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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: 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'.

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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 US 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.

The classification of PG was revisited during the fifth revision of the DSM (DSM-V; 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, among 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; World Health Organization 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-V categorization of the condition as a SAD (a decision based in part on DSM-V Research Workgroup efforts to systematically review the literature across multiple domains (Petry 2006; Potenza 2006; Potenza, Koran & Pallanti 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 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 previously mentioned 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.

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.

Substance-related and addictive disorders

The DSM-V 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 (World Health Organization 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 and 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.

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 (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-V process that refocused 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), because these are the only two disorders present in the existing and proposed ICD categories, respectively, in ICD-10 and ICD-11.

CO-OCCURRING DISORDERS (COMORBIDITIES)

Impulse Control Disorders (other than Pathological Gambling)

In clinical samples, kleptomania frequently co-occurs with other psychiatric disorders, primarily with other ICDs (20–46 percent), drug addiction (23–50 percent) and mood disorders (45–100 percent) (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).

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) support these findings. We found the highest comorbidity rates for PG and drug addiction (79 percent including nicotine dependence; 34 percent excluding nicotine dependence) (Mann, Lemenager & Fauth-Bühler 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, Stinson & Grant 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 percent 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 US 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).

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.

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 frontostriatal 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/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, Fassbender & Garavan 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 intertemporal choice tasks that measure the temporal discounting of rewards (e.g. Sellitto, Ciaramelli & di Pellegrino 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).

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, among 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.

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 [refer to 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-dependent and cocaine-dependent (e.g. Kirby & Petry 2004), alcohol-dependent (e.g. Petry 2001) and nicotine-dependent (e.g. Mitchell 1999) individuals. Moreover, patients with SAD 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).

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, Yucel & van Holst 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 with 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 with 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 dorsolateral prefrontal cortex and anterior cingulate cortex 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, Peters & Bu 2012). Furthermore, craving has been shown to affect impulsive choices: altered activity in the midbrain and striatum was observed during the making of impulsive choices in high-craving trials (Miedl, Büchel & Peters 2014).

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 handwashing 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 intradimensional/extradimensional 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 orbitofrontal cortex, 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 overactive striatal habit circuitry (caudate nucleus, putamen) may also underlie compulsive acts (Fineberg *et al.* 2014).

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).

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.

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 *et al.* 2014) and response perseveration (Frost *et al.* 2001; 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).

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, Tobler & Schultz 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 of the midbrain (Volman *et al.* 2013). Dopaminergic neurons, whose cell bodies are located in the ventral tegmental area 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.

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 drug-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 with non-addicted individuals [for a review of alcohol studies refer to 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 (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 patients with SAD. 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).

Impulse Control Disorders (other than Pathological Gambling)

Evidence on the neurobiological basis of reward processing in ICDsconsidered in this review (i.e. kleptomania and pyromania) other than PG is not available to date, to our knowledge.

Pathological Gambling

The presentation of gambling-related stimuli to individuals with PG has been shown to alter brain activity in several studies (Potenza *et al.* 2003; Crockford *et al.* 2005; Goudriaan *et al.* 2010; 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 with 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 with control subjects, for both monetary gains and losses (e.g. De Ruiter *et al.* 2009; Balodis *et al.* 2012). 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 with 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 with 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.

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 and fire-setting). In DSM-V, 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.* 2016).

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 obsessive-compulsive disorder 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 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 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 obsessive-compulsive disorder can also be effective in reducing gambling urges observed in PGs when presented with gambling-related cues (e.g. Park *et al.* 2015). However, this approach has also been successful in reducing drug-taking urges (e.g. Vollstädt-Klein *et al.* 2011; Kiefer & Dinter 2013). In our opinion, none of these arguments are sufficient to counter the classification of PG as SAD in DSM-V 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-V.

Research on PG has revealed substantial similarities between PG and SADs in many respects, including diagnostic criteria, comorbidities and neurobiological underpinnings such as brain structure and function and cognitive features, among other domains (refer to 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-V 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 and 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 do not support continuing to classify PG as an ICD.

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 because of 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.

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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References

Alvarez-Moya EM, Jiménez-Murcia S, Moragas L, Gómez-Peña M, Aymamí MN, Ochoa C, Sánchez-Díaz I, Menchón JM, Fernández-Aranda F (2009) Executive functioning among female pathological gambling and bulimia nervosa patients: preliminary findings. J Int Neuropsychol Soc 15:302–306.

American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn. American Psychiatric Association: Washington, DC.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. American Psychiatric Association: Washington, DC.

Balodis IM, Kober H, Worhunsky PD, Stevens MC, Pearlson GD, Potenza MN (2012) Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. Biol Psychiatry 71:749–757.

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7–15.

Berlin GS, Hollander E (2014) Compulsivity, impulsivity, and the DSM-5 process. CNS Spectr 19:62–68.

Blaszczynski A, Nower L. (2002) A pathways model of problem and pathological gambling. Addiction 97:487–99.

Boog M, Höppener P, Wetering BJ, Goudriaan AE, Boog MC, Franken IH (2014) Cognitive inflexibility in gamblers is primarily present in reward-related decision making. Front Hum Neurosci 8:569.

Brand M, Kalbe E, Labudda K, Fujiwara E, Kessler J, Markowitsch HJ (2005) Decision-making impairments in patients with pathological gambling. Psychiatry Res 133:91–9.

Brevers D, Cleeremans A, Verbruggen F, Bechara A, Kornreich C, Verbanck P, Noél X (2012) Impulsive action but not impulsive choice determines problem gambling severity. PLoS One 7: e50647. doi: 10.1371/journal.pone.0050647.

Brevers D, Koritzky G, Bechara A, Noél X (2014) Cognitive processes underlying impaired decision-making under uncertainty in gambling disorder. Addict Behav. 39:1533–6.

Bühler M, Mann K (2011) Alcohol and the human brain: a systematic review of different neuroimaging methods. Alcohol Clin Exp Res 35:1771–1793.

Bühler M, Vollstädt-Klein S, Kobiella A, Budde H, Reed LJ, Braus DF, Büchel C, Smolka MN (2010) Nicotine dependence is characterized by disordered reward processing in a network driving motivation. Biol Psychiatry 67:745–752.

Choi SW, Kim HS, Kim GY, Jeon Y, Park SM, Lee JY, Jung HY, Sohn BK, Choi JS, Kim DJ (2014) Similarities and differences among Internet gaming disorder, gambling disorder and alcohol use disorder: a focus on impulsivity and compulsivity. J Behav Addict 3:246–253.

Clark L, Averbeck B, Payer D, Sescousse G, Winstanley C, Xue G (2013) Pathological choice: the neuroscience of gambling and gambling addiction. J Neurosci Off J Soc Neurosci 33:17617–17623.

Crockford DN, Goodyear B, Edwards J, Quickfall J, el-Guebaly N (2005) Cue-induced brain activity in pathological gamblers. Biol Psychiatry 58:787–795.

Daruma J, Barnes P (1993) A neurodevelopmental view of impulsivity and its relationship to the superfactors of personality. In: McCown W, Johnson J, Shure M eds. *The Impulsive Client: Theory, Research and Treatment*. American Psychological Association: Washington DC.

De Ruiter MB, Veltman DJ, Goudriaan AE, Oosterlaan J, Sjoerds Z, van den Brink W (2009) Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 34:1027–1038.

De Ruiter MB, Oosterlaan J, Veltman DJ, van den Brink W, Goudriaan AE (2012) Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. Drug Alcohol Depend 121:81–89.

De Wit H (2009) Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addict Biol 14:22–31.

Di Chiara G, Bassareo V (2007) Reward system and addiction: what dopamine does and doesn't do. Curr Opin Pharmacol 7:69–76.

El-Guebaly N, Mudry T, Zohar J, Tavares H, Potenza MN (2012) Compulsive features in behavioural addictions: the case of pathological gambling. Addiction (Abingdon, England) 107:1726–1734.

Evenden JL (1999) Varieties of impulsivity. Psychopharmacology (Berl) 146:348–361.

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8:1481–1489.

Fauth-Bühler M, de Rover M, Rubia K, Garavan H, Abbott S, Clark L, Vollstädt-Klein S, Mann K, Schumann G, Robbins TW (2012) Brain networks subserving fixed versus performance-adjusted delay stop trials in a stop signal task. Behav Brain Res 235:89–97.

Fauth-Bühler M, Zois E, Vollstädt-Klein S, Lemenager T, Beutel M, Mann K (2014) Insula and striatum activity in effort-related monetary reward processing in gambling disorder: the role of depressive symptomatology. NeuroImage: Clinical 6:243–251.

Fineberg NA, Chamberlain SR, Goudriaan AE, Stein DJ, Vanderschuren LJ, Gillan CM, Shekar S, Gorwood PA, Voon V, Morein-Zamir S, Denys D, Sahakian BJ, Moeller FG, Robbins TW, Potenza MN (2014) New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. CNS Spectr 19:69–89.

Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. Science (New York, NY) 299:1898–1902.

First MB (2009) Harmonisation of ICD-11 and DSM-V: opportunities and challenges. Br J Psychiatry J Ment Sci 195:382–390.

Fontenelle LF, Oostermeijer S, Harrison BJ, Pantelis C, Yücel M (2011) Obsessive-compulsive disorder, impulse control disorders and drug addiction: common features and potential treatments. Drugs 71:827–840.

Frost RO, Meagher BM, Riskind JH (2001) Obsessive-compulsive features in pathological lottery and scratch-ticket gamblers. J Gambl Stud 17:5–19.

Garavan H, Hester R (2007) The role of cognitive control in cocaine dependence. Neuropsychol Rev 17:337–345.

Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W (2005) Decision making in pathological gambling: a comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. Brain Res Cogn Brain Res 23:137–151.

Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W (2006a) Neurocognitive functions in pathological gambling: a comparison with alcohol dependence, Tourette syndrome and normal controls. Addiction (Abingdon, England) 101:534–547.

Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W (2006b) Psychophysiological determinants and concomitants of deficient decision making in pathological gamblers. Drug Alcohol Depend 84:231–239.

Goudriaan AE, de Ruiter MB, van den Brink W, Oosterlaan J, Veltman DJ (2010) Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: an fMRI study. Addict Biol 15:491–503.

Goudriaan AE, Yucel M, van Holst RJ (2014) Getting a grip on problem gambling: what can neuroscience tell us? Front Behav Neurosci 8:141.

Grant JE, Odlaug BL (2008) Kleptomania: clinical characteristics and treatment. Revista Brasileira de Psiquiatria (São Paulo, Brazil: 1999) 30:S11–S15.

Grant JE, Potenza MN, Weinstein A, Gorelick DA (2010) Introduction to behavioral addictions. Am J Drug Alcohol Abuse 36:233–241.

Grant JE, Atmaca M, Fineberg NA, Fontenelle LF, Matsunaga H, Janardhan Reddy YC, Simpson HB, Thomsen PH, van den Heuvel OA, Veale D, Woods DW, Stein DJ (2014a) Impulse control disorders and "behavioural addictions" in the ICD-11. World Psychiatr 13:125–127.

Grant JE, Chamberlain SR (2014) Impulsive action and impulsive choice across substance and behavioral addictions: Cause or consequence? Addict Behav 39:1632–1639.

Grant JE, Kim SW (2014) Brain circuitry of compulsivity and impulsivity. CNS Spectr 19:21–27.

Hasson R, Fine JG (2012) Gender differences among children with ADHD on continuous performance tests: a meta-analytic review. J Atten Disord 16:190–198.

Hester R, Fassbender C, Garavan H (2004) Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the GO/NOGO task. Cerebr Cortex (New York, NY: 1991) 14:986–994.

Hollander E, Pallanti S, Allen A, Sood E, Baldini Rossi N (2005) Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? Am J Psychiatry 162:137–145.

Hommer DW, Bjork JM, Gilman (2011) Imaging brain response to reward in addictive disorders. Ann N Y Acad Sci 1216:50–61.

Hulka LM, Eisenegger C, Preller KH, Vonmoos M, Jenni D, Bendrick K, Baumgartner MR, Seifritz E, Quednow BB (2014) Altered social and non-social decision-making in recreational and dependent cocaine users. Psychol Med 44:1015–1028.

Jupp B, Dalley JW (2014) Convergent pharmacological mechanisms in impulsivity and addiction: insights from rodent models. Br J Pharmacol 171:4729–66.

Keramati M, Gutkin B (2013) Imbalanced decision hierarchy in addicts emerging from drug-hijacked dopamine spiraling circuit. PLoS One 8:e61489.

Kessler RC, Hwang I, LaBrie R, Petukhova M, Sampson NA, Winters KC, Shaffer HJ (2008) DSM-IV pathological gambling in the National Comorbidity Survey Replication. Psychol Med 38:1351–1360.

Kiefer F, Dinter C (2013) New approaches to addiction treatment based on learning and memory. Curr Top Behav Neurosci 13:671–684.

Kirby KN, Petry NM (2004) Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction (Abingdon, England) 99:461–471.

Knutson B, Adams CM, Fong GW, Hommer D (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 21:RC159.

Kräplin A, Dshemuchadse M, Behrendt S, Scherbaum S, Goschke T, Bühringer G (2014) Dysfunctional decision-making in pathological gambling: pattern specificity and the role of impulsivity. Psychiatry Res 215:675–682.

Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L (2009) Impulsivity and response inhibition in alcohol dependence and problem gambling. Psychopharmacology (Berl) 207:163–172.

Leeman RF, Potenza MN (2012) Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity. Psychopharmacology (Berl) 219:469–490.

Liao DL, Huang CY, Hu S, Fang SC, Wu CS, Chen WT, Lee TS, Chen PC, Li CS (2014) Cognitive control in opioid dependence and methadone maintenance treatment. PLoS One 9:e94589.

Limbrick-Oldfield EH, van Holst RJ, Clark L (2013) Fronto-striatal dysregulation in drug addiction and pathological gambling: Consistent inconsistencies? Neuroimage Clin 2:385–93.

Mann K, Lemenager T, Fauth-Bühler M (2013) Glücksspielsucht und verwandte Störungen: Patientenzentrierte Erfassung des Risikos und Entwicklung von Frühinterventionen für Gefährdete. Endbericht an das Ministerium für Arbeit und Soziale Ordnung, Familien und Senioren, Baden-Württemberg. [Pathological gambling and related disorders. Report to the Ministry of Social Welfare Baden Wurttemberg, Germany].

Marazziti D, Catena Dell'osso M, Conversano C, Consoli G, Vivarelli L, Mungai F, Di Nasso E, Golia F (2008) Executive function abnormalities in pathological gamblers. Clin Pract Epidemiol Ment Health 4:7.

Meng YJ, Deng W, Wang HY, Guo WJ, Li T, Lam C, Lin X (2014) Reward pathway dysfunction in gambling disorder: a meta-analysis of functional magnetic resonance imaging studies. Behav Brain Res 275:243–251.

Meyer C, Rumpf H, Kreuzer A, de Brito S, Glorius S, Jeske C, Kastirke N, Porz S, Schön D, Westram A, Klinger D, Goeze C, Bischof G, John U (2011). Pathologisches Glücksspielen und Epidemiologie (PAGE): Entstehung, Komorbidität, Remission und Behandlung. Endbericht an das Hessische Ministerium des Innern und für Sport. Greifswald/ Lübeck.

Miedl SF, Fehr T, Meyer G, Herrmann M (2010) Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. Psychiatry Res 181:165–173.

Miedl SF, Peters J, Bu C (2012) Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. Arch Gen Psychiatry 69:177–186.

Miedl SF, Büchel C, Peters J (2014) Cue-induced craving increases impulsivity via changes in striatal value signals in problem gamblers. J Neurosci Off J Soc Neurosci 34:4750–4755.

Milosevic A, Ledgerwood DM (2010) The subtyping of pathological gambling: a comprehensive review. Clin Psychol Rev 30:988–998.

Mitchell SH (1999) Measures of impulsivity in cigarette smokers and non-smokers. Psychopharmacology 146:455–64.

Monterosso JR, Aron AR, Cordova X, Xu J, London ED (2005) Deficits in response inhibition associated with chronic methamphetamine abuse. Drug Alcohol Depend 79:273–277.

Noël X, Van der Linden M, d'Acremont M, Bechara A, Dan B, Hanak C, Verbanck P (2007) Alcohol cues increase cognitive impulsivity in individuals with alcoholism. Psychopharmacology (Berl) 192:291–298.

Odlaug BL, Chamberlain SR, Kim SW, Schreiber LR, Grant JE (2011) A neurocognitive comparison of cognitive flexibility and response inhibition in gamblers with varying degrees of clinical severity. Psychol Med 41:2111–2119.

Park CB, Park SM, Gwak AR, Sohn BK, Lee JY, Jung HY, Choi SW, Kim DJ, Choi JS (2015) The effect of repeated exposure to

virtual gambling cues on the urge to gamble. Addict Behav 41:61–4.

Petry NM (2001) Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. Psychopharmacology (Berl) 154:243–250.

Petry NM (2006) Should the scope of addictive behaviors be broadened to include pathological gambling? Addiction 101:152–160.

Petry NM, Stinson FS, Grant BF (2005) Comorbidity of DSM-IV Pathological Gambling and Other Psychiatric Disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 66:564–574.

Potenza MN, Koran LM, Pallanti S (2009) The relationship between obsessive-compulsive and impulse control disorders: A current understanding and future research directions. Psychiatry Res 170:22–31.

Potenza MN, Steinberg MA, Skudlarski P, Fulbright RK, Lacadie CM, Wilber MK, Rounsaville BJ, Gore JC, Wexler BE (2003) Gambling urges in pathological gambling: a functional magnetic resonance imaging study. Arch Gen Psychiatry 60:828–836.

Potenza MN (2006) Should Addictive Disorders Include Non-Substance-Related Conditions? Addiction 101:142–151.

Potenza MN (2013) Neurobiology of gambling behaviors. Curr Op Neurobiol 23:660–667.

Premper V, Schulz W (2008) Komorbidität bei Pathologischem. Sucht 54:131–140.

Redish AD (2004) Addiction as a computational process gone awry. Science (New York, NY) 306:1944–1947.

Reuter J, Raedler T, Rose M, Hand I, Gläscher J, Büchel C (2005) Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci 8:147–148.

Robbins TW, Clark L (2014) Behavioral addictions. Curr Opin Neurobiol 30:66–72.

Robbins TW, Gillan CM, Smith DG, de Wi S, Ersche KD (2012) Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. Trends Cogn Sci 16:81–91.

Sellitto M, Ciaramelli E, di Pellegrino G (2010) Myopic discounting of future rewards after medial orbitofrontal damage in humans. J Neurosci Off J Soc Neurosci 30:16429–16436.

Sescousse G, Barbalat G, Domenech P, Dreher J-C (2013) Imbalance in the sensitivity to different types of rewards in pathological gambling. Brain: A Journal of Neurology 136:2527–2538.

Shaffer HJ (1999) Strange bedfellows: a critical view of pathological gambling and addiction. Addiction (Abingdon, England) 94:1445–1448.

Smith JL, Mattick RP, Jamadar SD, Iredale JM (2014) Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. Drug Alcohol Depend 145:1–33.

Stalnaker TA, Takahashi Y, Roesch MR, Schoenbaum G (2009) Neural substrates of cognitive inflexibility after chronic cocaine exposure. Neuropharmacology 56:63–72.

Tanabe J, Thompson L, Claus E, Dalwani M, Hutchison K, Banich MT (2007) Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. Hum Brain Mapp 28:1276–1286.

Van Holst RJ, van Holstein M, van den Brink W, Veltman DJ, Goudriaan AE (2012a) Response inhibition during cue reactivity in problem gamblers: an fMRI study. PLoS One 7: e30909.

Van Holst RJ, Veltman DJ, Büchel C, van den Brink W, Goudriaan AE (2012b) Distorted expectancy coding in problem gambling: is the addictive in the anticipation? Biol Psychiatry 71:741–748.

Vanes LD, van Holst RJ, Jansen JM, van den Brink W, Oosterlaan J, Goudriaan AE (2014) Contingency learning in alcohol dependence and pathological gambling: learning and unlearning reward contingencies. Alcohol Clin Exp Res 38:1602–10.

Vaughn MG, Fu Q, Delisi M, Wright JP, Beaver KM, Perron BE, Howard MO (2010) Prevalence and correlates of fire-setting in the United States: results from the National Epidemiological Survey on Alcohol and Related Conditions. Compr Psychiatry 51:217–223.

Vollstädt-Klein S, Wichert S, Rabinstein J, Bühler M, Klein O, Ende G, Hermann D, Mann K (2010) Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction 105:1741–1749.

Vollstädt-Klein S, Löber S, Kirsch M, Bach P, Richter A, Bühler M, von der Goltz C, Hermann D, Mann K, Kiefer F (2011) Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. Biol Psychiatry 69:1060–1066.

Volman SF, Lammel S, Margolis EB, Kim Y, Richard JM, Roitman MF, Lobo MK (2013) New insights into the specificity and plasticity of reward and aversion encoding in the mesolimbic system. J Neurosci Off J Soc Neurosci 33:17569–17576.

Wang G, Shi J, Chen N, Xu L, Li J, Li P, Sun Y, Lu L (2013) Effects of length of abstinence on decision-making and craving in methamphetamine abusers. PLoS One 8:e68791.

World Health Organization (1977) *International Classification of Diseases. 9th Revision*. World Health Organization: Geneva.

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization: Geneva.

Zois E, Kortlang N, Vollstädt-Klein S, Lemenager T, Beutel M, Mann K, Fauth-Bühler M (2014) Decision-making deficits in patients diagnosed with disordered gambling using the Cambridge Gambling task: the effects of substance use disorder comorbidity. Brain and Behavior 4:484–494.

Zois E, Kiefer F, Lemenager T, Vollstädt-Klein S, Mann K, Fauth-Bühler M (2016) Frontal cortex gray matter volume alterations in pathological gambling occur independently from substance use disorder Adiction Biol doi: 10.1111/adb.12368. [Epub ahead of print].