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Pathological Gambling and Substance Use Disorders

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Abstract

Pathological gambling (PG) has been considered as a behavioral addiction having similarities with substance use disorders (SUDs). Shared features exist in diagnostic, clinical, physiological, and behavioral domains. Current conceptualizations of addiction, as well as experimental studies of PG and SUDs, are reviewed in order to provide a perspective on the areas of convergence between addictive behaviors in PG and SUDs.

Keywords

Pathological gambling; gambling; substance use disorder; addiction; substance dependence; impulsivity

Introduction

Pathological gambling (PG) is classified as an Impulse Control Disorder (ICD) Not Elsewhere Classified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) (1). ICDs are characterized by repeated engagement in impulsive behaviors and a diminished ability to inhibit participation in these behaviors despite adverse consequences. PG is described as a maladaptive pattern of gambling behavior that may be associated with serious psychosocial and financial problems. Clinical features of PG overlap with those of substance use disorders (SUDs). On this basis, researchers have conceptualized PG as a non-substance or 'behavioral' addiction in which elements, such as impaired self-control, may be shared amongst individuals with PG and those with SUDs (2–4). Here, we review diagnostic, pharmacological, neurobiological, genetic, and behavioral features of PG in order to highlight similarities and differences between PG and SUDs.

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Epidemiology, Co-morbidity, Diagnostic Features and Clinical Phenomena

Although earlier reports have typically cited prevalence estimates in the 1%–2% range, more recent prevalence estimates using diagnostic rather than screening assessment typically range from 0.5–1% (5, 6). In community samples, PG co-occurs with a broad range of mental health conditions. For example, the St. Louis Epidemiologic Catchment Area Study found that individuals with PG symptomatology (both syndromal and subsyndromal PG) were more likely than those without to have substance use disorders (particularly relating to alcohol use), mood disorders, and psychotic disorders (7). More recent epidemiologic data (e.g., from the National Epidemiologic Survey of Alcohol and Related Conditions and the National Co-morbidity Study - Replication) indicate that PG co-occurs with a broad range of both Axis I and Axis II disorders (5, 6). Furthermore, subsyndromal patterns of gambling appear to be associated with multiple mental health disorders, suggesting that gambling behaviors might be best considered along a continuum rather than as discrete entities (8, 9). PG and other ICDs may go under-diagnosed in psychiatric populations. For example, in a sample of adult psychiatric inpatients, 2% of patients upon admission were diagnosed with an ICD, whereas additional screening found that 30% of patients met diagnostic criteria for an ICD, with about a quarter of these individuals meeting criteria for PG (10). A similar diagnostic pattern was observed amongst adolescent inpatients, with 1% being initially diagnosed with an ICD and approximately 40% found to meet criteria for an ICD following active screening and formal diagnostic assessment (11). Together, these findings suggest that, as in the case of SUDs, co-occurring psychiatric disorders are an important consideration for PG and other ICDs.

Substance dependence is defined in the DSM-IV-TR as a “maladaptive pattern of substance use, leading to clinically significant impairment or distress” (1). Diagnostic criteria for substance dependence state that “substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance” (1). Similarly, diagnostic features of PG describe a diminished ability to resist an impulse to gamble despite serious or adverse consequences of the gambling behaviors. The core behaviors of SUDs and PG (e.g., drug-seeking or participation in gambling activities, respectively) appear characterized by initial appetitive drives that lead to more compulsive motivational states (3).

PG and substance dependence share specific diagnostic features, including those of tolerance and withdrawal (1). Tolerance in substance dependence describes the use of increasing amounts of a substance in order to achieve an equivalent desired effect of previous consumptions, or a diminished desired response following the use of the same amount of a substance. In PG, tolerance is operationalized as gambling with increasing amounts of money in order to achieve the desired subjective effect (e.g., excitement), or that the same level of gambling leads to a diminished subjective response. Withdrawal in substance dependence relates to the onset of physiological or psychological symptoms upon the abrupt cessation or marked diminution of substance use. Features of withdrawal are present in the diagnostic criteria for PG, operationalized as becoming anxious or irritable when quitting or cutting down on gambling. The diagnostic criteria for PG and substance dependence also share common criteria relating to interference in major areas of life functioning and repeated unsuccessful attempts to cut back or quit. Several inclusionary criteria specific to PG (e.g., lying about gambling, gambling related “chasing” and financial bailouts, illegal behaviors related to gambling) may be analogous to substance-related behaviors in substance dependence, even if they are not directly reflected in the diagnostic criteria. For example, the term chasing in PG (going back to a gambling venue shortly after losing in an effort to regain money recently lost) may share features with “chasing a high” or being on a “drug run” (repeatedly seeking and using drugs), although further research is needed to examine this possibility.

Several studies have investigated the diagnostic criteria with respect to their frequencies of acknowledgement and their relationships with one another. One study of 399 US individuals from a nationally representative sample found that individual diagnostic criteria of PG overlapping with those for substance dependence were acknowledged frequently individuals meeting diagnostic for PG (9). For example, approximately 75% of individuals with PG reported withdrawal and 57% reported tolerance (9), although additional investigation of the nature of the similarities and differences of these sates in PG and SUDs is warranted. The same study, using principal components analysis, found that nine of the ten inclusionary criteria (all but the most frequently acknowledged criterion of chasing) loaded moderately to strongly onto a primary component, suggesting that the majority of the criteria (including those that predominantly overlap with those for drug dependence) may represent a unitary construct (9). However, again in the same study, multi-level regression analyses suggested the existence of four groups of individuals (at-risk, problem, low-severity pathological, and high-severity pathological), based on the number and precise criteria acknowledged (9). A second study using data from the National Epidemiologic Survey on Alcohol and Related Conditions found that among 11,153 individuals gambling at least five times in a single year, the diagnostic criteria were strongly unidimensional as assessed by Rasch modeling (12). While the criteria maintained a reliable ordering across a gambling continuum, the authors found that although there was sufficient reliability to distinguish the groups using the current threshold of five criteria, there was not sufficient reliability to distinguish groups acknowledging less than five criteria (12). The findings of a unitary construct (arguing for a single diagnostic entity) are similar to those observed when modeling together abuse and criteria dependence for alcohol using a similar approach (12).

Treatment

Currently, there are no FDA-approved pharmacotherapies for the treatment of PG. Pharmacological interventions have targeted serotonin, opioidergic, and glutamatergic systems, among others (13). A meta-analysis of pharmacotherapy studies in PG patients found a large (d=0.78) overall post-treatment effect size of medications (14). However, this effect size may be inflated due to the high placebo treatment response rates observed in PG.

Multiple medication classes, including serotonin reuptake inhibitors, opioid antagonists, mood stabilizers, and other agents like bupropion and N-acetyl-cysteine, have been evaluated for their efficacy and tolerability in treating PG (13). The findings from placebo-controlled, randomized clinical trials for serotonin reuptakes inhibitors (paroxetine, fluvoxamine and sertraline) have been mixed, with both positive and negative findings reported (13, 15–18). The mood stabilizer lithium was superior to placebo in reducing gambling and manic symptomatology in individuals with PG and co-occurring bipolar spectrum disorders (typically bipolar II disorder) (19). The nutriceutical N-acetyl cysteine, a glutamate-modulating agent with preliminary efficacy in the treatment of cocaine dependence and nicotine dependence, was efficacious and well-tolerated in an initial open-label trial followed by double-blind discontinuation (20). The most consistent data involve opioid antagonists, drugs that are efficacious in the treatment of alcohol dependence and opiate dependence. Specifically, two placebo-controlled trials of naltrexone and two placebo-controlled trials of nalmefene have had positive findings (21–24). Furthermore, the most robust clinical measures associated with treatment outcome in the opioid antagonist-treated individuals were a family history of alcoholism and strong gambling urges at treatment onset, findings consistent with those from the alcohol dependence treatment literature (25). Together, these findings suggest overlaps in the pharmacological treatments of PG and SUDs.

Behavioral therapies for the treatment of PG have also received empirical support. Cognitive-Behavioral Therapy (CBT) targets cognitive distortions, craving states, and poor

coping strategies in patients with PG (26). A meta-analysis of studies concluded that CBT had a significant beneficial post-treatment effect on PG patients (27). One randomized controlled study examining the use of CBT for PG found that 86% of patients who received CBT no longer met DSM criteria for PG post-treatment, whereas only 6% of control patients did not meet DSM criteria for PG (28). Subsequent studies utilizing CBT to treat PG have found similar beneficial treatment outcomes (29). In the largest behavioral therapy study performed to date involving PG subjects, a CBT package based on one initially developed for SUDs and modified for PG showed efficacy in the treatment of PG (26). Motivational therapies (e.g., motivational enhancement therapy, motivational interviewing) have shown efficacy in the treatment of both SUDs and PG (13). The use of brief motivational therapy strategies in the treatment of PG has been supported by randomized controlled trials demonstrating beneficial treatment outcomes in college students with PG (30) and other adult PG populations (31). Existing data also indicate that participation in Gamblers Anonymous, the most widely available intervention for PG, is associated with better treatment outcome (32). Together, these findings suggest that, like with pharmacotherapies, many behavioral therapies for SUDs appear promising when adapted for PG.

For both PG and SUDs, clinical trials and formalized treatments might be limited to individuals with disorders of greater severity. Recent analyses of community data indicate that, as in the case of SUDs (often termed “spontaneous recovery”), a majority of individuals recover from PG without apparent formal interventions (33). Thus, for many individuals with PG or SUDs, the natural histories may be relatively self-limited rather than chronic in nature, although additional direct investigation through longitudinal studies is needed to further substantiate this notion (34). Sex differences in the natural histories of PG and SUDs should be taken into consideration, e.g., sex differences in “telescoping” have been observed in both disorders (35, 36). Telescoping refers to a more rapid progression from initial to problematic engagement in the behavior that is the focus of the disorder (e.g., gambling in PG).

Neurobiology

Neurobiological models of PG, including roles for specific neurotransmitter systems, have been based, in part, on studies of drug addiction (37). For example, norepinephrine has been hypothesized to relate to aspects of arousal. Initial studies of men with PG have found elevated levels of noradrenergic metabolites in individuals with PG and levels have correlated with measures of extroversion (37). Serotonin has been hypothesized to underlie behavioral control and differences in subjective, biochemical, and neural responses to serotonergic challenges have been observed in individuals with PG and other ICDs (37). Dopamine has been implicated in reinforcement and learning processes related to drug and non-drug rewards, and data have been mixed with respect to dopamine involvement in PG. For example, one study of cerebrospinal fluid (CSF) from PG subjects found altered levels of dopamine and dopaminergic metabolites in men with PG, but these findings were no longer apparent when controlling for CSF flow rates (37). Another study found that the D2/D3 dopamine receptor antagonist haloperidol primed gambling motivations in individuals with PG (38), whereas other studies have found an association between D2/D3 dopamine receptor agonist use and PG and other ICDs in individuals with Parkinson’s disease (39–42). A precise role for dopamine in PG requires additional investigation.

Brain imaging studies have investigated PG and its relationship to SUDs (37). Functional magnetic resonance imaging studies of PG have repeatedly identified ventral components of cortico-striatal circuitry as demonstrating relatively reduced activation in PG. For example, in a study of simulated gambling, individuals with PG showed relatively diminished activation of ventromedial prefrontal cortex (vmPFC) and ventral striatum, with severity of gambling problem correlating inversely with the degree of activation within these brain

regions in the PG subjects (43). These findings of diminished activation of the vmPFC are consistent with prior studies that have identified diminished relative activation of the vmPFC during viewing of gambling-related videotapes (44) and during performance of the Stroop color-word interference task (45), an assessment of cognitive inhibitory control. The vmPFC has been implicated in risk-reward decision-making, and individuals with PG or SUDs have disadvantageous performance on cognitive tests (e.g., the Iowa Gambling Task – IGT) assessing risk-reward decision-making (46). An fMRI study of individuals with SUDs with or without PG found that these individuals, as compared to non-addicted control subjects, showed relatively diminished activation of vmPFC during IGT performance (47).

Few brain imaging studies have directly compared individuals with PG and those with SUDs. One such study found that cocaine-dependent men, as compared to control comparison men viewing cocaine-related videotapes, showed differences in brain activations that were similar to those observed when PG men were compared to control comparison men viewing gambling–related videotapes (37). In this study, both cocaine-dependent and PG subjects showed relatively diminished regional activation in the ventral striatum. These findings are similar to those from individuals with Parkinson's disease with and without ICDs (including PG). In those studies, individuals with ICDs showed relatively diminished blood flow to the ventral striatum (as assessed by fMRI arterial spin labeling) and relatively diminished activation of the ventral striatum during performance of a risk-taking task (48). Additionally, in the videotape tape study, PG and cocaine-dependent subjects showed similar differences from control subjects during viewing of the respective addiction-related tapes in other cortico-limbic brain regions, including ventral PFC, thalamus and posterior cingulate cortex (37). In each case, relatively diminished activation was observed. These findings suggest that appetitive states relating to responses to the object of the addiction show similar neural correlates across PG and cocaine dependence.

However, not all brain regions show similarities. Regions showing the most robust differences included the anterior cingulate cortex, in which relative activation was observed in cocaine-dependent men during viewing of the cocaine tapes, but not in PG men viewing the gambling tapes. This finding has since been replicated in an independent sample of cocaine-dependent, PG, and control comparison subjects of both sexes (49). Another study involving tobacco smokers, PG subjects, and a control comparison group found that PG subjects showed relatively diminished activation of ventrolateral PFC during reward processing, a finding consistent with that of PG subjects viewing gambling tapes, but one not extending to tobacco smokers (50). Together, these findings suggest multiple similarities, but also differences, in the neural correlates of PG and SUDs.

Although few studies have investigated neuropsychological function in individuals with PG, existing data indicate similarities with SUDs (51–53). For example, both groups tend to perform disadvantageously on gambling tasks and other measures of choice impulsivity. In contrast with some SUDs (e.g., cocaine dependence), PG appears characterized by normal executive functioning in some traditional domains (e.g., as assessed by the Wisconson Card Sorting Task or by working memory performance). Studies that have directly contrasted individuals with PG with those with SUDs have largely confirmed these findings, suggesting a more extensive pattern of neurocognitive dysfunction in SUDs than in PG (51–53). Certain cognitive distortions (e.g., illusion of control or gambler's fallacy) may be more specific to PG than SUDs (54). However, the extent to which these cognitive distortions may extend to individuals with SUDs warrants direct examination, particularly as some of these biases appear to extend to individuals without PG (54).

Preliminary findings have identified similarities between PG and SUDs using brain imaging modalities other than fMRI. For example, as in the case of cocaine dependent subjects,

corpus collsal genual differences in white matter integrity have been observed in PG subjects and these have correlated with impulsivity-related measures (49). A ligand-based positron emission tomography (PET) study of individuals with Parkinson's disease with and without PG found that individuals with PG demonstrated lower D2/D3 dopamine receptor availability, findings similar to those observed in SUDs (55). Additional studies employing larger and more diverse samples and a wider array of imaging modalities are needed to investigate the similarities and differences in the characteristics of individuals with PG and SUDs.

Genetics

In the Vietnam Era Twin (VET) Registry sample of male twins, a substantial portion of PG symptomatology was found to be attributable to genetic factors, with estimates increasing from 48% of the variance for one or more inclusionary criteria and 54% for two or more inclusionary criteria accounted for by genetic factors (56). Two additional VET Registry studies found common genetic contributions to various SUDs, including alcohol, nicotine, and cocaine dependence, and significant shared genetic vulnerabilities for both alcohol dependence and PG in men (56). Although both shared genetic and environmental factors contribute to the co-occurrence of PG and alcohol dependence and PG and anti-social behaviors in the VET Registry sample, the co-occurrence of PG and major depression is predominantly genetic in nature (57). These findings suggest, as in the case of SUDs, that genetic factors contribute significantly to PG. Given the overlap in genetic and environmental contributions to both PG and SUDs and their co-occurrence, more research is needed to identify specific genetic and environmental influences.

Molecular genetic investigations have been performed in PG and SUDs (3). For example, one allele of the gene encoding the dopamine D2 receptor (Taq 1A) has been associated with PG and SUDs, although more recent studies with improved assessments and a more carefully controlled design have failed to replicate the finding in PG subjects (37). Additional studies that investigate at a genome-wide level will be helpful to more precisely identify genetic factors associated with PG and how they relate to those identified in similar studies of SUDs.

Conceptual Models

PG is currently classified in the DSM-IV-TR as an ICD, but has been proposed as an addiction and as an obsessive-compulsive-spectrum disorder. Although these categorizations are not mutually exclusive, they have significant implications for how the disorders are approached from scientific and clinical perspectives. Recent reviews related to DSM-V research work groups have described the relationships between PG and SUDs and PG and obsessive-compulsive disorder (OCD), respectively (2, 58). These critical reviews indicate that PG shares greater similarities with SUDs than with OCD. A main difference between PG and SUDs involves the ingestion of a substance. However, if one does not consider the ingestion of a substance as a core element of addiction, then PG appears to fit very well within an addiction framework. The core features of addiction (i.e., 1) repeated engagement in a behavior despite adverse consequences; 2) compulsive engagement in the behavior; 3) reduced self-control over engagement and participation in the behavior; and 4) presence of a craving or appetitive urge states that typically precede engagement in the behavior (2)) appear to apply well to PG.

A recent important line of investigation in mental health disorders involves the identification and characterization of intermediary phenotypes or endophenotypes. Potential endophenotypes for PG and SUDs include facets of impulsivity (e.g., those related to choice and response impulsivity) (3, 4). Individuals with PG and SUDs tend to score high on self-

reported and behavioral measures of impulsivity in each domain. Further investigation into the nature of the relationship between domains of impulsivity and aspects of PG and SUDs (e.g., onset of engagement, progression, and treatment outcome) will be helpful in targeting prevention and treatment strategies. Additionally, understanding the progression from impulsive to compulsive behavioral engagement will involve careful consideration of compulsivity as a feature of SUDs and PG. As these features do not appear diametrically opposed (for example, individuals with PG have been reported to score high on measures of both impulsivity and compulsivity (59, 60), understanding how the core components of compulsivity relate to PG and SUDs will be an important future endeavor.

7.1 Conclusion

PG and SUDs share many clinical, phenomenological, and biological features that warrant strong consideration for their being grouped together as addictions. Additional research into possible endophenotypes should help better characterize PG and SUDs and lead to improved and more precisely targeted prevention and treatment strategies.

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