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Similarities and Differences between Pathological Gambling and Substance Use Disorders: A Focus on Impulsivity and Compulsivity

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Abstract

Rationale—Pathological gambling (PG) has recently been considered as a "behavioral" or non-substance addiction. A comparison of characteristics of PG and substance use disorders (SUDs) has clinical ramifications and could help advance future research on these conditions. Specific relationships with impulsivity and compulsivity may be central to understanding PG and SUDs.

Objectives—To compare and contrast research findings in PG and SUDs pertaining to neurocogntive tasks, brain function and neurochemistry, with a focus on impulsivity and compulsivity.

Results—Multiple similarities were found between PG and SUDs, including poor performance on neurocognitive tasks, specifically with respect to impulsive choice and response tendencies and compulsive features (e.g., response perseveration and action with diminished relationship to goals or reward). Findings suggest dysfunction involving similar brain regions, including the ventromedial prefrontal cortex (PFC) and striatum and similar neurotransmitter systems, including dopaminergic and serotonergic. Unique features exist which may in part reflect influences of acute or chronic exposures to specific substances.

Conclusions—Both similarities and differences exist between PG and SUDs. Understanding these similarities more precisely may facilitate treatment development across addictions, whereas understanding differences may provide insight into treatment development for specific disorders. Individual differences in features of impulsivity and compulsivity may represent important endophenotypic targets for prevention and treatment strategies.

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Keywords

Iowa Gambling Task; delay discounting; neuroimaging; alcohol; cocaine; dopamine; serotonin; glutamate; frontal cortex; striatum

Introduction

Although pathological gambling (PG) is currently categorized in the Diagnostic and Statistical Manual (DSM-IV text revision, APA 2000) as an impulse control disorder (ICD), parallels between PG and substance use disorders (SUDs) have been noted. Substance dependence and PG both include diagnostic criteria regarding continued engagement despite negative consequences, tolerance, withdrawal and repeated attempts to cut back or quit (APA 2000; Holden 2001; Wareham and Potenza, 2010). Given these similarities and biological data concerning PG and SUDs, there has been a shift toward consideration of PG as a "behavioral" or non-substance addiction (Frascella et al. 2010; Holden 2001; Petry 2006; Potenza 2006; 2008) with possible re-categorization in DSM-V (Holden 2010). Not only is SUD research likely to be illustrative for PG, the study of PG also may also inform our understanding of and future investigations into substance addictions. PG presents an opportunity to study addictive behaviors without necessarily being confounded by neurotoxicity associated with acute or chronic substance use (Lawrence et al. 2009b; Pallanti et al. 2010; Verdejo-Garcia et al. 2008).

Impulsivity, a multi-faceted construct with relevance to myriad psychiatric conditions including PG and SUDs (Leeman et al. 2009; Petry 2007), has been defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others" (Brewer and Potenza 2008; Moeller et al. 2001). Responsiveness to reward, at the expense of passive, inhibitory behaviors and reduced responsiveness to punishment, have been related to impulsivity (Patterson and Newman 1993). Recently, the construct has been fractionated into distinct components, including response and choice forms (Dalley et al. 2011; Potenza and de Wit 2010; Winstanley et al. 2004). These components have been found to relate differently to various aspects of addictive behaviors (Dick et al., 2010; Verdejo-Garcia et al., 2008; Whiteside & Lynam, 2001).

It has been proposed that the pathology of SUDs involves a shift from being more novelty-driven and impulsive to more habit-driven and compulsive (Brewer and Potenza 2008; Dalley et al. 2011; Everitt and Robbins 2005; Fineberg et al. 2010; Koob & LeMoal, 1997; Potenza 2008). Dalley et al. (2011, p. 680) define compulsive behaviors as "actions inappropriate to the situation which persist, have no obvious relationship to the overall goal and which often result in undesirable consequences." Data suggest that like impulsivity, compulsivity is multi-faceted (Fineberg et al. 2010). Dalley et al. (2011) identified two key, theoretically dissociable components in their definition: persistence or perseveration and actions that have no obvious relationship to an overall goal. Additional independent or related factors may exist as self-report measures of compulsivity have factored into multiple domains including those relating to impaired control over thoughts and behavior, and these may relate to clinically relevant aspects of psychiatric behaviors and conditions (Blanco et al. 2009).

Both impulsivity and compulsivity appear characterized by difficulties in self-control (Stein and Hollander 1995) and may relate in complex fashions to theoretically similar but distinct constructs (e.g., sensation-seeking, risk-taking, decision-making). Regarding clinical implications, persistent substance use despite knowledge of harm, which relates to

definitions of both impulsivity and compulsivity, is a criterion for dependence (APA, 2000) and considered a core component of addition (O'Brien et al. 2006). A key distinction between the constructs is that while impulsivity is often thought of as entailing rash action in pursuit of reward (Patterson and Newman, 1993), compulsive action is typically undertaken with diminished regard for reward (Everitt and Robbins, 2005; Fontenelle et al. 2011).

Evidence suggests that impulsivity is a longitudinal predictor of SUDs (Hicks et al. 2010; Mezzich et al. 2007). Further, greater similarity in self-reported impulsivity between stimulant-addicted and non-addicted siblings than between non-related individuals suggests impulsivity is an endophenotype that may mediate risk for SUD (Ersche et al. 2010). Given the importance of impulsivity to SUDs, along with evidence that those with PG tend to score highly on impulsivity measures, systematic examination of similarities and differences with regard to response and choice impulsivity in PG and SUDs is needed. Evidence of impulsivity in PG has come from use of self-reports (e.g., Petry 2001a) and observations of greater response impulsivity on the stop-signal and other such neurocognitive tasks (e.g., Goudriaan et al. 2006b) and choice impulsivity on delay discounting tasks (e.g., Petry and Casarella 1999). Similarities could indicate that SUDs and PG are characterized by overlapping risk factors, which suggest that treatments found to be efficacious for SUDs could also have utility in PG. In contrast, differences between conditions may indicate disparities in risk factors for the conditions, or factors related to the course of the specific disorders (e.g., recent or chronic exposures to specific substances) and point to unique treatment approaches for individual addictions.

Similarities and differences between PG and SUDs can be examined with regard to neurocognitive task performance, as well as relevant brain function or neurotransmitter activity. Frontal cortical and striatal regions are of particular relevance. Frontal cortical regions, particularly ventral areas (e.g., ventromedial prefrontal cortex [vmPFC] and orbitofrontal cortex [OFC]), have been implicated in reward responsiveness and by extension potentially to impulsivity and compulsivity in PG and SUDs (Brewer and Potenza 2008; Fineberg et al. 2010). The striatum (particularly the nucleus accumbens [NAcc] in the ventral striatum) is another key region underlying reward responsiveness and motivational drives and may contribute importantly to habit formation and compulsions (Everitt and Robbins 2005; Kalivas 2009; Volkow et al., 2007b). Regarding relevant neurochemistry, dopamine and serontonin have received much research attention. Dopaminergic activity contributes to rewarding effects of addictive substances (e.g., Schultz 2011), gambling behaviors (e.g., Campbell-Meiklejohn et al. 2011), and impulsivity (Buckholtz et al. 2010). Multiple lines of evidence link serotonin function to PG (Fineberg et al. 2010) and SUDs (Ratsma et al. 2002). Roles for opioidergic and gluatamatergic systems have been implicated in SUDs (Kalivas 2009; Volkow 2010) and PG (Grant et al. 2007; Grant et al. 2008a;). Endogenous opioids contribute to rewarding effects of addictive substances (Volkow 2010), and this effect may involve modulation of mesolimbic dopamine function through intermediary GABAergic mechanisms (Brewer and Potenza 2008). Glutamate, an excitatory neurotransmitter and GABA precursor (Brewer and Potenza 2008; Holmes 2011), has been proposed to mediate reward-seeking in SUDs (Kalivas and Volkow 2005) given its influences on mesolimbic dopamine function (Geisler et al. 2007; Grant et al. 2010), particularly in the NAcc (Kalivas and Volkow 2005; McFarland et al., 2003). Imbalance in glutamate homeostasis may also contribute to compulsive action in addictions (Kalivas 2009). Adrenergic systems may have a role in mediating drug-related reward (Weinshenker and Schroeder 2007) and adrenergic drugs may have an impact on impulsivity (Chamberlain et al. 2007) and thus may be relevant to PG and SUDs.

As with SUDs, it has been hypothesized that an impulsivity-to-compulsivity shift may take place with PG (Brewer and Potenza, 2008). The extent to which empirical data support this

hypothesis is a topic of research and clinical importance. If a similar impulsivity-to-compulsivity shift occurs in PG, performance indicative of response perseveration on reversal learning tasks, for instance (e.g., de Ruiter et al. 2009), may indicate a higher level of PG severity. Alternatively, compulsivity may characterize PG relatively early on, in which case suboptimal performance on such tasks may be indicative of risk for developing gambling problems. While research pertaining to compulsivity is not as developed as it is for impulsivity (Fineberg et al. 2010), examination of the available evidence could illustrate key similarities and differences between PG and SUDs.

In addition to impulsivity and compulsivity, the related construct of risk/reward decision-making is pertinent in that gambling typically involves this type of decision-making. Some neurocognitive tasks designed to assess risk/reward decision-making (e.g., the Iowa Gambling Task [IGT], Bechara et al. 1994) are also thought to capture aspects of response and choice impulsivity, as well as perseveration and outcome devaluation compulsivity (Verdejo-Garcia et al. 2008). Thus, it is important to consider risk/reward tasks as potentially measuring multiple constructs of interest. The IGT is a computerized test of risk/reward decision-making in which participants draw one card per trial for 100 trials from one of four decks. Each draw results in hypothetical monetary rewards and/or penalties. Although participants are instructed that some decks may be better than others, they do not know specifically that two are advantageous, leading to small, steady wins and intermittent small losses, yielding long-term gains, and two are disadvantageous, involving larger wins and intermittent large losses, yielding long-term losses. Optimal performance requires diminished choice impulsivity in that selecting from the advantageous decks entails privileging long-term gain over immediate, large rewards (Dymond et al. 2010). Optimal performance also involves aspects of reversal learning (Fellows and Farah 2005), which is the ability to note changes in contingencies and modify one's behavior accordingly (i.e., a lack of perseveration; Clark et al. 2004).

When comparing and contrasting PG with SUDs, it is important to note variability across addictions to various substances. Several characteristics apply to dependence across all substances, suggested by the use of the same abuse and dependence criteria for all substances in the DSM-IV-TR (APA 2000). There are, at the same time, differences in the clinical characteristics of dependence upon various substances (Fisher and Roget 2008a; 2008b). Similarly, aspects of PG resemble aspects of dependence on some substances more than others. For instance, evidence suggests PG has a great deal in common with alcohol dependence, including similarities relevant to impulsivity (Lawrence et al. 2009a; Rogers et al. 2010). To cite a contrasting example, findings suggesting lack of notable impairment on response inhibition and decision making on tasks such as the IGT in MDMA users (Verdejo-Garcia et al. 2008) suggests the possibility that clinical characteristics associated with problem MDMA use may differ from those associated with PG.

Behaviors indicative of ICDs in Parkinson's Disease (PD) offer a model for the study of impulsivity and compulsivity in PG and SUDs. PD is a condition characterized by dopaminergic neuronal loss and is often treated with dopamine replacement therapies (DRTs) that include dopamine agonists such as pramipexole or ropinirole and levodopa, a biochemical precursor to dopamine (Linazasoro 2009; Potenza et al. 2007; Voon et al. 2007). These medications have been hypothesized to lead to "dopamine overdosing" and ICDs in some patients (reviewed in Leeman and Potenza 2011). ICDs appear more prevalent among those with PD than in those without (Kenagil et al. 2010; Weintraub et al. 2010). While DRTs have been associated with ICDs in PD, evidence suggests non-PD individual factors (e.g., a family history of alcoholism, marital status and geographic location) also relate to ICDs in PD (Leeman and Potenza 2011; Weintraub et al. 2010). Thus ICDs in PD offer a clinically relevant and scientifically informative model; e.g., for investigating

dopaminergic influences. At the same time, the extent to which these findings extend to non-PD populations should be carefully considered given neural changes associated with PD, medications used to treat PD, and other factors associated with this disorder. PG is arguably the most well-studied ICD in the general population and in those with PD (Evans et al. 2009). Accordingly, there have been multiple tests of risk-reward decision-making relevant to gambling in PD patients (e.g., Kobayakawa et al. 2010; Pagonabarraga et al. 2007).

This review is comprised of three sections dedicated to findings involving neurocognitive tasks, brain function and neurochemistry. In the neurocognitive task section, we discuss results pertaining to response impulsivity, choice impulsivity, compulsivity, risk/reward decision-making and other theoretically related constructs. We address findings from PG and then compare and contrast them with findings from SUD studies. SUD findings are typically identified according to the substance in question. Where applicable, findings from healthy adult samples are addressed first, followed by studies in clinical non-PD samples, concluding with PD studies. A similar approach is taken in the brain function section. In our discussion of compulsivity, we differentiate perseveration from outcome devaluation forms when possible; however, behavioral and self-report measures of compulsivity have not yet been developed with demarcation as sharp as in the impulsivity literature. Regarding neurochemistry, research gaps exist that limit a fully systematic description. We conclude with suggestions for future studies.

Neurocognitive tasks assessing impulsivity, compulsivity and risk/reward decision-making

Findings involving neurocognitive tasks have provided evidence of similarity between PG and SUDs with regard to aspects of choice and response impulsivity, compulsivity and risk/reward decision-making. Some differences have been found as well, with regard to basic executive function and elements of risk/reward decision-making.

Impulsivity in PG

Response impulsivity—Individuals with PG have been found to differ from those without in response impulsivity. In go/no-go tasks (e.g., Marczinski and Fillmore 2003), participants are trained to respond to a one type of stimulus (“go” stimulus) and to inhibit response to another (“no-go” stimulus). Stop-signal tasks (e.g., Logan 1994) share features with go/no-go tasks except on a minority of trials, the “go” response must be withheld immediately when an auditory “stop signal” occurs. Lengthier reaction times on stop signal trials are thought to be indicative of greater difficulties inhibiting pre-potent responses. PG participants had longer reaction times on stop signal trials in the stop-signal task (Goudriaan et al. 2006b; Grant et al. 2010). However, Lawrence et al. (2009b) reported no significant differences in stop-signal performance between PG participants and healthy control subjects and Rodriguez-Jimenez et al. (2006) reported significant performance deficits only among those with co-occurring ADHD. PG participants had more commission errors controls on a go/no-go task (Fuentes et al. 2006; Goudriaan et al. 2005).

Choice impulsivity—One aspect of choice impulsivity is temporal or delay discounting, a phenomenon whereby distal reinforcers are devalued in comparison with immediate reinforcers (Bickel and Marsch 2001). The choice to engage in addictive behaviors entails selection of immediate (e.g., getting “high”) over delayed (e.g., better work performance) reinforcement (Dalley et al. 2011), making delay discounting relevant to the addictions. PG participants discounted delayed rewards to a greater extent than controls on a task in which they selected between small, immediate and larger, distal hypothetical rewards on index cards (Dixon et al. 2003; Petry 2001b; Petry and Casarella 1999).

Choice impulsivity has also been compared in PD patients with and without ICDs using the Experiential Discounting Task (EDT; Reynolds and Schiffbauer 2004). The computer-based EDT is an inter-temporal choice task that assesses real-time temporal discounting. In each trial, participants choose between a standard amount that is delayed and probabilistic and an adjusting amount that is certain and provided immediately. The probability of receiving the standard amount remains consistent across all blocks of trials, and the delay to receipt of the standard amount varies across blocks. When taking dopamine agonists, PD patients with ICDs made more impulsive choices than those without ICDs (Voon et al. 2010). Given the temporal aspect of the EDT, reaction time is also measured. Patients with ICDs had quicker reaction times overall and in high conflict trials on the EDT than those without ICDs. Thus, differences based on ICD status may involve both choice and response impulsivity.

Other relevant constructs—Tendencies not to make use of reflection may also pertain to choice and response impulsivity in that poor reflection involves making rapid choices without adequate information (Verdejo-Garcia et al. 2008). On an information sampling task, Lawrence et al. (2009b) found that PG participants engaged in less reflection than control subjects.

Attention and working memory are basic executive functions that are relevant to impulsivity (Finn 2002; Rugle and Melamed 1993). Findings suggest that those with PG without co-morbid SUDs may not have notable difficulties with working memory (Cavedini et al., 2002; Goudriaan et al. 2006b; Lawrence et al. 2009b) or attention (Marazziti et al. 2008a; Rugle and Melamed 1993). Complex cognition may be affected in PG, but basic executive functions may not be substantially impacted (Goudriaan et al. 2006b; Lawrence et al. 2009b; Potenza, 2009).

Similarities and differences regarding response and choice impulsivity in SUDs vs. PG

Findings suggest that response impulsivity is elevated in SUDs. Longer reaction times on stop signal trials have been found in cocaine (Fillmore and Rush 2002; Li et al. 2006) and alcohol dependence (Goudriaan et al. 2006b; Lawrence et al. 2009a; 2009b) and methamphetamine abuse (Monterosso et al. 2005). Alcohol dependent people have also displayed more commission errors than controls on a go/no-go task (Goudriaan et al. 2005; Kamarajan et al. 2005), as have cocaine users (Moeller et al. 2004; Verdejo-Garcia et al. 2007). A negative finding (Lawrence et al. 2009b) and a qualified result in PG (Rodriguez-Jimenez et al. 2006) notwithstanding, most results support response impulsivity in both PG and SUDs.

Those with various SUDs have been found to discount delayed rewards more than controls (see Bickel et al. 2007 for a review). Alcohol dependence (Lawrence et al. 2009b) and amphetamine and opiate use (Clark et al. 2006) have been linked to difficulties with reflection impulsivity, similar to findings in PG.

In contrast, differences in executive function have been found between PG and SUDs. People with SUDs often evince more working memory (Cavedini et al. 2002; Lawrence et al. 2009b) and attentional difficulties (De Wit 2009) than those with PG. These findings suggest more extensive cognitive dysfunction in SUDs such as alcohol dependence than in PG (Lawrence et al. 2009b), which may be a result of neurotoxicity from long-term substance use (Dalley et al. 2011). Thus, cognitive dysfunction may warrant greater consideration in treatment development for SUDs than for PG (Bickel et al. 2011; Wexler 2011).

To summarize, evidence suggests elevated choice and response impulsivity among those with PG and those with SUDs as compared to healthy control subjects. In contrast, attention

and working memory deficits may be more severe in SUDs (e.g., alcohol) than in PG (see Table 1).

Compulsivity in PG

Most published findings suggest heightened compulsivity, particularly response perseveration, in PG. Compared to control subjects, people with PG have demonstrated greater response perseveration on a card-playing task (Goudriaan et al. 2005). This task involves a series of choices regarding whether or not to play a card. In successive blocks, the ratio of win to loss cards decreases; thus, the optimal strategy involves deciding to play less frequently in later blocks. The task was classified as primarily assessing compulsivity, given the design to measure response perseveration and because continued frequent play in later blocks despite a high probability of punishment may reflect outcome devaluation. However, it is also a risk/reward decision-making task. Problem gamblers exhibited perseveration on a computerized, probabilistic reversal learning task. Participants were presented with two visual stimuli. Response to one stimulus was punished while response to the other was rewarded in an 80:20 ratio. The rewarded and punished stimuli reversed after a series of trials (de Ruiter et al. 2009). Those with PG also had more total errors than control subjects on the intradimensional/extradimensional set shifting (IDED) task (Grant et al. 2010) from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Downes et al. 1989; Sahakian and Owen, 1992). The IDED is a multi-stage task in which participants initially respond to one of two line stimuli and, based on feedback, must determine which response is correct. In a second stage, the correct response shifts. In later stages, shape stimuli are added and similar shifts as to which line stimulus is correct occur (intradimensional shifts). In the final stages, an extradimensional shift occurs in which response correctness depends upon selection of the proper shape, not the proper line.

There are differing findings regarding comparisons between PG participants and healthy controls on the Wisconsin Card Sorting Task (WCST; Grant and Berg 1948; Heaton et al. 1993), another measure of cognitive flexibility. On the WCST, participants match stimulus cards on a dimension (i.e., number, color, or shaped) not stated to them. After participants master the task on a trial-and-error basis based on feedback, the rule shifts and sorting must be done according to a different dimension. Marazziti et al. (2008a) found that PG participants made significantly more perseverative errors than healthy controls, but Goudriaan et al. (2006b) found no significant difference between PG participants and controls in perseverative errors.

Similarities and differences regarding compulsivity in SUDs vs. PG

Similar to PG, several neurocognitive task findings suggest response perseveration in SUDs, although findings have been more consistent in PG. Findings indicating response perseveration have not been borne out with all drugs in all studies. Chronic cocaine users made significantly more perseverative errors than control subjects on reversal learning tasks (Camchong et al. 2011; Ersche et al. 2008), although chronic amphetamine users, opiate users and former chronic cocaine users did not differ from control subjects (Ersche et al. 2008). Current amphetamine/methamphetamine users have shown response perseveration on the IDED task (Ersche and Sahakian 2007), although Ersche et al. (2006) found no significant differences between control subjects and those with current amphetamine dependence, current opiate dependence or past users of amphetamines and/or opiates. Cocaine dependent individuals have exhibited greater response perseveration on the WCST, (Woicik et al. 2011) but there have also been negative findings in comparisons between healthy controls and abstinent alcohol dependent individuals (Goudriaan et al. 2006b).

Regarding differences between PG and SUDs, Goudriaan et al. (2005) reported that unlike PGs, who had difficulty with perseveration on a card playing task, alcohol dependent individuals tended to play more conservatively. De Ruiter et al. (2009) reported smokers outperformed problem gamblers on reversal learning, but like PG subjects, they were outperformed by control subjects.

To summarize, most findings suggest response perseveration in PG. Some findings suggest the same in SUD; however, there are also a number of negative findings. This suggests that response perseveration may be more of an inherent aspect of PG than of SUD (Table 1).

Risk/reward decision-making in PG

Several studies have now been conducted comparing PG participants with healthy controls on the IGT. Compared to control subjects, those with PG perform disadvantageously (e.g., Cavedini et al. 2002; Goudriaan et al. 2005; 2006a; Petry 2001a). Specifically, PG participants have been found not to improve their performance in the later stages of the task (Goudriaan et al. 2005; 2006a) in the way healthy adults tend to (Bechara and Damasio 2002). Thus, these data are consistent with the notion that response perseveration--perhaps related to maintaining a response selection pattern consistent with preferences for large immediate reward or not learning from or changing behavior in the setting of losing outcomes--partly explains poor IGT performance among those with PG (Fellows and Farah 2005). As the failure to avoid large losses in the IGT from the outset could be indicative of outcome devaluation, IGT performance appears related to aspects of impulsivity and compulsivity.

In addition to being a risk/reward task, the IGT requires implicit learning as participants must recognize which decks are advantageous and disadvantageous and make subsequent selections accordingly. In contrast, the computerized Cambridge Gamble Test (CGT) assesses risk/reward decision-making without a learning component (Rogers et al. 1999). In each trial, participants are presented with 10 red or blue boxes. The number of boxes of each color varies across trials. Participants are asked to guess whether a hidden token is located behind a red or blue box; thus, the number of boxes of each color is an indicator of probability. Participants must then decide how many points from their bank they would like to bet on their response. Possible bets are presented by the computer with ascending or descending incremental changes. Larger bets in descending trials are ostensibly indicative of difficulty waiting for a smaller, more reasonable bet size. Both short latencies of initial response selection and larger bets on decreasing trials could be indicative of response impulsivity. In a recent study, those with PG bet more than controls regardless of task condition and were more likely to lose all of their points. There were no significant differences in response latency (Lawrence et al. 2009b).

Similarities and differences in risk/reward decision-making in SUDs vs. PG

Most gambling task results suggest similarities between PG and SUDs. Consistently, disadvantageous IGT performance has been observed in SUDs (Bechara and Damasio 2002): heavy alcohol use and dependence (Goudriaan et al. 2005; Kim et al. in press), chronic marijuana use (Whitlow et al. 2004), cocaine (Grant et al. 2000) and opiate dependence (Lemenager et al. 2011).

There have been some subtle differences in IGT performance. Alcohol dependent participants showed slightly more improvement in later quintiles than PG participants, who also responded faster than alcohol dependent individuals, which is potentially indicative of greater response impulsivity (Goudriaan et al. 2005). PG and alcohol dependent participants performed somewhat differently on the CGT in a recent study. Alcohol dependent

participants placed larger bets than healthy controls but only in descending trials and they were not significantly more likely than healthy controls to lose all of their points (Lawrence et al. 2009b). Thus, while both PG and alcohol dependent participants performed in a manner indicative of response impulsivity, PG participants' performance departed more dramatically from that of normal controls. Null differences on the CGT have also been found in opiate abusers (Rogers et al. 1999), although other studies have shown poorer performance in opiate users (Ersche et al. 2006; Fishbein et al. 2007) and in amphetamine abusers, compared to control subjects (Rogers et al. 1999).

To summarize, findings have shown that those with PG and dependence on several different substances perform worse than controls on the IGT. Fewer studies have been conducted with the CGT. Findings thus far suggest that those with PG perform worse than controls with findings mainly showing similar, suboptimal performance among substance users and those with various SUDs. While more research is needed, those with PG and with SUD may have particular difficulty with unique aspects of the IGT (e.g., reversal learning) (Table 1).

Summary of neurocogntive task findings

Neurocognitive task findings suggest similarities between PG and SUDs with respect to risk/reward decision-making, choice and response impulsivity and cognitive flexibility related to compulsivity. Possible exceptions involve the CGT and subtle differences on the IGT, suggesting some gambling-related tasks might measure deficits specific to PG. Neurocognitive task findings suggest compulsivity is relevant to both PG and SUDs though findings have been somewhat less consistent in SUDs. Performance on executive functioning tasks suggests greater impairments in SUDs than in PG. Together, these findings suggest both similarities and differences between those with PG and those with SUDs, with differences perhaps reflecting specific underlying vulnerabilities or effects of chronic substance use (Potenza 2009).

Brain Function underlying impulsivity, compulsivity and risk/reward decision-making

Neuroimaging has provided insight into regional contributions to impulsivity, compulsivity and risk/reward decision-making in PG and SUDs, providing directions for treatment development. This section will focus primarily on findings implicating the frontal cortices and striatum. Other brain regions and white matter integrity will be addressed briefly.

Frontal cortical activity in PG

Impulsivity—As much of the research attention in the neuroimaging literature in PG has addressed patterns of activation during risk/reward tasks, there has been little attention paid to tasks assessing aspects of impulsivity. In an fMRI study, participants with PG had reduced activity in the vmPFC compared to controls during the Stroop color-word interference task, which relates to cognitive control and response impulsivity (Potenza et al 2003a). In a recent investigation, de Ruiter et al. (in press) found weaker activation during the stop-signal task in the dorsomedial prefrontal cortex (dmPFC) in problem gamblers compared to healthy controls, though there were no significant differences in task performance. This pattern applied to failed as well as successful response inhibitions. No studies were found investigating frontal cortical activity associated with choice impulsivity in PG.

Compulsivity—While normative set-shifting task performance has been associated with ventrolateral PFC (vlPFC) activity (Hampshire and Owen 2006), problem gamblers exhibited severe response perseveration during reversal learning, which was related to

reduced activation in the right vlPFC in fMRI following monetary gain and loss during a computerized, probabilistic reversal learning task (de Ruiter et al. 2009). A lesion study relates closely to aspects of compulsivity despite use of a risk/reward decision-making task (the IGT) (Fellows and Farah 2005). Participants with lesions of the vmPFC and of the dorsolateral prefrontal cortex (dlPFC) were tested on the standard IGT and an alternate version in which initial draws from disadvantageous decks yielded large losses, thus negating the need for reversal learning in the standard IGT. While participants with vmPFC lesions performed disadvantageously on only the standard IGT, those with dlPFC lesions performed poorly on both versions. Thus, difficulties faced by those with vmPFC damage appear closely related to reversal learning deficits, while damage to the dlPFC relates to broader difficulties. The alternate IGT may have tapped more closely into outcome devaluation but not perseveration given punishment began from the outset. Those with dlPFC dysfunction could be more severely affected with regard to compulsivity.

Risk/reward decision-making—Multiple frontal cortical areas have been implicated in reward processing in gambling. Healthy adults have been found to activate the vmPFC along with other frontal cortical areas during the IGT (Li et al. 2010). In contrast, people with lesions in the vmPFC tend to perform poorly on the IGT (Bechara et al. 1994; 1998) and those with vmPFC damage have also performed poorly on the CGT, specifically making relatively high bets throughout, regardless of odds of winning (Clark et al. 2008). This proclivity fits with a normative role of the vmPFC to bias toward conservative options under risk (Clark et al. 2008).

“Loss chasing” (i.e., continued gambling, often in increasing amounts, in order to recover losses) is a cognitive/behavioral tendency particularly relevant to gambling (Campbell-Meiklejohn et al. 2008). A loss-chasing task, involving a “double-or-nothing” opportunity following losing wagers, was utilized in an fMRI study involving healthy participants. Participants began with a stake of hypothetical money and the opportunity to wager to win back the money lost. Wins led to elimination of the lost money whereas losses were followed by another choice to either quit or play with an opportunity to win back money lost that round. Decisions to chase losses were associated with increased activation in the vmPFC, while decisions to quit were associated with a different pattern of activations. The authors noted that the vmPFC and other activated regions are typically associated with representation of expected positive outcomes (Campbell-Meiklejohn et al. 2008).

In people with PG, diminished activity was found in the vmPFC during a guessing task in which participants chose between two playing cards of differing colors with red cards yielding monetary reward and other cards yielding monetary punishment. Significant inverse correlations were found between activation in this region and problem gambling severity (Reuter et al. 2005). Problem gambling severity was also significantly and negatively correlated with right middle and ventral medial frontal gyri activity among PG participants during a slot machine rating task (i.e., participants rated displays regarding closeness to winning) designed to model the “near miss” phenomenon (Habib and Dixon, 2010). Gamblers sometimes interpret near wins to be informative regarding likelihood of a subsequent win and increase upcoming bets accordingly.

Shifting to the PD literature, in an fMRI study involving only PD patients without ICDs, participants took part in a computerized roulette-style probabilistic reward task during scanning. Participants chose the color in which they thought the ball would drop among four single possibilities (25% probability of winning) in half the trials and among four trios of colors (75% chance of winning) in the other half. Winnings were paid in cash at the end. Dopamine agonist, but not levodopa, administration was associated with increased activation in the OFC to feedback from the task in general and during loss feedback

specifically (Van Eimeren et al. 2009). In a positron emission tomography (PET) study of PD patients given a dopamine agonist following overnight abstinence, neural activity was tested during a probabilistic feedback card game. The type of feedback provided by the game did not influence the results. PD patients with PG showed reduced activation in regions such as the lateral OFC and rostral cingulate, while PD patients without PG showed increased activation in these regions (van Eimeren et al. 2010) similar to this group's prior study (van Eimeren et al 2009). The authors surmised that hypoactivation in the PD/PG group was indicative of weaker impulse control (van Eimeren et al. 2010). Similarly, in an fMRI study, participants completed a task with options to take a sure monetary amount or to gamble for a larger amount (both amounts varied from trial to trial) under a "gain" condition in which they started with a $0 stake or a "loss" condition in which they began at a negative stake. PD patients with ICDs had lower OFC activity during the "gain" condition (in which larger gambles were typically made) than in the "loss" condition (when smaller gambles were typically made). The opposite pattern of activation was true for PD patients without ICDs (Voon et al. 2011).

Similarities and differences in frontal cortical activity in SUDs vs. PG

Regarding response impulsivity, in parallel with PG findings (Potenza et al. 2003a) those with cocaine use disorders displayed hypo-activation in the OFC during a Stroop task conducted during fMRI (Goldstein et al. 2007b). During the stop-signal task, de Ruiter et al. (in press) found similar hypoactivation of the dmPFC in smokers as they found in problem gamblers. Thus, sub-optimal activation in the PFC/OFC may characterize impulsive response in PG and SUDs. Regarding compulsivity, de Ruiter et al. (2009) found that problem gamblers and smokers showed hypoactivation in the vlPFC with loss feedback in a probabilistic reversal learning task.

There are parallels in terms of reduced frontal cortical activation tied to reward responsiveness in PG and SUDs. In an fMRI study, participants pressed or refrained from pressing a button according to instructions under three levels of monetary reward for compliance. Cocaine abusers showed reduced regional responsivity in the OFC and PFC to differences in monetary value across trials in comparison with controls (Goldstein et al. 2007a). Compared to controls, cocaine abusers had stronger activation in the right OFC and weaker activation in areas of the PFC (dorsolateral and medial regions) during the IGT (Bolla et al. 2003). In another fMRI study, despite similar task performance and compared to controls, those with comorbid PG and substance dependence and those with substance dependence only showed decreased activation in the vmPFC while playing a variant of the IGT. In this variant, the computer selected the deck and the participant opted to play or not. An exception was in cases when a disadvantageous deck was selected (i.e., high reward and high punishment). In these trials, those with PG and substance dependence had stronger activation than controls (Tanabe et al. 2007).

In summary, these findings highlight roles for prefrontal cortical function, particularly in ventrolateral and ventromedial components, in tasks related to impulsivity, compulsivity and risk-reward decision-making. Findings in PG have tended to resemble findings in SUDs.

Striatal activity in PG

Impulsivity—de Ruiter et al. (in press) reported no significant differences among problem gamblers, smokers and healthy controls in striatal activation during the stop-signal task.

Compulsivity—de Ruiter et al. (2009) reported no significant differences among problem gamblers, smokers and healthy controls in striatal activation during a reversal learning task.

Risk/reward decision-making—Studies of risk/reward and simulated gambling in healthy adults have provided bases for comparison with studies of those with PG. Li et al. (2010) found evidence for ventral striatal activation using fMRI during the IGT. In other fMRI studies, during a computerized slot machine task developed to model the "near miss" phenomenon, healthy adults (Clark et al. 2009) and a heterogeneous group of gamblers (Chase and Clark 2010) activated the ventral striatum during wins and "near misses" (i.e., when a reel stops one spot away from a win). Dorsal striatal activity (i.e., caudate) was observed during reward anticipation in a computerized gambling task in which healthy adults, following a cue, were asked to make rapid choices whether to opt for smaller or larger gambles (Cohen et al. 2005).

In an fMRI study utilizing a computerized "cup task" in which participants chose whether or not to gamble and then selected a cup associated with monetary gain or loss, healthy adults tended to bet conservatively following wins, which was associated with dorsal and ventral striatal activation. Participants tended to take more risks following losses, when they tended to show reduced activation in both regions (Xue et al. 2011). Similarly, in the aforementioned "loss chasing" paradigm tested by Campbell-Meiklejohn et al. (2008), healthy adults activated the ventral striatum during decisions not to chase. Thus surprisingly, in healthy adults increased ventral striatal activity has been associated with risk-taking and conservative decisions, and future studies should investigate the extent to which specific factors (genetic, environmental) might contribute to increased or decreased striatal activations during gambling behaviors.

Striatal dysfunction has been implicated in PG. Pallanti et al. (2010) reported those with PG had lower baseline ventral striatal glucose metabolism and higher levels in the dorsal striatum than healthy controls. In a different study (Linnet et al. 2011), PG participants did not differ significantly from healthy controls in D2-like receptor availability in the ventral striatum at baseline. PG participants have shown diminished ventral striatal activity during a card guessing gambling task involving monetary reward and punishment and significant inverse correlations between activation in this region and problem gambling severity (Reuter et al. 2005). According to these authors, under-stimulation in the ventral striatum may reflect reduced sensitivity to reward. During a slot machine rating task, Habib and Dixon (2010) found increased dorsal striatal activity during "near misses" in PG subjects, but not in controls, and reduced ventral striatal activity in PG. In contrast, Miedl et al. (2010) found an increased ventral striatal signal during win trials in simulated blackjack among problem and occasional gamblers using fMRI. Using PET, Linnet et al. (2011) found significant positive relationships between ventral striatal dopamine release and self-reported excitement in PG during the IGT, suggesting this activity may be tied to experiences of positive affect while gambling. This finding may help to explain observations of reduced activation in the ventral stratum in PG participants but increased activation in a study involving problem and occasional gamblers (Miedl et al. 2010) who may not have developed as strong tolerance to rewarding effects of gambling. Ventral striatal differences may also involve neurotransmitters other than dopamine as increased 5HT1B receptor availability in the ventral striatum have been found to correlate with problem gambling severity in PG (Potenza et al. in press).

Baseline PET studies of PG participants in PD have shown differences in ventral striatal dopamine transporter measures (Cilia et al 2010) and low D2-like receptor availability in the ventral striatum (Steeves et al. 2009) in scans following overnight abstinence from agonist medications. Other findings among PD patients with ICDs (Rao et al. 2010) suggest reduced ventral striatal activity compared to patients without ICDs, both at baseline and during the Balloon Analogue Risk Task (BART; Lejuez et al. 2002). ICD patients tested on dopamine

agonists showed increased risk sensitivity during a risk-taking task and reduced ventral striatal activity (Voon et al. 2011).

Similarities and differences in striatal activity in SUDs vs. PG

As in PG, findings suggest reduced ventral striatal activity with reward responsiveness in those using substances and having SUDs. In the monetary incentive delay task (MIDT), anticipation of working for monetary reward was associated with diminished ventral striatal activity in alcohol dependence (Beck et al. 2009; Hommer 2004; Wrase et al. 2007) and in adolescent smokers (Peters et al. 2011), similar to findings in PG (Potenza 2011). In both alcohol dependent and PG subjects, ventral striatal activation during reward anticipation correlated inversely with self-reported impulsivity (Beck et al. 2009; Potenza 2011). Divergent findings have been reported for substance involvement as in PG (Miedl et al. 2010). Increased ventral striatal activity during reward anticipation was found in heavy cannabis users (Nestor et al. 2010) and cocaine dependence (Jia et al. 2011).

The finding of elevated serotonin 5HT1B receptor availability in the ventral striatum in alcohol dependence (Hu et al., 2010) resonates with ventral striatal findings in PG (Potenza et al. in press). 5HT1B receptor function has been found to regulate multiple neurotransmitters, including dopamine, in the ventral striatum (Yan and Yan 2001a; b).

While relatively diminished D2-like receptor availability in the striatum has been observed in stimulant abuse (Volkow et al. 2003) as well as non-drug states sharing features of addictions (e.g., obesity [Wang et al. 2001]), initial findings have not been as consistent in PG (Linnet et al. 2011). Differences in activity in PG associated with PD may localize specifically to ventral components of striatum (Cilia et al 2010; Frosini et al. 2010; O'Sullivan et al. 2011; Steeves et al. 2009). Limited available evidence suggests hyperactivity in the dorsal striatum in PG (Habib and Dixon 2010; Pallanti et al. 2010). Likewise, dorsal striatal hyperactivity has also been observed in substance dependence (e.g., cocaine; Volkow et al. 2006).

In summary, resting state dysfunction has been observed in both the ventral and dorsal striatum in PG and SUDs. While many studies suggest relatively diminished activation of ventral striatum in processes involving risk/reward decision-making in PG, findings have been less consistent in drug addictions, suggesting, among other things, that drug exposure may influence striatal function and related activity.

Other brain function/key regions

The *anterior cingulate cortex (ACC)*, a component of the limbic system, is reciprocally connected with the amygdala and thought to have roles in mood and emotion responsivity (Childress et al. 1999), cognitive control (Botvinick et al. 2004), response inhibition (Dalley et al. 2011), and of particular relevance to PG, loss-chasing (Campbell-Meiklejohn et al. 2008). Findings suggest the ACC may play a role in risky decision-making among those with SUDs (Fishbein et al. 2005).

The *insula*, implicated in interoceptive processing, is relevant to risk/reward processing. It has extensive reciprocal connections with the vmPFC, amygdala and ventral striatum, making it well-positioned to contribute to emotional decision-making (Clark et al., 2008). Healthy adults activate the insula in gambling tasks (Cohen et al. 2005; Li et al. 2010) and in anticipation of reward (Beck et al. 2009; Cohen et al. 2005) and insula damage is associated with poor adjustments in betting behaviors (Clark et al. 2008). The insula may also contribute to rewarding effects as it has been activated in healthy adults in response to “near misses” and wins and this activity was correlated with desire to participate in a gambling task (Clark et al. 2009). Miedl et al. (2010) found occasional gamblers activated the insula

during simulated blackjack. In SUDs, de Ruiter et al. (2009) found that smokers activated the insula in response to monetary gain.

White matter integrity

Poorer white matter integrity, potentially resulting from drug-related neurotoxicity or reflecting individual differences, has been observed in association with heavy substance use and dependence, with some findings suggesting relationships with impulsivity (Verdejo-Garcia et al. 2008). In PG, reduced fractional anisotropy (FA) values were found in the left and right genu of the corpus callosum and were associated with measures of fun-seeking (Yip et al. in press). Poorer white matter integrity in PG persisted in models accounting for prior alcohol dependence. Poor white matter integrity has been observed diffusely in heavy alcohol users including binge-drinking adolescents (McQueeny et al. 2009) and alcohol dependent adults (Pfefferbaum et al. 2000). White matter integrity has also been linked with impulsivity in drug dependence, albeit inconsistently. In cocaine dependence, reduced FA was associated with higher scores on the Barratt Impulsiveness Scale (BIS-11; Patton et al. 1995) (Lim et al. 2008; see Moeller et al. 2005 for negative results).

Summary

Multiple brain regions, including the frontal cortices, striatum and insula, have been implicated in PG and SUDs. The precise nature of the involvement shows both similarities and differences (Table 2). Further, the extent to which brain function relates to impulsivity and compulsivity in these disorders is only beginning to be systematically examined.

Neurochemistry underlying impulsivity, compulsivity and risk/reward decision-making

Several neurotransmitter systems have been associated with impulsivity, compulsivity and risk/reward decision-making in PG and SUDs. Arguably, dopaminergic and serotonergic contributions have been most well investigated, with substantial research investigating dopamine function over the past several years. As such, these two transmitters will be the focus of this section. Opioidergic, glutamatergic, and noradrenergic systems will be addressed briefly.

Dopamine in PG

The extent to which dopaminergic activity contributes to impulsivity and compulsivity in PG has received little systematic examination. Using a rat IGT model, pro-dopaminergic and pro-adrenergic agent amphetamine was associated with an increase in perseverative responding, while D2/D3 agonist quinpirole and D1 antagonist SCH23390 were both associated with decreases in perseveration (Zeeb et al. 2009).

Studies assessing the impact of dopamine manipulation on risk/reward decision-making in normative human samples suggest a role for dopamine in gambling-related reward and reinforcement. On a task modeling “loss chasing”, D2-like receptor agonist pramipexole was associated with significant increases in perception of the value of losses chased and decreases in perceived value of losses not chased, suggesting increases in perceived value of rewards and minimization of punishment (Campbell-Meiklejohn et al. 2011). In a rat slot machine model, increases in “near miss” responses were found with D2-like receptor agonist quinpirole and amphetamine but not with the D1-like receptor agonist SKF 81297 (Winstanley et al. 2011). In a rat IGT model with somewhat contrasting findings, amphetamine increased selection of the second strongest option, offering the second largest reward and lowest punishment (Zeeb et al. 2009). While rats pursued and received rewards on amphetamine, the drug may have also increased punishment aversion.

Regarding relationships between risk/reward decision-making and dopaminergic activity in PG, those PG participants with ventral striatal dopamine release during the IGT reported more excitement than healthy control subjects (Linnet et al. 2011). Results also demonstrate the importance of individual differences as only 8/18 PG participants had findings suggestive of dopamine release (Linnet et al. 2011).

The impact of dopamine manipulation may be different among those with gambling problems. Amphetamine increased motivation to gamble in problem gamblers and problem gambling severity was related to the magnitude of positive subjective effects of amphetamine and ratings of motivation to gamble (Zack and Poulos 2004). There have been seemingly opposing findings with dopamine antagonists. The D2-like receptor antagonist haloperidol decreased a tendency in PG participants to bet more aggressively following payoffs in a slot machine task (Tremblay et al. 2011). However, in another study, haloperidol increased self-reported rewarding effects and primed desire to gamble in PG (Zack and Poulos 2007). These results may help to explain negative clinical trial findings for drugs with D2-like receptor antagonism (e.g., olanzapine; Fong et al. 2008; McElroy et al. 2008) in PG. These findings suggest a complex relationship between D2-like dopamine receptor function and gambling-related motivations and behaviors.

Studies in PD also suggest associations between reward responsiveness and dopamine (Leeman and Potenza 2011). Changes in risk/reward preferences may be associated with dopaminergic medications (Frank et al. 2004; Kobayakawa et al 2010; Pagonabarraga et al 2007) and, like the non-PD literature (Zack and Poulos 2004; 2007), differentially associated in those with and without ICDs (Bodi et al. 2009; Housden et al. 2010). Tested off DRTs, Cilia et al. (2010) found reduced striatal dopamine transporter binding in PD patients with PG, suggesting higher levels of synaptic dopamine, reduced mesolimbic dopamine function, or diminished cell-surface transporter protein levels. Also tested off DRTs, raclopride displacement in the ventral striatum during a gambling task was greater in PD patients with PG than in PD patients without, consistent with greater dopamine release in association with PG (Steeves et al. 2009).

DRT use and ICD status have also been associated with impulsive choice and response tendencies in PD patients. PD patients with ICDs tested on DRT were more likely than healthy control subjects and PD patients without ICDs to prefer immediately available rewards in a delay discounting task (Housden et al. 2010). In a within-subjects comparison in which patients were tested on and off medication, dopamine agonist use was associated with more impulsive choices on the EDT in those with ICDs, but not in those without (Voon et al., 2010). In contrast, with a non-PD sample, Hamidovic et al. (2008) found no significant influence of the dopamine agonist pramipexole on perseveration and performance of impulsive choice and response tasks.

Similarities and differences in dopaminergic contributions to PG and SUDs

Dopamine has been hypothesized to contribute to delay discounting in SUDs (Schultz 2011). Dopamine involvement in impulsive choice and response in PG has not received research attention in non-PD samples. While a contribution of dopamine to compulsivity in SUDs has been reported (Schultz 2011), little work has investigated dopamine's role in compulsivity in PG.

Similarities exist with respect to involvement of dopamine in PG and SUDs. As with gambling, substance use has been associated with dopamine release (Ritz et al. 1987), supported by recent findings from a PET study of alcohol administration in non-dependent individuals (Urban et al. 2010). At the same time, individual differences in dopamine responses have been identified in PG (Linnet et al. 2011) and SUD (Volkow 2010) samples.

As with gambling, dopamine may mediate reinforcing and rewarding effects of drugs (Goldstein and Volkow 2002). Continued substance seeking and taking may be perpetuated in part by reduced numbers of striatal dopamine D2-like receptors (Volkow et al. 2003). Regarding gambling, Zack and Poulos (2007) argued that haloperidol led to reduced D2-like receptor availability among PG participants, which, they believed, led to increased rewarding effects, although this hypothesis was not directly examined in their study.

PG may differ from some substance addictions with regard to dopaminergic response to particular manipulations. Amphetamine did not increase motivation to drink in problem drinkers as it did motivation to gamble in PG (Zack and Poulos 2004).

Serotonin in PG

Preliminary investigations have been performed into relationships among impulsivity, compulsivity and treatment outcome in a clinical trial to test the efficacy of a selective serotonin reuptake inhibitor (SSRI) for PG. In a placebo-controlled trial of paroxetine (Blanco et al. 2009), self-reported impulsiveness on the Eysenck Personality Questionnaire (Eysenck et al. 1985) and scores on the impaired control over mental activities subscale of the Padua Inventory (Sanavio 1988), a self-report measure of obsessional and compulsive tendencies, were correlated with problem gambling severity at treatment onset and declined by the end of treatment. Changes in problem gambling severity (assessed by the Yale-Brown Obsession Compulsion Scale Modified for Pathological Gambling [PG-YBOCS]; Pallanti et al. 2005) were related to changes in impulsiveness only, suggesting changes in gambling symptoms were tied more closely to changes in impulsivity than compulsivity (Blanco et al. 2009).

Findings from neurochemical studies indicate a role for serotonergic function in PG. Low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been found in cerebrospinal fluid samples from subjects with PG (Nordin and Eklundh 1999). In PG and healthy controls, ^{3}H-paroxetine ([^{3}H]-Par) binding to platelet membranes was used to investigate the serotonin transporter (SERT), a protein that regulates synaptic serotonin concentration through reuptake mechanisms. Maximum binding capacity values were lower in PG subjects, suggesting the involvement of serotonin in PG (Marazziti et al. 2008b). Administration of meta-chlorophenylpiperazine (mCPP), a mixed serotonin agonist with high affinities for 5HT1 and 5HT2 receptors, elicited subjective reports of a “high” or a buzz in individuals with PG. In contrast, control subjects tend to report aversive responses to mCPP (DeCaria et al. 1998; Pallanti et al. 2006). Blunted growth hormone response to sumatriptan, a selective 5-HT1B receptor agonist, has also been observed in PG (Pallanti et al. 2010), whereas increased growth hormone release has been seen in control subjects (Herdman et al. 1994).

Clinical trial findings of SSRIs (e.g., fluvoxamine and paroxetine), have been mixed (positive: Hollander et al. 2000; Kim et al. 2002; negative: Blanco et al. 2002; Grant et al. 2003; Saiz-Ruiz et al. 2005) and results with olanzapine, a drug with 5HT2 receptor antagonistic properties, were negative (Fong et al. 2008; McElroy et al. 2008). While the positive findings support serotonin’s role in PG, the mixed findings suggest that individual differences contribute to variability in efficacy of SSRIs in the treatment of PG.

Similarities and differences in serotonergic contributions to SUDs and PG

Neurochemical studies suggest serotonergic similarities in PG and SUDs. As in PG, low levels of 5-HIAA were found in alcohol dependence (Fils-Aime et al. 1996; Ratsma et al. 2002). As in PG, administration of mCPP elicits reports of subjective “high” in abstinent alcoholics (Krystal et al., 1994). Blunted growth hormone response to sumatriptan has been

observed in alcohol dependence (Vescovi and Coiro 1997) and PG. Given that mCPP and sumatriptin target serotonin 5HT1B receptors, it is tempting to speculate that similarly abnormal biochemical and behavioral responses in PG and alcohol dependence are mediated through this receptor. PET studies with the selective 5HT1B ligand [^{11}C]P943 have implicated 5HT1B receptor function in PG and alcohol dependence (Hu et al 2010; Potenza et al. in press). Alcohol dependent participants showed greater binding potentials than controls and problem gambling severity correlated positively with binding potentials in PG, suggesting increased 5HT1B receptor availability may contribute across non-substance and substance addictions.

Mixed clinical trial findings with serotonergic agents in PG are similar to results in SUDs. Both SSRIs (Torrens et al. 2005) and olanzapine (Amato et al. 2010; Guardia et al. 2004) have shown limited efficacy in the treatment of SUDs.

Differences in the relationship between serotonin function and gambling and substance use behaviors may also exist. Tryptophan depletion, which results in reduced central serotonin levels and altered serotonin neurotransmission, was related to less “loss chasing” in simulated gambling (Campbell-Meiklejohn et al. 2011). Among those at high risk of alcohol dependence, tryptophan depletion has been associated with increased response, but not choice, impulsivity (Crean et al. 2002; LeMarquand et al. 1999). These findings suggest tryptophan depletion, and by extension, serotonin function, may differentially influence aspects of decision-making and impulsivity. The extent to which these findings extend to PG and SUDs warrants investigation.

Opioids in PG

Elevated levels of the endogenous opioid beta-endorphin have been tied to gambling and related behaviors (Shinohara et al. 1999). Currently, opioid antagonists have the strongest empirical support amongst pharmacotherapeutic agents for PG. High-dose naltrexone was superior to placebo and especially efficacious in those reporting strong gambling urges at treatment onset (Kim et al. 2001). In a multi-site trial of nalmefene, 25mg and 50mg doses were associated with greater declines in PG-YBOCS scores than placebo. However, while efficacious, 50mg and 100mg doses were associated with adverse events and more treatment discontinuation (Grant et al. 2006). In a trial of naltrexone in PG patients reporting primarily urge-driven gambling, significant reductions were found in problem gambling severity, PG-YBOCS scores, self-reported urges and gambling behavior (Grant et al. 2008a). Subsequent analyses of early naltrexone and nalmefene data related family history of alcoholism to positive treatment response (Grant et al. 2008b). A subsequent study found that amongst subjects receiving active medications, nalmefene was superior to placebo, although the intent-to-treat analysis including early (placebo-lead-in) drop-outs was negative (Grant et al. 2011). Thus, results from four randomized, clinical trials of opioid antagonists yielded positive findings with respect to diminishing problem gambling severity and this effect seems particularly robust amongst in those with a family history of alcoholism or strong gambling urges. In contrast, Toneatto et al. (2009) reported no significant advantage for naltrexone over placebo for concurrent treatment of alcohol use disorder and PG. Although naltrexone was associated with decreased gambling and alcohol use, there was a strong placebo response, and studies designed to anticipate and account adequately for placebo responses in co-occurring patient populations appear warranted.

Similarities and differences in opioidergic contributions to SUDs and PG

Clinical trial results with opioid antagonists for PG follow multiple positive results for SUDs, particularly alcohol and opiate dependence. Naltrexone is effective in blocking rewarding effects of opiates. Its lack of success in treatment trials appears related to non-

compliance rather than pharmacologic efficacy (Lobmaier et al. 2008; Minozzi et al. 2011). Naltrexone, in conjunction with psychosocial therapy, has demonstrated efficacy in alcohol use reduction (Rosner et al. 2010), although there have been negative trials (e.g., Krystal et al. 2001). Mechanisms for naltrexone's efficacy include reductions in urges to drink (Monti et al. 1999; Palfai et al. 1999). Thus, findings suggest that naltrexone may reduce urges in PG and problem drinking. Evidence also suggests naltrexone's effects in PG and alcohol dependence (Krishnan-Sarin et al. 2007) may be particularly strong among those with a family history of alcoholism.

While there is evidence of a role for opioid activity in reward related directly to substance use, opioid activity may not contribute as robustly to reward responsiveness or all facets of impulsivity more broadly. Unlike findings with amphetamine, naltrexone reduced alcohol consumption in a mouse model but had no tangible effect on impulsive choice or attention in a delay discounting task (Oberlin et al. 2010). Similarly, in a rat delayed reward task, the opioid antagonist naloxone did not have a notable effect on impulsive choice, but did ameliorate response impulsivity on the five-choice serial reaction time task (Wiskerke et al. 2011).

Glutamate in PG

Open-label n-acetyl cysteine (NAC), a glutamatergic nutriceutical, was associated with significant decreases in problem gambling severity. These changes largely persisted in a double-blind discontinuation phase, with a large effect size (Grant et al., 2007). NAC is believed to restore extracellular glutamate concentration and influence neurotransmission in regions including the ventral striatum.

Reductions in PG-YBOCS scores and decreased gambling were noted with open-label memantine, a N-methyl d-aspartate receptor antagonist (Grant et al. 2010). Though stop-signal reaction time did not improve significantly, the performance of PG subjects at trial end no longer differed from that of control subjects. Amongst PG subjects, there was significant improvement at the end of treatment in IDED performance. Decreases in numbers of errors on the IDED from pre- to post-treatment were correlated significantly and positively with baseline problem gambling severity. This finding may have been due to modulation of glutamatergic neurotransmission in the PFC due to memantine (van Wageningen et al., 2010), although this hypothesis was not directly examined. Thus, memantine may reduce aspects of impulsivity and perhaps particularly compulsivity in PG, and larger, controlled studies are indicated.

Similarities and differences in glutamatergic contributions to SUDs and PG

Medications that alter glutamate neurotransmission may decrease both gambling and substance use. Paralleling gambling findings, NAC was associated with reduced reward-seeking in rats trained to self-administer cocaine (Baker et al. 2003) and in reduced heroin-induced drug seeking in rats (Zhou and Kalivas 2008). NAC may reduce cigarette (Knackstedt et al. 2009) and marijuana use and craving in humans (Grey et al. 2010). Memantine may also have a role in treating alcohol dependence. In human alcohol administration studies, memantine was associated with reduced positive subjective effects (Krupitsky et al. 2007). The extent to which memantine exerts its influences on substance use through effects on impulsivity or compulsivity is unclear, particularly given that memantine reduced alcohol consumption in mice without tangibly influencing attention or impulsive choice on a delay discounting task (Oberlin et al. 2010).

Evidence suggests that an imbalance in glutamate neurotransmission may underlie impulsive and compulsive behavior in both PG (Grant et al. 2010) and SUDs (Kalivas 2009).

Accordingly, findings suggest medications that modulate glutamate neurotransmission may lead to reduced impulsive and compulsive action in PG and SUDs (Grant et al. 2010; Kalivas 2009).

Norepinephrine in PG and SUDs

Norepinephrine, which has been linked to arousal, has been found to increase during gambling behavior (Shinohara et al. 1999), including in individuals with PG, consistent with elevations in peripheral measures of arousal like heart rate (Meyer et al. 2004). People with PG have been found in non-gambling situations to have elevated measures of adrenergic agents and their metabolites (Roy et al. 1988; 1989). Given that adrenergic systems may mediate rewarding effects of addictive behaviors (Weinshenker and Schroeder 2007) and adrenergic drugs may influence impulsivity (Chamberlain et al. 2007) and treatment outcomes in SUDs (Jobes et al. in press; Shaham et al. 2000; Sinha et al. 2007), more work is needed to investigate relationships between adrenergic systems and agents in PG and as related to impulsivity and compulsivity.

Summary

Evidence supports roles for dopamine, serotonin, opioids, glutamate and norepinephrine in PG and SUDs (Table 3). Overlaps exist in many cases, especially PG and alcohol dependence.

Future directions for research related to impulsivity and compulsivity in SUD and PG

This review suggests multiple avenues for future research. These include the prediction of risk for PG and SUDs, laboratory models and treatment studies.

Regarding vulnerability, studies involving subgroups at risk for PG (e.g., those with a positive family history of this or other ICDs), along the lines of similar studies in SUDs (e.g., LeMarquand et al. 1999), could offer valuable information regarding the characteristics that are associated with risk for developing PG. Also, longitudinal studies in those at high risk and those with PG, SUDs and both, in humans as well as in animal models, could provide important information regarding risk and vulnerability, as well as the natural history of these disorders.

Future studies could be designed to address complex and contrasting findings regarding dopaminergic and serotonergic activity in SUDs and PG, along with the nature of activation in the various brain regions in PG and SUDs. Such investigations could intergrate multiple modes of imaging (PET, fMRI, diffusion tensor imaging) to understand better the relationships among neurochemistry, functional activation and white matter integrity. Advanced analytic techniques could be applied data to investigate functionally integrated activations during fMRI as related to task function and other imaging and clinically relevant measures.

A challenge in comparing results in PG and SUD research is that laboratory research in SUDs (Haney 2009) arguably comes closer to duplicating actual substance use than PG research does in duplicating actual gambling. While actual substances can be administered, most gambling studies utilize simulated tasks. While some studies (e.g., Breen and Zuckerman 1999) have used actual money, these have been rare. Data suggest use of actual versus hypothetical money may influence subjective and neural responses (Hollander et al. 2005). In recent years, there has been progress in modeling aspects of gambling (e.g., models of the “near miss” and “loss chasing” phenomena). These models could be utilized

in more PG studies and in laboratory studies of medication development similar to what has been done in SUDs (e.g., O'Malley et al. 2002). PG and SUD research would benefit from development of more human and animal models of aspects of addiction. Recent progress in animal models in PG (Rivalan et al. 2009; Winstanley et al. 2011; Zeeb et al. 2009) is promising. If rats or mice could be bred selectively or genetically engineered to gamble in a manner analogous to PG, akin to SUD models (e.g., alcohol preferring rats; Bell et al. 2006), they would represent powerful research tools.

Additional research on aspects of impulsivity and compulsivity should be conducted both in PG and SUDs. Relationships between impulsivity and compulsivity are inadequately understood and should be examined further (Blanco et al., 2009; Dalley et al. 2011). Subsequent work is needed to define clearly and to fractionate the heterogeneous concept of compulsivity (Dalley et al. 2011; Fineberg et al. 2010), along similar lines of work conducted in the impulsivity literature (see Dick et al. 2010). In particular, self-report measures and neurocognitive tasks that can isolate facets of compulsivity such as response perseveration and outcome devaluation would be particularly useful. Imaging research to identify the neurochemistry and brain function underlying impulsivity and compulsivity in PG and SUDs would be valuable, as would continued research of these constructs in people and animal models. In particular, the use of both self-report and behavioral measures of impulsivity and compulsivity in clinical trials for PG and SUDs could yield clinically valuable information for understanding how treatments work and for whom specific treatments work best (Potenza et al 2011).

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Table 1

Similarities and differences between pathological gambling (PG) and substance use disorders (SUDs) with regard to neurocognitive task performance findings (see text for details)

Primary construct	PG results	SUD results: similarities/differences with PG
Response impulsivity	PG groups exhibit more commission errors than do controls on go/no-go tasks. PG groups demonstrate longer stop-signal reaction times on stop-signal task than do controls but also negative and qualified findings.	SUD groups also exhibit more commission errors than do controls. SUD groups also demonstrate longer stop-signal reaction times on stop-signal task than do controls.
Choice impulsivity (delay discounting)	PG groups discount delayed rewards to a greater extent than do controls. PD patients with ICDs discount delayed rewards to a greater extent than patients without ICDs.	SUD groups also discount delayed rewards to a greater extent than do controls.
Reflection impulsivity	PG groups demonstrate greater difficulty with reflection than do controls.	SUD groups also demonstrate greater difficulty with reflection than do controls.
Attention and working memory	Lack of strong evidence that attention and working memory are compromised in PG.	SUD groups demonstrate greater difficulties with attention and working memory than do controls.
Response perseveration compulsivity	Most findings suggest greater response perseveration in PG groups as compared with controls.	Some findings also suggest greater response perseveration in SUD groups than in controls but several negative findings as well.
Risk/reward decision-making	PG groups draw from disadvantageous decks more frequently than do controls on IGT and bet more and lose more money than do controls on CGT.	SUD groups also draw from disadvantageous decks more frequently than do controls on IGT, but evidence of some differences from PG. SUD and substance using groups bet more and lose more than do controls on CGT, but negative findings as well.

PD: Parkinson’s Disease, ICD: impulse control disorder, IGT: Iowa Gambling Task, CGT: Cambridge Gamble Task

Table 2

Similarities and differences between pathological gambling (PG) and substance use disorders (SUDs) with regard to brain function research findings related to impulsivity and compulsivity (see text for details)

Brain region/structure	PG results	SUD: similarities/differences with PG
Frontal cortical regions	*Response impulsivity tasks*: PG/problem gamblers demonstrate less activity than do controls.	SUD/substance users also demonstrate less activity than controls.
	Compulsivity tasks: PG/problem gamblers demonstrate less activity than do controls. Lesion studies suggest vmPFC and dlPFC are important for task performance.	Smokers also demonstrate less activity than do controls.
	Risk/reward tasks: PG/problem gamblers demonstrate less activity than do controls. In PD, less activity among those with ICDs, greater activity in those without ICDs.	Most findings also suggest less activity in SUD groups than in controls.
Striatum	*Baseline*: Limited results have been variable regarding D2-like receptor availability in PG. Limited evidence suggests dorsal hyperactivity.	Reduced D2-like receptor availability in SUD/substance users. Dorsal hyperactivity in SUD also.
	Impulsivity and compulsivity tasks: Limited findings suggest no differences between PG and controls.	Limited findings suggest no differences between substance users and controls.
	Risk/reward tasks: In PG, less ventral activity than in controls and association with impulsivity. Some evidence of elevated dorsal activity in PG. Findings more variable in PD studies.	Some similar findings of diminished ventral activity in SUD/substance users with similar associations with impulsivity (particularly in alcoholism), but opposing findings of elevated activity as well.
Anterior cingulate cortex (ACC)	Findings that “loss chasing” is associated with elevated activity in healthy adults suggest a role in gambling.	Associated with risky decision-making in SUDs.
Insula	Activated by healthy adults and occasional gamblers during gambling tasks and by healthy adults in response to “near misses” during gambling tasks.	Activated in response to reward by substance users.
White matter integrity	PG reduced FA values in the corpus collosum	Poor white matter integrity observed diffusely both in heavy substance users and in SUDs

PD: Parkinson’s Disease, ICD: impulse control disorder, FA: fractional anisotropy

Table 3

Similarities and differences between pathological gambling (PG) and substance use disorders (SUDs) with regard to neurotransmitter system research findings (see text for details)

Neurotrans-mitter	PG results	SUD results: similarities/differences with PG
Dopamine	Limited impulsivity findings: In PD, agonist use associated with increased delay discounting in those with ICD.	Activity proposed to contribute to delay discounting in SUDs.
	Limited compulsivity findings: Equivocal results with agonists in animal models.	Activity proposed to contribute to compulsivity in SUDs.
	Elevated release during gambling task performance in some with PG (with and without PD), but also individual differences.	Substance use typically associated with release, but also individual differences.
	Equivocal findings with antagonist use	Also equivocal findings with antagonist use
Serotonin	Low levels of 5-HIAA in PG	Low levels of 5-HIAA in SUDs
	mCPP associated with subjective “high” in PG	mCPP associated with subjective “high” in SUDs
	Blunted growth hormone response to sumatriptan	Blunted growth hormone response to sumatriptan
	Evidence suggests role for 5HT1B receptor function	Evidence suggests role for 5HT1B receptor function
	Mixed results in efficacy of SSRIs for PG	Mixed results in efficacy of SSRIs for SUDs
Opioids	Evidence of involvement in gambling behavior and urges. Strong evidence for treatment efficacy of antagonists.	Evidence of involvement in substance use behavior and urges. Strong evidence for treatment efficacy of antagonists, particularly for alcohol and opioid dependence.
Glutamate	Preliminary evidence for efficacy of medications that alter transmission, with possible involvement in impulsive and compulsive behaviors.	Preliminary evidence for efficacy of medications that alter transmission, with possible involvement in impulsive and compulsive behaviors.
Norepineprine	Elevated activity in PG, particularly during gambling.	Elevated during use of some substances, particularly stimulants like cocaine.

5-HIAA: 5-hydroxyindoleacetic acid, PD: Parkinson’s Disease, ICD: impulse control disorder, mCPP: meta-chlorophenylpiperazine, SSRI: selective serotonin reuptake inhibitor