Published in final edited form as:
Trends Cogn Sci. 2014 August ; 18(8): 429–438. doi:10.1016/j.tics.2014.03.007.

The neural bases of cognitive processes in gambling disorder

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Abstract

Functional imaging is offering powerful new tools to investigate the neurobiology of cognitive functioning in people with and without psychiatric conditions like gambling disorder. Based on similarities between gambling and substance-use disorders in neurocognitive and other domains, gambling disorder has recently been classified in DSM-5 as a behavioral addiction. Despite the advances in understanding, there exist multiple unanswered questions about the pathophysiology underlying gambling disorder and the promise for translating the neurobiological understanding into treatment advances remains largely unrealized. Here we review the neurocognitive underpinnings of gambling disorder with an eye towards improving prevention, treatment and policy efforts.

Keywords

Gambling; neuroimaging; neurobiology; cognition

Introduction

Evidence of gambling extends back to the earliest recorded cultures in human history [1]. Gambling may take many forms including lotteries, electronic gambling machines (i.e., slot machines), cards, and sports, and may occur in multiple venues (e.g., in casinos, convenience stores or bars or on the Internet), either legally or illegally [2]. Most adults gamble, as do most adolescents, making gambling a normative behavior for these groups [3, 4]. Although most people gamble without experiencing problems, a minority develops gambling problems with lifetime estimates amongst adults typically cited in the range of 0.2%–5.3%, with precise estimates depending on the threshold used for considering gambling problematic [2].

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Disclosures: The author reports that he has no financial conflicts of interest with respect to the content of this manuscript.

The diagnostic entity in the fifth edition of the Diagnostic and Statistical Manual (DSM-5) relating to gambling is gambling disorder (previously termed “pathological gambling” in the third and fourth editions of the DSM [5, 6]). The inclusionary criteria for pathological gambling and gambling disorder (Box 1) share similarities with those for substance abuse, dependence and use disorders across DSM-IV and DSM-5. For example, the inclusionary criteria for gambling disorder, like those for substance use disorders, include criteria targeting tolerance, withdrawal, repeated unsuccessful attempts to cut back or quit and interference in major areas of life functioning. Although certain criteria are specifically listed for gambling and substance-use disorders, they often have applicability to both. For example, cravings (strong desires or urges to use substances) are listed in the inclusionary criteria for substance-use but not gambling disorders, although gambling urges are present in people with gambling disorder and a target of clinical interventions [7]. On the other hand, gambling when feeling distressed is an inclusionary criterion for gambling but not substance-use disorders, although negative-reinforcement motivations are clinically relevant for substance addictions, particularly women [8].

Based on existing data from epidemiological, clinical, genetic, and neurobiological domains [9], pathological gambling was reclassified from the category of “Impulse Control Disorders Not Elsewhere Classified” in DSM-IV to the category of “Addictive and Related Disorders” in DSM-5 [10]. Although gambling and substance-use disorders are now classified together, the DSM-5 applies a threshold of relatively greater stringency for the diagnosis of gambling disorder (meeting 4 of 9 inclusionary criteria) compared to substance-use disorders (meeting 2 of 11 inclusionary criteria) [10]. This situation has the potential to underestimate the societal impact of gambling relative to substance-use disorders. As levels of gambling not meeting the threshold for gambling disorder have been associated with adverse measures of functioning (e.g., psychopathology [11]), consideration of both risky and disordered gambling is warranted from neurobiological and public health perspectives [12].

Unlike many other psychiatric disorders, there are no medications with indications for treating gambling disorder (i.e., no drug with an indication approval from the US Food and Drug Administration for treating the disorder) [13]. Thus, there is a significant need for medications development efforts to help advance the treatment of gambling disorder. In order to facilitate these efforts, an improved understanding of the biological underpinnings of gambling disorder is needed. Additionally, an improved understanding of the neural features underlying gambling disorder will generate an improved understanding of the mechanisms underlying effective behavioral therapies for gambling disorder and may lead to improved or better targeted therapies [14]. In this article, a current understanding of the neurobiology of gambling disorder will be presented. The term gambling disorder will be used in place of pathological gambling given the changes in DSM-5, albeit with the understanding that most neurobiological investigations to date have studied populations with pathological gambling. When relevant, findings described will be placed within the context of other psychiatric conditions (most notably substance-use disorders) given biological similarities across the conditions [15]. Given recent reviews into the neurobiology of gambling disorder [12, 15–18], an emphasis will be placed on recent data published over the past several years, with a focus on current controversies like whether gambling disorder is associated with hyper-or hypo-responsive reward systems and the extent to which dopamine

dysfunction exists and predominates in gambling disorder. The review will cover cognitive/behavioral, neuroimaging and neurochemistry domains, and a schematic is included describing key components in these areas (Figure 1). A glossary with definitions for some terms relevant to gambling disorder, including less widely used gambling-related terms, is provided.

Cognitions and Gambling Behaviors in Gambling Disorder

Cognitive Processes

Cognitive factors (e.g., relating to decision-making) may contribute importantly to gambling behaviors and gambling disorder. Individuals with gambling disorder have shown differences in multiple cognitive processes. Early studies indicated that individuals with gambling disorder showed differences from healthy comparison subjects on measures of executive function relating to attention, learning and reversal learning, and planning, attending and decision-making [19]. More recent studies have identified cognitive differences that seem particularly related to ventral prefrontal cortical function. For example, in a study comparing individuals with gambling problems to those with alcohol-use problems and those with neither, those with gambling problems performed similar to healthy comparison subjects (who both performed better than those with alcoholuse problems) on tasks assessing visuospatial working memory and the maintenance and manipulation of verbal information in working memory [20]. However, both the problem gambling and alcohol-abusing groups performed worse than the non-addicted comparison group on measures of reflection impulsivity and gamblingrelated decision-making [20]. These findings resonate with those of independent investigations that have identified disadvantageous patterns of decision-making in individuals with gambling disorders [21], as well as other studies that have compared individuals with gambling problems, alcohol-use problems and healthy comparison subjects [22]. However, in some of these studies between-group differences extended to a broader range of cognitive functions relating to inhibition (including aspects of cognitive control and stopping an ongoing action when rapidly responding), time estimation, cognitive flexibility, and planning [22]. In general, in each of these domains with the possible exception of cognitive flexibility, individuals with gambling problems and those with alcohol-use problems performed more poorly than did non-addicted comparison subjects [22]. Although findings and their interpretations are not entirely consistent across studies [23], the extant literature suggests similarities across gambling and substance-use disorders, consistent with the reclassification of gambling disorder together with substance-use disorders in DSM-5 [10]. They also suggest that multiple cognitive domains contribute to gambling disorder and that understanding the clinical and neurobiological correlates may help in guiding treatment development efforts. However, the most consistently identified cognitive disturbances in gambling disorder appear related to risk-reward decision-making, cognitive processes linked to functioning of ventromedial prefrontal cortex (vmPFC) rather than dorsolateral PFC (dlPFC), consistent with findings from neuroimaging studies (discussed later in this article).

Gambling-related Cognitions

In addition to the "traditional" cognitive domains described above, gambling behaviors may be associated with more unique cognitive features that may contribute importantly to gambling disorder. For example, irrational cognitions relating to gambling behaviors have been observed in people who gamble, including those with and without gambling problems. These cognitions may relate to superstitions, gambler's fallacy, illusion of control, inaccurate processing of wins, losses or near-wins (so-called "near-miss" effect), persistence of gambling despite often recurrent losses (so-called "chasing") or other gambling-related domains [24]. Given that studies have found that non-problematic gamblers experience irrational gambling-related cognitions [25], behavioral measures of gambling seem not to be substantially influenced by cognitive biases [26], and cognition-related information alone (e.g., relating to odds of winning) may not influence gambling behaviors significantly [27], the centrality of irrational cognitions to gambling disorders has been questioned [28]. However, structured assessments of irrational gambling-related cognitions are now permitting more nuanced and systematic investigations into the relationships between irrational gambling-related cognitions, gambling behaviors and gambling problems.

A widely used scale to assess irrational cognitions related to gambling is the gambling related cognitions scale (GRCS) [29]. The GRCS is a 23-item measure with good psychometric properties [29]. It has been found to identify and assess five factors relating to interpretative control/bias (e.g., "Relating my winnings to my skill and ability makes me continue gambling"), illusion of control (e.g., "I have specific rituals and behaviors that increase my chances of winning"), predictive control (e.g., "Losses when gambling, are bound to be followed by a series of wins"), gambling-related expectancies (e.g., "Gambling makes things seem better"), and a perceived inability to stop (e.g., "It is difficult to stop gambling as I am so out of control") [29], although there is considerable correlation between the factors (mean =0.55), raising questions about a one-factor or five factor model [30]. Amongst non-problem gamblers, there exist individual differences that relate to gender, with men scoring higher overall and on all subscales except for the illusion-of-control subscale [29]. Among adolescents, boys scored higher than girls on the GRCS; additionally, GRCS scores were associated with disordered gambling across gender groups, with the GRCS scores (particularly subscales relating to perceived inability to stop, gambling-related expectancies, and illusion of control) statistically predicting problem-gambling severity [30]. Amongst adults, the subscale of the GRCS relating to perceived inability to stop was related to persistence of slot-machine gambling behavior, and gambling-related cognitions more broadly were related to subjective effects of desires to continuing to gamble following multiple types of outcomes including near-misses [31]. Together, these findings indicate important relationships between gambling-related cognitions and persistence and severity of gambling across different developmental epochs, and more research is needed into the neural factors that relate to these cognitions in groups with and without gambling disorders.

Neuroimaging

Neural Underpinnings

Functional neuroimaging has provided insight into the regional brain activation patterns underlying specific cognitive processes in gambling disorder. These studies have identified in individuals with and without gambling disorder differences in corticostriatal-limbic activations. In multiple cases, relatively blunted activation of corticostriatal-limbic regions, in particular the vmPFC and ventral striatum (VS), has been observed in individuals with gambling disorder [15]. For example, relatively diminished activation of the vmPFC and/or VS has been observed during task performance interrogating cognitive control (Stroop) [32], gambling urges [33, 34], simulated gambling [35], decision-making (Iowa gambling task) [36], and the processing of monetary rewards and losses (monetary incentive delay task) [37, 38]. These findings show similarities to those involving individuals with or at-risk for substance-use disorders. For example, like individuals with gambling disorder during the anticipatory phase of reward processing on the monetary incentive delay task [37, 38], individuals with alcohol-use disorder [39, 40], tobacco-use disorder [41], or a familial history of alcoholism [42] show relatively blunted VS activation as compared to those without or at lower risk for addictions. These findings appear to extend to other groups characterized by impaired impulse control (e.g., individuals with binge-eating disorder [43]), relate to impulsivity in gambling and alcohol-use disorders (e.g., with less VS activation during reward anticipation linked to greater impulsivity [37]), and relate prospectively to treatment outcome in preliminary studies (e.g., with individuals with binge-eating disorder who continued to binge following treatment as compared to those who ceased bingeing following treatment demonstrating at treatment onset relatively blunted VS activation during reward anticipation [44]). Additionally, problem-gambling severity amongst individuals with gambling disorders has been associated inversely with activation of the VS and/or vmPFC during simulated gambling [35, 45] and the encoding of value signals for delayed rewards in the vmPFC, VS and substantia nigra during performance of an intertemporal choice task [46]. Together, these findings suggest that blunted activation of VS, vmPFC and other neural regions linked to reward processing contribute importantly to a range of cognitive processes in gambling disorder and other conditions characterized by impaired impulse control. These findings suggest that gambling disorder might be conceptualized as a reward-processing disorder; alternatively, alterations in function of vmPFC, VS and/or other brain regions contributing to ventral-prefrontal/subcortical circuits may give rise to key features (abnormalities in reward processing, craving, decision-making, delay discounting, cognitive control) of gambling disorder. These possibilities warrant further examination, with longitudinal and translational studies (across species) offering possible avenues of further study.

Despite these data, there is debate as to the extent to which blunted neuronal sensitivity to rewards may underlie gambling disorder. Several studies investigating gambling urges [47, 48] and monetary processing [49] have identified relatively increased neuronal activations of corticostriatal circuitry in individuals with, as compared to those without, gambling disorder. Although seemingly contradictory to findings described in the prior paragraph, differences in task designs, participants, and other features like context may contribute to differences in

findings [50–53]. Specifically, different contexts may exert important influences, with situations or cues that are more closely related to the addiction (i.e., to gambling in gambling disorder) more likely to elicit increased activation of the VS and other reward-related brain regions [51–53]. Additionally, the risk associated with the gambling may influence brain activations as individuals who gambled problematically and those who gambled occasionally demonstrated opposite patterns of regional brain activations to high- and lowrisk conditions [54]. Given that gambling-related contexts may be more physiologically arousing for individuals with gambling problems as compared to those without [55], the effect of context on neuroendocrine response and brain function should be examined further. Further supporting the relevance of these lines of research are data suggesting greater functional connectivity between ventral affective and dorsal executive systems during affective processing in an emotional/motivational Go/No-Go task in individuals with gambling problems as compared to those without [56]. The findings from this study resonate with those from a study of cocaine dependence in which greater connectivity with ventral cortical and subcortical regions were identified during a cognitive control task in the cocaine-dependent as compared to the control group [57].

Future studies are needed to investigate systematically context, not only relating to the object of addiction (i.e., gambling for gambling disorder), but also to mood, stress and other possible factors that might relate to or influence motivational tendencies to engage in addictive behaviors [58, 59]. For example, negative mood states or stress might promote gambling behaviors in certain individuals with gambling disorders, consistent with negative reinforcement models of addiction and findings linking gambling disorder and related cognitive processes (e.g., gambling urges) to stress and trauma [58, 60]. These relationships may be particularly relevant to women given their greater acknowledgement of gambling to escape negative affective states and links between gambling disorder in trauma in women as compared with men [60, 61]. Subjective responses to emotional or gambling-related cues may also provide additional insight; for example, activation of the temporal pole, a brain region implicated in the recollection of personally relevant events, was related to the magnitude of gambling urges in response to gambling cues during the onset of subjective awareness of these feelings [62]. As personalized cues relating to stress more strongly elicited corticostriatal-limbic activations in cocaine-dependent women and cocaine cues more strongly elicited corticostriatal-limbic activations in cocainedependent women [8], similar studies of gambling-disordered women and men are needed to investigate the extent to which similar neurobiological processes might underlie sex differences in gambling disorder. While stress might operate through increasing urges to gamble in individuals with gambling disorder, it might also operate by comprising prefrontal control mechanisms in individuals with addictions [63], mechanisms that have been linked to regulation of craving states amongst drug-dependent individuals [64], and direct examination of these possibilities is warranted.

Other contexts also warrant examination. For example, peer influence might promote risk-taking behaviors particularly amongst adolescents, and certain adolescents might be particularly prone to risk-taking behaviors under peer influence. For example, adolescent smokers but not non-smokers increased risk-taking on a laboratory task under peer influence, and this peer-related increase in risk-taking was linked to self-reported impulsive

tendencies [65]. The extent to which such contexts may increase gambling behaviors, particularly adolescents with gambling disorders, warrants direct examination. Additionally, other cognitive constructs underlying aspects of reward processing and related behaviors (near-miss effects [66], loss-chasing [67]) that have been investigated in people without gambling problems warrant further study in individuals with gambling disorder, both amongst adolescents and adults.

Neurochemistry

Neurochemical Contributions to Gambling Disorder

Recent reviews has described in detail neurochemical contributions to gambling disorder [15, 17, 18, 52]. For decades, biogenic amines and other neurochemicals have been implicated in the pathophysiology of gambling disorder [15]. Noradrenergic, serotonergic, dopaminergic, and opioidergic contributions have been proposed to contribute to arousal/excitement, impulse control, reward/reinforcement and urges/cravings, respectively [15]. Recently communicated data suggest more extensive contributions to cognit ive factors underlying gambling behaviors; e.g., with respect to dopamine and executive functioning [68]. Additionally roles for alpha-adrenergic mechanisms, particularly in relationship to stress responsiveness [69], and glutamatergic mechanisms that may relate to compulsive engagement in gambling [70, 71] have been suggested and supported, although other pathways may also contribute to identified findings [72]. Given the importance of dopamine in substance addictions, dopaminergic systems have been an important focus of recent neurochemical investigations of gambling disorder.

Dopamine in Gambling Disorder

Debate exists regarding the centrality of dopamine to gambling disorder [73]. Although multiple lines of evidence associate dopamine with gambling, gambling disorder, substance use and substance-use disorders, the precise relationships between dopamine and these behaviors and disorders remain incompletely understood. For example, dopamine replacement therapies (including dopamine agonists acting upon dopamine D2-like receptors, which include D2, D3 and D4) have been associated with gambling disorder and other “behavioral” addictions [74], dopamine agonists influence impulsive choices differentially in people with Parkinson’s disease with and without gambling disorder and other behavioral addictions [75], and amphetamine administration has been found to prime/promote gambling urges in individuals with gambling problems [76]. These findings suggest that pro-dopaminergic agents or states may promote problematic gambling and underlie the pathophysiology observed in gambling disorder. However, drugs antagonizing dopamine D2-like receptors (e.g., haloperidol) have been associated with increasing the rewarding and priming effects of a gambling in people with gambling problems but not in those without [77]. Furthermore, drugs that antagonize dopamine D2-like receptors like olanzapine have not shown clinical utility in randomized clinical trials involving people with gambling disorder [78, 79].

There may be multiple reasons for the seemingly conflicting results regarding a role for dopamine in gambling disorder. Among these is the homology between D2, D3 and D4

dopamine receptors that translate into overlapping affinities for drugs, and this situation has important research and clinical implications. Specifically, each dopamine receptor may play a role in gambling behaviors and gambling disorder. For example, in animal studies for which drugs with greater specificity are available, the D4 dopamine receptor has been implicated in slot-machine gambling behaviors in rodents [80]. In humans, positron emission tomography (PET) studies have used [^{11}C]raclopride in preliminary studies to investigate D2/D3 receptors in relationship to gambling behaviors and gambling disorder. In one study of individuals with Parkinson's disease, less [^{11}C]raclopride availability in the VS at baseline and greater [^{11}C]raclopride displacement following performance of a gambling task was observed in individuals with gambling disorder as compared to those without, suggesting greater VS dopamine release in the group with gambling disorder [81]. However, the extent to which dopaminergic or other brain pathology associated with Parkinson's disease may have contributed to these findings is unclear. In studies of individuals without Parkinson's disease, between-group differences in individuals with and without gambling disorder in [^{11}C]raclopride binding have typically not been identified [82–85]. However, individual differences in VS [^{11}C]raclopride binding have correlated inversely with negative urgency [82] and money lost and other aspects of Iowa gambling task performance [83, 84] in preliminary studies. These findings suggest potential roles for dopamine neurotransmission in the VS as related to specific cognitive aspects of gambling disorder.

An important advancement with respect to dissecting dopamine D2 and D3 receptor contributions to cognitive aspects of gambling disorder relates to the availability of [11C]-(+)-propyl-hexahydro-naphtho-oxazin ([^{11}C]PHNO) as a radio-ligand available for use in humans. [^{11}C]PHNO is a dopamine-D3-receptor-preferring radioligand. In regions like the substantia nigra, where the D2-like dopamine signal is primarily attributable to dopamine D3 receptors, [^{11}C]PHNO can provide specific insight into a role for D3 versus D2 dopamine receptors. In individuals with gambling disorder, binding values of [^{11}C]PHNO did not differ between individuals with or without gambling disorder; however, among individuals with gambling disorder, [^{11}C]PHNO binding values in the substantia nigra correlated positively with problem-gambling severity and impulsiveness [85]. Furthermore, following amphetamine administration, the individuals with gambling disorder exhibited findings consistent with greater dopamine release in the dorsal striatum, with the dopaminergic response to amphetamine relating positively to [^{11}C]PHNO binding (or dopamine D3 receptor levels) in the substantia nigra [86]. These findings suggest in gambling disorder a hyper-dopaminergic state involving the substantia nigra and dorsal striatum, and suggest possible differences between gambling and drug addictions. The extent to which these findings relate to specific cognitive functions in gambling disorders, represent potential vulnerability factors, or relate importantly to clinical outcomes requires additional investigation.

Intermediate Phenotypes and Trans-diagnostic Considerations

An important approach to understanding psychiatric conditions involves the identification and characterization of relevant intermediate phenotypes or endophenotypes [87]. Such constructs may link more closely to underlying biological factors than do heterogeneous

psychiatric disorders. NIH initiatives like the Research Domain Criteria (RDoC) and Phen-X (https://www.phenxtoolkit.org) reflect current efforts related to this line of research [88].

Among the most widely studied intermediary phenotypes in gambling disorder is impulsivity, a construct that has been related to multiple psychiatric conditions [89–92]. Impulsivity has been found to factor into multiple domains (e.g., choice and motor or response forms), and behavioral and self-report measures may factor separately or not correlate with one another, even within the same domain [90]. Compulsivity has historically received less research attention but may also relate importantly to gambling disorder, particularly as behavior becomes more engrained or habitual [90]. Although early models conceptualized impulsivity and compulsivity as lying along a continuous linear spectrum [93], data indicate that certain groups like those with gambling disorder may score high both on measures relating to impulsivity and compulsivit y [94]. As measures of impulsivity and compulsivity have been linked to treatment outcomes in gambling disorder [95, 96], both constructs warrant further investigation into how they may relate to specific biological measures in gambling disorder. Additional intermediate phenotypes (e.g., relating to emotional regulation and stress responsiveness) also warrant investigation [58, 59, 62].

Future Directions

Although significant advances have been made with respect to understanding the cognitive processes underlying gambling behaviors and gambling disorder, there remain many unanswered questions and clinical needs. Among the clinical needs is the identification of effective treatments for people with gambling disorder. Although multiple behavioral therapies have shown promise and are used in clinical settings, little is known about the biological mechanisms of action underlying these therapies or the extent to which specific therapies might best help specific groups of people with gambling problems [14]. For example, opioid antagonists in the treatment of gambling disorder have received support from multiple randomized clinical trials [13]. However, human studies into their biological mechanisms of action are lacking. Unlike many other psychiatric conditions, there is no medication with an approved indication from the US Food and Drug Administration for gambling disorder. As such, there is a distinct need for medications development efforts.

Technologies currently available afford great opportunities for investigating the neurobiological underpinnings of cognitive processes in gambling disorder. While much of the current article has focused on functional neuroimaging, other approaches, such as magnetization-prepared rapid gradient-echo (MPRAGE) and diffusion tensor imaging (DTI) that can be used to assess regional brain volume and white matter integrity, respectively, are available. These have been used to identify differences between individuals with and without gambling disorder and relate the biological measures to individual differences related to avoidance and approach tendencies [97–99]. Additionally, PET studies using non-dopaminergic radioligands in individuals with and without gambling disorder have implicated other neurochemical systems (e.g., the serotonin 1B receptor system [100], one also implicated in alcohol and cocaine-use disorders [101, 102]). While few studies to date have used multiple radioligand probes in the same individuals, such approaches have significant potential to advance our understanding of how neurochemical systems may

interact in psychiatric conditions [103]. Given data implicating dopaminergic, serotonergic, noradrenergic, opioidergic, glutamatergic and other neurochemical systems in gambling disorder, the investigation of these systems and how they interact and relate to specific aspects of gambling disorder (e.g., reward processing, urges/cravings, risk/reward decision-making) warrants direct examination. Along a similar line of reasoning, employing multiple imaging modalities concurrently (functional magnetic resonance imaging, MPRAGE, DTI, PET and others) may offer complementary insight into brain biology and promote an understanding of how these multiple domains (brain activation patterns, gray-matter structure, white-matter integrity, and neurochemical processes) interact and underlie individual differences in clinically relevant phenomena (e.g., impulsivity, treatment outcomes) in gambling disorder, as is currently the case for substance-use disorders [104]. Integrating information from functional neuroimaging with that from other domains (molecular genetic, clinical outcomes) is in early stages, with preliminary studies in gambling disorder suggesting promise and providing insight into future lines of investigation [14, 68, 105]. Additionally, utilizing alternative analytic strategies (e.g., independent component analysis or intrinsic connectivity distributions) may help to identify brain networks underlying cognitive constructs and relate them to clinically relevant measures like treatment outcome as is being done for substanceuse disorders [57, 106, 107]. In these efforts, longitudinal studies may help identify biological factors that may predispose people to developing gambling problems, as well as biological changes that occur during the progression of developing and recovering from the disorder. “Deep phenotyping” using both valid, reliable assessments of psychiatric conditions, detailed gambling information and assessments of intermediate phenotypes used in studies of other psychiatric conditions (e.g., measures of impulsivity or other research RDoC constructs [88, 90]) will ultimately help to understand gambling disorder and how it relates to other disorders, identify and intervene to assist people at risk, and help best those currently suffering from the disorder.

Concluding Remarks

While gambling and gambling problems have long been recognized, there has been a recent shift in the classification of the disorder based in considerable part on neurobiological similarities between gambling and substance-use disorders. Despite the advances over the past dozen years (prior to which no brain imaging study of people with gambling disorder had been published), there exist significant gaps in our understanding of the biological underpinnings of gambling disorder, how they are similar to and distinct from those underlying other psychiatric disorders, how they relate to specific cognitive functions in gambling disorder and how they mat be targeted therapeutically. In addition to the future directions cited above for research in people with gambling disorder, the field would benefit from additional translational research. Over the past five years, important inroads have been made with respect to generating rodent models of slot-machine and other gambling behaviors [108, 109]. These tasks have allowed for the initial investigation of dopaminergic and serotonergic systems involved in specific aspects of gambling behaviors and gambling-related decision-making and provide complementary data to human investigations. For example, studies in rats suggest that the D4 dopamine receptor may contribute importantly to slot-machine behaviors, shedding additional insight into potential roles for dopamine in

gambling disorder and providing potential novel targets for drug development [80]. Similarly, development of tasks for use in other species might generate important knowledge regarding gambling behaviors in humans; for example, development of analogous tasks for use in mice might capitalize on knowledge about and experimental capacities relating to murine genetics. Additional technologies (involving targeted gene regulation via optogenetics, viral mediation and other techniques) could be used to understand gambling-related behaviors.

Additionally, studies of gambling behaviors in non-human primates might offer insight into electrophysiological brain function and how such brain function might be targeted therapeutically to influence gambling behaviors. For example, gambling-related tasks in which specific manipulation of risk and uncertainty have been developed for use in non-human primates, and an alpha-2 adrenergic agonist (guanfacine) was found to influence choice of larger later rewards only when the reward was certain, and that guanfacine influenced time preference (selecting of larger later rewards) but not risk preference [110]. These behaviors were accompanied by guanfacine-related changes in prefrontal cortical function that suggested the drug may enhance top-down control over subcortical regions that may promote impulsive choices [110]. These findings complement human studies suggesting a role for alpha-2 adrenergic involvement in gambling disorder [69] and suggest the potential utility of guanfacine in the treatment of gambling disorder. While in these rodent and nonhuman- primate examples gambling-related behaviors and not gambling disorder *per se* is being studied, the findings have important implications for the study of gambling disorder in humans.

As a behavioral addiction, gambling disorder has the potential to provide important insight into substance addictions (e.g., the effects that chronic or recent exposure to drugs may have on brain structure and function and behavior). The concurrent study of individuals with substance-use disorders and those with gambling disorders thus is likely to provide important insight into substance addictions, as well as into gambling disorder. The improved understanding should thus diminish the currently large impact that addictions have on individuals, their families and society in general.

Acknowledgments

This research was funded in part by NIH grants from NIDA (P20 DA027844, R01 DA018647, R01 DA035058, P50 DA09241), the National Center for Responsible Gaming, the Connecticut State Department of Mental Health and Addictions Services, and the Connecticut Mental Health Center. The funding agencies did not provide input or comment on the content of the manuscript, and the content of the manuscript reflects the contributions and thoughts of the author and not necessarily reflect the views of the funding agencies.

Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised Lundbeck and Ironwood pharmaceuticals; has received research support from the Mohegan Sun Casino and the National Center for Responsible Gaming; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for legal and gambling entities on issues related to gambling behaviors and disorders; provides clinical care in a Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

Glossary

Compulsivity	relating to tendencies to engage in repetitive and functionally impairing overt or covert behaviors without apparent adaptive function; may involve perseverative or stereotypic features
Craving	a strong desire or urge to engage in a behavior; typically applied to substance-use disorders and may motivate an individual to engage in the addictive behavior; frequently a therapeutic target in the treatment of addictions
Decision-making	a cognitive process considered by some to be a core element of addictions in which decisions to engage in addictive behaviors take precedent over ones that may be more adaptive (e.g., engaging in work, family functions or other pro-social roles)
Delay Discounting	Also termed temporal discounting; refers to preferences for smaller, sooner as compared to larger, later rewards; greater or steeper delay discounting is often seen in individuals with addictions; reflecting a greater tendency to prefer or select smaller, sooner as opposed to larger, later rewards
Executive Functioning	a term applied to a broad range of cognitive processes that includes working memory, attention monitoring, reasoning, and flexibility
Gambling	placing something of value (usually money) at risk in the hopes of gaining something of greater value
Gambler's Fallacy	the belief that an independent event is more or less likely on the basis of prior independent events; e.g., that the odds of a coin-flip outcome is not 50% heads or 50% tails if three consecutive heads outcomes were observed
Illusion of Control	a tendency to believe that one has control over events over which he or she has no influence
Impulsivity	a predisposition to rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of the reactions to the impulsive individual or others
Loss-chasing	the behavior of trying to win back money recently lost gambling by engaging in more gambling; for example, "double or nothing" bets
Near-miss	the occurrence of a nearly winning event, usually on a slot machine (or other electronic gambling machine); for example, when the first two reels of a slot machine stop on the same symbol and the third ends on a different symbol

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Box 1. A) DSM-IV Diagnostic Criteria for 312.31 Pathological Gambling

A. Persistent and the current maladaptive gambling behavior as indicated by five (or more) of the following:

1. is preoccupied with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)
2. needs to gamble with increasing amounts of money in order to achieve the desired excitement
3. has repeated unsuccessful efforts to control, cut back, or stop gambling
4. is restless or irritable when attempting to cut down or stop gambling
5. gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety, depression)
6. after losing money gambling, often returns another day to get even (“chasing” one’s losses)
7. lies to family members, therapist, or others to conceal the extent of involvement with gambling
8. has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling
9. has jeopardized or lost a significant relationship, job, or education or career opportunity because of gambling
10. relies on others to provide money to relieve a desperate financial situat ion caused by gambling

B. The gambling behavior is not better accounted for by a Manic Episode.

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Box 1. B) DSM-5 Diagnostic Criteria for 312.31 Gambling Disorder

A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cutback, or stop gambling.

4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

B. Gambling behavior is not better explained by a manic episode

Specify if:

Episodic: Meeting diagnostic criteria at more than one time 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.

Specify if:

In early remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have 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 have been met during a period of 12 months or longer.

Specify current severity:

Mild: 4–5 criteria met.

Moderate: 6–7 criteria met.

Severe: 8–9 criteria met.

Note: Although some behavioral conditions that do not involve ingestion of substances have similarities to substance-related disorders, only one disorder – gambling disorder – sufficient data to be included in this section.

Highlights

Debate exists regarding the extent to which blunted or exaggerated reward responsiveness underlies gambling disorder.

Seemingly conflicting data exist for a role for dopamine in gambling disorder and its related cognitive processes.

Further examination of intermediate phenotypes like impulsivity and compulsivity will help understand gambling disorder and other addictions.

There exists a need to translate a neurocognitive understanding of gambling disorder into improved prevention, treatment and policy initiatives.

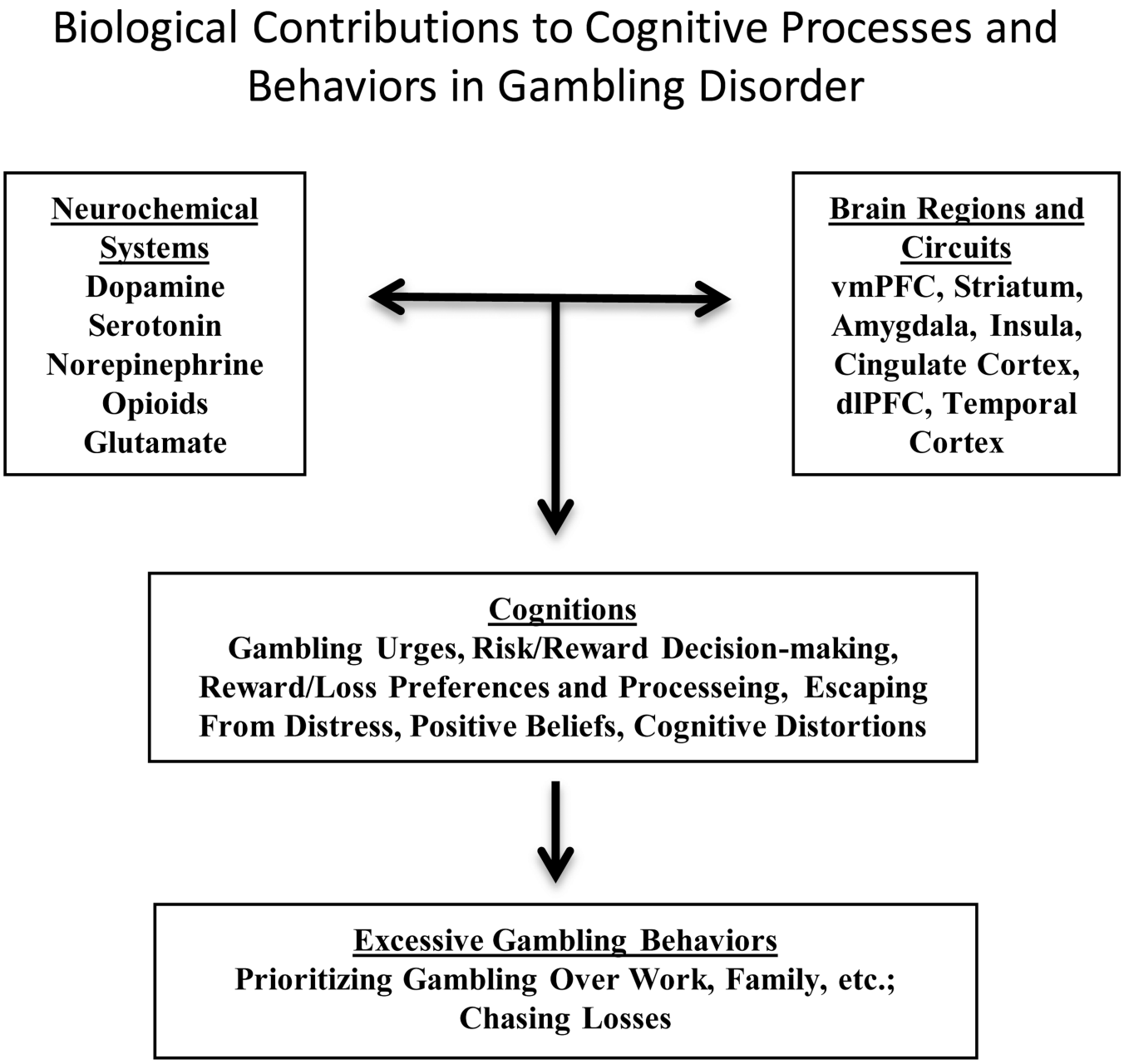

Figure 1.

Schematic Diagram Relating Biological Measures to Cognitions and Behaviors in Gambling Disorder. A diagram linking the domains of "Neurochemical Systems" and "Brain Regions and Circuits" to "Cognitions" which then influence the domain of "Excessive Gambling Behaviors" is presented. Salient representative factors within each domain are presented. Each domain has potential as targets for possible prevention and treatment interventions.