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Pathological gambling: a review of the neurobiological evidence relevant for its classification as an addictive disorder

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Abstract

In light of the upcoming eleventh edition of the International Classification of Diseases (ICD-11), the question arises as to the most appropriate classification of “Pathological Gambling” (“PG”). Some academic opinion favors leaving “PG” in the “Impulse Control Disorder” (“ICD”) category, as in ICD-10, whereas others argue that new data especially from the neurobiological area favor allocating it to the category of “Substance-related and Addictive Disorders” (“SADs”), following the decision in the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders.

The current review examines important findings in relation to “PG”, with the aim of enabling a well-informed decision to be made with respect to the classification of “PG” as a “SAD” or “ICD” in ICD-11. Particular attention is given to cognitive deficits and underlying neurobiological mechanisms that play a role in “SADs” and “ICDs”. These processes are impulsivity, compulsivity, reward/punishment processing and decision making.

In summary, the strongest arguments for subsuming “PG” under a larger “SAD” category relate to the existence of similar diagnostic characteristics; the high co-morbidity rates between the disorders; their common core features including reward-related aspects (positive reinforcement:

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6. Authors contribution

MFB was responsible for drafting the manuscript. KM and MNP provided critical revision of the manuscript, contributing important intellectual content. All authors critically reviewed content and approved final version for publication.

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behaviors are pleasurable at the beginning which is not the case for “ICDs”); the findings that the same brain structures are involved in “PG” and “SADs”, including the ventral striatum. Research on compulsivity suggests a relationship with “PG” and “SAD”, particularly in later stages of the disorders. Although research is limited for “ICDs”, current data do not support continuing to classify “PG” as an “ICD”.

Keywords

ICD-11; “Impulse Control Disorder”; “Pathological Gambling”; reclassification; “Substance-related and Addictive Disorder

1. Introduction

Gambling can be defined as the wagering of something of value (typically money) on an event with an uncertain outcome with the primary intent of winning a larger reward.

Excessive gambling was first officially recognized as a psychiatric disorder in the ninth edition of the International Classification of Diseases (World Health Organization, 1977). Three years later it was first included in U.S. diagnostic coding, the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III; American Psychiatric Association, 1980) where it was classified as “Impulse Control Disorder” (“ICD”). The DSM-III diagnostic criteria began with a description of the individual experiencing a progressive loss of control, followed by seven other items, with an emphasis on damage and disruption to the individual’s family, personal or vocational pursuits and money-related issues. In the next edition (DSM-IV; American Psychiatric Association, 1994), the diagnostic criteria for “Pathological Gambling” (“PG”) were revised to reflect its similarity to substance dependence. A key element was the addition of “repeated unsuccessful attempts to control, cut back or stop gambling” as a diagnostic criterion (Reilly & Smith, 2013).

The classification of “PG” was revisited during the fifth revision of the DSM (DSM-5; American Psychiatric Association, 2013). Following suggestions of the working groups on Obsessive-compulsive-related Disorders (OCRDs) and Substance-related Disorders, “PG” was moved from the “ICD” category to the category of “Substance-related and Addictive Disorders” (“SAD”) because of its striking similarities to drug addiction in several respects; i.e., genetic predisposition, treatment response, clinical characteristics, cognitive deficits and underlying neurobiological mechanisms, amongst other domains (e.g. Grant et al., 2010). “PG” is thus far the only non-substance-related disorder in the “SAD” category.

In accordance with the early DSM classification of “PG” as an “ICD”, the World Health Organization’s tenth revision of the International Classification of Diseases (ICD-10; WHO, 1992) listed “PG” in the category “F63 Habit and impulse disorders”. Endeavors relating to the generation of ICD-11 are currently underway, offering an excellent opportunity to revise and adjust diagnostic criteria that have been proven to be suboptimal in clinical use and research settings. Particular attention is being paid to clinical utility, global applicability, and scientific validity (Grant et al., 2014a).

An important question currently under debate is whether the diagnostic category for “PG” in ICD-11 should follow the DSM-5 categorization of the condition as a “SAD” (a decision based in part on DSM-5 Research Workgroup efforts to systematically review the literature across multiple domains (Petry, 2006; Potenza, 2006; Potenza et al., 2009), or whether there is sufficiently convincing evidence for leaving “PG” in the ICD-10 category of “ICDs”, as proposed by the ICD-11 Working Group on OCRDs. Some arguments for this decision have been recently outlined in the opinion paper by Grant et al. (2014a). The views expressed in this paper are those of the authors and do not necessarily represent the official positions of the Working Group. In order to make a scientifically well-informed decision, the similarities and differences between “PG” and various disorders represented in the “ICD” category should be compared with respect to several different dimensions. These dimensions include clinical (including co-occurring or co-morbid conditions), phenomenological, cognitive and neurobiological underpinnings. We will review these domains and elaborate in the discussion on how these relate to the views communicated in Grant et al. (2014a).

Several excellent reviews have already been published on “PG” (e.g. El-Guebaly et al., 2012; Potenza, 2013). However, new findings have since emerged that need to be taken into account when considering a possible (re)classification of “PG”. Moreover, the aforementioned reviews did not cover all the dimensions of interest (or current data in these dimensions) that are, in our opinion, relevant for a (re)classification of “PG”. Dimensions of interest refer to cognitive features that play an important role in the development and maintenance of “ICDs” and “SADs” such as impulsivity, compulsivity, reward/punishment processing and decision-making. This paper aims to improve the current understanding of “PG” by highlighting several important findings in various areas of research that are pertinent to a (re)classification of the disorder, with a particular focus on neurobiology. This will allow for a well-informed decision to be made on the matter.

2. Possible diagnostic categories for “Pathological Gambling” and their characteristics

The ICD-11 working groups are considering “SADs” and “ICDs” as potential categories in which to classify “PG” (although please note that the terminology may differ in the ICD-11). The following paragraph summarizes the key characteristics of each category.

2.1 “Substance-related and Addictive Disorders”

The DSM-5 category “SADs” encompasses 10 separate classes of drugs. “SADs” have been defined as repeated use of a psychoactive substance (or substances) to such an extent that the addicted individual is periodically or chronically intoxicated, exhibits a compulsion to use the preferred substance (or substances), has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain psychoactive substances by almost any means. Typically, an increased tolerance to the substance can be observed and withdrawal syndrome frequently occurs when substance use is interrupted (WHO, 1992). Drug taking is usually reported to be pleasurable and rewarding (“positive reinforcement”) at the beginning.

The core elements of addiction (dependence), according to the diagnostic criteria in the ICD-10, are as follows: (1) Diminished control: an impaired capacity to control substance-taking behavior in terms of its onset, termination, or levels of use; persistent desire or unsuccessful efforts to reduce or control substance use; persistent use despite clear evidence of harmful consequences. (2) Craving: a strong desire or sense of compulsion to take the substance. (3) Tolerance: a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance. (4) Withdrawal state: a group of symptoms that occurs upon the abrupt discontinuation/separation or a decrease in dosage of the intake of substance.

2.2 “Impulse control disorders“

The “ICD” category in the DSM finds its equivalent in the ICD-10 category “Habit and impulse disorders”, and includes “PG”, pathological fire-setting (pyromania), pathological stealing (kleptomania) and trichotillomania (hair-pulling disorder).

The main aspect of impulsive behaviors is a tendency to act prematurely and without foresight. A core feature of these disorders involves problems of emotional and behavioral self-control. According to Grant et al. (2014a), the ICD-11 working group on OCRDs has called for revision of the “ICD” criteria. It recommends that these disorders be defined by the repeated failure to resist an impulse, drive, or urge to perform an act that is rewarding to the person (at least in the short-term), despite long-term harm either to the individual or to others. The working group suggests including “PG”, intermittent explosive disorder, kleptomania, pyromania and compulsive sexual behavior disorder in this category. These suggested core criteria for “ICD”, as laid out by Grant et al. (2014a), seem to bear a remarkable similarity to the core features of addiction (as described by Potenza et al. (2006), referencing Shaffer (1999)). This raises the crucial question of whether significantly overlapping core features for two distinct categories of disorders (namely “SADs” and “ICDs”) only serve to complicate diagnosis and classification efforts. An alternative approach would be to reclassify disorders that do not fulfill the original diagnostic criteria of the “ICD” category, without modifying the criteria of the category itself. This would mirror the DSM-5 process that re-focused the heterogeneous “Impulse Control Disorders Not Elsewhere Classified” category into a “Disruptive, Impulse-Control and Conduct Disorders” category based on data that had emerged since DSM-IV and linked specific “ICDs” to specific disorders in other categories (thus prompting the reclassification of “PG” into the “SADs” category and trichotillomania into the “OCRDs” category).

In this review, we will focus on pathological fire-setting (pyromania) and pathological stealing (kleptomania), since these are the only two disorders present in the existing and proposed “ICD” categories, respectively, in ICD-10 and ICD-11.

3. Co-occurring disorders (comorbidities)

3.1 “Impulse control disorders” (other than “Pathological Gambling”)

In clinical samples, kleptomania frequently co-occurs with other psychiatric disorders, primarily with other “ICDs” (20–46%), drug addiction (23–50%) and mood disorders (45–100%) (Grant & Odlaug, 2008). Pyromania frequently co-occurs with “SADs”, conduct disorder, antisocial and obsessive-compulsive personality disorders, and a family history of antisocial behavior; however, pyromania was not reported to co-occur with “PG” (Vaughn et al., 2010).

3.2 “Pathological Gambling”

In the German epidemiological PAGE study, telephone assessments were conducted of 15,023 participants representative of the German population, of whom 442 were diagnosed as having “PG” (Meyer et al., 2011). Additional data from N=101 gamblers undergoing inpatient treatment were also incorporated into analyses (Premper & Schulz, 2008). “PG” revealed high comorbidity rates with “SADs”, mood disorders, anxiety disorders and personality disorders, with “SADs” demonstrating the strongest comorbidity. Our data from the Baden-Württemberg Study on “PG” (N=675 PGs) supports these findings. We found the highest comorbidity rates for “PG” and drug addiction (79% including nicotine dependence; 34% excluding nicotine dependence) (Mann et al., 2013).

The largest psychiatric epidemiological study undertaken in this field thus far has been the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which was conducted in the USA. Over 43,000 individuals were interviewed in this survey, with 195 of individuals meeting criteria for “PG” (Petry et al., 2005). The highest odds ratios (ORs) of DSM-IV lifetime “PG” and other psychiatric axis I disorders (adjusted for sociodemographic and socioeconomic characteristics) were observed for drug addiction. For nicotine dependence the OR was 6.7 (4.6 to 9.9; 95% confidence interval (CI)), for any alcohol use disorder the OR was 6.0 (3.8 to 9.2; CI) and for any drug use disorder the OR was 4.4 (2.9 to 6.6; CI). After drug addiction, the second highest ORs were found for mood disorders 4.4 (2.9 to 6.6; CI). Comparable comorbidity rates of “PG” and psychiatric disorders were observed in the National Comorbidity Survey Replication (NCS-R), another large-scale U.S. survey on mental disorders, similar. The strongest ORs involve substance use disorders (OR=5.5). Of those diagnosed with “PG”, the OR of having a mood disorder was increased by a factor of 3.7, and the OR of having an anxiety disorder increased by a factor of 3.1 Even weaker ORs were found for associations between “PG” and other “ICDs” with ORs of 2.2 (Kessler et al., 2008).

4. Cognitive and neurobiological changes

When debating the merits of a possible reclassification of “PG” in the upcoming ICD-11, it is crucial to consider common cognitive features, as well as the underlying functional and structural neurobiological features of both “PG” and the disorders listed in the other possible diagnostic categories. An explicit aim in the development of the ICD-11 is to group disorders according to common underlying etiological factors to the furthest extent possible.

Although the presence of common neurobiological mechanisms in various disorders is arguably the most valid indicator of whether these disorders are related, research comparing the neurobiological correlates of “ICDs” and “SADs” has been sparse. The cognitive features that play an important role in the development and maintenance of psychiatric disorders such as “ICDs” and “SADs” include impulsivity, compulsivity, reward/punishment processing and decision-making. The following paragraphs summarize important research results relating to the various diagnostic categories in which “PG” may be classified, as well as exploring the commonalities and differences between “PG” and the other members of each category.

4.1 Impulsivity

Impulsivity refers to behavior that is disinhibited to a degree where it is poorly conceived, premature, unduly risky and inappropriate to the context in which it is carried out, with potential adverse consequences likely to follow (Daruma & Barnes, 1993). Alterations in fronto-striatal circuits have been proposed to contribute to impulsive behaviors, with a striatal component (including the ventral striatum) driving behavior and a prefrontal component (involving the anterior cingulate cortex (ACC)/ventromedial prefrontal cortex (VMPFC)) failing to exert inhibitory control (Fineberg et al., 2014). Several different constructs of impulsivity have been proposed. Impulsivity consists of at least two major components: motor or response impulsivity (also termed impulsive action), and cognitive or decision-making impulsivity (also termed impulsive choice) (Evenden, 1999).

Impulsive action is typically defined as diminished ability to inhibit motor responses. It has been studied using behavioral tasks such as Go/No-Go Tasks (e.g. Hester et al., 2004), continuous performance tests (e.g. Hasson & Fine, 2012) and stop-signal tasks (e.g. Fauth-Bühler et al., 2012).

Impulsive choice refers to the preference for selecting more modest immediate (smaller, sooner) rewards instead of more sizable long-term (larger, later) rewards. Impulsive choice has been assessed using inter-temporal choice tasks that measure the temporal discounting of rewards (e.g. Sellitto et al., 2010). Related to impulsive choice are diminished tendencies to delay gratification and disadvantageous decision-making which have been assessed using such measures as the Cambridge Gambling Task (e.g. Zois et al., 2014) and the Iowa Gambling Task (Bechara et al., 1994).

4.1.1 “Impulse control disorders” (other than “Pathological Gambling”)—

Impulsivity is by definition considered a core feature of “ICDs”. A comparative analysis of different aspects of impulsivity across various putative “behavioral addictions”/”ICDs” indicates impaired impulse control (assessed with a stop-signal task) in patients diagnosed with “PG” and/or kleptomania, amongst other disorders (including compulsive buying/shopping and Internet addiction) (Grant & Chamberlain, 2014). It is not currently known whether impulsive choice behavior is also exhibited in “ICDs” other than “PG”.

4.1.2 “Substance-related and Addictive Disorders”—

A recent review of studies of “SADs” has described significant inhibitory deficits in heavy users and dependent individuals of most classes of drugs, such as cocaine, MDMA (ecstasy), methamphetamine,

tobacco and alcohol, with the greatest deficits observed in users of psychostimulants (Smith et al., 2014). No behavioral control deficit was found for patients addicted to opioids or cannabis. Evidence has been gathered in relation to both major components of impulsivity - impulsive action and impulsive choice- in relation to several classes of drugs (see Jupp & Dalley, 2014 for more details). Increased impulsive action (assessed using go/no-go paradigms or SSTs) has been reported in alcohol- (e.g. Noël et al., 2007), cocaine- (e.g. Garavan & Hester, 2007), methamphetamine- (e.g. Monterosso et al., 2005) and opioid-dependent individuals (e.g. Liao et al., 2014). The making of impulsive choices has been observed in heroin- and cocaine-dependent (e.g. Kirby & Petry, 2004), alcohol-dependent (e.g. Petry, 2001) and nicotine-dependent (e.g. Bickel 1999) individuals. Moreover, "SAD" patients have been shown to prefer immediate profit even in the face of negative future outcomes (e.g. Brevers et al., 2014 for alcohol; Wang et al., 2013 for methamphetamine and Hulka et al., 2014 for cocaine).

Several strands of evidence suggest that, on the one hand, impulsivity may be an endophenotypic marker for addiction risk. Conversely, drug use has also been shown to increase levels of impulsivity in patients (de Wit, 2009). Thus, there is evidence to support the idea that impulse-control deficits represent a risk factor for substance addiction (Leeman & Potenza 2012) and, conversely, that substance abuse induces or exacerbates impulsivity with respect to most classes of drug (de Wit, 2009).

4.1.3 "Pathological Gambling"—While studies on impulsivity in pyromania and kleptomania are relatively rare, various facets of impulsivity have been assessed more extensively in relation to "PG". Impulsive action and response-inhibition performance (i.e. prolonged latency of motor response inhibition) have been studied in patients with "PG" using the Stop-signal and the Go/No-Go Tasks. Studies of impulsive action have produced less consistent results than one may have expected, given that impulsivity is considered a core feature of "PG" and one that has contributed to its classification as an "ICD". While some investigators have found no differences in the time required to stop a response (stop-signal reaction time; SSRT) in "PG" in comparison to control subjects (e.g. de Ruiter et al., 2009; Lawrence et al., 2009; unpublished own data), others have observed some deficits in motor response (Goudriaan et al., 2006a; Odlaug et al., 2011). A recent meta-analysis found no performance deficits in "PG" in the Go/No-Go Tasks but a medium to large effect in relation to SSRT (g=0.625) (Smith et al., 2014). Multiple factors could account for the heterogeneous findings, such as a variation in sample characteristics (patients who do not fulfill criteria for "PG"), comorbidities, and potential differences between subtypes of gamblers, as proposed, for example, in the pathway model by Blaszczynski and Nower (2002), although these subtypes have rarely been studied directly in neurocognitive investigations (Goudriaan et al., 2014).

In "PG", impulsive-choice behavior has been studied using decision-making tasks as well as tasks measuring the discounting of rewards by probability and delay. Decision-making has been studied using the Cambridge Gambling Task. In a study by Lawrence et al. (2009), participants suffering from either "PG" or alcohol addiction did not differ significantly in their decision-making capabilities (rational choices) compared to controls. However, patients suffering from either alcohol addiction or "PG" exhibited elevated risk-taking, with those

with alcohol addiction also being slower decision-makers compared to control and “PG” participants.

In a separate study, the impact of comorbid “SAD” on the decision-making capabilities of patients with “PG” was assessed. Patients with “PG” revealed disadvantageous decision-making, regardless of whether they had a comorbid “SAD” (Zois et al., 2014). However, patients with an alcohol or nicotine dependence as well as “PG” tended to take relatively more risks, in addition to making disadvantageous decisions. Increased risk-taking in the Cambridge Gambling Task has been shown to co-vary with steeper delay-discounting tendencies (Kräplin et al., 2014). Individuals with “PG” may have difficulties anticipating the negative consequences associated with risky choices they make during the Iowa Gambling Task, and as a result they perform poorly (e.g. Goudriaan et al., 2005, 2006b). Comparable performance on the Iowa Gambling Task is observed in “PG” and “SADs” (Leeman & Potenza, 2012). Disadvantageous decision-making in “PG” has also been documented in other in studies using similar tasks, such as the Game of Dice Task (e.g. Brand et al., 2005). Individuals with “PG” exhibit disadvantageous decision making in risky situations, irrespective of task performance. Comparing problem and “PG”, a study by Brevers et al. (2012) found abnormal impulsive choice-making in both groups, while only the group with “PG” revealed greater action impulsivity.

Several neuroimaging studies have assessed the neural correlates of impulsive choice and action behavior using a variety of tasks. With regards to altered impulsive action in PGs, a functional neuroimaging study by de Ruiter et al. (2012) found reduced dorsomedial prefrontal cortex activity in problem gambling, even though in tests using SST the “PG” group showed similar behavioral stopping performance as the control group. Increased DLPFC and ACC activity was observed in “PG” during response inhibition when presented with neutral go stimuli, in a study by van Holst et al. (2012a) using a Go/No-Go Task. Behaviorally, patients were slower than healthy control subjects, although equally as accurate.

Impulsive-choice-related behavior has been studied using the Iowa Gambling Task (Tanabe et al., 2007). Research shows that in decision-making tasks involving risk, the presence of gambling problems is related to altered VMPFC activity. Neuroimaging has revealed altered neural reward representations in “PG”, using Delay and Probability Discounting Tasks (Miedl et al., 2012). Furthermore, craving has been shown to affect impulsive choices: altered activity in the midbrain and striatum were observed during the making of impulsive choices in high-craving trials (Miedl et al., 2014).

4.2 Compulsivity

Compulsivity appears to be less well-defined and/or well-investigated than impulsivity. Furthermore, the relationship between impulsivity and compulsivity is still a matter of debate, with some authors advancing a dimensional model, while others prefer a spectrum or orthogonal model. A full discussion of the impulsivity/compulsivity debate is outside the scope of the present paper, but the reader may refer to reviews by Berlin & Hollander (2014) or Fineberg et al. (2014) for further details. Nonetheless, an important difference between

the two constructs is that impulsivity involves rash action in pursuit of reward, while compulsive behavior is typically undertaken regardless of reward (Fontenelle et al., 2011).

Compulsivity can be characterized by perseverative, repetitive actions that are excessive and inappropriate in a given situation (Robbins et al., 2012). Obsessive compulsive disorder is the prototypical disorder that exemplifies compulsivity (Berlin & Hollander, 2014). Compulsions can manifest as simple motor behaviors (such as hand-washing or tapping rituals) or cognitive behaviors/mental acts (such as mentally repeating a conversation or counting a series of numbers). Tasks previously used to assess compulsivity focused on the repetitive component of compulsions and were designed to measure the ability to flexibly adapt behavior after negative feedback (probabilistic reversal learning tasks) or the ability to switch attention between stimuli (e.g. an intra-dimensional/extra-dimensional set-shifting task). Other tasks that measure attentional bias or habit formation are less common, but may in the future contribute to a better understanding of the nature of compulsions.

The brain circuits thought to be implicated in compulsivity include the circuits of reversal learning (DLPFC, lateral OFC, and caudate nucleus) and habit learning (the supplementary motor area, the premotor area, and the putamen) (Grant & Kim, 2014). A failure in the top-down control (frontal) regions and an over-active striatal habit circuitry (caudate nucleus, putamen) may also underlie compulsive acts (Fineberg et al., 2014).

4.2.1 “Substance-related and Addictive Disorders”—Habit formation is thought to play a major role in drug addiction, as initially impulsive drug-seeking may become compulsive with continued use (Everitt & Robbins, 2005). A growing body of evidence from both human and animal studies suggests that the dorsal part of the striatum plays a role in both habitual responding and in initiating automatic stimulus-response tendencies (Everitt & Robbins, 2005). Functional magnetic resonance imaging (fMRI) data in humans have shown that a shift in processing from the ventral to the dorsal parts of the striatum accompanies the progression of alcohol dependence (Vollstädt-Klein et al., 2010).

Impairments in probabilistic reversal-learning and set-shifting have been reported in individuals with cocaine addiction (Stalnaker et al., 2009).

It is still unclear whether compulsive tendencies constitute a risk factor for addiction, or whether compulsive behaviors occur as a consequence of prolonged drug use, or whether both hold true. In any case, the relationship between compulsivity and addiction is likely to be influenced by specific facets of compulsivity and types and patterns of substance use (Fineberg et al., 2014).

4.2.2 “Impulse control disorders” (other than “Pathological Gambling”)—No neurocognitive and neuroimaging studies exploring the compulsive aspects of pathological fire-setting (pyromania) and pathological stealing (kleptomania) have been undertaken to date, to our knowledge.

4.2.3 “Pathological Gambling”—Although “PG” is characterized by compulsivity-related behaviors, such as loss chasing and lucky rituals, relatively few studies have

systematically examined compulsivity in “PG”. Several compulsive tendencies have been revealed in PGs, such as slower contingency learning (Vanes, 2014) and response perseveration (Frost, 2001, 2012, de Ruiter et al., 2009). Cognitive "rigidity" has been observed in studies that used the Wisconsin card-sorting test (e.g. Marazziti et al., 2008; Alvarez-Moya et al., 2009) and Set-shifting tasks (e.g. Choi et al., 2014). It is important to note that the reduced cognitive flexibility observed in “PG” has recently been suggested to be more likely the result of aberrant reward-based learning, rather than a general problem with cognitive flexibility (Boog et al., 2014).

4.3 Reward and punishment sensitivity

The reward system of the brain drives the reinforcement of reward-related behavior and learning, as well as promoting goal-directed behavior (Fiorillo et al., 2003). It is activated by natural reinforcers, such as food, water, sex and maternal behavior, thus promoting behavior necessary for self-preservation and the survival of the species. Structurally speaking, the reward circuitry consists of highly interconnected cortical and subcortical structures, including the prefrontal cortex, amygdala, nucleus accumbens (NAc) / ventral striatum, the subiculum of the hippocampal formation and the ventral tegmental area (VTA) of the midbrain (Volman et al., 2013). Dopaminergic neurons, whose cell bodies are located in the VTA and which project primarily to the NAc, are especially important in the processing of rewarding stimuli. The NAc also receives efferent glutamatergic projections from the prefrontal cortex, amygdala, and other brain regions involved in reward processing.

Reward and punishment sensitivity has been monitored in studies employing fMRI, using tasks that assess specific phases of reward processing, such as anticipation, motor response and feedback (Limbrick-Oldfield et al., 2013). A well-known and widely-used task that assesses reward sensitivity during neuroimaging is the Monetary Incentive Delay Task (Knutson et al., 2001). In this task, the subject is asked to respond to a target stimulus within a given timeframe, and may potentially be rewarded for the response according to his/her reaction time.

Other tasks have been designed to study the impact of risk, effort, stakes and reward type on brain activation. The effects of salient stimuli on brain function have been studied using cue-reactivity paradigms. In these tasks, brain response is measured while both salient stimuli (such as drug-related pictures for patients with “SADs”) and neutral control stimuli (visual, olfactory etc.) are presented to the participants.

4.3.1 “Substance-related and Addictive Disorders”—“SADs” are characterized by altered functioning of the brain’s “natural reward system”, also referred to as the mesocorticolimbic dopamine system. Drugs that are prone to being abused are thought to pharmacologically “hijack” the brain’s reward-based reinforcement learning system (Keramati & Gutkin, 2013). Almost all drugs of abuse induce a large and rapid increase in dopamine release in the ventral striatum of addicted and non-addicted drug users, thereby triggering the initial reinforcing effects of the drug (Di Chiara & Bassareo, 2007). Temporal-difference reinforcement-learning models predict that the repeated dopamine release triggered by drug consumption results in a progressive increase of the value attributed to

drug use, which finally ends up exceeding the value of alternative behaviors (Redish, 2004). This theory conceptualizes the dysfunctional preference for drug use in addiction as a pharmacologically induced failure of reward prediction in the dopaminergic system. The theory of instrumental behavior highlights the importance of Pavlovian and instrumental conditioning processes in the development of addiction (Everitt & Robbins, 2005). Accordingly, formerly neutral environmental stimuli become associated with substance use and turn into conditioned stimuli (CS). The linking of the CS to the reinforcing effect produced by drugs of abuse enables the CS to act as a reinforcer in and of itself, thereby raising the likelihood of drug-seeking and -taking behavior (Pavlovian-instrumental transfer).

According to cue-reactivity studies, dependent patients show increased brain activity in response to visual drug-related cues in parts of the mesocorticolimbic dopamine system, the medial prefrontal cortices, the visuospatial attention network (fronto-occipito-parietal regions) and the temporal lobe, compared to non-addicted individuals (for a review of alcohol studies see Bühler & Mann, 2011). Furthermore, studies show that responses to alcohol-related cues can also include behaviors such as increased craving intensity and a higher subsequent relapse risk (Bühler & Mann, 2011). While most studies on appetitive processing in “SADs” have found increased activity in addiction-related brain regions, other studies have reported hypoactivation in those regions (see Hommer et al., 2011). However, these seemingly contradictory findings can be explained by examining in further detail the processing of non-drug related salient stimuli in “SAD” patients. Neuroimaging studies have revealed diminished brain response to non-drug-related cues in drug-addicted groups (e.g. Bühler et al., 2010). Taking these findings together, researchers have argued that “SADs” are characterized by an increased sensitivity to drug rewards and a reduced response to non-drug rewards, that leads vulnerable individuals to seek drugs in preference over more socially acceptable goals (e.g. Bühler et al., 2010).

4.3.2 “Impulse control disorders” (other than “Pathological Gambling”)— Evidence on the neurobiological basis of reward processing in “ICDs” considered in this review (i.e., kleptomania and pyromania) other than “PG” is not available to date, to our knowledge.

4.3.3 “Pathological Gambling”—The presentation of gambling-related stimuli to individuals with “PG” has been shown to alter brain activity in several studies (Crockford et al., 2005; Goudriaan et al., 2010; Potenza et al., 2003; van Holst et al., 2012b). With the exception of an early study (Potenza et al., 2003) that made use of complex film sequences, subsequent cue-reactivity studies using static images reported increased activity in the prefrontal cortex, parahippocampal areas, ventral striatum, amygdala and occipital regions (Crockford et al., 2005; Goudriaan et al., 2010; van Holst et al., 2012b).

A recent meta-analysis of fMRI cue-reactivity studies in “PG” assessed 62 candidate studies, of which 13 eventually met the selection criteria (Meng et al., 2014). The researchers observed increased activation in the right lentiform nucleus (putamen and globus pallidus) and the left middle occipital gyrus across the selected studies. Increased activity in both areas was also present when controlling for “SADs”. Furthermore, activity in the right

lentiform nucleus and bilateral parahippocampus was found to be positively correlated with problem-gambling severity, as measured by the South Oaks Gambling Screen (SOGS). On the other hand, activity in the right middle frontal gyrus was negatively correlated with SOGS scores. Taken together, these findings support the idea of dysfunction in the frontostriatal pathways in “PG” during reward processing.

An early fMRI study in “PG” found reduced responses in the striatum and VMPFC in a Card Guessing Task, compared to control subjects (Reuter et al., 2005). Subsequent fMRI studies that used primarily gambling-related tasks or tasks involving some sort of uncertainty about monetary outcome found significantly diminished fronto-striatal activation in “PG” compared to control subjects, for both monetary gains and losses (e.g. Balodis et al., 2012; de Ruiter et al., 2009). Additionally, research has shown reduced VMPFC activation in “PG” undertaking a Probabilistic Reversal Task, where participants were given positive reinforcement for their correct responses (monetary gain) and punished for giving incorrect answers (monetary loss) (de Ruiter et al., 2009). In contrast, several studies have found increased activity in the mesocorticolimbic brain regions, such as experiments that vary the amount of risk involved (e.g. Miedl et al., 2010) or that use different probabilities of winning or losing varying amounts of money (e.g. van Holst et al., 2012b).

A proposed explanation for these seemingly contradictory findings is that “PG” individuals generally exhibit a hypo-responsive reward circuitry. However, highly salient cues or reward anticipation are capable of heightening attention in “PG” individuals, which can enable normal or even heightened levels of striatal activation (e.g., van Holst et al., 2012b).

Another possible explanation, stemming from studies of individuals with “SADs”, focuses on the sensitivity to non-monetary (non-addiction related) rewards in “PG” (Clark et al., 2013). Research has demonstrated that “PG” individuals reveal a decreased response in the ventral striatum when exposed to erotic cues, as opposed to monetary cues, compared to control subjects (Sescousse et al., 2013). In fact, the differential response observed in “PG” subjects was correlated with the severity of problem gambling, and accompanied by a similarly reduced behavioral motivation for erotic rewards.

Another likely explanation is the existence of different subgroups of gamblers (Milosevic & Ledgerwood, 2010). Our fMRI data collected from a large sample of “PG” and control subjects suggest that comorbid depressive symptomatology in “PG” has a significant impact on effort-related reward processing (Fauth-Bühler et al., 2014). We found a significant group-by-depression interaction. During receipt of monetary reward, “PG” subjects with higher depression scores compared to those with lower scores showed greater brain activity in the right insula and dorsal striatum. No differences were observed for control subjects with higher versus lower depression scores. These findings further highlight the importance of subgroup specific differences in “PG” (Milosevic & Ledgerwood, 2010), which necessitate further examination.

5. Discussion and Conclusion

From a diagnostic perspective, the criteria for “PG” (as proposed for ICD-11) overlap considerably with those for substance abuse/dependence; i.e., preoccupation with the behavior in question, diminished control over behavioral engagement and adverse psychosocial consequences related to behavior. Even tolerance and withdrawal-like symptoms have been reported for behavioral addictions (el-Guebaly et al., 2012). Gambling is a pleasurable leisure activity for many people, whereas most other behaviors that are the focus of “ICDs” are not (e.g. stealing, fire-setting). In DSM-5, the “ICD” category is now also characterized by behaviors that violate the rights of others or bring an individual into conflict with social norms or authority figures. While compulsive acts are repetitive and purposeless behavioral or mental acts performed with the aim of reducing anxiety or distress (“negative reinforcement”), gambling is rewarding (“positive reinforcement”) for controlled and addicted gamblers individuals alike. Only at a later stage the behavior may become more compulsive, in the sense that the behavior might not be accompanied by pleasurable, hedonic emotions or conducted for the sake of pleasure. This pattern also holds true for “SADs” (Robbins & Clark, 2014), but we would strongly argue not for “ICDs”.

“PG” has not frequently co-occurred with “ICDs”, such as kleptomania or pyromania but is highly comorbid with other psychiatric disorders. Only weak associations (OR=2.2) have observed between “PG” and “ICDs” in the NCS-R study. The strongest evidence relates “PG” to “SADs”. In the NESARC-study, associations between any alcohol use disorder and alcohol dependence were especially strong (Petry et al., 2005). This stronger association between alcohol use disorders and “PG” may indicate that similar environmental, social, and/or genetic factors may be associated with both of these disorders. Comorbid psychiatric disorders in “PG” need to be carefully considered in future research as they have been shown to impact behavior (Zois et al., 2014), brain function (Fauth-Bühler et al., 2014) and brain structure (Zois et al., 2015).

Research findings to date indicate elevated choice impulsivity among patients suffering from “SADs” and “PG”. While impulsive action (motor response inhibition) has been found to be impaired in patients diagnosed with “ICDs” (specifically kleptomania) and “SADs”, results for “PG” have been less consistent and merit further examination.

Compulsive behavior contributes to “SADs” and “PG”, and may become increasingly more significant with the progression of each disease. Cognitive inflexibility is a hallmark of patients suffering from OCD and has also been observed in “PG”. However, in the latter group, it is likely the result of aberrant reward-based learning rather than a more general problem of cognitive inflexibility. Research on cognitive flexibility for “ICDs” other than “PG” is lacking to date.

Altered reward processing brought on by functional and structural changes in the mesocorticolimbic reward system, resembling those that occur in “SADs”, is a hallmark of “PG”. An increased salience of stimuli linked to problematic behavior is a unique feature of “SADs” and “PG”. So far this has not been studied in patients suffering from “ICDs” like kleptomania or pyromania.

With respect to reward sensitivity, reward anticipation is dysfunctional irrespective of the type of reward, be it drugs or gambling. This suggests that dopaminergic dysfunction during reward anticipation may constitute a common feature of both substance-related and behavioral addictions, although this notion warrants further study.

Despite great similarities between “PG” and “SADs” in diagnostic criteria, comorbidities and neurobiological characteristics among other domains the grouping of “PG” as “SAD” is controversial. Only recently, in the context of ICD-11, has the working group on OCRDs recommended keeping a category of “ICDs” in ICD-11. This would include “PG” alongside pyromania, kleptomania, compulsive sexual disorder, and intermittent explosive disorder (Grant et al., 2014a). However, the arguments supporting this suggestion are difficult to follow. Firstly, the authors note that “PG” not only shows brain abnormalities in reward circuits, but also reveal prefrontal cortical dysfunctions comparable to those seen in manic patients. They cite a paper in which gamblers displayed altered VMPFC functioning while performing a Stroop Task (Potenza et al., 2003). The VMPFC plays a crucial role in response inhibition. As such, altered VMPFC activity can be observed in a number of psychiatric disorders characterized by poor impulse control including drug addiction. As impaired impulse control and VMPFC dysfunction is also a hallmark of drug addiction, it is difficult to see why “PG” should remain placed in the “ICD” category because of this finding.

Secondly, Grant et al. (2014a) have put forward the shared genetic vulnerability factors between “PG” and major depression as an argument for grouping “PG” in the IC category. The existence of these shared factors is not surprising, given that mood disorders are the second most common co-occurring disorders in “PG”, after “SADs”. This finding does not, in our opinion, explain why “PG” should be grouped as an “ICD” rather than as an addictive disorder.

Thirdly, the paper argues that categorizing “PG” as an addictive disorder has no obvious clinical utility, given that a range of treatment approaches other than those used in the treatment of “SAD” may be useful for “PG”, such as lithium and exposure therapies. However, we argue that lithium is likely to be effective in reducing excessive gambling mostly because of its effectiveness in treating comorbid bipolar symptoms (e.g. Hollander et al., 2005).

Finally, we agree with Grant et al. (2014a) that exposure therapies that are successful in treating OCD can also be effective in reducing gambling urges observed in PGs when presented with gambling-related cues (e.g. Park, 2015). However, this approach has also been successful in reducing drug-taking urges (e.g. Kiefer & Dinter, 2013; Vollstädt-Klein, et al., 2011). In our opinion, none of these arguments are sufficient to counter the classification of “PG” as “SAD” in DSM-5 and moving forward in ICD-11.

It is important to mention that the ICD-10 groups the “ICDs” together not because of any broad descriptive similarities or other shared features, but simply because “they are poorly understood”. A greater understanding of the etiologies of these disorders is therefore needed in order to move them to diagnostic categories that are better suited. This is already the case

for trichotillomania, which will very likely be moved from the “ICD” to the OCRD category in ICD-11, similar to what has occurred in DSM-5.

Research on “PG” has revealed substantial similarities between “PG” and “SADs” in many respects, including diagnostic criteria, comorbidities, neurobiological underpinnings such as brain structure and function and cognitive features, among other domains (see Table 1 for an overview). This suggests that the “SAD” category is far better suited for “PG” than the “ICD” one.

It is also important to highlight that harmonization between ICD-11 and DSM-5 classifications would reduce mismatch in diagnosis, which should always be a common aim for different classification systems (First, 2009).

In summary, there is substantial overlap between “SADs” and “PG”, with communalities in diagnostic criteria, comorbidities, neurobiological underpinnings such as brain function and cognitive features. The strongest arguments for subsuming “PG” under a larger “SAD” category relate to the existence of similar diagnostic characteristics; the high co-morbidity rates between the disorders; their common reward-related aspects (positive reinforcement: behaviors are pleasurable at the beginning which is not the case for “ICDs”); the findings that the same brain structures are involved in “PG” and “SADs”, including the ventral striatum; and the overlap in pharmacological and behavioral treatments (not part of this review). Research on compulsivity suggests a relationship with “PG” and “SAD”, particularly in later stages of the disorders. Although research is very limited for “ICDs” such as kleptomania and pyromania, current data on these disorders does not support continuing to classify “PG” as an “ICD”.

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Table 1

Overview of possible disorder categories for “PG” and central research findings in relation to “PG”.

	Impulse Control Disorders	**Substance-related and Addictive Disorder**	**Pathological Gambling**
Primary diagnostic criteria	Repeated, intense urges Tension before the act and relief afterwards Preoccupation with thoughts or mental images	A strong desire or sense of compulsion to take the drug Lack of control	A strong desire or sense of compulsion to gamble Lack of control
Key behavioral characteristics	Repetitive behaviors that are **not pleasurable**; characterized by tension beforehand and relief afterwards	Repetitive, **reward-related** acts that are pleasurable at the beginning	Repetitive **reward-related** acts that are pleasurable at the beginning
Comorbidities	Not frequently co-occurring with “PG”	Frequently co-occurring with “PG”	Frequently co-occurring with “SADs” but not with “ICDs”
Key brain structures	Not known for pyromania and kleptomania; likely IFC due to its role in impulse control	PFC-striatum circuitry At the beginning ventral striatum; later stages dorsal striatum	PFC-striatum circuitry At the beginning ventral striatum; later stages dorsal striatum
Compulsivity and/or impulsivity	Impulsivity	At the beginning impulsivity; later stages compulsivity	At the beginning impulsivity; later stages compulsivity
Reward sensitivity	Not known; not a central aspect of the disease	Decreased sensitivity to non-drug rewards; increased sensitivity to drug rewards	Decreased sensitivity to non-drug rewards; increased sensitivity to gambling-related rewards

Abbreviations: IFC: inferior frontal cortex; PFC: prefrontal cortex