Published in final edited form as:
Rev Bras Psiquiatr. 2008 May ; 30(0 1): S24–S30.

The Neurobiology of Impulse Control Disorders

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Abstract

Objective—To review the neurobiological substrates of impulse control disorders (ICDs). Pathological gambling (PG) is a main focus of the review in that most biological studies of the formal ICDs have examined this disorder.

Methods—The medical database MedLine from 1966 to present was searched to identify relevant articles that were subsequently reviewed to generate this manuscript.

Results—Preclinical studies suggest that differential brain monoamine neuromodulation is associated with impulsive decision-making and risk-taking behaviors. Clinical studies implicate multiple neurotransmitter systems (serotonergic, dopaminergic, adrenergic, and opioidergic) in the pathophysiology of PG and other ICDs. Initial neuroimaging studies have implicated the ventromedial prefrontal cortex and ventral striatum in the pathophysiology of PG and other ICDs. Genetic contributions to PG seem substantial and initial studies have implicated specific allelic polymorphisms, although genome-wide analyses have yet to be published.

Conclusion—Although significant advances have been made in our understanding of the neurobiology of ICDs, more research is needed to extend existing knowledge and translate these findings into clinical advances.

Keywords

Pathological Gambling; Serotonin; Norepinephrine; Dopamine; Opioids; Impulsivity; Stress; Genetics; Brain Imaging; Biochemistry

Introduction

In the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV-TR), Impulse Control Disorders (ICDs) are grouped as a heterogeneous cluster of disorders linked by a “failure to resist” impulses to engage in harmful, disturbing or distressing behaviors. The formal group of ICDs Not Elsewhere Classified include pathological gambling (PG), intermittent explosive disorder, kleptomania, pyromania, trichotillomania, and ICDs not otherwise specified. Criteria for other ICDs have been proposed including compulsive sexual behavior, compulsive shopping, and compulsive computer use [(1)]. Other disorders characterized by impaired impulse control (for example, substance use disorders,

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Tourette's Syndrome, Attention Deficit Hyperactivity Disorder (ADHD)) are categorized in other sections of DSM-IV-TR. ICDs are typically characterized by a common core of clinical features: 1) compulsive and repetitive performance of the problematic behavior despite adverse consequences; 2) progressive loss of control over the behavior; 3) an appetitive urge or "craving" state before starting the behavior; and 4) a pleasurable quality associated with its performance [(2)].

In this article, we review the neurobiology of ICDs. Disordered monoamine neurotransmission has been implicated in the pathophysiology of PG and other ICDs. Three main neurotransmitter systems will be discussed: 1) serotonin (5-HT) function in the initiation and cessation of the problematic behavior [(3, 4)]; 2) abnormal dopamine (DA) function contributing to modulation of reward and reinforcement pathways, particularly with regard to aggressive and other impulsive behaviors; and, 3) norepinephrine (NE) dysfunction associated with arousal and excitement. Of the formal ICDs, PG is arguably the best studied to date from a neurobiological perspective. Therefore, this article will focus on PG and data from other ICDs, other non-ICD disorders characterized by impaired impulse control, and studies of impulsivity which will be integrated as appropriate.

Methods

The Medline (1966 to present) database was searched using the MeSH (Medical Subject Heading) and textwords "pathological gambling" and "impulse control disorders", each with sub-categories (for example, pathological gambling, dopamine) to identify candidate articles for review. Potential articles were examined to determine if they met the following eligibility criteria: 1) were published in peer-reviewed journals between 1966 and 2007, 2) were written in English and involved pre-clinical and clinical experimentation, 3) discussed the neurobiology of pathological gambling and impulse control disorders, 4) discussed imaging of pathological gambling and impulse control disorders, and, 5) discussed genetics of pathological gambling and impulse control disorders. Articles not meeting these criteria were not included in the review. All eligible citations were appraised to identify those related to the neurobiology of PG and ICDs.

Results

The initial Medline search yielded over a thousand citations. Citations that were listed as addresses, bibliographies, biographies, classical articles, dictionaries, directories, duplicate publications, editorials, festschrifts, historical articles, interviews, lectures, legal cases, letters, news, periodical indices, published errata, or retracted publications were excluded. MeSH and textword searches for, as an example, "serotonin" (MeSH ="serotonin"), "dopamine" (MeSH ="dopamine"), and "Impulse control disorder" were used in Medline and combined in a "Boolean Or" and subsequently combined in a "Boolean And" to limit the set of Medline citations. All eligible citations were appraised to identify those related to neurobiology of impulse control disorders, and in particular, pathological gambling, and 169 publications were selected for further review.

Biochemistry and Neurophysiology

Abnormalities in dopamine, serotonin, and noradrenergic neurotransmitter activity have been reported in PG [(5)]. Indirect evidence for involvement of these neurotransmitter systems is derived from diagnostic and pharmacological treatment considerations.

Serotonin

5-HT is one of the most widely-implicated neurotransmitter systems in ICDs and, in particular, with PG [5]. 5-HT is involved in the regulation of mood states, sleep, and appetitive behaviors. Reduced 5-HT neurotransmission has been associated with increased impulsivity in humans and animal models [1, 6].

A role for a 5-HT in PG and ICDs is supported from results of pharmacological challenge studies that suggest decreased 5-HT synaptic activity in PG [7], postsynaptic 5-HT receptor hypersensitivity and reduced 5-HT availability [8], and decreased platelet monoamine oxidase B (MAO-B) activity in PG [9, 10]. In a double-blind placebo-controlled trial, obsessive-compulsive adolescents were treated with clomipramine (CMI), which produced a marked decrease in platelet 5-HT, a non-significant reduction in platelet MAO activity, and an increase in plasma NE. Significant clinical improvement correlated with pretreatment platelet 5-HT concentration and MAO activity; also observed were post-treatment decreases in both measures [11].

In a subsequent study of PG, intravenous CMI (12.5 mg) was used to target the 5-HT transporter, yielding a blunted prolactin response which suggested diminished 5-HT transporter binding [7]. The efficacy and tolerability of treatment with the SSRI, fluvoxamine, in PG was tested in an 8-week single-blind trial [12]. 70% of patients with PG who completed the trial were treatment responders as determined by decreases in gambling behavior (Yale-Brown Obsessive Compulsive Scale modified for PG) and improvement in clinical status (Clinical Global Impression score) [12]. Findings from this and other open-label trials of drugs in the treatment of PG should be considered with caution given high rates of placebo response often observed in controlled trials, including those with SSRIs. Placebo-controlled, randomized clinical trials with SSRIs have shown mixed results, with some trials of paroxetine and fluvoxamine showing superior responses as compared with placebo and others showing no statistically significant difference [2].

Meta-chlorophenylpiperazine (m-CPP), a metabolite of trazodone acting as a high affinity partial 5-HT_{1A} agonist, produces euphoria in individuals with PG [13], and an effect analogous to that reported in individuals with alcohol use disorders exposed to the agonist [13]. Subjects with PG who were administered 0.5 mg/kg of m-CPP had a significantly increased prolactin response, a reported “high” sensation, and a neuroendocrine response that correlated with gambling severity [14]. Similar behavioral responses to m-CPP have been reported in individuals with other disorders in which impulsive or compulsive behaviors are prominent; for example, antisocial personality disorder, borderline personality disorder, trichotillomania, and alcohol abuse/dependence [1].

In a study examining cognitive neurotoxicity of 3, 4-methylendioxymethamphetamine (MDMA or “Ecstasy”, a drug that leads to loss of presynaptic 5-HT neurons) on impulsivity and decision-making, heavy users showed heightened behavioral impulsivity and impaired decision-making, suggesting an association between 5-HT dysfunction and impulsive decision-making [15]. Decreased levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) have been found in cerebrospinal fluid (CSF) of individuals with impulsive characteristics, people attempting suicide, impulsive alcoholic criminals, fire setters, and alcohol use disorders [1]; when correcting for CSF flow rates, decreased CSF 5-HIAA concentration was observed in men with PG [1].

The influence of allelic variants of the 5-HT transporter gene promoter (5HTTLPR *s* vs. *l* alleles) on eating symptoms, psychopathologic traits, and platelet [^{3}H-] paroxetine binding in women with bulimia spectrum syndromes was investigated. Carriers of the *s* allele of 5-HTTLPR showed significantly more affective instability and behavioral impulsivity, as well

as fewer paroxetine-binding sites. The authors suggest that impulsive behavior and dysregulated affective states may be related to, if not determined by, reduced central 5-HT reuptake and the 5-HTTLPR polymorphism [16]. Lumbar punctures were done in men with PG to investigate the biochemistry, genetics, and personality profiles of PG. Men with PG had lower CSF concentrations of tryptophan and 5-HT than did men without PG [1].

Dopamine

The dopamine (DA) system influences reward and reinforcement behaviors in animal and human experimentation, and has been implicated in both substance and behavioral addictions [1]. Alterations in dopaminergic pathways may underlie the seeking of rewards (gambling, drugs) that trigger release of dopamine and produce pleasurable feelings [17]. A mechanism of addiction has been proposed that is driven by diminished DA involving multiple genes and environmental stimuli, termed the “Reward Deficiency Syndrome”, and places vulnerable individuals at high risk for addictive, impulsive, and compulsive behaviors [17]. However, no ligand-based imaging studies of individuals with PG or other ICDs have been published to support this hypothesis. A subset of dopaminergic neurons project directly from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) via the medial forebrain bundle. These neurons appear crucial for reward reinforcement because interruptions in DA impulse trafficking along axonal routes or at the receptor level, decrease the reward valence of VTA DA-stimulation [18].

It has been hypothesized that discrete areas of frontal cortex (implicated in impulse control), are divided into functionally “dissociable areas” [6, 19]; for example, the ventral and dorsal pre-frontal regions representing distinct neuroanatomical substrates of impulsive behavior with differentially regulated monoamine neurotransmission. To test this hypothesis, DA, 5-HT, and metabolite concentrations were measured in rat medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) using *in vivo* microdialysis during a delay-discounting model of impulsive choice [6]. During task performance, the investigators observed significant increases in mPFC- but not OFC-related 5-HT efflux. 3, 4-di-hydroxyphenylacetic acid (DOPAC, a DA metabolite) levels increased in OFC during the performance task but not under control conditions, whereas mPFC-DOPAC levels increased in all animals. These data suggest what has been termed a double dissociation in fronto-cortical 5-HT and DA neuromodulation during impulsive decision-making [6].

Cortico-limbic brain activation is seen in subjects with cocaine dependence after cocaine-induced rush [20] or following viewing of cocaine-related videotapes [21], and occupancy of the DA transporter is correlated with cocaine's euphorigenic effect [22]. However, a different pattern of corticolimbic activation has been observed in individuals with PG [23]. These findings raise the possibility that chronic or acute effects of cocaine exposure may contribute to corticolimbic activations seen in cocaine dependent subjects. Peripheral measures of DA have been observed to be elevated in problem gamblers during casino gambling [24] and in people playing Pachinko, a form of gaming combining elements of pinball and slot machines [25]. Data on central DA function in PG indicate abnormalities including altered CSF levels of DA (decreased) and its metabolite 3,4-dihydroxyphenylacetic acid (DHPA) (increased), together suggesting an increase in DA neurotransmission [26]. However, when corrected for flow rate perturbation, CSF levels of homovanillic acid (HVA) were not decreased [1]. Taken together, these data raise questions regarding the precise role for DA in PG.

DA involvement in PG and other ICDs also comes from studies of individuals with Parkinson's disease (PD) [27]. Psychiatric behaviors and disorders reported in PD may be related to the degradation of dopaminergic pathways related to PD pathology or to the

treatment of PD. Repetitive and reward-seeking behaviors have been reported in patients with PD, and these behaviors include compulsive gambling, pathologic hypersexuality, binge eating, and compulsive shopping [1]. Although many initial reports involved case reports, case series, and retrospective chart reviews, two recent studies screened larger samples of individuals with PD subjects for ICDs. A survey of 297 patients with PD found that estimates of pathologic hypersexuality of 2.4% and compulsive shopping of 0.7% [28]. The estimates of ICDs in the sample (excessive shopping, sex, and gambling) was 6.1%, which increased to 13.7% in patients exposed to dopamine agonists [28]. Concurrent levo-dopa therapy in conjunction with a DA agonist was also associated with the presence of an ICD [28]. An independent study of 272 patients with PD identified an association between DA agonist treatment and presence of an ICD (compulsive gambling, compulsive shopping or compulsive sexual behaviors) [29]. In this study, 6.6% of subjects experienced an ICD at some point during treatment for PD and levo-dopa equivalency dose was higher in individuals with an ICD as compared to those without. In both studies, an association between DA agonist treatment and ICD occurrence was reported, and, in contrast to several case series, no difference was observed between specific DA agonists and their associations with ICDs. These findings suggest that confounding factors (for example, prescribing patterns related to DA agonist selection and dosage) may have contributed to these results [29]. From a biological perspective, these findings suggest that speculations regarding the involvement of specific dopamine receptor subtypes, for example, the DRD3 receptor that is primarily localized to brain limbic regions [30], be entertained cautiously in the absence of data directly investigating the underlying brain biology of PD subjects with and without ICDs. Additionally, a family history of alcoholism [28] or a personal history of an ICD prior to PD onset [29] was associated with ICD presence suggesting that specific biological factors exist that place certain individuals with PD at greater risk to experience ICDs in association with DA agonist treatment.

Norepinephrine

Norepinephrine (NE) is involved in cognitive processes, particularly with regard to attention and arousal, and has been implicated in PG [4]. Central noradrenergic activity is increased in PG [1]. Other findings suggest that the noradrenergic system mediates selective attention in PG and is related to heightened arousal, readiness for gambling or risk-taking [1]. Higher measures of norepinephrine and its metabolites have been found in urine and CSF samples from men with PG as compared to control comparison subjects without PG. Measures of extraversion in PG subjects correlated positively with CSF, plasma and urinary levels of NE and NE metabolites [1]. In an independent study examining physiological changes in Pachinko, NE levels were found to increase as winning commenced [1].

Monoamine Oxidase Activity

The MAOs, subtypes MAO-A and MAO-B, are enzymes that metabolize NE, 5-HT, and DA [1]. Peripheral MAO derived from platelets is of the MAO B subtype and has been suggested to be an indicator of 5-HT function [1], although MAO B also binds with high affinity to and catabolizes DA [1]. Decreased platelet MAO activity has been reported in association with impulsive behaviors [1], high levels of sensation-seeking [1], and other disorders characterized by impaired impulse control, including PG and eating disorders [1].

In one study, men with PG as compared to those without were found to have MAO activities 26% lower [1]. A separate study with a similar male PG cohort found MAO activity levels 41% lower than closely matched control subjects [1]. Each group investigated personality and sensation-seeking characteristics of the PG and control groups and found statistically significant between-group differences. However, no clear picture emerged regarding

correlation of the characteristics with MAO levels: no associations persisted after Bonferroni correction application in one study [1] and a positive correlation between MAO and several measures of sensation-seeking was observed in the other study [1]. A recent investigation demonstrated a significant interaction between childhood maltreatment and reduced MAO-A enzymatic activity in modulating the risk for antisocial behavior, aggressiveness, and violence during adolescence [31]. Future studies are needed to investigate the relationship between MAO-A enzymatic activity, childhood maltreatment and ICDs, particularly as childhood trauma has been found in association with ICDs such as PG [32].

Stress Response Systems

Cortisol, adrenergic, and heart rate measures represent key components of stress responses. Stress responsiveness has been implicated in ICDs and other disorders characterized by impaired impulse control. Amongst Australian Aboriginals, urinary epinephrine and cortisol hormone output was approximately two-fold higher in individuals during gambling [33]. Non-pathological or recreational gamblers demonstrate increases in salivary cortisol during casino gambling [34]. In a study analyzing the effect of casino gambling on cardiovascular and neuroendocrine activity in PG, elevated epinephrine and NE levels were found in problem gamblers at baseline and throughout a session of gambling [24]. In problem gamblers, adrenocorticotropic hormone (ACTH) and cortisol levels were transiently increased during gambling. Positive correlations were found between gambling outcomes and NE plasma concentrations. The desire for starting and continuing gambling was positively correlated with plasma NE at baseline and following gambling sessions [24]. In a group of recreational, problem and pathological gamblers, researchers found that heart rate and cortisol levels significantly increased with the onset of gambling and remained elevated throughout the gambling sessions [35]. Subjects with high levels of impulsivity showed significantly higher heart rate compared to those with low levels of impulsivity. Correlation analyses in this study revealed a positive relationship between impulsivity scores and severity of PG [35]. Together, these findings implicate stress response pathways in PG and subsyndromal levels of gambling.

Opioidergic Pathways

Data suggest an important role for endogenous opioids in mediating hedonia and for μ-opioid receptors (mORs) in the mediation of reward and reinforcement. Particularly relevant is opioidergic influence of DA pathways via disinhibition of γ-aminobutyric acid (GABA) input to DA neurons in the VTA [1]. In an investigation of β-endorphin function in gaming behaviors, blood levels of β-endorphins were elevated during Pachinko play, which peaked at the start of high-pitched play [1]. However, β –endorphin levels did not change during casino gambling sessions in problem and non-problem gamblers, and problem gamblers tended to have lower levels than did non-problem gamblers [24]. Opioidergic involvement in PG is supported by clinical studies demonstrating the efficacy of the opioid antagonists naltrexone and nalfemene in the treatment of ICDs [13]. As allelic variants of the mu-opioid receptor have been related to naltrexone treatment outcome in alcoholism, further work is needed to investigate the impact of specific genetic factors on treatment outcome in PG and other ICDs. Taken together, although multiple findings implicate opioidergic factors in PG, the precise nature of their involvement remains incompletely understood.

Neuroimaging

Relatively few brain imaging studies of ICDs have been performed to date, and existing studies have focused on PG. These studies suggest similarities and differences between PG and other psychiatric disorders. In one investigation, gambling cues were presented to men with PG (n = 10) and control subjects (n = 11) [36]. Two gambling scenarios and two

emotional scenarios were presented. For each scenario, subjects were instructed to push a button at the onset of an emotional (for example, happiness, sadness, or anger) or motivational (for example, desire to eat, drink, or gamble) response. After each scenario, participants were asked to describe the quality and rate the peak and average intensities of their emotions and motivations (including gambling urges) using visual analog scales from 0 to 10. During three time periods, comparisons in brain activation were made between PG and control subjects: (1) initial portion of videotape viewing as compared with pre-tape baseline; (2) immediately after a subjective response as compared with immediately before a subjective response; and, (3) the final period of videotape viewing when the most provocative stimuli were presented as compared with the post-tape baseline. As compared to control subjects, PG subjects reported stronger gambling urges after viewing gambling scenarios. The most pronounced between-group differences in brain activations were observed during the initial period of viewing of the gambling scenarios: PG subjects displayed relatively decreased activity in frontal and orbitofrontal cortex, caudate/basal ganglia, and thalamus. The relatively decreased activation in PG as compared with control subjects of the cortico-basal-ganglionic-thalamo-cortical circuitry is different from the relatively increased activation of this network observed in cue provocation studies in OCD [37]. During the period of videotape viewing corresponding to the most intense gambling cues, individuals with PG showed relatively diminished activation in the ventromedial PFC, a brain region previously implicated in disadvantageous decision-making and disorders characterized by impaired impulse control (for example, impulsive aggression) [38]. Together, the data suggest that a complex network of brain regions distinguishes PG and control subjects during gambling-related motivational states, and that these neural processes are dynamic over time.

The neural correlates of cognitive control were examined with fMRI using an event-related Stroop paradigm in men with and without PG [36]. Following the presentation of infrequent incongruent stimuli (mismatched color-word pairs), both subject groups demonstrated similar activity changes in multiple brain regions, including activation of the dorsal anterior cingulate and dorsolateral frontal cortex. As compared with control subjects, those with PG demonstrated greater deactivation of the vmPFC, resulting in a between-group difference in left vmPFC. A similar region of left vmPFC was found to distinguish subjects with bipolar disorder from those without during the performance of the same fMRI task [36]. These findings suggest a common neurocircuitry underlying impaired impulse control across diagnostic boundaries.

An independent group studied 12 subjects with PG and matched-controls without PG using an fMRI task that simulates gambling and involves the processing of monetary rewards and losses [39]. Significantly lower activation of the right ventral striatum was observed in subjects with PG as compared to those without in winning vs. losing contrasts. The PG cohort also showed relatively diminished activation in the vmPFC, consistent with prior studies of PG subjects [23, 36]. Severity of gambling in PG showed significant negative correlations with both the ventral striatal and vmPFC activations. Potential confounding factors (e.g., depression or smoking) did not account for the findings. Relatively diminished activation of the ventral striatum during fMRI tasks of reward processing has been observed in individuals at risk for alcoholism or those with alcoholism [38], suggesting that similar neurocircuits operate in PG and substance use disorders and that diminished striatal activation during reward processing might represent a meaningful endophenotype across addictive disorders [38].

Another fMRI study examined whether subjects with PG exhibited differential brain activity when exposed to gambling cues [40]. The investigators found that PG subjects exhibited greater activity in the right DLPFC, the right parahippocampal gyrus, and left occipital

cortex. They also reported that after the study, PG subjects experienced a significant increase in craving for gambling [40]. Hollander and colleagues (2005) performed two [^{18}F]FDG PET scans 7-days apart on subjects with PG who were playing computerized blackjack under two different reward conditions: monetary reward and computer game points only. The investigators observed significantly higher relative metabolic rate in the primary visual cortex, the cingulate gyrus, the putamen and prefrontal areas during the monetary reward condition vs. the point reward condition. The authors interpret this pattern of activation as indicative of heightened limbic and sensory activity with regard to risk vs. reward incentives. They suggest that these data provide confirmatory evidence of the salience of monetary reward in the development of PG [41].

Genetic Considerations

Data from studies of twin samples suggest that a substantial degree of the risk for PG is heritable [42]. Eisen and colleagues (1998) determined that the prevalence of PG in the Vietnam Era Twin (VET) Registry was 1.4%. Of twins reporting gambling at least 25 times in a year in their life-time, 29% (7.6% of the total cohort) also reported at least one symptom of PG [42, 43]. Familial factors contribute between 35% and 54% of the liability for each of five individual PG-related factors. Higher degrees of familial contribution were estimated for the reporting of three (56%) or four (62%) or more of the individual PG-related factors. More recent investigations of the same sample indicate that genetic and environmental factors contribute to PG, that there exists overlap in the genetic and environmental contributions between PG and alcohol dependence and PG and adult antisocial behaviors, and that the majority of the co-occurrence between PG and major depression appears to be determined by common genetic factors. As this sample is comprised of a unique group of men, the extent to which these findings extend to other groups, particularly women, warrants additional investigation.

Differential frequencies of allelic variants involving mainly serotonergic and dopaminergic genes have been implicated in preliminary studies of PG. The 2A1 allele of the DA D2 receptor gene has been implicated in compulsive and addictive behaviors, including drug abuse, compulsive eating, and smoking. In 171 non-Latino whites with PG, 51% carried the D2A1 allele as compared with 26% of controls [44]. Frequency of homozygosity of the DA Dde I allele of the D1 receptor has also been found to be elevated in PG, tobacco smokers, and Tourette Syndrome probands [45]. Allelic variants of the DRD4 gene containing five of eight copies of an incorporated 48 base pair nucleotide repeat have also been associated with PG [46,47].

Some of differences in allelic variation related to PG appear influenced by sex status, raising the possibility that the genetic contributions to PG differ for men and women [48]. Some of the mechanisms by which genes may influence vulnerability to PG include DNA polymorphisms in MAO-A genes [48], the serotonin transporter gene [49], and DA D1, D2, and D4 receptor genes [17,45,49]. One should view the findings from these association studies cautiously, particularly as methodological limitations often exist with these initial investigations (for example, in the areas of diagnostic evaluation and lack of stratification by racial/ethnic identity) [48]. The extent to which these preliminary findings generalize to other ICDs, and the precise manner in which allelic distributions of these and other genes may contribute to the development of PG requires further investigation. Ongoing studies using more comprehensive diagnostic evaluations, larger samples, and genome-wide analytic approaches should provide important information with respect to the genetic contributions to PG and other ICDs.

Discussion

Multiple factors, including behavioral initiation, arousal, reward and reinforcement, and behavioral disinhibition, have been implicated in PG [13]. In addition to these features, ICDs share criteria with substance use disorders aspects of tolerance, withdrawal, repeated attempts to cut back or stop, and impairment in major areas of life functioning [13]. Phenomenological data [38] further support a relationship between PG and substance addictions (for example, high rates of PG and substance use disorders have been reported during adolescence and young adulthood and low rates in older adulthood) and the telescoping phenomenon (reflecting the rapid rate of progression from initial to problematic behavioral engagement in women as compared to men) initially described for alcoholism has also been observed in problem and pathological gambling [38]. Multiple neurotransmitter systems have been similarly implicated in ICDs and substance use disorders [5, 38]. Further research is needed to understand the molecular and biochemical factors underlying the behavioral features seen in PG and other ICDs. An improved understanding of the neurobiology of ICDs will facilitate clinical advances in the identification, prevention, and treatment of PG and other ICDs.

Acknowledgments

Supported in part by: (1) National Institute on Drug Abuse (K12-DA00166 and R01-DA019039); and (2) the Veterans Administration VISN1 MIRECC and REAP.

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