% of participants who received nalmefene for 16 weeks had significant reductions in gambling urges, thoughts and behaviour, compared with only 34% of participants who received placebo[242]. In the second study, the primary and secondary outcomes in the intent-to-treat population were not significantly different with nalmefene compared with placebo, but post-hoc analyses of participants who received a full titration of nalmefene for at least 1 week demonstrated a significantly greater reduction in the primary outcome measure as compared with placebo[243]. Finally, a pooled analysis of 284 participants in two of these studies demonstrated that a positive response to either nalmefene or naltrexone was significantly associated with a positive family history of alcoholism, and that an individual's intensity of gambling urges was associated with a positive response to higher doses[244]. Recent investigation of as-needed naltrexone for the treatment of GD failed to identify differences from placebo[245]. Given these mixed findings, the overall clinical effectiveness of opioid antagonists for the treatment of GD has been questioned[236].

Monoaminergic drugs. Early models of pathological gambling and GD proposed a role for serotonin, particularly with respect to impulse control[246,247]. Five double-blind, placebo-controlled pharmacological studies of serotonin reuptake inhibitors for GD have been conducted. Although initial studies of fluvoxamine and paroxetine demonstrated some benefits compared with placebo, subsequent studies of fluvoxamine, paroxetine and sertraline have failed to separate these effects from those of placebo[236,238].

Given the early proposed roles for dopaminergic and serotoninergic systems in GD[248], two studies have investigated the efficacy of olanzapine, a dopamine-receptor and serotonin-receptor antagonist, for the treatment of GD, but neither study demonstrated superiority

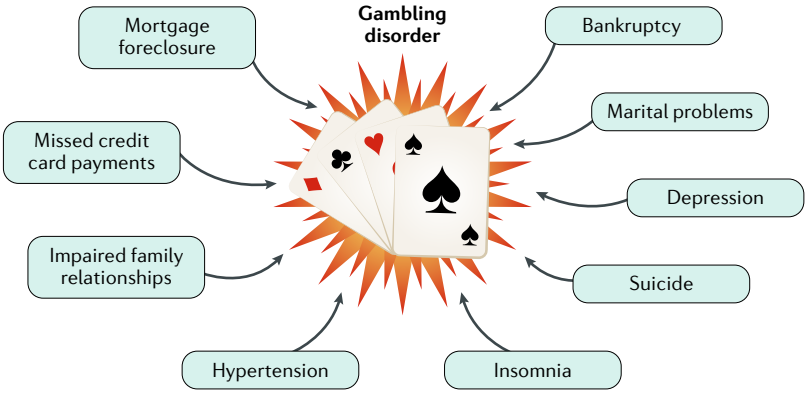

Fig. 5 | **Quality of life in gambling disorder.** Poor quality of life has been linked to gambling disorder. Indeed, alterations in several domains are associated with gambling disorder, including financial, social, physical and mental health.

of olanzapine over placebo[249,250]. These findings are consistent with those from studies of the dopamine-receptor antagonist haloperidol, which was found not to reduce, but rather to promote, gambling urges in GD[251]. Interestingly, the pro-dopaminergic drug amphetamine has demonstrated similar effects[252]. Other drugs with dopaminergic effects, such as bupropion, have not demonstrated efficacy superior to placebo for the treatment of GD[253].

Despite the above mixed findings, prefrontal dopamine could be a target for the treatment of GD, as cognitive deficits have been reported across prefrontal-dependent domains in GD adults (for example, in inhibition, cognitive flexibility and decision-making)[254]. In the frontal lobes, dopamine reuptake transporters and COMT are in part responsible for the regulation of synaptic dopamine and its inactivation[255]. In one open-label pilot study, tolcapone (a COMT inhibitor) significantly reduced gambling behaviour in 24 adults with GD, and the behavioural improvement was correlated with planning-related frontoparietal activation observed using functional MRI and the val/val *COMT* polymorphism[87]. However, given the substantial placebo response in trials of GD (which can be >70%)[250], further controlled trials are needed.

Translational approaches to medication development for GD might also offer promise. Animal studies of gambling behaviour (such as rodent gambling and slot-machine tasks)[256,257] provide support for the involvement of serotonergic and dopaminergic systems, particularly for the dopamine D4 receptor in regions including the anterior cingulate cortex and the insula[258,259]. As animal models of gambling become further developed[260], they could provide novel methods for evaluating potential pharmacological interventions for treatment development in GD.

Glutamatergic drugs. Preclinical data have also suggested a possible role for glutamate transmission and receptors in reward, reinforcement and relapse[261,262], and a potential role for glutamate in medication development for addictions has also been suggested[263,264]. Given preliminary data from humans suggesting a dysfunctional glutamate system in GD[265], in one study *N*-acetylcysteine (NAC), a glutamate-modulating agent that seems to be helpful for treating people with SUDs, was administered to 27 adults with GD, with responders then receiving an additional 6-week double-blind trial of NAC or placebo. In the open-label phase, 59% of participants experienced significant reductions in gambling symptoms, and at the end of the double-blind phase, 83% of those who received NAC were still classified as responders compared with 29% of those who received placebo[266]. A follow-up 12-week, double-blind, placebo-controlled study combining NAC with CBT that included elements of motivational interviewing and imaginal desensitization[267] (BOX 1) in 28 individuals who also had nicotine dependence demonstrated a significant benefit with NAC treatment compared with placebo on nicotine-dependence symptoms during treatment, and on problem-gambling symptoms 3 months after formal treatment ended[268].

Comorbidities and pharmacological therapies

The assessment of co-occurring disorders in individuals presenting with gambling problems could help to inform appropriate treatment approaches[269,270]. Data from clinical trials indicate that naltrexone and nalmefene could be most effective in those with a family history of alcoholism[244], whereas NAC could be particularly effective in those with co-occurring nicotine dependence[268,269]. Mood stabilizers, such as lithium, might be effective in individuals with co-occurring bipolar disorder[271], but perhaps not for those without bipolar disorder[237]. Topiramate combined with behavioural therapy might be helpful for patients without co-occurring disorders[272]. By contrast, selective serotonin reuptake inhibitors such as escitalopram may be effective for the treatment of pathological gambling symptoms in individuals with affective disorders[270,273]. These differential treatment recommendations highlight the importance of assessing for co-occurring disorders in individuals presenting with gambling problems, as well as that of screening for gambling problems in clinical (particularly psychiatric) populations.

Quality of life

GD has been associated with poor quality of life (FIG. 5). Indeed, two studies using the Quality of Life Inventory and the Short-Form Health Survey demonstrated significantly lower quality-of-life scores in individuals with GD[274,275]. Subsequent studies have identified subgroups of individuals with GD that are particularly likely to struggle with quality-of-life issues. For example, of 150 adults calling a gambling helpline in New Zealand, female callers reported greater psychological distress and lower quality of life[276]. Of 201 adults in Hong Kong with pathological gambling, those with co-occurring psychiatric disorders reported more severe impairment in at least one major area of functioning, such as occupational or academic achievement and interpersonal relationships[277]. In addition, co-occurring trauma could in part explain the poor quality of life in GD; of 230 young adult gamblers with and without gambling problems, those with a history of trauma reported lower scores on measures of quality of life and self-esteem compared

with those without a history of trauma[278]. Furthermore, among 350 young adult gamblers in China and Australia, a poorer quality of life was associated with stronger gambling urges and more distorted gambling-related cognitions[279]. Although effective psychological and pharmacological treatments for GD also generally improve overall functioning and quality of life[217,242], a study of 281 gamblers treated with CBT and followed for 1 year found that high levels of psychological distress and low levels of quality of life at the treatment endpoint were associated with subsequent relapse[280].

GD is frequently associated with marital problems, diminished intimacy and trust within the family, and health problems (such as hypertension, obesity and insomnia)[281]. In epidemiological studies, individuals with pathological gambling have increased likelihood of tachycardia, angina, cirrhosis and other liver diseases[281]. Moreover, in the same sample, problem-gambling features were associated prospectively with an increased incidence of cardiovascular conditions among older adults[282]. Financial problems such as bankruptcy, defaulting on credit cards, mortgage foreclosures and delinquent bank loans are common among individuals seeking treatment for GD[283], and are linked to treatment-seeking; for example, 92% of gambling helpline callers initiating treatment reported financial problems, compared with ~75% of non-initiators[284]. Many individuals with GD require psychiatric hospitalization owing to depression and suicidality related to their gambling, which can be associated with financial problems and guilt. Indeed, ~17–24% of individuals with GD report attempting suicide owing to gambling[285]. In Sweden, individuals with GD had a 1.8-fold increase in mortality and a 15-fold increase in suicide mortality[286], whereas in the United Kingdom, 46% of individuals seeking help for gambling problems reported current suicidal ideation[287]. Personality disorders (particularly antisocial personality disorder) may relate importantly to suicide attempts in individuals with gambling problems[288]. Shame may be an important consideration, as shame-proneness has been linked to gambling problems[289]. Legal problems are also common in individuals with gambling problems, with 21% of callers to a gambling helpline reporting gambling-related illegal activities and >50% of these reporting gambling-related arrests[290].

Outlook

Although many research contributions over the past several decades have contributed to understanding the epidemiology and health correlates of GD, substantial needs and gaps exist in understanding with respect to prevention, policy and treatment.

Epidemiology

Although large prevalence-estimates studies have been conducted in many countries, fewer longitudinal studies have been performed. Existing studies suggest that, despite prevalence estimates for GD remaining relatively stable over time, specific individuals transition between varying severities of problem gambling over time[291]; understanding the factors related to this variation would help to target policy, prevention and treatment efforts. Existing data suggest that psychopathology could be an important consideration. For example, retrospective data estimate that psychopathology precedes GD in 76% of cases[24] and that psychopathology (in particular, attention-deficit/hyperactivity disorder) may predict persistence or worsening of GD[40]. Identifying the risk factors for GD with greater precision and developing prevention and treatment initiatives that are based on these approaches will be important. Of note, the effective treatment of a co-occurring disorder often results in a reduction in problem gambling severity[237]. However, even in psychiatric settings, a diagnosis of co-occurring GD in adolescents and adults with other psychiatric disorders often goes overlooked[292,293], highlighting the need for effective identification through improved, systematic screening.

Aetiology

Little is known about the precise molecular genetic contributions to GD. It is likely that multiple genetic factors each make small contributions to the risk of GD, and that these genetic factors interact with various environmental factors in complex manners. To elucidate these contributions, large studies involving >10,000 individuals will probably be needed, as has been the case for schizophrenia[294]. Such large-scale studies might best be conducted by consortia. In addition, integrating GD measures into molecular genetic studies of other psychiatric disorders would probably be a cost-effective approach and one that has a high likelihood of success given the frequent co-occurrences between GD and other psychiatric disorders[295]. Identifying the specific environmental factors that place individuals at risk of GD would permit policy interventions. For example, minors receiving lottery tickets as gifts has been associated with greater severity of problem gambling, more permissive attitudes towards gambling and a stronger link between age of gambling onset and severity of problem gambling[296]. As such, restricting access to underage lottery gambling (and likely other forms) seems important. Empirically validating policy approaches and implementations will be important in such efforts.

Although many advances have been made with respect to understanding the neurobiology of GD, additional advances are needed. For example, analytical approaches to neuroimaging data continue to advance, and both data-driven and theory-based connectivity-based analyses (such as independent component analysis and tractography) are providing better insight into how brain circuitry features relate to gambling and GD[297,298]. Such approaches could also be applied to ligand-based imaging, which has been used in studies of SUDs but not yet GD[107]. Until very recently, neuroimaging studies in GD consisted of small numbers of individuals, thereby making results less stable and preventing the study of subgroups to explore sex, gambling preferences, mood or comorbidity influences. In addition, explorations of comorbid subgroups and studies directly comparing psychiatric groups remain scarce. Prospective studies of GD are needed to clarify whether frontostriatal alterations may represent a cause or a consequence of GD. Despite these shortcomings, neuroimaging findings

suggest that certain neural measures may represent important treatment targets for GD and other addictions; combining imaging, pharmacological, genetic and neuropsychological testing could help to identify which subgroups might best respond to certain treatments and identify the mechanisms by which treatments are working[87]. In addition, multimodal approaches that integrate data across multiple neuroimaging techniques may provide important structure–function–phenomenology relationships and help to resolve some heterogeneity-related considerations that might currently be impeding treatment development for GD. This is important as the improved neurobiological understanding has yet to be translated into treatment advances, and such approaches could permit advances towards precision medicine for GD.

Treatment

Some treatments for GD, such as mindfulness-based[299] and positive-psychology-based approaches including assessment of recovery capital[300] and spirituality[301], are only just beginning to be studied. A substantial barrier to helping people with GD is that most individuals with GD never engage in treatment. Although many individuals recover without formal intervention[16,302], many experience substantial problems that can last for years. Such concerns are particularly relevant for youths given the high rates of GD among adolescents and the potential effect that GD might have on their developmental trajectories. Understanding the barriers related to not seeking treatment is, therefore, of paramount importance. One barrier might be the lack of GD treatment availability and limited investment in this area. For example, treatment for GD is much less available than it is for SUDs in the United States and substantially less support exists for GD treatment. Indeed, in 2016, $73 million ($0.23 per capita) was invested in GD treatment services from public funds, compared with $24.4 billion invested in SUD treatment services[303]. Furthermore, ten states and the District of Columbia do not provide funding for GD services[303].

In addition, GD research is poorly funded[304]. In the United States, the NIH has institutes that support addiction research focused on alcohol and drugs (the National Institute on Alcoholism and Alcohol Abuse and the National Institute on Drug Abuse, respectively); however, no institute exists focused on the research of GD and other behavioural addictions[305]. Thus, little NIH support is provided for GD research, limiting the size and scope of research and related treatment advances. This occurs in the setting of the US government receiving considerable gambling revenues, with state revenues estimated at $27.7 billion in 2015 (REF.[306]).

Changing gambling landscape

Additional research is needed to examine the potential effects of changes in gambling behaviours. For example, Internet gambling has been becoming increasingly popular, with the online gambling market estimated at a value of $47.1 billion in 2017 (REFS[307,308]). Data suggest that differences exist between Internet and non-Internet gambling; for example, in adolescents, Internet gambling is associated with greater severity of problem gambling, stronger links between severity of problem gambling and both heavy alcohol use and poor academic performance, and weaker links between problem-gambling severity and gambling with friends, compared with non-Internet gambling[193]. The last finding, in particular, suggests that a different population of youths might be vulnerable to experiencing Internet-related gambling problems, as Internet-related gambling may be a more solitary activity. However, other data suggest that the Internet could provide another outlet for gambling for individuals who already have difficulty controlling their gambling[309]. Other developments include how daily fantasy sports are considered and regulated, particularly as adolescents participating in daily fantasy sports are more likely to have gambling problems[310]. A substantial portion of online gambling involves sports wagering, and changes in sports gambling legislation (with more states in the United States legalizing sports wagering) could affect potentially vulnerable individuals, such as college students and student athletes[311]. The effect of advertising and other marketing strategies that include aspects of sports wagering also warrants further consideration and study[312].

Another domain that warrants consideration is the interaction of gaming and gambling, with gaming elements being incorporated into forms of gambling and vice versa. For example, video-gaming aspects are being integrated into electronic gambling machines[313], and gambling elements incorporated into gaming through skins gambling and loot boxes[314,315] (BOX 1). Competitive gaming (eSports) has also been linked to gambling on both virtual and real items[314,316]. Additionally, social casino and other games can offer opportunities to pay for additional time or to advance levels, and such microtransactions have been linked to gambling initiation, further blurring the boundaries between gaming and gambling and potentially placing individuals at risk[191].

Both gaming and gambling disorders have been included as disorders due to addictive behaviours in the ICD-11 (REF.[317]) (BOX 2). Additionally, hazardous forms of gaming and gambling are also included, in that subsyndromal patterns of these behaviours may be associated with harm, and hazardous engagement may apply to a larger proportion of the general population than does disordered engagement; thus, hazardous levels of gambling and gaming may be particularly relevant from a public health perspective[317,318]. In anticipation of the ICD-11, the WHO organized five international workgroup meetings to discuss Internet-related behaviours and gaming and gambling disorders. A recent outcome was the need to develop culturally informed and empirically validated instruments to assess hazardous and disordered gambling and gaming, with gaming-related assessments currently lagging behind gambling-related ones. A better understanding is needed regarding the extent to which gaming disorder overlaps with GD, and the degree to which the harms are similar or unique. Ultimately, these processes could guide research in other areas of behavioural addictions.

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Author contributions

Introduction (M.N.P.); Epidemiology (S.W.Y. and M.N.P.); Mechanisms/pathophysiology (A.V.-G., S.W.Y., M.N.P. and I.M.B.); Diagnosis, screening and prevention (N.M.P. and J.D.); Management (N.M.P. and J.E.G.); Quality of life (J.E.G.); Outlook (M.N.P.); Overview of Primer (M.N.P.). The authors alone are responsible for the content and writing of this manuscript.

Competing interests

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