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Parallel Roles for Dopamine in Pathological Gambling and Psychostimulant Addiction

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Abstract: A variety of evidence suggests important commonalities in the neurochemical basis of reinforcement in pathological gambling (PG) and psychostimulant addiction. This article focuses on the parallel and specific roles that dopamine (DA) activation plays in these two disorders, beyond its generic role in reinforcement. A psychostimulant-mimetic model for PG is proposed based on evidence from the following domains: Acute subjective-behavioral effects of gambling and psychostimulants; Effects of anticipated rewards and uncertainty of reward delivery (key elements of gambling) on DA release; Relationship between DA release and positive arousal; Cross-priming of motivation for gambling by amphetamine; Effects of DA D2 antagonists on gambling and amphetamine reward; Effects of mixed D1-D2 antagonists on clinical symptoms of PG; Effects of DA D2 agonists on experimental measures of risk-taking, gambling, and induction of PG in patients with Parkinson's disease; Electrophysiological and cognitive disturbances associated with chronic exposure to gambling and psychostimulants, and the possible role of sensitization in these effects. Limitations of the model regarding the exclusive role of DA are discussed with particular reference to genetic risk, co-morbidity, and sub-types of PG. Suggestions for future research include isolating the roles of DA receptor subtypes in PG, and parallel within-subject assessment of DA manipulations on gambling and psychostimulant reinforcement in PG subjects and controls.

Keywords: Pathological gambling, psychostimulant, dopamine, addiction, sensitization.

THE NATURE AND SCOPE OF THE PROBLEM

Pathological gambling (PG) is a disorder whose prevalence has grown rapidly with the liberalization of gambling laws and increased availability of gambling venues in the last decade. Current estimates indicate that PG afflicts 1-3% of the general population in developed countries [1-3], a rate that is likely to increase with the proliferation of poker and other gambling sites on the Internet.

PG is linked with social and vocational disruption, criminality, cardiac problems, depression, and suicide [4-7]. In addition, PG often results in enormous debt that remains even after abstinence is achieved, which can often lead to relapse to gambling, the proverbial vicious cycle. Together, this constellation of features makes PG a debilitating psychiatric disorder and a serious public health problem.

DIAGNOSIS AND CLASSIFICATION OF PG

From a clinical standpoint, management of PG is impeded by uncertainty around its appropriate classification. The bellwether Diagnostic and Statistical Manual [8, 9] of the American Psychiatric Association classifies PG as an Impulse Control Disorder. However, accumulating evidence has led to the suggestion that PG may be better characterized as a substance-less or behavioral addiction [10]. With a view towards the next version of the DSM, recent accounts have described PG as a hybrid disorder that challenges current classification systems and may require a broadening of the category now reserved for substance dependence disorders [11, 12].

Such formal definitions could benefit from research designed to operationalize or objectively define the fundamental processes that mediate PG. Although important insights have been gained in this regard, much of this work has occurred outside the context of a unifying framework. This has made it difficult to identify important linkages among symptoms, functions, and physiology. Research and treatment of PG could benefit from a model or heuristic to guide hypothesis testing at the pre-clinical and clinical levels. The present article outlines one such model.

Specifically, we propose that PG resembles psychostimulant addiction on a number of important dimensions. We present evidence that the correspondence between PG and psychostimulant addiction goes well beyond the generic overlap between PG and substance addictions as a class of disorders. In particular, a range of evidence converges to suggest a parallel and dominant role for dopamine (DA) in the pathophysiology and symptom profile of the two disorders. This model of PG could be referred to as the psychostimulant-mimetic model. As with all heuristic models, there are limitations to the present framework. These will be outlined, along with suggestions for future research. We begin with a brief overview of epidemiology and key points from previous reviews to serve as context for our model.

Co-Occurrence of PG and Psychostimulant Addiction

Indirect evidence for a common role of DA in PG and psychostimulant addiction can be gleaned from co-occurrence

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patterns for these disorders. Among diverse outpatients (n = 111), Baldo *et al.* [13] found a greater prevalence of pathological gamblers among drug users than alcoholics. Among alcohol-dependent outpatients (n = 124), PG was seen in 4.0%, or slightly more than in the general population [14]. In a 1992 study of cocaine dependent outpatients (n = 298) lifetime prevalence of PG was 14.8% [15] which, at that time was *10 times the rate* found in community samples. In that study, subjects with PG also had higher rates of ADHD and alcohol use disorders, indicating a more severe diagnostic profile. More recently, Hall *et al.* [16] found that lifetime prevalence of PG in cocaine dependent outpatients (n = 313) was 8.0%. In 72.0% of these cases, PG preceded cocaine dependence. These data indicate a somewhat greater than expected rate of PG among alcoholic patients but a much higher rate of PG in psychostimulant addicts, and suggest that PG may escalate to psychostimulant abuse.

OVERALL NEUROBIOLOGY OF PG AND SUBTYPES

Brewer and Potenza [17] describe PG and other impulse control disorders as 'behavioral addictions', which, like substance use disorders (SUD's), involve disturbances in the neural circuitry that mediates reward sensitivity, decision-making, habit formation, and impulse control. Both PG and SUD's involve disturbances in glutamate, GABA, serotonin, and endogenous opioid systems. Both SUD's and PG are also heterogeneous in terms of etiology and symptom profile.

Iancu *et al.* [18] proposed three subtypes of PG, each of which should respond preferentially to different medications: The Impulsive Subtype (25-35% of cases), is characterized by frontal lobe dysfunction and includes individuals with ADHD. These patients should respond best to mood stabilizers. The Obsessive-Compulsive Subtype (5-10% of cases) is mostly female with a history of trauma, and should respond best to serotonin reuptake inhibitors (SSRI's). The Addictive Subtype (50-60% of cases) often have co-morbid alcohol use disorders and should respond to mixed noradrenergic-dopaminergic antidepressants, like bupropion, which restore reward function.

Goudriaan *et al.* [19] noted that conceptual models applied to SUD's have relevance in PG. For example, Koob and Le Moal's [20] 'allostatic' model of progressive reward and stress system dysregulation may explain why artificial rewards, like gambling, become preferred by patients with PG and why these individuals exhibit excessive stress-related responses (e.g., cortisol release) when they engage in gambling. In this framework, chronic exposure to gambling, like drugs of abuse, is considered the critical pathogenic factor. Goudriaan *et al.* also emphasize the importance of subgroups in PG and cite Blaszczynski and Nower's [21] seminal model, which proposes three distinct etiological pathways to PG: Behavioral conditioning, emotional vulnerability, and impulsivity.

Heterogeneity was a common theme in each of these reviews. In this respect, PG is no different than other psychiatric disorders like schizophrenia, depression, or anxiety disorders, each of which is characterized by clearly definable sub-types. Nevertheless, core pathologies have been identified for each disorder. Thus, DA dysfunction is essential to schizophrenia; serotonin dysfunction to depression; and GABA dysfunction to anxiety disorders. It is possible that a similar 'core pathology' exists in PG.

One way to identify a core pathology is to focus on the neurochemical effects of the addictive behavior rather than on the patients who engage in it. This is in keeping with current theories of addiction, like allostasis [20] or incentive-sensitization [22], which focus on *how addictive drugs change brain function*. In this respect, gambling is notable insofar as its neurochemical effects result exclusively from exposure to conditioned signals for reward. Both the cues that predict reward (e.g., spinning wheels, tumbling dice) and the reward itself (credits, money) have no intrinsic value apart from that acquired through prior learning. Therefore, one way to understand the intoxicating, reinforcing, and addictive properties of gambling is to consider the neurochemical basis of conditioned reward signaling. From this perspective, DA, the neurotransmitter that directly (though not exclusively) governs conditioned reward signaling in the mammalian brain would be expected to be a critical neurotransmitter in mediating gambling behavior and pathological aspects of this behavior [23].

TOWARDS A PROCESS-ORIENTED DEFINITION OF PG

Research on 'classic' addictions – substance dependence – has relied heavily on animal behavioral models to investigate the effects of environmental (e.g., stress, cues) and neurochemical (e.g., drug probes, receptor cloning) manipulations. This has led to critical advances in the understanding and treatment of these disorders. To date, no corresponding animal behavioral model of PG has been validated, although models do exist that appear to capture some key elements of the disorder, which we discuss later [24].

In humans, functional magnetic resonance imaging (fMRI) permits on-line evaluation of brain activity while subjects engage in gambling-like activities. Event-related fMRI, which has high temporal resolution to track moment-to-moment neural responses, has been used very successfully to isolate the brain regions activated during anticipation, receipt and loss of monetary reward [25-33]. The findings from this line of research consistently identify the ventral striatum (which includes the nucleus accumbens) and medial prefrontal cortex as critical substrates mediating responses to gambling-like stimuli. Notably, these brain regions are also critical components of the neural circuitry of drug reward and substance addiction. Activation of these circuits has been consistently linked with a subjective state described as 'positive arousal' or 'excitement,' which contrasts with 'negative arousal' or 'fear' [34, 35]. An fMRI-monetary guessing game has been used to compare brain activity in PG subjects and controls. The findings reveal relatively lower levels of prefrontal response and less pleasure in PG *vs* controls, with the decrement increasing with the severity of PG symptoms [36]. These findings are suggestive of tolerance to a standard 'dose' of gambling (i.e., an episode of wagering of a given duration and intensity) in PG, similar to that which is observed in response to a standard dose of a drug in substance dependent individuals.

Activation of the striatum and prefrontal cortex can be induced by administration of natural reinforcers, like food

and water as well as by drugs, as has been found for gambling [37, 38]. Similarly, tolerance to the pleasurable effects of most addictive drugs is common following chronic exposure, despite the wide variability in their subjective and neurochemical properties [39-42]. Thus, the neural effects seen in the fMRI monetary-guessing game procedure primarily serve to confirm that gambling can recruit the same processes as other drug and non-drug reinforcers. However, when taken together with the self-report data from the fMRI procedure, a picture begins to emerge of a more specific profile of bio-behavioral effects for gambling.

PHENOMENOLOGY OF PG

Excitement is one way to describe the positive arousal evoked by the expectation of reward, and to distinguish it from negative arousal or fear [34]. A more nuanced description of the phenomenology of gambling can be obtained from subjective descriptions of PG subjects themselves. Using this self-report strategy with subjects addicted to a variety of different drugs of abuse, Haertzen compiled the Addiction Research Center Inventory [ARCI; 43] to evaluate and discriminate psychoactive agents on a number of core dimensions. The ARCI includes sub-scales comprised of statements describing the subjective effects of Amphetamine, Morphine, LSD and other drugs that typify their respective drug classes.

In an early effort to extend this approach to PG, Haertzen and colleagues asked PG subjects to describe the effects of an imagined bout of gambling using the ARCI [44]. These investigators found that the profile of items endorsed was *strikingly similar* to those endorsed by psychostimulant abusers in response to amphetamine. Thus, a scale that reliably characterizes the effects of a psychostimulant and distinguishes these effects from other drugs also appears to capture the subjective effects of gambling in PG subjects.

These findings are provocative but limited as they were based on imagined rather than actual gambling. If the experience of gambling resembles a psychostimulant drug effect, then PG subjects should find a psychostimulant drug more enjoyable than subjects who prefer other mood-altering drugs (e.g., problem drinkers; opiate abusers) or control subjects, who have no strong affinity for drug reinforcers. Furthermore, the underlying neurochemical processes that mediate this subjective commonality can be investigated using a cross-priming strategy. Priming refers to the increase in motivation for a reinforcer that results from non-contingent exposure to a dose of that reinforcer or, in the case of cross-priming, a related reinforcer. Thus, amphetamine cross-primes motivation for cocaine in cocaine-experienced animals [45], but this effect is not elicited by drugs from other classes (e.g., THC) or even by drugs from the same class whose subjective reinforcing effects are mediated by different neurochemicals than cocaine (e.g., nicotine). Based on this evidence, the psychostimulant-mimetic model predicts that amphetamine should cross-prime motivation to gamble in PG subjects.

ACUTE EFFECTS OF A PSYCHOSTIMULANT IN PG SUBJECTS

Zack and Poulos [46] adopted this cross-priming strategy to investigate the commonalities between psychostimulant and gambling reinforcement mechanisms. The study examined the effects of a moderate dose (30-mg) of the prototypic psychostimulant, d-amphetamine on measures of intrinsic and gambling-related reinforcement. The results revealed that self-reported desire to take the drug again was more pronounced in PG subjects than in problem drinkers or controls. Thus, relative to other subjects, those for whom gambling is a preferred activity also preferred amphetamine. Critically, amphetamine was found to prime desire to gamble in PG subjects whereas the drug did not prime desire for alcohol in problem drinkers or controls without PG. This selective cross-priming effect provides evidence that gambling and amphetamine share important neurochemical commonalities that are not a generic feature of addiction.

In addition to the self-reported effects of amphetamine, Zack and Poulos [46] also assessed the ability of amphetamine to facilitate or improve response time to Gambling words (e.g., Wager) on a rapid reading task. This procedure was modified from a widely utilized cognitive science paradigm in which exposure to a word 'prime' has been found to facilitate reading responses to categorically (e.g., Table-Chair) or conceptually associated (e.g., Doctor-Hospital) word targets. Such semantic priming effects are considered to reflect activation of a network of associations in memory. In the amphetamine study, a drug rather than a word served as the priming stimulus on the assumption that the subjective state evoked by the drug would activate the gambling memory network. The findings supported this hypothesis: Amphetamine selectively facilitated reading of Gambling words in PG subjects. The drug also selectively and profoundly inhibited reading of motivationally irrelevant Neutral words (e.g., Window) in these subjects. Notably, amphetamine did not facilitate reading of Alcohol words in either PG or non-PG subjects. Instead, in problem drinkers and controls amphetamine led to a uniform facilitation of response to all classes of words including Neutral ones. This undifferentiated response is consistent with the expected generic improvement in mental fluency under a psychostimulant drug.

The reading task results are important for two reasons: First, they provide an objective index of the 'incentive salience' (i.e., automatic allocation of cognitive resources) of gambling-related stimuli under the influence of the drug prime. Incentive salience is considered to be a critical feature of the addicted state [47]. Second, priming effects like these occur involuntarily and are therefore relatively insensitive to experimental demand. As such, they help to corroborate the self-report data. Together, the selective profile of priming effects for amphetamine in this study confirmed and extended the initial findings with the ARCI [44]. Given the literature on cross-priming, the amphetamine results further suggested that gambling and psychostimulants might be mediated by common neurochemical substrates in PG subjects [45, 48].

Psychomotor activation is the defining feature of drugs like amphetamine. Therefore, the finding that amphetamine greatly slowed reading responses to Neutral words in PG subjects was remarkable. Such an effect would be expected if the prime preferentially activated a network of associations that were incompatible with Neutral words [49]. In other words, under amphetamine, PG subjects responded as if thoughts about neutral stimuli, like Windows and Doors,

were the "furthest thing from their mind." Seminal research on priming by Konorski [50] indicates that priming of one motivational system involves the collateral suppression of alternative motivations. This provides some insight into the pathological nature of incentive motivation in PG [51]. That is, the failure to select alternative, more adaptive courses of action (e.g., cut your losses and go home) may in part reflect inhibition of these alternative networks when the gambling network is activated. In this sense, the inhibition of reading of Neutral words recapitulates the cognitive rigidity or compulsive persistence in gambling by PG subjects, especially when exposed to a priming 'dose' of gambling (i.e., a brief gambling episode).

DOPAMINE AND THE ACUTE REINFORCING-MOTIVATIONAL EFFECTS OF GAMBLING

Robust, sustained activation of mesolimbic dopamine is the primary effect of d-amphetamine. However, amphetamine also activates neurochemicals apart from DA, including norepinephrine, serotonin, and endogenous opioids. Thus, the amphetamine findings in themselves do not provide conclusive evidence that DA activation mediates gambling reinforcement in PG subjects.

Before proceeding to the evidence that bears on this issue, some clarification around common and specific roles of DA is warranted. It is well-established that drugs of abuse and natural reinforcers share the capacity to activate limbic DA. However, limbic DA does not universally mediate or account for the acute subjective effects of these stimuli. Thus, food remains palatable when DA transmission is blocked pharmacologically [52, 53]. Similarly, DA antagonists or selective DA lesions do not reliably disturb the ability of animals to discriminate drugs based on their interoceptive properties including alcohol, opiates and nicotine [54-57]. This is not the case for psychostimulants like cocaine and amphetamine, where DA antagonists reliably impede discrimination of the drug by animals [58-61].

In a recent review article, Pierce and Kumaresan [62] examined the evidence regarding the role of the mesolimbic DA system as the final pathway for the reinforcing effects of five classes of abused drugs: psychostimulants, opiates, alcohol, cannabinoids, and nicotine. The authors evaluated behavioral pharmacological experiments, with particular emphasis on animal drug self-administration studies. For the four classes of drugs other than psychostimulants, the authors concluded that, although increasing mesolimbic transmission plays an important role, "there are also dopamine-independent processes that contribute significantly to the reinforcing effects of these compounds" (p. 1898). In contrast, "Behavioral pharmacological experiments indicate that increased dopamine transmission is clearly both necessary and sufficient to promote psychostimulant reinforcement" (p. 1898). The psychostimulant-mimetic model also implies a predominant role of DA in gambling reinforcement.

Unpredictable Rewards and DA Release In a pivotal study, Fiorillo *et al*. [13] explored the role of uncertainty in cue-induced DA release. These investigators made recordings from electrodes directly implanted in the midbrain DA neurons of monkeys. The monkeys were trained to associate distinctive conditioned cues with delivery of a sucrose solution under varying reinforcement schedules: 0%, 25%, 50%, 75%, and 100%. On test trials they found, in line with previous research, that the discrepancy between predicted and actual reward related monotonically to the magnitude of phasic activation of DA neurons upon delivery of the sucrose. When reward was completely unexpected (0%) phasic activation was maximal; when reward was completely expected (100%), phasic activation was minimal. The critical finding was, "a previously unobserved response [to the discriminative cue, which] co-varied with uncertainty and consisted of a gradual increase in activity until the potential time of reward" (p. 1898). That is, the magnitude of signal-induced DA activation co-varied with the uncertainty of reward delivery, such that activation was greatest following a signal that predicted reward on 50% of occasions – i.e., the signal associated with maximal uncertainty. The investigators pointed out that their findings could account for the reinforcing effects of gambling in humans, noting that "the sustained, uncertainty-induced increase in dopamine could act to reinforce risk-taking behavior and its consequent reward information, whereas the phasic response after prediction error could mediate the more dominant reinforcement of reward itself" (p. 1901).

The findings of Fiorillo *et al*. [24] imply that, with respect to gambling, the spinning of the slot machine reels or the actual rolling of the dice, quite apart from their outcomes, activates the limbic DA system in a profound manner. Interestingly, in a recent study ([63], see below) using a standard commercial slot machine in our laboratory, we found that, over thousands of spins, the percentage of trials that yielded a non-zero outcome - i.e., some rather than no winnings (credits) - was 45.8%, strikingly similar to the maximal uncertainty condition in the Fiorillo *et al*. study [24]. Likewise, in roulette, the probability of winning on black versus red is just under 50%; only the numerals 0 and 00 are designated as green. Similarly, near-maximally uncertain outcomes characterize many bets that can be placed in the dice game of craps. These payoff schedules would be expected to elicit maximal DA release immediately following the *placing* of each and every bet, thereby reinforcing the act of gambling itself. This seems to account for an apparent paradox in gambling, namely, that even losing can reinforce and promote further gambling behavior.

There is also some evidence suggesting that PG subjects may be hyper-sensitive to the DA response to unpredictable rewards. Meyer *et al*. [64] found that PG subjects displayed significantly higher heart rate response and greater increases in plasma DA during an actual game of blackjack than did non-PG controls. Although these effects cannot be attributed exclusively to central DA transmission, other evidence suggests that sympatho-adrenal response to a psychostimulant is tightly linked with striatal DA release [65]. These results imply that, relative to controls, PG subjects may experience heightened positive arousal from actual gambling, and that this difference may be mediated by limbic DA. However, because subjects in the blackjack study could raise the stakes of the game it is possible that those with PG also self-administered a greater functional 'dose' of gambling than controls (i.e., amplified the consequences [win/loss] associated with the conditioned signal). Nevertheless, the findings collectively implicate sustained physiological arousal as an important feature of gambling reinforcement for PG subjects.

The results of Fiorillo *et al.* [24] imply that exposure to unpredictable rewards on multiple occasions would result in repeated episodes of robust DA release, mimicking some of the effects of chronic amphetamine. By extension, animals chronically exposed to unpredictable reward should display heightened locomotor activation in response to an acute challenge dose of amphetamine much like animals chronically exposed to amphetamine (also see section on Sensitization below).

Preliminary evidence supports this possibility. Scott-Railton and Vezina [66] exposed healthy male rats to escalating fixed ratio (FR) or variable ratio (VR) schedules of saccharin reinforcement over a ~8 week training period. Schedules were designed such that total saccharin exposure did not differ; only the predictability of reward delivery varied between the groups. Two weeks after the final training session, a low dose (0.5 mg/kg) amphetamine challenge led to significant increases in locomotion in VR but not FR rats. In addition, a sub-chronic regimen of amphetamine (5 x 1 mg/kg systemic injections every third day) led to significantly more locomotor activity and sensitization in VR than FR rats. The authors concluded that "the *experience* (sic) of intermittency mimicked drug-like neuronal activity during training, ultimately resulting in drug-like neuroplasticity. That intermittent reinforcement can induce such plasticity may shed light on the neuroplastic changes posited to underlie behavioral addictions such as gambling" (p.1). These findings were reported in a poster format and currently await peer-reviewed publication. Nevertheless, they are consistent with the overarching hypothesis of this article that repeated engagement in gambling can induce a pathological neurobehavioral syndrome akin to that produced by chronic exposure to a psychostimulant drug.

DA Activation and Its Possible Relationship to Pleasure

There has been much controversy surrounding the role of DA in motivation and the subjective-experiential aspects of addictive behavior. The terms *pleasure*, *reward*, *reinforcement*, '*high*,' and *liking* have all been used to characterize different components of these states. In animal research, reward has been operationalized by the conditioned place preference paradigm: When an animal returns to a location previously associated with exposure to a stimulus (e.g., drug), this is taken as evidence that the drug was 'rewarding'. Reinforcement has been operationalized by the self-administration paradigm and particularly, by progressive-ratio and other labor-intensive response schedules, whereby the willingness to work to receive another dose of a stimulus (drug) is considered to reflect the 'reinforcing' properties of that stimulus. The terms, 'high' and 'liking' have been used in human studies to index the subjective euphoric or hedonic effects of the drug by means of self-report. These terms approximate what might generally be referred to as pleasure.

KC Berridge [67] has argued convincingly against the hypothesis that DA transmission mediates a subjective state of pleasure or 'liking' occasioned by food, for example. Instead, he shows that DA is much more strongly involved in the appetitive or seeking aspects of motivated behavior – the 'wanting' of a stimulus. By 'wanting', Berridge means the ability of a stimulus to be recognized as a *signal* for reward and to elicit *approach* behavior. Robbins and Everitt [68] note that behavioral activation is another critical result of DA transmission that is clearly necessary for approach. DA transmission may also mediate avoidance such as locomotion away from an aversive stimulus (e.g., tail-pinch stress in rodents).

In gambling, the distinction between wanting and liking becomes blurred because the appetitive/seeking component of the activity (wanting) is inseparable from the game itself. As noted earlier, the placing of the bet, execution of the play, and anticipation of its outcome may induce a subjective state (suspense/thrill) quite apart from the outcome itself (win/lose). Thus, in gambling, it is possible to subjectively *like* the state of *wanting*. This is not unique to gambling; it is seen in seduction or striptease, as well as in activities like hunting. In each case, the subject enjoys the state of pursuit *per se*. Indeed, Panksepp [69] characterized DA as the SEEKING system, reflecting its functional role in the mammalian brain (e.g., stalking prey, foraging, pursuing a sexual partner). One likely subjective correlate of such pursuit is arousal. Arousal is one of four poles in the "circumplex" model of emotion [70], which posits two independent dimensions: valence (positive, negative) and activity (arousal, sedation). States considered as most pleasurable (e.g., ecstasy) combine very strong positive valence with very strong arousal. In the context of gambling, such arousal may be subjectively pleasurable/ enjoyable when the prospect of reward exists (i.e., until the last bet). However, when paired with persistent losses (negative valence) such arousal may be aversive – something to be squelched. Because each new bet reinstates the opportunity for reward, continued gambling could be a very effective (though maladaptive) way to squelch aversive arousal.

There is ample evidence that DA critically mediates the arousal induced by psychostimulant drugs [71]. The model outlined here implies that DA may play a similar role in the state of arousal that occurs in gambling. It should be noted that states of arousal may be perceived as highly aversive to some, but highly pleasurable to others. For example, jumping from a plane with a parachute on one's back may be terrifying or exhilarating, depending on the individual. High arousal situations like these juxtapose the potential for extreme negative outcomes with the potential for escape. Gambling with high stakes may approximate this effect: Although the hoped-for outcome is positive, the actual outcome is uncertain. This uncertainty will further activate DA [24]. Whether the activity is gambling or skydiving, it would be very difficult to describe the state as inherently or uniformly pleasurable. However, to the extent that such activities are endorsed as 'enjoyable' by a subject, we may conclude that they involve a form of pleasure. Moreover, if selective DA manipulations induce parallel alterations in self-reported enjoyment and excitement, this is *prima facie* evidence that DA contributes to these subjectively pleasurable and arousing states, at least for some individuals.

Drug challenge studies in PG subjects are rare. However, in one experiment, Pallanti *et al.* [72] found that the 5-HT (5-hydroxytryptamine; serotonin)-2C receptor agonist, m-CPP led to stronger neuroendocrine responses in PG than in control subjects, that the strength of this effect correlated with PG severity, and that the drug induced a significantly greater subjective 'high' in PG subjects than controls. Based on their findings, the authors concluded that, "the 5-HT dys-

function related to the experience of 'high' might represent the pathway that leads to dyscontrolled behavior in pathological gamblers" (p. 956). Buydens-Branchey *et al*. [73] found a similar pattern in cocaine addicts, who reported significantly more "activation-euphoria" and "high" responses following m-CPP than controls. The mechanism of this effect is elucidated by Bagdy *et al*. [74] who found that, "intravenous administration of the serotonin agonist, m-chlorophenylpiperazine (m-CPP), produced large, dose-dependent increases in epinephrine, norepinephrine and dopamine in plasma in normal, conscious rats" (p. 975). Eriksson *et al*. [75] subsequently found that systemic m-CPP injections in rats "induce an increase in extracellular concentrations of dopamine in the nucleus accumbens and the striatum" (p. 287). These findings suggest that elevation of limbic DA may contribute to the subjective 'high' produced by m-CPP in PG subjects and cocaine abusers.

Volkow *et al*. [76] have shown that the degree of striatal DA release from a standard dose of methylphenidate directly predicted the self-reported 'high' in healthy volunteers. Because methylphenidate is a DA reuptake inhibitor, these effects would involve a compensatory response by presynaptic DA neurons in the absence of an inhibitory feedback signal (mediated by the reuptake transporter) from synaptic DA. A subsequent study with the combined DA releaser and reuptake inhibitor, d-amphetamine found a similar correlation between degree of DA release and reported 'high' in healthy volunteers [77]. The parallel pattern of effects across the two studies is important as it suggests that the manner in which DA release comes about does not influence the link between release and subjective reward. It is also important because methylphenidate and d-amphetamine differ with respect to other pharmacological factors like kinetics (i.e., rate of dissociation from the reuptake transporter) and their effects on other neurochemicals (e.g., serotonin). Together, the PET findings confirm that sustained robust activation of DA neurons coincides with subjective pleasure in humans, which mirrors the self-reported 'positive arousal' evoked by anticipation of money in the fMRI studies.

It should be noted that the evidence linking DA release with the 'high' induced by psychostimulants or arousing effects of monetary reward is correlational. As such, increased subjective effects may be the cause rather than the effect of DA release, or may be a separate manifestation of a third process that directly mediates pleasure (e.g., opioid receptor activation). Nevertheless, the ability of selective DA manipulations to alter the subjective pleasurable response to psychostimulant drugs as indexed by self-report in humans [78, 79] and by specific types of vocalizations in animals [80] indicates that the role of DA in these subjective effects is not epiphenomenal.

Along with the caveats concerning DA's causal role in subjective positive states, it must be acknowledged that DA is only one of a network of neurochemicals that have been linked with these states. Considerable evidence indicates important roles for endogenous opioids, serotonin, norepinephrine, GABA, and glutamate in the subjective positive effects of drugs in general and psychostimulants in particular [81]. By extension, these transmitters (all of which converge on DA) very likely contribute to the subjective effects of gambling as well.

DYNAMIC ASPECTS OF DA TRANSMISSION AND GAMBLING REINFORCEMENT

Grace [82] drew attention to the dynamic aspects of DA transmission for understanding the subjective and behavioral effects of psychostimulants. In particular, he distinguished between tonic DA transmission, low level baseline activity, and phasic DA transmission, which is more intense and results from exposure to a stimulus. Chronic exposure to drugs of abuse would be expected to elevate tonic DA transmission through sensitization. However, "the increase in tonic dopamine levels that occurs with repeated drug administration would serve to oppose phasic dopamine release *via* stimulation of dopamine terminal autoreceptors, causing the subject to increase drug administration to restore the phasic response" (p. S119). Hence the vicious cycle of escalating drug use that typifies substance dependence.

Redish [83] incorporated conditioning principles into this model. DA has been widely shown to mediate the signaling properties of conditioned stimuli [CS; 23]. However, drugs of abuse, and particularly psychostimulants, can cause unconditional DA release. As a result, drugs differ from rewarding non-drug unconditioned stimuli (US; e.g., food), whose capacity to evoke (phasic) DA release transfers to the CS as learning progresses, to the point where the DA-eliciting effects of the US eventually become redundant. Based on this, Redish argued that the incentive value of drugs of abuse, and psychostimulants in particular, would continue to grow with each exposure. In this way, the drug effect itself would never become redundant to the CS that predicted it. In this respect, addictive drugs like cocaine are qualitatively different than non-drug reinforcers. Such a process could account for the positive-feedback or intensifying effects of each drug exposure on motivation for future drug use.

Redish's model implies that a US capable of continuing to induce DA release despite chronic learning (*via* repeated exposure) would be expected to promote a similar positive feedback cycle. Gambling, by definition, entails imperfect prediction of reward in the presence of physical (e.g., machines, cards) or behavioral (i.e., the act of betting) CS. Thus, Redish's formulation implies that gambling should escalate perpetually, much like psychostimulant addiction, and activation of DA should directly mediate this effect.

Redish *et al.* [84] went on to describe another aspect of DA function that may contribute to PG. Specifically, they note that the outcome of the CS (i.e., delivery or non-delivery of reward) has critical effects on DA transmission, to confirm or refute the expectancy evoked by the CS. As noted by Shultz [23], "dopamine neurons are activated by rewarding events that are better than predicted, remain uninfluenced by events that are as good as predicted, and are depressed by [i.e., cease firing] events that are worse than predicted"(p. 1). This process applies to all reinforcers and explains the acquisition of rewarded responses and extinction of unrewarded ones. This is congruent with the Rescorla-Wagner model of learning [85]. In the case of gambling, Redish *et al.* emphasize how a 'big win' can disrupt this normal learning and extinction process. Big wins establish a pathological expectancy that renders the gambler relatively immune to normal extinction. As a result, pauses in DA following non-reinforcement fail to extinguish wagering as they

would extinguish most learned responses. Unlike most instrumentally learned responses, the prospect of a big win - capable of negating prior losses and thereby validating the gambler's persistence - actually exists on every gambling trial. As such, the memory of the big win (expectancy) persists and can continue to drive betting behavior.

Thus, for Redish, the persistence of cocaine-seeking in cocaine abusers derives from the capacity of the drug to unconditionally activate DA and perpetually reinforce learned behavior, so that the strength of the CS-US association never reaches an asymptote. In gambling, Redish *et al.* posit, there is also a distortion in the role of DA-based learning processes: The persistence of betting behavior in PG subjects derives from the ability of a big win to establish a pathological expectancy, whereby pauses in DA transmission due to losses or small wins lose their capacity to extinguish wagering since the expectancy can be reinstated (i.e., primed) by each new wager. Thus, in both psychostimulant addiction and PG, it is DA that mediates the persistent supra-normal pattern of responding.

Dopamine Receptor Sub-types and Gambling Reinforcement Psychostimulant-induced DA release could activate a range of dopamine receptors. Therefore, the specific contribution of DA receptor sub-types to amphetamine-induced priming of gambling motivation cannot be ascertained from our original study [46]. This issue is important for understanding gambling pathology and developing effective interventions for PG. Genetic evidence had linked deficits in D2 receptor availability or sensitivity to increased risk for addictive-compulsive disorders, including PG [86, 87]. Accordingly, we examined the effects of the preferential dopamine D2 receptor antagonist, haloperidol on the subjective rewarding and priming effects of actual slot machine gambling in PG subjects and controls [63]. An oral dose of 3-mg was chosen based on previous evidence that it was well-tolerated and could be expected to occupy 65-70% of D2 receptors in physically healthy subjects [88-90].

The findings for PG subjects in this study were clear and convergent. Pre-treatment with haloperidol consistently augmented the subjective pleasurable effects of the slot machine (e.g., Enjoyment, Excitement, Involvement), post-game Desire to Gamble, and the salience of Gambling words on the reading task, as well as the gambling-induced increase in systolic blood pressure. In contrast, for controls, who were essentially non-gamblers, haloperidol had no significant effects apart from an enhanced post-game increase in blood pressure. It is conceivable that the dissociation between the physiological activating and reinforcing effects of the game in the two groups reflected differences in the preferred level of physiological arousal in PG subjects versus non-gambler controls.

The finding that a D2 antagonist increased gambling reinforcement is consonant with findings on the inverse relationship between D2 receptor availability and subjective rewarding effects of the psychostimulant methylphenidate found in PET studies [91, 92]. The haloperidol findings are also consistent with evidence on the effects of low-dose pimozide (1-mg, 2-mg), a selective D2 antagonist, on d-amphetamine (10-mg, 20-mg) reinforcement. Brauer and de Wit [78] found that healthy subjects pre-treated with pimozide (1-mg, 2-mg) more readily discriminated amphetamine from placebo and reported greater 'liking' and stimulant effects of the drug. The findings with low-dose pimozide contrast with other studies using higher doses of D2 antagonists that found no effects on amphetamine reinforcement in healthy subjects [93, 94].

The lack of increase in gambling reinforcement in controls under haloperidol may reflect differences in dose-response sensitivity. For example, higher doses of pimozide (4-mg, 8-mg) failed to alter the subjective reinforcing effects of d-amphetamine in healthy volunteers [94]. Similarly, 3-mg haloperidol, the dose used in our gambling study, failed to alter the subjective reinforcing effects of methamphetamine in healthy volunteers [90]. The contribution of receptor sensitivity to group differences in the antagonist effect could be resolved by directly comparing the effects of 3-mg haloperidol on gambling and amphetamine reinforcement in PG subjects and controls. If receptor sensitivity differences accounted for the differential effects of low dose pimozide *vs* haloperidol, 3-mg haloperidol would be expected to have no effect on either gambling or amphetamine reinforcement in controls, but should enhance both gambling and amphetamine reinforcement in PG subjects. A parallel assessment study of this kind would provide strong evidence for the psychostimulant-mimetic model and role of DA D2 receptors in PG.

The enhancing effects of D2 antagonists on gambling and amphetamine reinforcement may be attributable to multiple factors. One highly plausible explanation is that partial D2 blockade reduced the feedback inhibition that D2 receptors normally exert on striatal DA release. Such disinhibition would have led to increased DA release and preferential activation of D1 receptors that remained unaffected by the selective D2 ligand [95]. Indeed, pre-treatment with haloperidol has been shown to increase basal DA release in the cortex and striatum of rats and also to augment the DA releasing effects of amphetamine in these brain regions [96]. Together, the evidence suggests that the increase in gambling reinforcement seen in PG subjects under haloperidol reflected heightened DA-releasing effects of the slot machine and preferential activation of D1 receptors.

Self and colleagues have shown that, in animals with a history of cocaine self-administration, cocaine's rewarding and incentive motivational properties are mediated respectively by activation of D1 and D2 receptors [97]. Based on this, Self [98] argued that neuroadaptations in DA receptor signalling in the accumbens produced "tolerance to the rewarding effects of D1-receptor stimulation, leading to increased drug intake during self-administration" (p. 379). In human cocaine abusers, selective blockade of D1 receptors dose-dependently reduces the self-reported euphoric effects of cocaine [79]. Taken together, these findings suggest that psychostimulant-induced activation of D1 receptors directly contributes to the perceived pleasurable effects of these drugs. Interestingly, blockade of D1 receptors does not alter the subjective pleasurable effects of nicotine [99]. This is consistent with animal research showing that, in contrast to amphetamine, nicotine fails to cross-prime cocaine self-administration in animals [45], supporting the specific role of the DA-D1 receptor in the interoceptive effects of psychostimulants.

The possibility that increased activation of D1 receptors contributed to the findings in our haloperidol study received indirect support from two clinical trials of the atypical antipsychotic medication, olanzapine in PG subjects. In a 12-week trial, McElroy *et al.* [100] found that a mean dose of 8.9 mg/day of olanzapine led to a reduction in overall illness severity and gambling episodes per week in PG subjects. In a seven-week trial with PG subjects whose primary activity was video-poker, Fong *et al.* [101] found that a mean dose of 7.9 mg/day olanzapine led to a marginally significant ($p < .08$) reduction in craving to gamble relative to pre-treatment. In both of these studies the drug effect did not differ from placebo. Nevertheless, the direction of the effects -- decreased motivation to gamble under olanzapine -- differed from the increased motivation to gamble and enjoyment of the game found in PG subjects under haloperidol. The directionally opposite effects of olanzapine and haloperidol are consistent with the possibility that a selective increase in activation of D1 receptors accounted for the enhanced reinforcing effects of gambling under haloperidol. This can be inferred from the binding profile of the two medications: Whereas both drugs are strong D2 antagonists, olanzapine is also a potent D1 antagonist: Its relative affinity for D2 *vs* D1 receptors is ~2:1 [102], whereas the relative affinity (D2:D1) for haloperidol is ~226:1 [103]. Thus, gambling-induced DA release, and the potentiation of this effect by D2 blockade, would have permitted robust activation of D1 receptors under haloperidol but not olanzapine. Although the evidence for this conclusion is indirect, it suggests that investigation of the effects of D1 receptor probes on gambling reinforcement is in order.

Combined Effects of Amphetamine and Gambling-Like Activity Another remaining issue is the role of DA activation on responses to gambling-like activity in healthy non-PG subjects. To investigate this issue, Knutson and colleagues [34] administered a weight-adjusted dose of d-amphetamine (~20 mg in an adult) to healthy non-gamblers who then underwent the fMRI-monetary guessing game procedure. The investigators found no change in the phasic DA-release in medial prefrontal cortex occasioned by receipt of money under the drug. In contrast, they observed an increase in the duration of DA activation during the anticipatory portions of the game. Subjectively, this translated into a decrease in positive arousal during the anticipation of large wins together with a conversion of negative arousal (i.e., fear) to positive arousal (excitement) in anticipation of large losses. In this way, the authors note, "AMPH [amphetamine] treatment appeared to 'equalize' activation during anticipation of large positive and negative incentives" (p. 263-264). Put simply, the prospect of reward became less exciting and the prospect of loss became less aversive in these non-PG subjects. How amphetamine might affect gambling reinforcement in PG subjects remains an open question.

Combined Effects of Gambling and the Atypical Stimulant, Modafinil Some indication as to the effects of a stimulant drug on gambling reinforcement in PG subjects may be gleaned from research we recently undertook with the atypical stimulant, modafinil (200-mg) in the slot machine protocol [104]. As in the previous haloperidol study, we assessed the drug effect on responses to actual slot machine gambling in PG subjects. Modafinil is used for the treatment of narcolepsy but has also proven effective in the treatment of ADHD and cocaine addiction [105,106]. In experiments, acute doses of modafinil improve impulse control and reduce risk-taking in ADHD subjects [107], and also reduce the rewarding effects of injected or smoked cocaine in cocaine abusers [108, 109]. These findings indicate a direct therapeutic effect of modafinil on core aspects of impulsivity and psychostimulant reinforcement. Notably, studies with cocaine abusers and controls have found no evidence of abuse liability for modafinil. Although well-tolerated it does not appear to produce the characteristic 'high' of classic stimulants like amphetamine or cocaine. This may be due to its complex pharmacology, which includes activation of glutamate, norepinephrine, serotonin, histamine, and orexin in addition to DA [110]. Like amphetamine, modafinil causes striatal DA release in healthy subjects [111]. Recent electrophysiological evidence further suggests that modafinil's primary mechanism of action may be as an agonist at the DA D2 receptor [112]. However, because each of the other transmitters engaged by modafinil also modulates DA, its net effect may depend on the balance of facilitatory and inhibitory effects on DA exerted by these other systems.

The modafinil-gambling study employed two additional tasks in the protocol: the Stop Signal Task (SST) [113], which measures the ability to withhold a pre-potent psychomotor response to a visual cue when faced with an unexpected stop-signal tone; and the Iowa Gambling Task (IGT) [114], which measures the tendency to choose high- versus low-risk options based on the win/loss profile of those options and the outcomes of early trials (i.e., which response options yield high *vs* low monetary payoffs and losses). The clinical evidence on modafinil in ADHD suggested that impulsivity might be an important moderator of the drug's effects in PG. To assess the influence of this factor in our study, subjects were recruited to represent high *vs* low impulsivity with respect to the normative mean on The Eysenck Impulsiveness Scale [115] found in a prior sizeable sample of PG subjects [116]. Based on the literature, we predicted that modafinil (200-mg) would reduce the reinforcing effects of the slot machine, improve inhibitory control on the SST, and promote low-risk decisions on the IGT, and that these effects would be greater in high versus low impulsivity subjects.

The findings were internally consistent across multiple indices but also somewhat unexpected. In high impulsivity subjects, modafinil reduced post-game desire to gamble and salience of Gambling words while increasing inhibitory control on the SST and promoting low-risk decisions on the IGT. In low impulsivity subjects, modafinil induced a generally opposite profile of effects, increasing desire to gamble before the game and the post-game salience of Gambling words; while impairing inhibitory control and promoting high-risk decisions. Although only evident at trend levels of statistical significance, the same bi-directional pattern was seen for the subjective pleasurable effects of the game. That is, the high impulsivity subjects enjoyed the game less whereas the low impulsivity subjects enjoyed it more. Modafinil also differentially affected sympatho-adrenal response to the game, occasioning a large post-game spike in systolic blood pressure in high impulsivity subjects as opposed to an undifferentiated elevation in blood pressure before and after the game in low impulsivity subjects. The only index that yielded consistent effects of modafinil across

groups was bet size on the slot machine itself, which declined uniformly in both groups under the drug.

The bi-directional effect of modafinil on inhibitory function in PG subjects parallels the pattern seen in response to direct D2 agonists on various measures of cognitive function in non-clinical populations. For example, cabergoline improves inhibitory control on a probabilistic Go/No-Go task in volunteers with low working memory (a reliable correlate of high impulsivity [117-119]) but impairs inhibitory control in those with high working memory [120]. Similarly, bromocriptine augments frontal control of striatal activity in high impulsivity volunteers but reduces the frontal cortex's regulatory influence on limbic regions in low impulsivity subjects [121]. Thus, direct D2 agonists have baseline-dependent bi-directional effects on cognitive mediators of impulse control in high *vs* low impulsivity individuals.

Modafinil is an indirect DA agonist, and therefore activates D1 as well as D2 receptors. Based on a comprehensive review of the electrophysiological and behavioral literature, Seamans and Yang [122] noted that, "D1 receptor activation can have exactly opposing functional effects depending on the level of stimulation. There is an inverted-'U' (bell-shaped) function relating cognitive performance to D1 stimulation levels" (p. 7). Given the hypothesized linkage between D1 receptor activation and subjective-motivational aspects of gambling in PG subjects alluded to earlier, and the established correspondence between low D1 function and impulsivity, it is conceivable that modafinil normalized D1 signaling in high impulsive subjects (with a low basal D1 signal), but led to supra-normal D1 signaling in low impulsive subjects (with a high basal D1 signal). Together, the evidence suggests that D1 and D2 receptors may both contribute to the effects of modafinil in PG subjects and underscores the importance of investigating D1 as well as D2 related processes in PG. Furthermore, regardless of the mechanism, the modafinil findings suggest that impulsivity is an important factor to consider for matching purposes, when developing medications for treatment of PG.

It should be noted that impulsivity is not simply one of many possible correlates of PG; it is also considered to be the defining feature of a particular sub-type of PG subject, as reflected in two empirically based conceptual models [18, 21]. The prominent role of impulsivity in PG typology is important for understanding the etiology of the disorder, which could inform prevention efforts; and also for pharmacological patient-treatment matching, which could increase efficacy and reduce relapse. Although the Eysenck Impulsiveness scale appears to provide a reasonable index of impulsivity, a growing literature supports the utility of cognitive-behavioral tasks to operationalize this construct in PG subjects [123-125]. Combined use of these paradigms with pharmacological probes should help to map specific neurocognitive dimensions onto specific neurochemical substrates in PG subjects.

In the modafinil study, high impulsivity subjects also evidenced higher scores than low impulsivity subjects on the DSM-based symptom questionnaire for PG [126]. Although this pattern is consistent with the clinical literature on impulsivity and PG severity [124,127] it precludes categorical conclusions as to whether impulsivity was the primary moderator of response to modafinil in this sample. Given that increased PG severity would be expected to involve greater chronic exposure to gambling, the high severity/high impulsivity PG subjects in this sample may also have undergone more sensitization of DA pathways. The relative contribution of impulsivity and PG severity to the effects of modafinil and the possible role of sensitization in these effects is another issue for future investigation.

Direct DA Agonists and Induction of PG in Parkinson's Patients The modafinil findings for low impulsivity subjects may provide an experimental analogue to the clinical side-effects of direct D2/D3 agonists increasingly seen in patients with Parkinson's disease. Once considered rare, agonist-induced PG and other addictive-compulsive disorders are now recognized as a major side effect of D2/D3 agonist treatment in Parkinson's patients. Recent estimates suggest that the prevalence of PG in agonist-treated Parkinson's patients is 7-8%, or more than twice the general population rate [128,129]. The temporal profile of these effects strongly indicates a causal role for the agonists: PG typically emerges soon after the introduction of the agonist and remits soon after it is withdrawn. Augmentation of basal DA levels does not appear to be sufficient for this effect, as PG rates are not elevated in patients only receiving the DA precursor, L-DOPA [130]. Men are much more likely than women to develop agonist-induced PG. This is consistent with the stronger interoceptive and mood effects of psychostimulants seen in men [131], and with the strong positive correlation between stimulant-induced DA release and sensation seeking seen in men but not women [132]. Given that most anti-Parkinson medications engage both D2 and D3 receptors the relative contribution of each of these receptor subtypes cannot be inferred from the clinical data.

Pre-morbid factors also appear to confer risk for developing PG under DA agonist medications. Generally speaking, younger males and those with a mood disorder, alcohol use disorder, or OCD prior to the onset of Parkinson's are more likely to develop agonist-induced PG [133]. In addition, DA agonists often promote excessive-compulsive behaviors apart from PG, including compulsive sexual behavior and in some cases, alcohol abuse [134,135]. Although psychostimulant abuse secondary to DA agonist medication has not been reported in Parkinson's patients, this may well reflect social factors and availability. Whereas alcohol is legal and readily accessed, cocaine and amphetamines are not, and would therefore be very difficult for physically challenged Parkinson's patients to procure. By contrast, DA agonist medication itself is both legal and available to Parkinson's patients. This is noteworthy because, as Voon and Fox [136] point out, Parkinson's patients treated with DA agonists not only show an increased risk of developing PG; they also show a tendency to develop 'compulsive medication use', a syndrome defined in DSM-IV by "a need for increasing dopamine replacement therapy in excess of that required for motor signs and symptoms; pathological use despite severe behavioral disturbances and drug-induced dyskinesias; social or occupational impairment; and development of a dopaminergic withdrawal state with dose reduction" (p. 1090). Thus, the same agents that promote PG in Parkinson's patients can also increase the incentive value of selective DA-enhancing drugs.

PD has been linked with up-regulation of DA D2 receptors [137, 138]. This is noteworthy given that high D2 receptor availability is associated with low impulsivity and neophobia [139-141]. This correspondence raises the possibility that the enhancement of desire to gamble by modafinil in low impulsivity PG subjects may have involved relatively higher D2 receptor sensitivity or availability in these subjects. This possibility could be tested directly by means of neuroimaging.

CHRONIC EFFECTS OF PSYCHOSTIMULANTS AND IMPLICATIONS FOR PG

Chronic exposure to addictive reinforcers is believed to induce profound and long lasting changes in brain function that promote compulsive drug / reinforcement seeking and vulnerability to relapse following periods of abstinence. Sensitization of limbic DA pathways is considered a critical process underlying these pathological effects [47]. Sensitization refers to the increase in response to a stimulus with repeated exposure to that stimulus. With respect to addiction, sensitization is evidenced by an increased overt response to a drug (e.g., increased locomotion) as well as by increased neuronal response in terms of limbic DA release. Although chronic exposure to most drugs of abuse can produce sensitization, there is considerable variability in this effect across drug classes [142]. This is not the case with psychostimulants, which reliably induce robust behavioral (locomotor) and neuronal (DA release) sensitization along with increased self-administration following repeated exposure in animals [143]. Animal studies further reveal that a sensitizing regimen of amphetamine induces characteristic cognitive deficits in terms of impaired set-shifting or perseveration [144] and decreased pre-pulse inhibition (PPI) of the acoustic startle response i.e., poor stimulus-response calibration [145]. Similar deficits are seen in patients with schizophrenia, a human population thought to typify the sensitized DA state [146-149]. Recent research with stimulant-naïve human subjects shows that repeated intermittent exposure to amphetamine (3 doses @ 0.3 mg/kg) is sufficient to induce long-lasting increases in psychomotor response and DA-release from a challenge dose of the drug [150]. The degree of sensitization correlated positively with self-reported novelty-seeking and impulsivity in this study.

Although never directly tested, sensitization may explain some of the findings for PG subjects. For example, PG subjects exhibit abnormally high levels of DA metabolites in their cerebrospinal fluid [151, 152]. This is indicative of higher basal brain DA activity. PG subjects also exhibit characteristic excesses in perseverative behavior, especially in pursuit of reward [153, 154], and this has been implicated in their compulsive "chasing" of monetary payoffs despite mounting losses [155]. Like amphetamine-sensitized animals, PG subjects display deficits in PPI under drug-free conditions [156]. Deficient PPI is said to reflect impaired 'sensorimotor gating' or hyper-reactivity to unconditioned stimuli (a loud noise) despite conditioned warning signals (a soft noise). Such deficits reflect a failure of habituation, which would be expected to promote perseverative behavior, and are consistent with Redish *et al.* [83, 84] perpetual learning model of cocaine addiction and PG.

Psychostimulant-Induced Delusions and Cognitive Distortions in PG Chronic exposure to high doses of psychostimulants can produce a psychotic syndrome in some users. The nature of the delusions in psychostimulant psychosis conforms closely to that seen in patients with schizophrenia, a disorder characterized by limbic hyper-DA activation [157-159]. Evidence from methamphetamine abusers shows that risk for psychosis can persist despite prolonged abstinence [160]. This lasting vulnerability has been found to be mediated by DA and is exacerbated by re-exposure to the drug or by stress [161]. These findings suggest that sensitization of DA pathways can produce a state that is hyper-reactive to acute DA-releasing stimuli, and which manifests in the form of profound cognitive distortions.

Cognitive distortions or irrational beliefs are extremely prevalent in PG subjects. These often go beyond errors in reasoning or lack of statistical knowledge (e.g., that the outcome of every trial is independent) [162, 163]. Therapists have noted that cognitive distortions are among the most intractable symptoms of PG [164, 165]. The qualitative nature of these distortions, their resistance to treatment, and the tendency for them to manifest during the course of a gambling episode are consistent with a sensitization-induced thought disturbance.

Some notable examples of cognitive distortions in PG include 'anthropomorphism' and perceived 'omnipotence' [166]. These correspond closely to Thoughts of Reference (e.g., "The machine is sensitive to my thoughts or wishes") and Delusions of Grandeur (e.g., "I can't lose"), respectively, which are common in amphetamine psychosis and schizophrenia [8, 9]. The belief that one can predict or control gambling outcomes is pervasive in PG subjects [167], and is especially problematic as it promotes persistence in gambling despite accumulating evidence to the contrary. The belief that one's thoughts can directly influence environmental events is one of the first-order delusional symptoms of schizophrenia [168]. The importance of acute gambling-induced DA release in 'activating' these distortions – giving them their potency - is implied by clinical findings showing that cognitive restructuring interventions are much more effective when applied while the individual is actually gambling [169, 170].

It should be noted that frank psychosis, like that of schizophrenia and in some cases chronic psychostimulant abuse, involves an inability to question the veracity of the delusion. To the patient, reality and (false) perception/belief are identical. In contrast, subjects with PG can acknowledge their cognitive distortions when confronted with them. However, they cannot act in accordance with this rational knowledge. In this regard, the erroneous beliefs espoused by PG subjects are similar to the obsessions held by patients with obsessive-compulsive disorder (OCD). In both cases, the patient has insight into their distortions but is unable to resist them. This disconnection between conscious thought and behavior implies that the systems responsible for integrating thought and action are compromised in PG patients as they are in OCD. The valence of the cognitive distortions differs between PG and OCD: In PG patients the cognitive trigger (prospect of reward) is positive or desirable, whereas in OCD it is usually aversive or undesirable (prospect of harm or contamination).

There is little epidemiologic overlap between OCD and PG or other impulse control disorders [171]. This suggests that uncontrollable cognitive distortions in PG may be an effect (e.g., sensitization) rather than a cause of excessive gambling. This is consistent with animal studies, which suggest that "psychostimulant-induced" stereotypic behavior provides an animal model of OCD [172,173] in that "rats treated chronically with the D2/D3 agonist quinpirole show a pattern of behavior that meets a set of ethologically derived criteria for compulsive behavior in obsessive-compulsive behavior (OCD)" (p. 191). Interestingly, medications with a combined D2/D3 agonist profile (like quinpirole), are the agents most consistently linked with PG in Parkinson's patients [174].

LIMITATIONS OF AN EXPLANATORY FRAMEWORK OF PG BASED EXCLUSIVELY ON DA ACTIVATION

PG is a complex disorder. Like most psychiatric disorders, no single process or system can adequately account for all aspects of its etiology or symptom profile. PG is characterized by high rates of co-morbidity including major depressive disorder (~50% prevalence in PG [6]) and alcohol use disorder (as noted above [14]). In cases like these, it is unclear whether PG is a cause, effect, or correlate of the co-morbid condition. Both depression and alcohol use disorder are strongly linked with disturbances in serotonin function [175], indirectly implying an important role for serotonin in co-morbid PG and possibly in non-co-morbid PG as well. Evidence from clinical studies has shown that naltrexone and nalmefene are beneficial in the treatment of PG [176, 177]. These drugs block central opioid receptors and inhibit DA release in the nucleus accumbens [178]. Thus, the brain opioid system may also play an important role in gambling reinforcement. However, it should be noted that naltrexone also reduces the acute rewarding effects of amphetamine in healthy volunteers [179].

On the basis of epidemiological and clinical evidence, theoretical accounts have emphasized the importance of heterogeneity in PG, and particularly in the different etiological pathways to this disorder. As noted earlier, Blaszczynski and Nower's [21] pathways model defines three independent sub-types of PG: one based on chronic exposure alone, a second based on mood-instability-related risk, and a third based on impulsivity. It seems unlikely that disturbances in DA alone can fully account for all three sub-types. In line with this, genetic studies indicate that risk for PG is mediated roughly equally by genes for all three mono-amine transmitters (serotonin, norepinephrine and DA [180]).

OVERVIEW AND CONCLUSIONS

The critical distinction between a general model of PG as a behavioral addiction and a model specifically linked to psychostimulant addiction focuses on the extent to which limbic DA activation is required in order to experience the acute reinforcing effects of gambling and psychostimulants. From a subjective standpoint the sense of avidity (see [181]) or active engagement in a particular activity (i.e., 'positive arousal' [34]) is the feature that we suspect is a direct result of gambling-induced limbic DA activation [182]. It is this feature in particular that lends gambling its psychostimulant-mimetic effects and that, following chronic exposure, leads to the characteristic symptoms (e.g., chasing, cognitive distortions) of PG.

Evidence from imaging studies suggests that PG may involve a deficit in arousal that is rectified to some extent by gambling. Thus, individuals with genetic deficits in arousal would find gambling especially reinforcing, while those who have developed the disorder would come to rely on gambling to reverse this deficit. The putative role of sensitization in PG suggests that for the full syndrome to emerge, chronic exposure to gambling may be necessary. This reasoning implies that individuals *at risk* for PG may resemble individuals without such risk after they have been exposed to gambling for some time. That is, in functional terms, risk for PG may involve a sub-clinical ('prodromal') sensitized brain state. Comparing pre-morbid individuals at high epidemiologic risk for PG with those at low risk in terms of their response to amphetamine would permit a test of this hypothesis, and could conceivably serve as a bio-behavioral marker or endophenotype for PG, in line with Brewer and Potenza's [17] recommendation.

Like all models, the psychostimulant mimetic model involves a trade-off between parsimony and comprehensiveness. In this regard, the utility of the model lies in its ability to inform hypothesis-testing, to explain etiology and symptom profiles, and to suggest the kinds of interventions that may ultimately help in the prevention and treatment of PG.

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Key Learning Objectives:

1. The neurotransmitter, dopamine (DA) is widely implicated in reinforcement and in the pathological processes underlying addiction. However, DA also appears to play a distinct role in psychostimulant addiction that goes beyond these generic effects. The overall goal of this article is to summarize evidence indicating that DA plays a similar distinct role in pathological gambling (PG) as it does in psychostimulant addiction.
2. To illustrate the parallel roles of DA in the effects of gambling and psychostimulants across several domains: reward-reinforcement, motivational-priming, subjective-experiential, cognitive-information processing.
3. To highlight the importance of DA-mediated positive arousal as an intrinsically positive aspect of gambling – to those who enjoy gambling - and describe parallels between this state and the state of avidity induced by psychostimulants.
4. To begin to delineate the roles of DA receptor sub-types in gambling reinforcement in PG subjects and controls.
5. To describe the critical role of conditioned signals (cues) for uncertain reward in gambling reinforcement. Such signals lead to dynamic changes in DA release, much like that induced by psychostimulant drugs, and may reinforce gambling behavior regardless of its outcome (win or lose).
6. To characterize the consequences of chronic exposure to gambling and psychostimulants with respect to DA. The role of sensitization is discussed as it relates to the cognitive distortions seen in PG and psychostimulant addiction, and to the compulsive perseveration to gamble (i.e., chasing) that typifies PG subjects.

Future Research Directions:

1. To directly assess the parallel effects of DA-specific probes on gambling and on psychostimulant reinforcement in PG subjects and controls.
2. To isolate the respective roles of DA receptor sub-types in gambling reinforcement in PG.
3. To identify possible differences in DA-mediation of gambling reinforcement in subtypes of PG.
4. To directly assess sensitization in PG subjects using neuroimaging and an amphetamine challenge.
5. To determine if preference for amphetamine coincides with epidemiological or genetic risk for PG in pre-morbid samples.

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