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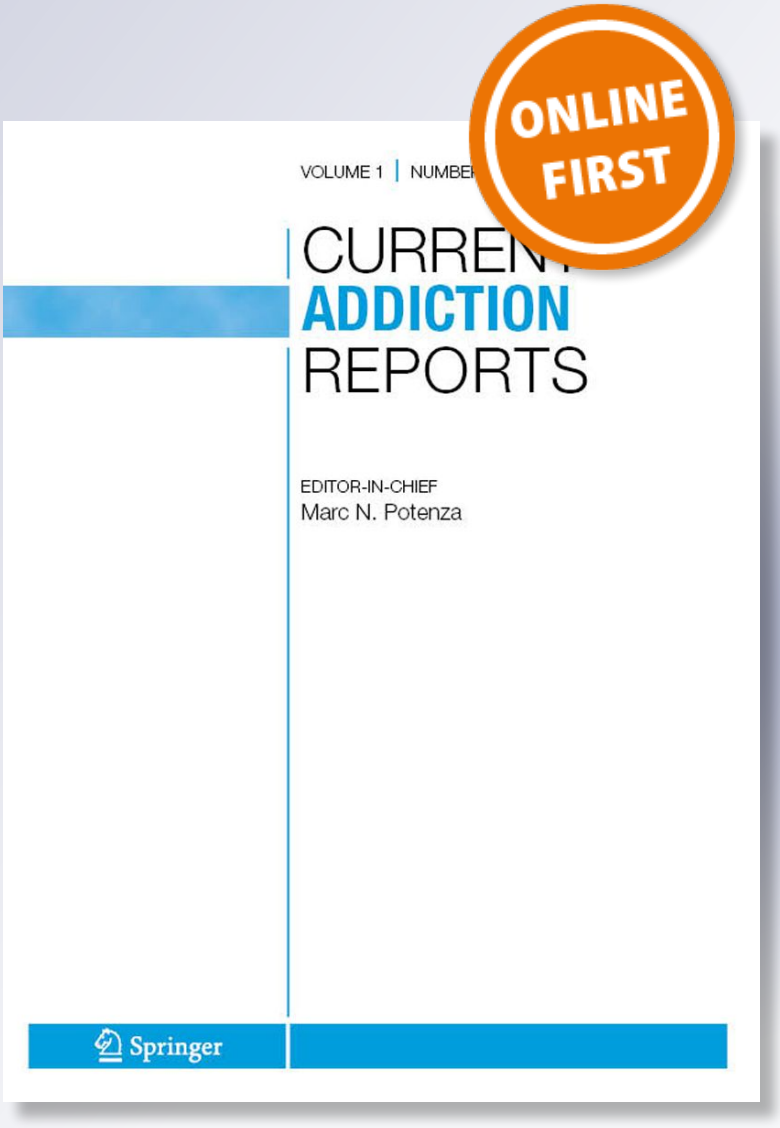
Current Addiction Reports

e-ISSN 2196-2952

Curr Addict Rep
DOI 10.1007/s40429-019-00240-8



Springer

Current Addiction Reports
https://doi.org/10.1007/s40429-019-00240-8

GAMBLING (L CLARK, SECTION EDITOR)

Dopamine and Gambling Disorder: Prospects for Personalized Treatment

Andrew Kayser [1,2]

Abstract

Purpose of Review To address variation in the severity of gambling disorder, this review evaluates the contribution of mesocorticolimbic dopamine neurons to potential behavioral endophenotypes, the influence of individual differences in the dopamine system on gambling and related behaviors, and the possible role for dopaminergic medications in the treatment of gambling disorder.

Recent Findings Newer work has suggested that dopaminergic dysfunction can lead to increased reward anticipation and a greater sensitivity to uncertainty, which in turn may drive addictive gambling behaviors. In addition, increased impulsivity, a well-recognized risk factor for gambling disorder, has been linked to dopaminergic dysfunction. More recently, emerging evidence has suggested that dopaminergic medications can influence the discounting of delayed rewards.

Summary Dopaminergic drugs that increase the salience of long-term over short-term goals may ameliorate symptoms of impulsive individuals with gambling disorder. More broadly, improved understanding of intermediate behavioral and other phenotypes with a defined neurobiological substrate may allow for personalized treatment of gambling disorder and other psychiatric conditions.

Keywords Dopamine · Gambling · Addiction · Impulsivity · Delay discounting · Computational psychiatry

Introduction

Gambling disorder, like other substance-related and addictive disorders, is syndromic. A shared phenotype reflecting functional impairment need not imply that the underlying etiologies are also shared. In fact, consistent with work in substance use disorders, the various influences on the development and perpetuation of gambling disorder, reviewed below, have been shown to include different psychiatric comorbidities, different cognitive and social processes, and different games of chance, among other factors. It should therefore be unsurprising that treatment approaches to mitigate the impact of gambling disorder may need to be personalized in order to be effective therapeutically. Current pharmacological treatment approaches do take such differences into account, but they focus primarily on psychiatric comorbidities that can contribute to problematic gambling behavior, such as alcohol use disorder, bipolar disorder, and others. Taking biologically motivated steps toward novel treatments will require us to better understand the neuroscience of gambling disorder itself.

This article is part of the Topical Collection on *Gambling*

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Group and Subgroup Analyses A first step toward this goal has been taken by studies that evaluate the features distinguishing individuals with gambling disorder from healthy controls, and different hypothetical subgroups of gambling disordered individuals from each other. Consistent with work characterizing individuals with substance use disorders [1–3], a meta-analysis of 44 studies that included personality traits from an aggregate of more than 2000 problem gamblers and 5000 healthy controls suggested that blunting of reward processing, increases in stress responses and associated cognitive changes may characterize gambling disorders [4]. In particular, significant differences between gamblers and healthy controls were found for traits along the impulsivity spectrum, characterized as negative

Published online: 07 March 2019

urgency, low premeditation, unconscientious disinhibition, disagreeable disinhibition, and negative affect [4].

These broad differences, however, likely conceal important individual variability [3] (Table 1). A series of studies have consequently evaluated whether subjects with gambling disorder can be clustered into subgroups based on characteristics such as comorbid mental health disorders, cognitive phenotypes, and preferred form of gambling. In a group of 212 Australian gamblers, four clusters differing in alcohol use, psychological distress, and impulsivity could be defined [5], consistent with a study in 158 Canadian gamblers who could be divided into 3 clusters based on situational negative and positive emotions related to gambling, and who differed in both game of choice and alcohol use [6]. In 372 Swiss Internet gamblers who completed a series of questionnaires, three clusters could be identified, segregated based on loneliness and indebtedness [7]. Intriguingly, these clusters also differed significantly on scores in the Urgency, Premeditation, Perseverance, and Sensation Seeking (UPPS) impulsive behavior scale, with highest total scores in the lonely, indebted subgroup. A larger study of 628 gamblers in France suggested that different traits were associated with different forms of gambling: for example, roulette gamblers showed more cognitive distortions around gambling play, while scratch card gamblers showed fewer cognitive distortions [8]. An even larger study in a Finnish cohort (4428 gamblers) demonstrated that the greatest incidence of problem gambling occurred in male-dominated sports and electronic gaming gambling [9]. Together, these studies suggest that differences in mental health comorbidities, cognitive distortions, impulsivity, and game of choice may significantly inform treatment, factors that proposed psychiatric treatment algorithms for comorbid disease have begun to recognize [10]. They also provide empirical support consistent with conceptual models describing the development of gambling disorder via different pathways—i.e., through behavioral conditioning, emotional vulnerability, and antisocial impulsivity [11].

Table 1 Possible etiologies and treatments

Sources of individual variability	*Examples*
(1) Biochemical, as reflected by different laboratory-based assays	Blood/serum metabolites
	CSF metabolites
	Urine metabolites
(2) Clinical comorbidities	Depression
	Bipolar disorder
	Alcohol use disorder
(3) Cognitive processes[a]	Impulsivity
	Working memory
(4) Digital biomarkers	Smartphone usage
	Wearable biosensor-related
(5) Genetics	Dopamine receptor polymorphisms
	Epigenetic changes
(6) Imaging data[a]	EEG
	Functional MRI
	PET
Potential treatment modalities	*Examples*
(1) Behavioral/psychological	Cognitive-behavioral therapy
	Motivational interviewing
	Mindfulness
(2) Brain stimulation	Transcranial magnetic stimulation (TMS)
	Transcranial direct current stimulation (TDCS)
(3) Pharmacological[a]	Dopamine-related medications
	Agents acting on multiple other neurotransmitter and neuromodulatory systems

[a] The primary focus of this review

Genetics The reasons for, and specific importance of, these potential group and subgroup differences remain unclear. Because a number of the differences between substance use disordered individuals and healthy controls have been hypothesized to result from changes in dopamine-related reward systems [12] (though other neurochemical changes are certainly present [3]), such differences have also been evaluated in gambling-disordered subjects. One approach has been to evaluate whether genetic polymorphisms might distinguish patients with gambling disorders from those without. All of these studies are limited by small sample sizes, and perhaps as a consequence, most generally focus on hypotheses about specific genes. One of the few GWAS studies, conducted in a general population of 1312 Australian twins who completed a structured telephone interview, evaluated which of 2.38 million SNPs were associated with a gambling composite score based upon four indices of gambling frequency, preferred game, and other traits, coupled with the DSM-IV gambling screen and South Oaks Gambling Scale (SOGS) scores [13]. No SNPs reached significance, and none of the six best-scoring SNPs, as defined by a specific p value threshold ($p < 1 \times 10^{-5}$), were found within the dopamine pathway.

A number of studies have thus taken a more focused approach by directly evaluating dopaminergic genes (Fig. 1). In an innovative effort to reconcile clinical and pre-clinical data, Lobo and colleagues genotyped 38 addiction-related genes in 400 gamblers and 345 matched controls, then used genetic tools to test variants reaching trend-level significance in a rodent model [14]. Sprague-Dawley rats performed an analog of the Iowa gambling task known as the rodent gambling task. Of the gene candidates derived from human genotyping, only a variant of the dopamine D3 receptor (DRD3) gene, as reflected by its expression within the islands of Calleja (the largest group of which forms the medial border of the nucleus accumbens), was significantly associated with behavior. This result is potentially consistent with work implicating the

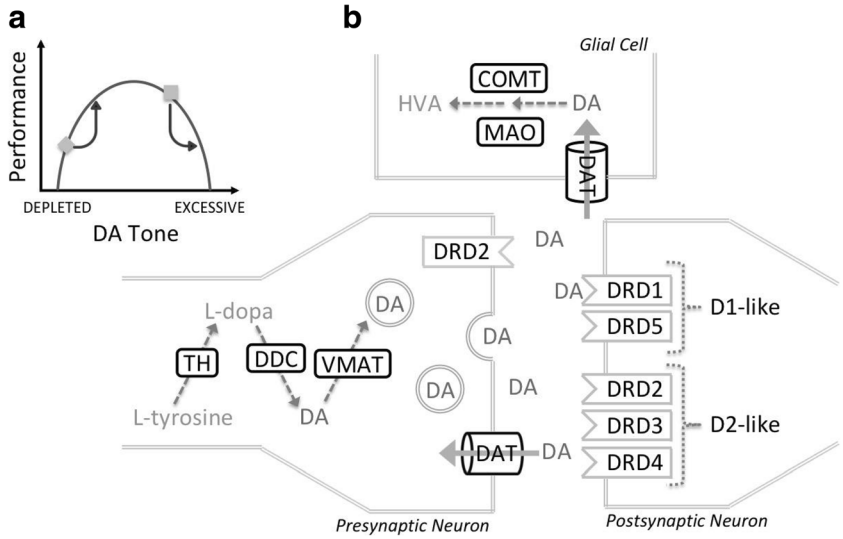

Fig. 1 Factors contributing to the importance of individual differences in the response to dopaminergic agents. **a** Behavioral performance (*y*-axis) is thought to be an inverted U-shaped function of dopamine tone (*x*-axis): both too little ("depleted") and too much ("excessive") tone can adversely impact behavior. This function has at least two implications. A similar medication-induced increase in dopamine tone can either help or hinder performance, depending on whether a subject starts in a relatively low (diamond) or relatively high (square) state. Moreover, within an individual, the position of the curve along the dopamine axis may vary for different cognitive functions—i.e., there is no one optimal level of dopamine for all cognitive processes. **b** This simplified overview of a dopaminergic synapse suggests multiple potential sources for individual variability within the dopamine system. Proteins related to dopamine synthesis and packaging (TH, DDC, VMAT), action at receptors (DRD1–5), and termination of signaling (DAT, COMT, MAO) may represent points of greater or lesser leverage over system function in different individuals. Additionally, interactions between dopamine gene products, epistatic or otherwise, can complicate enhancement or disruption of function in single targets. Abbreviations: COMT = catechol-O-methyltransferase; DA = dopamine; DAT = dopamine transporter; DDC = dopamine decarboxylase; DRD1–5 = dopamine receptor subtypes 1–5; HVA = homovanillic acid; MAO = monoamine oxidase; VMAT = vesicular monoamine transporter

DRD3 receptor, especially in dopamine-agonist-induced impulse control disorders (see below); but it is compromised by concerns including the relevance of the gambling task to human gambling behavior (a concern also noted in the context of other tasks [15]), and the demonstrated ability of a single genetic variant to lead to different, sometimes opposite, effects in different rodent strains [16••]. These results also contrast somewhat with a previous study focusing on dopamine receptors D1–3 in 242 healthy Caucasian subjects who had gambled at least once; the authors found no significant relationships between gambling metrics and DRD3, but did find trend-level associations with DRD2-like receptors [17]. Here, too, the specific population may matter: a case-control study evaluating the DRD1–4 polymorphisms in a Korean sample of 104 DG patients and 114 controls found no evidence for a link to any of these genes [18]. Similarly, in a case-control study in Parkinson's disease patients with (N = 48) and without (N = 41) gambling and impulse control disorders, no differences were seen in frequency of the DRD2 Taq1A, catechol-O-methyltransferase (COMT) Val158Met, and dopamine transporter (DAT) VNTR gene variants [19]. Epigenetic factors may further complicate such work—e.g., the finding that the methylation status of DRD2 may decline during abstinence from gambling [20]. Other, typically smaller studies have focused on variants in single genes including COMT [21], dopamine beta-hydroxylase [22], and DRD2 and DAT1 [23]. Overall, while some results are suggestive, the small subject numbers and lack of replication in larger studies point to general problems with such work, heroic as it is, in small patient populations. In that spirit, one study evaluated the relationship between a broader panel of dopamine genes and delay discounting behavior in 175 weekly gamblers of European ancestry and found that a dopamine composite score based on 11 of these genes could explain approximately 17% of the variance in discounting [24]. However, this large effect size was determined post hoc, and further studies will be necessary to confirm it.

Neurochemistry The neurobiological underpinnings of gambling disorder have also been assessed by studies examining differences in dopamine binding within the brain using positron emission tomography (PET), typically to evaluate potential differences in dopamine synthesis capacity and receptor availability within the striatum. One early motivation for this effort was a now well-known side effect of dopamine agonist therapy in Parkinson's disease. A small subset of Parkinson's patients so treated have developed pathological gambling, as well as impulse control disorders such as compulsive shopping, eating, and sexual behaviors [25]. Intriguingly, Moore et al. noted that the strongest effects on such behaviors were seen for pramipexole and ropinirole, two agonists with stronger dopamine D3 receptor activity [26],

though other drugs with different dopamine pharmacodynamics and receptor selectivity have also been implicated. Recent meta-analyses have suggested that frontal-executive dysfunction may represent a risk factor for the development of these disorders, as measured by set shifting and reward-related decision making [27, 28], and that behavioral risk factors also contribute, including subjective psychiatric symptoms (anxiety, depression, anhedonia) and impulsivity [27]. Other studies have suggested that an increased risk for the development of gambling and impulse control disorders is not specific to the use of agonist treatment in Parkinson's disease itself: an increased incidence of reduced impulse control with use of dopamine replacement therapies may also be seen in the treatment of prolactinomas [29, 30] and restless leg syndrome [31–33], as confirmed by recent reviews of the Food & Drug Administration's adverse events database [26, 34].

Given these findings in Parkinson's disease, as well as longstanding evidence that dopamine dysfunction may be a hallmark of substance use disorders (especially those involving stimulants [12]), neurochemical differences between gambling disorder, and healthy controls have been sought. However, PET studies have not identified consistent differences. Direct evaluation of D3-receptor availability using the D3 agonist ^{11}C-PHNO did not differ between these two groups, although intriguingly, a direct relationship between increased PHNO binding in substantia nigra and increased gambling severity and impulsivity was found in the gambling disordered group [35]. Similarly, a study by Clark and colleagues demonstrated that although striatal binding of the D2/D3 antagonist ^{11}C-raclopride did not differ between gambling disordered subjects and healthy controls, raclopride binding showed an inverse relationship with urgency, a form of impulsivity under positive or negative mood states, in gamblers [36], as did ventral striatal raclopride binding in a subsequent study by a different group [37]. Dopamine synthesis capacity has also shown an inconsistent relationship with gambling disorder, with some groups seeing striatal differences between GD and HC groups [38], and others not [39]. Perhaps the most suggestive difference between gamblers and controls has been the finding that amphetamine-induced dopamine release may be greater in the dorsal striatum of gamblers than in a control group, in a manner that correlates directly with gambling severity as measured by the SOGS [40]. Similar findings were seen by Joutsa and colleagues, who evaluated gambling (slot machine)-induced dopamine release in the striatum [41]. Other researchers have evaluated the correlation between Iowa Gambling Task performance and PET data and suggested that dopamine release in response to uncertainty may explain these findings [42]. Together, these studies suggest that, if any differences are apparent, they might be found in increased dopamine release, though past criticisms about a lack of reproducibility in PET data in this population are noted [43].

Other imaging findings, primarily using functional MRI, suggest that changes in reward circuitry, and therefore potentially in dopamine function, can distinguish gambling disordered patients from healthy controls [44]. A meta-analysis of 25 functional MRI studies evaluating reward anticipation in individuals with substance use disorders and gambling disorder, compared to healthy controls, found that both patient groups demonstrated decreased striatal activity during reward anticipation [45•]. Curiously, during reward receipt, substance use disordered individuals showed an increase in BOLD activity, whereas gambling disordered individuals showed a decrease. Because of the prominent role of the striatum (particularly the ventral striatum) in reward processing, the PET data suggestive of increases in dopamine release, and the data implicating dopamine in ventral striatal function, this evidence has inspired pharmacological attempts to interrogate dopamine's role in gambling disorder and to develop potential dopamine-based treatments.

Pharmacology The evidence from cognitive neuroscience studies as a whole demonstrates that dopaminergic agents have a multiplicity of effects on gambling-related cognitive processing. In a between-subject design of 40 healthy controls, methylphenidate, a dopamine and norepinephrine reuptake inhibitor, prevented the typical reduction in risky choice as stakes increased [46]. However, in a clever study to isolate the D1 receptor, Zack and colleagues administered d-amphetamine in the setting of pretreatment with either the specific D2R antagonist haloperidol, or the combined D1R-D2R antagonist fluphenazine [47]. Their data on a slot machine task suggest that relative to fluphenazine, haloperidol pretreatment of methylphenidate-treated subjects decreased the desire to gamble again. Similarly, L-dopa, a dopamine precursor, increased baseline gambling propensity in a sample of 32 healthy controls [48], and in a functional MRI study, it increased impulsivity as measured by a delay discounting task in a group of 14 controls [49]. However, in a larger study of 200 healthy male controls, L-dopa did not increase risk-taking on a sequential risk task, although the subset of individuals with the 7-repeat version of the DRD4 exon III VNTR did increase risky responding [50]. As with the cognitive neuroscience literature more generally, variations in the behavioral assay and medication complicate a summary interpretation of these sometimes-conflicting results.

Other work has directly evaluated dopamine agonists and antagonists. In a hint at why not all subjects who receive dopamine agonists develop impulse control disorders, Norbury and colleagues found that the effects of the D2/3 agonist cabergoline on risky choice in 20 healthy men were modulated by baseline sensation seeking, with the largest effects of drug in those subjects with the lowest baseline sensation seeking scores [51]. In contrast, a D2 antagonist, haloperidol, reduced the relationship between payoff and subsequent bet size in 20 pathological gamblers playing a commercial slot machine [52].

However, haloperidol did not modify performance on a slot machine task in male recreational gamblers [53], nor did use of the D2 antagonist sulpiride alter reward- and punishment-based reversal learning in 18 pathological gamblers [54]. Despite these negative findings, a subsequent study in 16 pathological gamblers and 21 healthy controls suggested that sulpiride could attenuate probability distortions when rewards (as opposed to losses) were present, but this finding was not specific to the gambling disordered group [55]. These variable findings speak to the need to better understand the cognitive and behavioral factors that may predict drug response.

Of course, the idea that dopaminergic drugs might have clinical applications draws directly from the aforementioned unexpectedly deleterious effects of the dopamine agonists in a subset of patients. In keeping with the Parkinson's literature, data from a large US claims database collecting adverse drug events documents that the dopamine agonists ropinirole and pramipexole, as well as the D2 modulating agent aripiprazole, are associated with an increased risk of gambling disorder [56]. Thus, despite the variable findings in cognitive studies, one might nonetheless hope that a dopamine antagonist could provide benefit for patients with gambling disorder. However, at the time of this paper, no dopaminergic medications have been approved for gambling disorder. As reviewed by Potenza and others [10, 57, 58], neither of the two dopamine-targeted drugs evaluated in randomized controlled trials for gambling disorder—the dopamine and serotonin antagonist olanzapine, and the dopamine and norepinephrine reuptake inhibitor bupropion—have shown any benefit for gambling disorder over placebo, as assessed by changes in the Yale Brown Obsessive Compulsive Score adapted for Pathological Gambling (PG-YBOCS).

Individual Differences

The above variable, sometimes contradictory findings revealed by studies of dopamine in gambling disorder are consistent with the larger idea that enriching for a gambling endpoint does not identify a homogenous population. Nonetheless, some of the above evidence suggests that alterations in dopamine function might contribute to the development and persistence of gambling disorder. Are there systematic relationships that might explain this variability in dopamine function and pharmacological response? Optimistically, the idea that specific subgroups might respond more favorably to specific interventions is consistent with the syndromic nature of the disease. As it turns out, there is substantial evidence, primarily from the cognitive neuroscience literature, that individual differences in dopamine tone underlie differences in specific cognitive processes and the response to dopaminergic agents. Thus, better defining a specific cognitive process of interest might be beneficial.

Working Memory Perhaps the strongest evidence that dopamine can impact cognition comes from the literature on working memory, the ability of lateral prefrontal cortex and connected regions to promote the temporary maintenance of information for use during cognitive processing. In seminal studies in both macaques and humans (reviewed in [59–61]), working memory was shown to be dependent upon the state of the dopamine system, such that both dopamine depletion and dopamine excess, through their effects on dopamine receptor signaling in lateral frontal cortex, impaired working memory performance (Fig. 1). This observation led to the concept that an optimal level of dopamine was important within the frontostriatal circuits that instantiate working memory processes, and to studies whose data supported the idea that variations in baseline dopamine tone across individuals might explain differences in working memory performance [60, 62, 63]. This concept of an inverted U-shaped response to dopamine—i.e., an optimal level of dopamine, flanked by worsening performance in the setting of higher or lower dopamine tone—was soon found to support findings related to other dopamine-dependent processes, such as impulsivity [49, 64–66]. In addition, it was recognized that the optimal level of dopamine for one cognitive process might not be the same for another—e.g., dopamine tone that optimized working memory might not optimally modulate impulsivity [64, 67•]—or even that the form of the function linking dopamine to behavior may vary [68].

Between the poles of genes and behavior, then, it may be important to search for intermediate cognitive phenotypes that correlate with the presence or severity of gambling disorder (Table 1). This third approach draws heavily on the recent NIMH work to define specific research domain criteria (RDoC) "based on dimensions of observable behavior and neurobiological measures" (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml). Aligned with past studies suggesting that a more general impairment in executive function may be present in gambling disorder [69], one such candidate cognitive process is impulsivity, the tendency to take actions leading toward an immediate goal that may conflict with long-term goals. Impulsivity represents a risk factor not only for gambling severity but also for substance use disorders (e.g. [70]; reviewed in [71]), arguing that it represents an endophenotype that is a potentially relevant treatment target. Intertemporal discounting, one of the most widely used task to assess impulsivity, evaluates the degree to which people devalue the passage of time in economic choices. When offered the choice between a smaller, typically monetary award available sooner, and a larger reward available later ("Would you like $20 now or $30 in one month?"), different subjects have variable thresholds for waiting for the larger reward. The tendency to choose the smaller, sooner reward is consistently greater in subjects with gambling disorders [72, 73, 74•, 75]. However, impulsivity is not itself a

unitary construct. Targeting non-planning impulsivity (the type of impulsivity described above) can require it to be distinguished from motor and attentional impulsivity. Non-planning impulsivity itself has subcomponents including the perception of the passage of time independent of decision making, the ability to prospect (i.e., to imagine/forecast future states), and subjective valuation [76••]—the latter of which is presumably a primary focus in studies of intertemporal discounting. In addition, "discounting" behavior itself is not uniform if not only delay discounting, but also probability and effort discounting are considered. For example, gambling use disordered subjects may even be more normatively rational, rather than less so, when compared to controls on the discounting of probabilities [74•]. These important complexities aside, impulsivity represents a potential endophenotype for addictive disorders that may be useful in guiding treatment [71].

Also promising is work on intertemporal discounting showing that impulsivity in controls depends upon the state of the dopamine system. In a non-pharmacological functional MRI study in problem gamblers, Miedl and colleagues found that, while increased craving also increased delay discounting, it did so in a manner that reversed a positive correlation between subjective value and ventral striatal activity when craving was low [77]. In a PET study, impulsivity in control subjects, as assessed by the Barratt Impulsiveness Scale (BIS), correlated inversely with D2/D3 receptor availability in the SN/VTA [78]. This effect was mediated by an inverse relationship between D2/D3 availability in the SN/VTA and amphetamine-induced striatal dopamine release. Changing the state of the dopamine system via the administration of L-dopa, a dopamine precursor (Fig. 1) increased impulsive choice in control subjects [49]. However, a 20 mg, but not a 10 mg, dose of D-amphetamine reduced intertemporal discounting in controls for choices based on the amount, not the probability, of a later reward [79]. These studies raise the possibility that dopaminergic agents might modulate impulsivity in patients with gambling disorder. For therapeutic purposes, however, reducing, not modulating, impulsivity using medications without significant risks (as amphetamines might have) would be critical.

An important additional consideration in the development of potential therapeutics is the neuroanatomical and neurophysiological basis for these behaviors—i.e., understanding where in the brain dopamine is acting. Cognitive neuroscience argues that the cognitive control necessary for future-oriented behaviors—i.e., less impulsive decision making—is implemented via top-down, goal-based control over more immediate stimulus-based responding [61, 80]. This form of control is thought to be instantiated by prefrontal and other higher-order cortical influences over subcortical brain regions including the striatum (e.g., [66, 81–83]). By this hypothesis, augmenting prefrontal control by whatever means should improve goal-oriented behaviors. For example, in a behavioral test of this hypothesis in controls, subjects asked to envision themselves in personally relevant future situations, such as a vacation, while they performed an intertemporal choice task chose fewer smaller, sooner options and demonstrated increased coupling between the anterior cingulate cortex and hippocampus [84].

By this logic, we and others have argued that medications that augment prefrontal cortical activity might also reduce impulsive choice, which in turn may reduce problematic gambling behaviors. One such medication is the brain-penetrant catechol-O-methyltransferase (COMT) inhibitor tolcapone. In most brain areas, the dopamine transporter terminates the action of synaptic dopamine via reuptake. However, dopamine transporter density is low in prefrontal cortex; consequently, COMT metabolism accounts for approximately half of the reduction in cortical dopamine levels following evoked dopamine release, as measured by voltammetry [85, 86]. In addition, mice with inactivated COMT genes show increased cortical but not subcortical (striatal) dopamine levels [86, 87]. The possibility therefore arises that selectively increasing dopamine tone in frontal cortex via COMT inhibition may improve top-down control, and thereby reduce discounting of delayed rewards.

To date, we have identified evidence supportive of this hypothesis. In controls, tolcapone reduced impulsivity in a fashion that varied inversely with an independent measure of baseline impulsivity, the Barratt Impulsiveness Scale (BIS) [66]. Consistent with this influence, tolcapone also impacts other cognitive processes contributing to impulsivity: it improved the accuracy of time perception, specifically by ameliorating the tendency to consider specific time intervals to be longer than they actually are [88]; and in keeping with influences on prospection, it increased exploratory over exploitative behaviors in subjects with the Met/Met COMT allele [89]. In a pilot study of 17 subjects with gambling use disorder, tolcapone also decreased delay discounting in direct proportion to the cognitive subscale of the BIS, suggestive in combination with our previous data of an inverted U-shaped dopamine response [82]. More recently, in an attempt to link tolcapone's effects to real-world behaviors, we demonstrated that tolcapone reduced alcohol consumption in non-treatment seeking subjects with alcohol use disorder in proportion to reductions in impulsive choice on a delay discounting task [90]. While alcohol use disorder and gambling disorder certainly differ, the relationship between tolcapone's effect on delay discounting and a real-world behavior suggests that by improving decision making, tolcapone might benefit other conditions as well. Of course, these data need to be replicated, the influence of tolcapone on real-world gambling behaviors needs to be established, and (assuming both of those results are positive) larger clinical trials remain to be done. With these important caveats, this approach suggests that, by stratifying

individuals by a relevant cognitive endophenotype, specific treatments might someday be targeted to those individuals most likely to benefit.

Of course, other approaches to treating impulsivity, and thereby treating gambling use disorder, based on individual differences in behavioral and neural phenotypes may be possible (Table 1). From the diagnostic side, defining a more homogeneous subgroup within the larger syndromic population—e.g., impulsive problem slot machine gamblers—might permit more targeted therapies. Another possibility is to define subgroups based on an intermediate behavior related to impulsivity—e.g., impaired time perception. Yet, a third tack is to use genetics to define subgroups—e.g., those impulsive GD individuals with specific (or specific combinations of) genetic polymorphisms—although genetic approaches have not been revealing to date, as noted above. One can also imagine subgroups based on other traits previously mentioned, such as age at onset of gambling disorder, psychiatric comorbidities, and the like (however, combinatorial approaches greatly increase the number of subjects necessary to assess such hypotheses). On the treatment side, one might argue for the development of more specific dopaminergic agents that better address the impulsivity associated with gambling disorder. By analogy to working memory deficits, for example, for which the need to develop and test dopamine D1 receptor-specific agonists has been argued [91], the aforementioned induction of impulsive behaviors by dopamine agonists would potentially support the importance of testing specific dopamine D3 receptor antagonists in gambling use disorder, using impulsivity as a covariate.

Conclusions and Future Directions

Taken together, the results reviewed here present mixed support for the notion of general differences in dopaminergic functioning between healthy controls and gambling disordered subjects. As a result, the expectation that a single dopaminergic agent should show group differences between gambling use-disordered and control subjects in studies evaluating gambling-relevant endpoints is likely unrealistic. While gambling disorders may well be enriched for certain behavioral and cognitive phenotypes, the current data suggest that unrecognized heterogeneity within this group could confound efforts to develop treatments. However, rather than arguing definitively against the role of dopaminergic agents in this group, the data also suggest that stratifying treatments by intermediate phenotypes that include value-based decision making, cognitive flexibility, and—importantly—an understanding of their neurobiological substrate may provide a way forward. Specifically, multiple studies suggest that impulsivity should be an important covariate in treatment, and our work, albeit preliminary, argues that considering factors such as the neurobiological locus of dopamine action may be critical when considering dopaminergic therapies.

In the future, multiple avenues for treatment development are possible. With respect to characterization of subgroups, computational psychiatry approaches to endophenotype identification have shown promise. For example, characterizing subjects based on whether they pursue rewards in a more goal-directed ("model-based") or habitual ("model-free") manner might differentiate individuals with greater cognitive flexibility from those with more compulsive traits [92]. Notably—and perhaps counterintuitively—initial studies suggest that a tendency to employ more model-based strategies correlates with greater presynaptic ventral striatal dopamine levels [93], and is increased by L-dopa administration [94, 95]. With respect to pharmacology, the development of more specific D3 receptor antagonists, as noted above, remains of interest. More broadly, complementary diagnostic and therapeutic approaches based on an understanding of the syndromic nature of gambling disorder (Table 1) will be important in guiding treatment development moving forward.

Acknowledgments Thanks go to Howard Fields and Jan Peters for reading through an earlier version of this manuscript, and to the colleagues and research subjects who contributed to our studies included in this review. Of course, any errors belong to the author alone.

Funding Information This work was supported by NIH grants AA026587 and MH112775.

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- • Of importance
- •• Of major importance

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