Neural and psychological underpinnings of gambling disorder: A review

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Abstract

Gambling disorder affects 0.4 to 1.6% of adults worldwide, and is highly comorbid with other mental health disorders. This article provides a concise primer on the neural and psychological underpinnings of gambling disorder based on a selective review of the literature. Gambling disorder is associated with dysfunction across multiple cognitive domains which can be considered in terms of impulsivity and compulsivity. Neuroimaging data suggest structural and functional abnormalities of networks involved in reward processing and top-down control. Gambling disorder shows 50-60% heritability and it is likely that various neurochemical systems are implicated in the pathophysiology (including dopaminergic, glutamatergic, serotonergic, noradrenergic, and opioidergic). Elevated rates of certain personality traits (e.g. negative urgency, disinhibition), and personality disorders, are found. More research is required to evaluate whether cognitive dysfunction and personality aspects influence the longitudinal course and treatment outcome for gambling disorder. It is hoped that improved understanding of the biological and psychological components of gambling disorder, and their interactions, may lead to improved treatment approaches and raise the profile of this neglected condition.

Keywords: gambling; cognition; personality; genetics; imaging

1. Introduction

Gambling disorder is characterized by persistent and recurrent maladaptive patterns of gambling behavior, leading to impaired functioning (1). Although most people who engage in gambling do so responsibly and without consequent functional impairment, some individuals find that they become preoccupied with gambling and cannot control their behavior despite multiple negative consequences (2). Surveys suggest that the prevalence of gambling disorder in the general United States population ranges from 0.42% to 1.9%, and similar rates have been reported worldwide (3-5). As such, recognition of why some individuals cannot control their gambling behavior appears worthy of attention from a global public health perspective (6). In recognition of Gambling disorder representing a prototypical 'behavioral addiction', it has been recently reclassified as a 'Substance-Related and Addictive Disorder) in the Diagnostic and Statistical Manual Version 5 (DSM-5) (1).

There exist several comprehensive reviews of specific aspects of gambling disorder (7-12). The aim of this paper is to provide a concise primer examining the neurobiological and psychological underpinnings of gambling disorder, incorporating recent evidence derived from the neurosciences. We highlight implications for new treatment directions, along with limitations of this approach and areas in which research is lacking.

2. Pathophysiology of gambling disorder

The behaviors that characterize gambling disorder can be regarded as impulsive, in that they are often poorly thought out (or undertaken without adequate forethought), risky, and result in deleterious long-term outcomes (13). Developmentally, impulsive behavior that underlies

gambling disorder tends to begin during late adolescence or early adulthood (14). While the longitudinal profile of Gambling disorder has received little research attention, for some individuals it is likely that patterns of behavior become ingrained and persist over time, especially in the absence of prompt treatment interventions (3, 9).

2.1. Neurocognition

People with gambling disorder often manifest cognitive deficits consistent with tendencies towards impulsivity. Objective brain-based measurable traits that deconstruct top-level phenotypes into meaningful markers more closely related to the underlying etiology are important in trying to understand the neurobiology of Gambling disorder and its relationship with other conditions (15). Deficits in aspects of inhibition, working memory, planning, cognitive flexibility, and time management/estimation have been reported in individuals with gambling disorder compared to healthy volunteers (12). Individuals with gambling disorder also tend to prefer small immediate rewards rather than larger delayed rewards, to the detriment of long-term task outcomes (i.e. they show abnormally elevated ‘delay discounting’) (16).

Impulsivity is not the only aspect of gambling disorder with other cognitive domains likely present to varying degrees in gambling disorder. Gambling disorder for many individuals, for example, is associated with features of compulsivity (17). People with gambling disorder often describe the behavior in ritualistic terms such as the need for “lucky” numbers or clothing to result in favorable outcome. In addition, the nature of gambling behavior may change over time, with early gambling being driven by reward, and later (more chronic) gambling being triggered by aversive/stressful stimuli (3), or being undertaken in order to avert anxiety (17). As such,

there may be a shift from an initial behavior that is reward-seeking (impulsive) towards one that persists to avoid negative consequences or in a habitual fashion (compulsive). Individuals with gambling disorder often score high on the Padua Inventory, a measure of compulsivity (18) and display marked response perseveration (19,20) and difficulties with cognitive flexibility (21).

Although studies of gambling disorder demonstrate that the behavior is associated with diminished performance on inhibition, time estimation, cognitive flexibility, decision-making, spatial working memory, and planning tasks, a temporal relationship has not been established between cognitive deficits and clinically significant symptoms. Most likely, some cognitive deficits predispose (perhaps running in families and representing candidate 'endophenotypes' or intermediate markers of risk), while others could be a consequence of recurrent engagement in gambling itself. While studies of cognitive functioning in unaffected close relatives of people with gambling disorder are lacking, findings from people 'at-risk' of gambling disorders suggest that deficits in decision-making (dependent on neural circuitry including the orbitofrontal and insular cortices) are evident before the illness, while some other domains may be relatively spared (22). Gambling addiction represents a useful model for exploring the 'cause versus effect' issue in addiction more broadly, since chronic gambling is presumably unlikely to exert toxic effects on the brain, as compared to chronic substance misuse.

2.2. Neuroimaging

A sparse amount of research on possible neurobiological correlates of gambling disorder currently exists (for reviews, please see 11-12). Most studies have focused on functional rather than structural neuroimaging abnormalities. One functional magnetic resonance imaging (fMRI)

study of gambling urges in male pathological gamblers suggested that gambling disorder is associated with relatively decreased activation within cortical, basal ganglionic and thalamic brain regions compared to control subjects (23). Recent neuroimaging studies have demonstrated that gamblers also show hyporesponsiveness of the dorsomedial prefrontal cortex compared to healthy controls during successful (as well as failed) response inhibition, along with a hypoactive reward system (24-26). Using a graph theoretical approach (network modeling), there was evidence for abnormalities in distributed brain networks in gambling disorder versus controls, such as reduced local efficiency in the left supplementary motor area, and hyperconnectivity between frontal brain regions including the right inferior frontal gyrus (27). In terms of brain structure, there is some evidence that gambling disorder is associated with excess volume of the ventral striatum and right prefrontal cortex (28).

Another area of neuroimaging research in gambling disorder is the use of radioligand measures in conjunction with positron emission tomography (PET). Using this technique, the status of neurochemical systems in people with gambling disorder, both in the resting state and in response to pharmacological challenge, can be explored. Research so far has focused on the dopamine system, given its established importance in substance addiction and more generally in reward-processing (29). In substance addictions, there is considerable evidence that chronic substance intake is associated with downregulation of striatal D2 receptors (30). Interestingly, radioligand studies so far suggest that gambling disorder is not associated with such dopaminergic D2 downregulation. In a study using raclopride (D2/D3 receptor binding) and propyl-hexahydro-naphtho-oxazin (PHNO; D3 receptor binding), no significant differences in inferred striatal dopamine receptor binding were found between people with gambling disorder

and healthy controls (31). However, PHNO binding in the substantia nigra correlated significantly with gambling symptom severity. In another study, using raclopride (D2/D3 receptor binding), no significant differences were found between gambling disorder subjects and controls in terms of inferred striatal dopamine receptor binding (32); but 'urgency' correlated negatively with raclopride binding in the gambling disorder group. Another study, using raclopride, similarly reported no group differences between gambling disorder and controls; but did find that dopamine receptor binding was associated with sensation-seeking in general (33). In all, these radioligand studies suggest that D2 receptor downregulation is not a general feature of gambling disorder, in contrast to findings in substance use disorders. This is consistent with the view that D2/D3 receptor abnormalities in substance use disorders are a consequence of the effects of chronic drug intake on the reward pathways. Dopamine status is relevant to personality-related factors (e.g. sensation-seeking) implicated in the development of gambling disorder. It may also be that other aspects of the dopamine system, not measured using the above ligands, are abnormal in gambling disorder. For example, one raclopride-PET study found an inverted 'U' relationship between striatal dopamine release and gambling task performance in pathological gamblers but not in controls, suggesting enhanced dopaminergic sensitivity to uncertainty in gamblers (34).

Neuroimaging studies to date, do not permit characterization of the temporal relationship between the manifestation of neural abnormalities and the symptoms that comprise gambling disorder. As with the neurocognitive findings, abnormal brain structure and function could occur in people 'at-risk' before symptoms develop, alternatively stem from the disorder itself, or perhaps even reflect a secondary or incidental epiphenomenon.

2.3. Genetic predisposition

Studies have found that approximately 20% of the first-degree relatives of individuals with gambling disorder also have gambling disorder (3). Research examining familial aggregation of gambling disorder found that individuals with a problem gambling parent were 3.3 times more likely to have gambling disorder (35). In a study using a control group to examine familial aggregation, lifetime estimates of gambling disorder were significantly higher in family members of gamblers (8.3%) compared to control subjects (2.1%) (36). Data from the Vietnam Era Twin Registry (male adults) have shown that the heritability of gambling disorder is approximately 50-60% (37-38). Further analyses of personality features and their association with the heritability of gambling disorder have found that low self-control is associated with the genetic risk for gambling disorder in women (39). As discussed in the subsequent section, various polymorphisms in genes coding for components of brain neurochemical systems (e.g. dopaminergic and serotonergic systems) have been associated with gambling disorder.

2.4. Neurobiological factors

Multiple neurotransmitter systems (e.g., dopaminergic, glutamatergic, serotonergic, noradrenergic, opioidergic) have been implicated in the pathophysiology of gambling disorder (3, 40-41). Dopamine is involved in learning, motivation, and the salience of stimuli, including rewards. As discussed in section 2.3, radioligand PET studies militate against an obvious D2/D3 receptor binding abnormality being evident in gambling disorder in the resting state. Nonetheless, alterations in dopaminergic pathways have been proposed as underlying the seeking of rewards that trigger the release of dopamine and produce feelings of pleasure. In addition,

neuroimaging studies examining pharmacological challenges using dopamine agonists have reported that during the anticipation of monetary rewards, a dopamine agonist increases the activity of the nucleus accumbens and weakens the interaction between the nucleus accumbens and the prefrontal cortex, leading to an increase in impulsive behaviors (42). Dopamine receptor agonist medication appears to predispose the dopaminergic reward system to mediate an increased appetitive drive leading to changed neural processing of negative consequences and learning of contingencies (43). In terms of molecular genetic studies, the D2A1 allele of the D2 dopamine receptor gene (DRD2) has been reported as increased in frequency in individuals with gambling disorder (for a review see 39). Other research has also implicated allelic variants of the DRD1 and DRD3 genes as having an association with gambling disorder (3).

There is also a persuasive body of preclinical evidence suggesting a critical role for glutamate transmission and glutamate receptors in drug reward, reinforcement, and relapse. Glutamate appears to be implicated in long-lasting neuroadaptations in the corticostriatal circuitry (44). An imbalance in glutamate homeostasis results in changes in neuroplasticity that adversely affects communication between the prefrontal cortex and the nucleus accumbens, thereby resulting in reward-seeking behaviors (45). Glutamate is also involved in associative learning between stimuli and promotes the immediate approach response through its link to the dopamine reward system (41). Data from cerebrospinal fluid studies also suggest a dysfunctional glutamate system in gambling disorder (46).

Animal studies of gambling behavior provide evidence that the serotonergic system also appears to play a role in poor decision-making (47) and impaired performance on a gambling task (48).

Serotonin is known as a modulator of neuroplasticity events. A polymorphism in the serotonin transporter gene has been associated with gambling disorder and is found more frequently in males with gambling disorder (49). More recent research found a significant association of the C/C genotype of the serotonin receptor 2A T102C (rs 6313) polymorphism and the gambling disorder phenotype (50). Other support for dysfunction within the serotonergic system in gambling disorder has been shown with decreased levels of platelet monoamine oxidase B (MAO-B) (a peripheral marker of serotonergic function), low levels of serotonin metabolites (5-HIAA) in the cerebrospinal fluid, and a euphoric response to serotonergic pharmacologic challenge studies (3, 40).

Norepinephrine (noradrenaline) appears to be especially involved in decision-making when contingencies are unexpectedly changed and alternatives are explored (51-52). Selective inhibition of norepinephrine reuptake results in reduced premature responding, especially under circumstances when task performance is suboptimal due to demanding task conditions or inherently high baseline levels of impulsive action (53-54*)*. Studies have found that individuals with gambling disorder have significantly higher cerebrospinal fluid levels of 3-methoxy-4-hydroxy-phenylglycol, the main metabolite of the noradrenergic system (55). In addition, individuals with gambling disorder maintained significantly higher noradrenergic levels throughout an entire gambling session whereas healthy controls exhibited elevated levels only at the onset of the gambling session (56).

Preclinical evidence indicates that opioid receptors are distributed widely in the mesolimbic system, and are implicated in the hedonic aspects of reward processing (57-58).

An fMRI study of the μ-opioid antagonist naloxone found attenuated reward-related responses in the ventral striatum and enhanced loss-related activity in the medial prefrontal cortex on a wheel of fortune task in healthy volunteers (59). Specifically, the authors used an fMRI gambling task and found that naloxone reduced pleasure ratings for larger rewards and dampened the associated brain responses in the anterior cingulate cortex. Naloxone was also associated with negative outcomes being rated as being more unpleasant, implicating the opioid system both in reward- and aversive-processing (59). Gambling has been associated with elevated blood levels of the endogenous opioid β-endorphin (60), and modulation of the opioid system through opioid receptor antagonists (61) and partial agonists (62-63) has shown significant promise in the treatment of gambling disorder.

3. Psychological aspects of gambling disorder

Relationships between gambling disorder and aspects of personality can be considered from several perspectives, including in relation to personality traits (typically measured using questionnaires such as the Barratt Impulsivity Questionnaire), in relation to formal personality disorders, and in relation to other potentially life-long enduring traits (such as aspects of cognition).

3.1. Gambling disorder and personality traits

The assessment of personality traits is an evolving field. While questionnaire-based measures relating to personality have proven useful in exploring aspects of gambling disorder, it can be difficult to relate them to underlying brain function (64-65).

Support for impulsivity as a personality characteristic of individuals with gambling disorder rather than transient impulsive behavior, comes from numerous studies over the years (for a review, please see 66), including a recent study of 37 individuals which found that trait, rather than state, questionnaire-based impulsivity is associated with gambling disorder (67).

The relationship between impulsivity and gambling, however, may be impacted by a variety of factors, including socioeconomic status, age of onset, and gender. One study found that self-reported impulsivity was associated with the onset of gambling behavior but only in the case of individuals reporting a low socioeconomic background (68). Similarly, in a sample of 1004 males from low socioeconomic status areas, impulsivity at age 14 was related to gambling problems at age 17 (69). With respect to age of onset, one study found that early onset gambling disorder was associated with a more severe clinical presentation and with higher novelty seeking and lower self-directedness (70). In addition, gender appears to have an influence on impulsivity, as men with gambling problems may be more impulsive and score higher on measures of sensation-seeking compared to women (71).

Several researchers have attempted to categorize gambling disorder based on dimensions of personality, such as impulsivity, and co-occurring psychopathology. One study identified three subtypes of gambling disorder based on self-report questionnaires measuring impulsivity, depression, and anxiety (72). The first subtype consists of behaviorally conditioned gamblers, who develop gambling disorder through continual exposure to gambling and is the least severe type of gambling disorder. A second type, the emotionally vulnerable individual, has poor coping

skills, and gambles to regulate emotions. Third, antisocial impulsivity gamblers gamble to regulate affect, but are also characterized by high rates of psychopathology and impulsivity.

Another study sought to categorize gamblers into four groups (73): Cluster 1 had high impulsivity, rates of psychopathology, early onset, and severe gambling problems; Cluster 2 had low sensation seeking and high avoidant, controlling, and distant behavior, with high rates of alcohol abuse; Cluster 3 was characterized by high impulsivity and early onset, but also had high rates of sensation seeking without psychopathological impairments; and Cluster 4 was defined by low impulsivity and psychopathology, and a late age of onset.

In a meta-analysis of studies, significantly higher rates of several personality traits were identified in people with gambling disorder compared to controls (medium-large effect sizes), including negative urgency, low premeditation, unconscientious disinhibition (low conscientiousness), negative affect, and disagreeable disinhibition (low agreeableness) (74). The authors suggested that these findings in gambling disorder were similar to those observed in substance use disorders, suggesting that it may be part of a broader group of conditions characterized by externalizing psychopathology.

Some personality traits have been found to correlate with dopamine functioning. For example, in healthy males, it was found that striatal dopamine receptor binding (measured using raclopride-PET) correlated with sensation-seeking according to an inverted ‘U’ shaped model (75). As noted in section 2.2, dopamine receptor binding – again with raclopride-PET – was associated with sensation-seeking across gambling disorder and control subjects (33).

Current research has just begun to examine how personality dimensions and disorders influence treatment outcome. One study found that treatment dropout was significantly related to impulsivity (76). Other studies have found that although certain personality aspects such as high novelty seeking have been associated with more severe gambling and a young age of gambling disorder onset, these variables were not associated with treatment outcome (70).

3.2. Gambling disorder and personality disorders

Personality disorders appear to be relatively common in people with gambling disorder, and are likely to contribute to chronic symptoms. In one study, 45.5% of individuals with gambling disorder met criteria for at least one personality disorder (76). However, the presence of a personality disorder was not clearly related with the severity of gambling symptoms.

There is evidence that rates of personality disorders in gambling disorder may be influenced by other psychiatric comorbidities. In a sample derived from a national survey, one or more personality disorders was evident in 71.4% of gambling disordered individuals with a comorbid anxiety disorder (versus 40.86% of low frequency gamblers with an anxiety disorder), and in 52.9% of gambling disordered individuals without a comorbid anxiety disorder (versus 11.3% of low frequency gamblers without an anxiety disorder) (77).

3.3. Gambling disorder and other potentially enduring traits

It is conceivable that some of the cognitive deficits that occur in Gambling disorder could represent enduring traits that predispose towards the development of symptoms. As such, cognitive measures may be useful as proxy 'personality measures' in that they may be enduring and more readily linked to underlying neurobiology than formal personality disorders or scores from personality questionnaires. In order to examine impulsivity at an endophenotypic level, cognitive research has attempted to delineate the complex construct of impulsivity observed in individuals with gambling disorder. Individuals with gambling disorder demonstrate deficiencies in planning, decision-making, motor inhibition, and cognitive flexibility (3). Perceived inability to stop gambling and positive gambling expectancies have also been associated with high school students, college students, and adults with gambling disorder (78). However, it is not known the extent to which these different deficits are trait in nature. To address this issue would require studies in unaffected first degree relatives and also, ideally, longitudinal studies capturing cognitive function before, during, and after the development of Gambling disorder. There is some evidence that decision-making deficits could represent a trait marker, based on findings in people at risk of gambling disorder but without fully developed pathological symptoms (22).

4. Conclusions

The literature suggests that gambling disorder is a heterogeneous condition; however, impulsivity appears to be characteristic of the majority of individuals with gambling disorder. The relatively paucity of neuroimaging data (especially functional imaging), genetic studies, and translational studies from animals to humans in gambling disorder, however, limits our ability in defining gambling disorder as a deficit of a particular component(s) of the brain although

dysfunction in dopaminergic, glutamatergic, and serotonergic transmission have all been implicated. Further, the evidence of a genetic link between gambling disorder and other addictive behaviors is supported by high rates of familial transmission and the cross-beneficial efficacy of opioid antagonists and partial agonists in gambling and substance addiction. More holistic studies involving a number of research paradigms (genetics, cognition, imaging, etc) that explore the pathology of gambling disorder over time may be useful in furthering our understanding of the onset and course of gambling disorder.

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JEG drafted the first version of the manuscript. BLO and SRC critically revised the initial version of the manuscript for important intellectual content. All authors approve the final version of the manuscript.

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