

*Review*

# The neurobiology of pathological gambling and drug addiction: an overview and new findings

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Gambling is a prevalent recreational behaviour. Approximately 5% of adults have been estimated to experience problems with gambling. The most severe form of gambling, pathological gambling (PG), is recognized as a mental health condition. Two alternate non-mutually exclusive conceptualizations of PG have considered it as an obsessive-compulsive spectrum disorder and a 'behavioural' addiction. The most appropriate conceptualization of PG has important theoretical and practical implications. Data suggest a closer relationship between PG and substance use disorders than exists between PG and obsessive-compulsive disorder. This paper will review data on the neurobiology of PG, consider its conceptualization as a behavioural addiction, discuss impulsivity as an underlying construct, and present new brain imaging findings investigating the neural correlates of craving states in PG as compared to those in cocaine dependence. Implications for prevention and treatment strategies will be discussed.

**Keywords:** gambling; addiction; impulsivity; impulse control disorder; brain imaging; functional magnetic resonance imaging

## 1. RECREATIONAL, PROBLEM AND PATHOLOGICAL GAMBLING

Gambling can be defined as placing something of value at risk in the hopes of gaining something of greater value (Potenza 2006). A majority of adults gamble, and most do so without encountering significant problems. Nonetheless, gambling problems among adults have been estimated as high as 5%, with certain groups (young adults, people with mental health disorders and incarcerated individuals) having estimates several fold higher (Shaffer *et al.* 1999). Pathological gambling (PG), representing the most severe form of problem gambling (see below), has prevalence estimates of approximately 0.5–1% (Petry *et al.* 2005). Given the increased availability of legalized gambling and its popularity over the past several decades, increased attention to the health impacts of specific levels of gambling behaviours is warranted (Shaffer & Korn 2002).

It was not until 1980 that the *Diagnostic and statistical manual* (DSM) defined criteria for a gambling disorder (American Psychiatric Association 1980). The term 'PG' was selected in favour of other terms (e.g. compulsive gambling) that were arguably more widely used at the time, perhaps in an effort to distinguish the disorder from obsessive-compulsive disorder. Along with pyromania, kleptomania, trichotillomania

and intermittent explosive disorder, PG is currently classified as an 'impulse control disorder (ICD) not elsewhere categorized' in the DSM. Similarly, in the International Classification of Disorders, the disorder is classified under 'Habit and impulse disorders' along with pyromania, kleptomania and trichotillomania. Many of the current diagnostic criteria for PG share features with those for drug dependence (DD). For example, criteria targeting tolerance, withdrawal, repeated unsuccessful attempts to cut back or quit, and interference in major areas of life functioning are contained in the criteria for both PG and DD. Similarities extend to phenomenological, epidemiological, clinical, genetic and other biological domains (Goudriaan *et al.* 2004; Potenza 2006; Brewer & Potenza 2008), raising questions about whether PG might best be characterized as a 'behavioural' addiction.

## 2. PG AS AN ADDICTION

If PG represents an addiction, it should share with DD core features. Core components of addictions have been proposed including (i) continued engagement in a behaviour despite adverse consequences, (ii) diminished self-control over engagement in the behaviour, (iii) compulsive engagement in the behaviour, and (iv) an appetitive urge or craving state prior to the engagement in the behaviour (Potenza 2006). Many of these features, as well as others, such as tolerance and withdrawal, appear relevant to PG and DD (Potenza 2006). Concurrent studies of both PG and DD should help define aspects that are related to drugs. That is, drugs may influence brain structure and function in ways that are central or unrelated to the addiction

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process. In that PG may be conceptualized as an addiction without the drug, direct comparison of both disorders may provide insight into the core neurobiological features of addiction and guide the development and testing of effective treatments.

### 3. NEUROTRANSMITTER SYSTEMS AND PG

Specific neurotransmitters have been hypothesized to relate to different aspects of PG. Based on studies of PG and/or other disorders, noradrenaline has been hypothesized in ICDs to be particularly relevant to aspects of arousal and excitement, serotonin to behavioural initiation and cessation, dopamine to reward and reinforcement, and opioids to pleasure or urges. These and other systems are considered below.

#### (a) *Noradrenaline*

Studies performed during the 1980s compared men with PG to those without and found higher levels of noradrenaline or its metabolites in urine, blood or cerebrospinal fluid samples in the former (Roy *et al.* 1988), and noradrenergic measures correlated with measures of extraversion (Roy *et al.* 1989). Gambling or related behaviours have been associated with autonomic arousal, with pachinko play and casino blackjack each associated with heart rate elevations and increases in noradrenergic measures (Shinohara *et al.* 1999; Meyer *et al.* 2000). During casino blackjack gambling, heart rate and noradrenergic measures become elevated to a greater degree in men with gambling problems as compared to those without (Meyer *et al.* 2004). In addition to a possible role in arousal or excitement, noradrenaline may be related to other aspects of PG. For example, noradrenergic activity influences prefrontal cortical function and posterior attention networks, and medications (e.g. the noradrenaline transport inhibitor atomoxetine and the alpha-2 adrenergic agonists clonidine and guanfacine) that operate through adrenergic mechanisms have been shown to be efficacious in the treatment of attention-deficit hyperactivity disorder and other psychiatric disorders (Arnsten 2006). Adrenergic drugs have been shown to influence specific aspects of impulse control in animal and human studies (Chamberlain & Sahakian 2007). These findings suggest several possible roles for adrenergic function in PG and its treatment, and further investigation is needed in this area to examine these possibilities.

#### (b) *Serotonin*

Traditionally, serotonin function has been considered to be of substantial importance in mediating impulse control. People with clinically relevant levels of impaired impulse control, including those with PG (Nordin & Eklundh 1999) or impulsive aggression (Linnoila *et al.* 1983), have demonstrated low levels of the serotonin metabolite 5-hydroxy indoleacetic acid. Individuals with PG or other disorders or behaviours characterized by impaired impulse control (e.g. impulsive aggression) display different behavioural and biochemical responses to serotonergic drugs than do healthy control subjects. Individuals with PG reported a 'high' following administration of *meta*-chlorophenylpiperazine (m-CPP),

a partial serotonin agonist that binds to multiple 5HT<sub>1</sub> and 5HT<sub>2</sub> receptors with particularly high affinity for the 5HT<sub>2c</sub> receptor (DeCaria *et al.* 1998; Pallanti *et al.* 2006). This response contrasted with that of control subjects and was similar to the high ratings reported previously by antisocial, borderline and alcoholic subjects after receiving the drug. Prolactin response to m-CPP also distinguished the PG and control groups, with greater elevation observed in the former.

Serotonergic probes have been used in conjunction with brain imaging in individuals with impaired impulse control. In individuals with impulsive aggression as compared to those without, a blunted response in the ventromedial prefrontal cortex (vmPFC) is seen in response to m-CPP (New *et al.* 2002) or the indirect agonist fenfluramine (Siever *et al.* 1999), consistent with the findings in alcoholics (Hommer *et al.* 1997). Similar studies have not been performed to date in PG, although other investigations have implicated vmPFC function in PG (see below).

Given the data suggesting an important role for serotonin function in PG and impulse dyscontrol, serotonergic drugs have been investigated in the treatment of PG (Brewer *et al.* 2008). Serotonin reuptake inhibitors show mixed results. In one small, placebo-controlled, double-blind, crossover trial of fluvoxamine, active and placebo arms were significantly distinguished during the second half of the trial, with active drug being superior to placebo (Hollander *et al.* 2000). A separate small placebo-controlled trial observed no difference between active fluvoxamine and placebo (Blanco *et al.* 2002). Similarly, one randomized, controlled, double-blind study of paroxetine demonstrated superiority of active drug over placebo (Kim *et al.* 2002), whereas a larger, multi-centre, randomized, placebo-controlled, double-blind study found no significant difference between active drug and placebo (Grant *et al.* 2003). These initial trials typically excluded individuals with co-occurring psychiatric disorders. A small, open-label trial of escitalopram followed by double-blind discontinuation was performed in individuals with PG and co-occurring anxiety disorders (Grant & Potenza 2006). During the open-label phase, gambling and anxiety measures improved in a largely parallel fashion. Randomization to placebo was associated with a resumption of gambling and anxiety measures, whereas randomization to active drug was associated with sustained responses. Although preliminary, these findings suggest that important individual differences exist among individuals with PG, and that these differences have important implications for treatment response.

#### (c) *Dopamine*

Dopamine is implicated in rewarding and reinforcing behaviours and drug addiction (Nestler 2004). However, few studies have investigated directly a role for dopamine in PG. Ambiguous findings have been reported for cerebrospinal fluid measures of dopamine and its metabolites in PG (Bergh *et al.* 1997; Nordin & Eklundh 1999). Similarly, one early molecular genetic study on PG implicated the TaqA1 allele of the dopamine receptor gene DRD2 similarly across PG, substance abuse and other psychiatric disorders

(Comings 1998). Early molecular genetic studies of PG often included methodological limitations such as lack of stratification by race or ethnicity and incomplete diagnostic assessments, and subsequent studies using methods controlling for race/ethnicity and obtaining DSM-IV diagnoses have not observed differences in TaqA1 allelic frequencies in PG (da Silva Lobo *et al.* 2007). Peer-reviewed publications involving PG subjects and investigating dopamine (or other) systems using ligand-based methodologies do not exist, and such studies represent an important area of future investigation.

PG and other ICDs have been observed in individuals with Parkinson's disease (PD), a disorder characterized by degeneration of dopamine and other systems (Jellinger 1991; Potenza *et al.* 2007). Individuals with PD are treated with drugs that promote dopamine function (e.g. levodopa or dopamine agonists, such as pramipexole or ropinirole) or interventions (e.g. deep brain stimulation) that promote neurotransmission through related circuitries (Lang & Obeso 2004). As such, ICDs in PD could potentially emerge from the pathophysiology of the disorder, its treatment, or some combination thereof. Two studies investigated ICDs in several hundred individuals with PD (Voon *et al.* 2006; Weintraub *et al.* 2006). ICDs were associated with the class of dopamine agonists rather than specific agents, and individuals with ICDs were younger and had earlier ages at PD onset. Individuals with and without ICDs also differed on other factors related to impaired impulse control. In one study, those with an ICD were more likely to have experienced an ICD prior to PD onset (Weintraub *et al.* 2006). In another, PD subjects with and without PG were distinguished by measures of impulsivity, novelty seeking and personal or familial alcoholism (Voon *et al.* 2007). The potential contribution of these and other individual difference variables warrants further consideration in investigations into the pathophysiologies of and treatments for ICDs in PD. Although anecdotal and case series report improvement in ICD symptomatology with discontinuation or diminished dosing of dopamine agonists (Mamikonyan *et al.* 2008), these studies are preliminary in nature and subject to typical biases of uncontrolled trials. Furthermore, some patients may not tolerate higher doses of levodopa used to control symptoms of PD whereas others might abuse these drugs (Giovannoni *et al.* 2000; Evans *et al.* 2005). Together, these findings indicate that more research is needed into the pathophysiologies of and treatments for ICDs in PD.

#### (d) Opioids

Opioids have been implicated in pleasurable and rewarding processes, and opioid function can influence neurotransmission in the mesolimbic pathway that extends from the ventral tegmental area to the nucleus accumbens or ventral striatum (Spanagel *et al.* 1992). On the basis of these findings and similarities between PG and addictions, such as alcohol dependence, opioid antagonists have been evaluated in the treatment of PG and other ICDs. Placebo-controlled, double-blind, randomized trials have evaluated the efficacies and tolerabilities of naltrexone and nalmefene. High-dose

naltrexone (average end of study dose = 188 mg d<sup>-1</sup>; range up to 250 mg d<sup>-1</sup>) was superior to placebo in the treatment of PG (Kim *et al.* 2001). Like in alcohol dependence, the medication appeared particularly helpful for individuals with strong gambling urges at treatment onset. However, liver function test abnormalities were observed in over 20% of subjects receiving active drug during the short trial. Nalmefene, an opioid antagonist not associated with liver function impairment, was subsequently evaluated (Grant *et al.* 2006). Nalmefene was superior to placebo, and liver function test abnormalities were not observed. The dose showing the most efficacy and tolerability was the 25 mg d<sup>-1</sup> dose, one that is roughly equivalent to the 50 mg d<sup>-1</sup> dose typically used in the treatments of alcohol or opiate dependence. A subsequent analysis of the treatment outcome in PG receiving opioid antagonists identified a family history of alcoholism as most strongly associated with a positive drug response, a finding consistent with the alcoholism literature (Grant *et al.* 2008). The extent to which other factors associated with treatment response to opioid antagonists in alcoholism (e.g. allelic variants of the gene encoding the  $\mu$ -opioid receptor; Oslin *et al.* 2003) extend to the treatment of PG warrants direct investigation.

#### (e) Glutamate

Glutamate, the most abundant excitatory neurotransmitter, has been implicated in motivational processes and drug addiction (Chambers *et al.* 2003; Kalivas & Volkow 2005). Based on these data and preliminary findings suggesting a role for glutamatergic therapies in other ICDs (Coric *et al.* 2007), the glutamatergic modulating agent *N*-acetyl cysteine was investigated in the treatment of PG (Grant *et al.* 2007). The study design involved open-label treatment followed by double-blind discontinuation. During the open-label phase, gambling symptomatology improved significantly. Following double-blind discontinuation, improvement was maintained in 83% of responders randomized to active drug as compared to 29% of those randomized to placebo. These preliminary data indicate a need for additional investigations into glutamatergic contributions to PG and glutamatergic therapies for its treatment.

## 4. NEURAL SYSTEMS

Relatively few investigations have examined how brain activities differ in individuals with PG or other ICDs as compared to those without. One initial functional magnetic resonance imaging (fMRI) study investigated urge or craving states in men with PG (Potenza *et al.* 2003b). When viewing gambling tapes and prior to the onset of subjective motivational or emotional response, the pathological gamblers (PGers) as compared to recreational ones showed relatively less blood oxygen level-dependent (BOLD) signal change in frontal cortical, basal ganglionic and thalamic brain regions. These between-group differences were not observed during the happy or sad videotape conditions during the comparable epochs of viewing, and the findings are distinct from studies of individuals with



obsessive-compulsive disorder, who typically show relatively increased activation of these regions during symptom provocation studies (Breiter & Rauch 1996). During the final period of tape viewing, the time at which the most robust gambling stimuli were presented, men with PG as compared to those without were most distinguished by showing relatively diminished BOLD signal change in vmPFC. These findings appear consistent with those from studies of impaired impulse control in other behavioural domains, notably aggression (Siever *et al.* 1999; New *et al.* 2002) and decision making (Bechara 2003).

Although other imaging studies have implicated frontal regions in PG (Crockford *et al.* 2005), multiple investigations have observed differences in vmPFC function in PG. A study of cognitive control using an event-related version of the Stroop colour-word interference task found that men with PG as compared to those without were most distinguished by a relatively diminished BOLD signal change in left vmPFC following the presentation of incongruent stimuli (Potenza *et al.* 2003a). When performing the same fMRI Stroop paradigm, individuals with bipolar disorder were distinguished most from control subjects in a similar region of vmPFC (Blumberg *et al.* 2003), suggesting that some elements common to the disorders (e.g. impaired impulse control, poor emotional regulation) share neural substrates across diagnostic boundaries. Analogously, individuals with substance dependence with or without PG showed less activation of vmPFC than did control subjects in a 'gambling' task assessing decision making (Tanabe *et al.* 2007).

In another fMRI study, individuals with PG as compared to those without showed less activation of vmPFC during simulated gambling in contrasts comparing winning and losing conditions, and BOLD signal change in vmPFC correlated inversely with gambling severity among PGers (Reuter *et al.* 2005). In the same study and using the same contrasts, a similar pattern of diminished activation was observed in PGers in the ventral striatum, a brain region with dopaminergic innervation and which is widely implicated in drug addiction and reward processing (Everitt & Robbins 2005). Based on work in primates (Schultz *et al.* 2000), studies of reward processing in humans have associated activation of the ventral striatum with anticipation of working for monetary reward and activation of vmPFC with receipt of monetary rewards (Knutson *et al.* 2003). This circuitry appears particularly relevant to the processing of immediate rewards as the selection of larger delayed reward involves more dorsal cortical networks (McClure *et al.* 2004). Blackjack gambling as compared to playing blackjack for points is associated with greater corticostriatal activations in PGers (Hollander *et al.* 2005). However, this study did not include subjects without PG and thus did not investigate how PG subjects differed from those without the disorder. The finding of relatively diminished activation of ventral striatum in PGers in the simulated gambling paradigm (Reuter *et al.* 2005) is consistent with the findings from studies of reward anticipation in individuals with addictions or seemingly at risk for such disorders. For example,

relatively diminished activation of ventral striatum during anticipation of monetary rewards has been reported in individuals with alcohol dependence (Hommer 2004; Wrase *et al.* 2007) or cocaine dependence (CD; Pearson *et al.* 2007) as well as in adolescents as compared to adults (Bjork *et al.* 2004) and those with a family history of alcoholism as compared to those without (Hommer *et al.* 2004). Together, these findings suggest that relatively diminished activation of ventral striatum during anticipation phases of reward processing might represent an important intermediary phenotype for substance addiction and ICDs.

## 5. APPETITIVE URGE STATES IN PG AND CD

Appetitive urge or craving states often immediately precede engagement in problematic behaviours such as gambling for PGers or drug use in drug addiction. As such, an understanding of the neural correlates of these states has important clinical implications (Kosten *et al.* 2006). From a scientific perspective, studies of similar processes, such as craving states in individuals with PG or those with DD, may clarify aspects that are central to the underlying motivational processes across disorders, independent of the effects of acute or chronic drug exposure.

To investigate, we employed data from our published studies of gambling urges in PG (Potenza *et al.* 2003b) and drug craving in CD (Wexler *et al.* 2001). As our gambling study involved only male subjects, we restricted analyses to men, yielding a sample including 10 PG subjects and 11 recreational gamblers ( $C_{PG}$  subjects) who viewed the gambling, sad and happy videotapes during fMRI, and 9 CD subjects and 6 non-cocaine-using control comparison men ( $C_{CD}$  subjects) who viewed the cocaine, sad and happy scenarios, as described previously. We investigated in the following manner the extent to which brain activations in motivational and emotional processing were similar or distinct in a behavioural addiction like PG as compared to the drug addiction CD. We hypothesized that brain regions whose function was influenced by cocaine exposure, such as frontal and anterior cingulate cortex, would be differentially involved in cocaine cravings in CD and gambling urges in PG.

We used a voxel-based randomization procedure to assign statistical significance in the generation of  $p$ -maps that identify differences in the manner in which affected subjects' brain function differs from that of controls across the gambling and cocaine groups during viewing of the addiction, happy and sad videotapes (Wexler *et al.* 2001; Potenza *et al.* 2003b). For each subject group viewing each tape type, we generated a  $t$ -map comparing the period of scenario viewing as compared to the average pre- and post-tape grey screen baselines. Next, for each tape type, we generated  $t$ -maps contrasting the manners in which the affected subjects (e.g. PG) differed from their respective controls (e.g.  $C_{PG}$ ), generating a PG- $C_{PG}$  contrast. Next, we contrasted the manner in which the affected groups differed from controls across the addictions ((PG- $C_{PG}$ ) - (CD- $C_{CD}$ ); table 1a, see figure 1A in the electronic supplementary material). At  $p < 0.005$  and

Table 1. Brain activations in PG and CD as compared to control subjects.

brain region	Talairach coordinates <sup>a</sup> ( $x, y, z$ )	radius (mm <sup>2</sup> )	subject groups <sup>b</sup>			
			gambling tapes		cocaine tapes	
			PG subjects	PG controls	CD subjects	CD controls
<i>(a) differences in addiction-related BOLD signal changes <math>((PG-C_{PG}) - (CD-C_{CD}))^c</math></i>						
right inferior parietal lobule	(-49, -44, 32)	4.20	no change	increased, 0.01	no change	decreased, 0.05
bilateral dorsal anterior cingulate	(-1, 31, 23)	4.96	decreased, 0.05	no change	increased, 0.02	no change
bilateral ventral anterior cingulate	(0, 36, -1)	8.05	decreased, 0.05	no change	increased, 0.005	no change
<i>(b) similarities in addiction-related BOLD signal changes <math>((PG-C_{PG}) + (CD-C_{CD}))^d</math></i>						
right posterior cingulate	(-9, -39, 41)	4.21	decreased, 0.01	increased, 0.01	no change	increased, 0.02
bilateral precuneus	(3, -59, 32)	5.45	decreased, 0.02	increased, 0.05	no change	increased, 0.05
right thalamus	(-7, -23, 14)	6.62	decreased, 0.01	increased, 0.05	decreased, 0.05	no change
left insula/ventrolateral prefrontal cortex	(34, 19, 0)	9.62	decreased, 0.02	increased, 0.01	no change	increased, 0.05
right ventral striatum/ventral prefrontal cortex	(-19, 12, -5)	4.88	decreased, 0.05	increased, 0.01	no change	increased, 0.02
left lingual gyrus	(24, -59, -5)	5.09	no change	increased, 0.05	no change	increased, 0.02

<sup>a</sup> Coordinates listed identify approximate Talairach coordinates for the average centre of mass for an activity change. Negative  $x$  values indicate the right side of the brain and negative  $y$  values indicate brain posterior to the anterior commissure. An activity change centred on white matter (corpus callosum) at (15, 25, 14) was observed in the contrast differentially distinguishing addicted from control subjects (*b*). This activity change was considered artefactual, removed from further analysis, and not listed in the table.

<sup>b</sup> Directions of changes in activity indicated are those observed in individual within-group  $p$ -maps contributing to the between-group comparison maps. Individual within-group  $p$ -maps were evaluated at successive significance thresholds of  $p < 0.005, 0.01, 0.02$  and  $0.05$  to identify contributions.  $p$  values listed following the direction of change to indicate the significance level of the  $p$ -map in which the indicated within-subject group change is observed. In cases in which activity changes span across  $z$ -levels of image acquisition (as determined by the Yale fMRI imaging software), the listed value reflects the lowest significance value of a contributing map at a given  $z$ -level.

<sup>c</sup> Brain activity changes differentially distinguishing addicted from control subjects were identified during the entire period of viewing of addiction videotapes (gambling for PG and  $C_{PG}$  subjects and cocaine for CD and  $C_{CD}$  subjects). No activity changes were identified in the corresponding  $((PG-C_{PG}) - (CD-C_{CD}))$  comparisons for the sad and happy videotapes. Directions of changes in activity indicated are those observed in individual within-group  $p$ -maps contributing to the between-group comparison maps. Individual within-group  $p$ -maps were evaluated at successive significance thresholds of  $p < 0.005, 0.01, 0.02$  and  $0.05$  to identify contributions. The  $p$  values are listed following the direction of change to indicate the significance level of the  $p$ -map in which the indicated within-subject group change is observed. In cases in which activity changes span across  $z$ -levels of image acquisition (as determined by the Yale fMRI imaging software), the listed value reflects the lowest significance value of a contributing map at a given  $z$ -level.

<sup>d</sup> Brain activity changes similarly distinguishing addicted from control subjects were identified during the initial period of viewing of addiction videotapes (gambling for PG and  $C_{PG}$  subjects and cocaine for CD and  $C_{CD}$  subjects). No activity changes were identified in the corresponding  $((PG-C_{PG}) - (CD-C_{CD}))$  comparisons for the sad and happy videotapes.

using a cluster of 25 to increase stringency (Friston *et al.* 1994), disorder-related differences in the contrasts between affected and non-affected subject groups were observed during viewing of the addiction tapes (table 1*a*; see figure 1A in the electronic supplementary material) but not the sad or happy scenarios (not shown). The regions of ventral and dorsal anterior cingulate and right inferior parietal lobule were identified during viewing of the addiction scenarios, with relatively decreased activity in the  $(PG-C_{PG})$  contrast as compared to the  $(CD-C_{CD})$  comparison. Within-subject group contributions to these differences are tabulated (table 1*a*). The anterior cingulate cortex, a brain region implicated in emotional processing and cognitive control in healthy (Bush *et al.* 2000) and CD subjects (Goldstein *et al.* 2007), has been shown to activate during cocaine craving (Childress *et al.* 1999). Cocaine administration activates the anterior cingulate (Febo *et al.* 2005), and the timing and the pattern of cocaine administration influence anterior cingulate function (Harvey 2004). The difference in inferior parietal lobule activation across subject groups reflects

mainly a difference in the neural responses of the control groups to the gambling and cocaine videotapes. The inferior parietal lobule has been implicated in response inhibition components of impulse regulation (Menon *et al.* 2001; Garavan *et al.* 2006). Thus, the findings indicate that viewing tapes of different content (e.g. descriptions of a socially sanctioned behaviour (gambling) as compared to an illegal activity (simulated cocaine use)) is associated with differential activation in control subjects of a brain region involved in mediating response inhibition.

We next investigated brain regions common to cocaine cravings and gambling urges, hypothesizing that we would identify brain regions that have been similarly implicated in CD and PG, such as diminished activation of the ventral striatum in reward processing in affected as compared to control subjects (Reuter *et al.* 2005; Pearson *et al.* 2007). For each subject group viewing each tape type, we generated a  $t$ -map comparing the period of scenario viewing to the average pre- and post-tape baselines. Next, for each tape type, we created  $t$ -maps showing activation abnormalities in

the patient groups by contrasting each patient group with its respective control, generating PG-C<sub>PG</sub> and CD-C<sub>CD</sub> contrasts. Computer-generated comparisons at successive significance thresholds ( $p < 0.005$ ,  $p < 0.01$ ,  $p < 0.02$  and  $p < 0.05$ ) were made to identify regions in which the PG-C<sub>PG</sub> and CD-C<sub>CD</sub> contrasts demonstrated similar findings. Individual group  $p$ -maps were used to identify brain regions contributing to these findings. No brain regions were identified using this procedure for the addiction, happy and sad tapes. As our prior studies demonstrated that the initial period of tape viewing, prior to the reported onset of motivational/emotional response, was associated with significant between-group differences in responses to the addiction videotapes (Wexler *et al.* 2001; Potenza *et al.* 2003b), we performed similar analyses focusing on the initial period of tape viewing as compared to the pre-tape baseline. This procedure identified multiple brain regions (table 1b; see figure 1B in the electronic supplementary material) showing similar activity changes in the contrasts between addicted and control subjects during viewing of the respective addiction tapes, and no regions were identified in comparisons involving the sad or happy tapes (not shown).

The brain regions identified as showing common activation patterns in the addicted versus non-addicted subject groups include regions that contribute to emotional and motivational processing, reward evaluation and decision making, response inhibition, and outcome in addiction treatment. In most cases, these regions were activated in control subjects but not in addicted ones. Relatively diminished activation of ventral striatum was observed in the addicted subjects as compared to control subjects, consistent with the findings on tasks involving reward processing in PG and CD subject groups (Reuter *et al.* 2005; Pearson *et al.* 2007). Ventral components of prefrontal cortex, notably the orbitofrontal cortex, have been implicated in the processing of rewards (Schultz *et al.* 2000; Knutson *et al.* 2003; McClure *et al.* 2004), and the lateral region is thought to activate when additional information is needed to guide behavioural actions or when decision making involves the suppression of previously rewarded responses (Elliott *et al.* 2000). Lateral regions of ventral prefrontal cortex, such as the inferior frontal gyrus, are also considered to be of significant importance in response inhibition and impulse control (Chamberlain & Sahakian 2007). Other brain regions whose activation patterns distinguished addicted and non-addicted subjects in the present study have also been implicated in mediating impulse control. For example, in a Go/NoGo paradigm involving healthy subjects, the insula, precuneus and posterior cingulate were activated during error processing and orbitofrontal cortex and lingual gyrus during response inhibition (Menon *et al.* 2001). Insular activation also contributes to conscious urges and thus may influence decision-making processes in addiction (Craig 2002; Naqvi *et al.* 2007). The failure of addicted subjects to activate these regions in the early stages of response to cues that serve as triggers could contribute to poor self-control and subsequent drug use. These findings have implications for

treatment outcome for both PG and drug addiction. For example, insula damage has been associated with impaired betting behaviour as evidenced by a failure to adjust bets with respect to odds of winning, and thus impaired activation might be particularly relevant to PG (Clark *et al.* 2008). Posterior cingulate activation during viewing of cocaine videotapes was associated with treatment outcome in CD subjects, with those who were able to abstain showing greater activation of this brain region (Kosten *et al.* 2006). Thus, although these results should be considered preliminary given the relatively small samples of each group of subjects, the findings complement the larger literature on PG, drug addiction, impulse control and the neural correlates of treatment outcome for drug addiction. Additional investigations involving larger and more diverse samples are needed to substantiate and extend these findings.

## 6. CONCLUSIONS AND FUTURE DIRECTIONS

Although significant advances have been made in our understanding of PG over the past decade, substantial gaps remain in our understanding of the disorder. Most biological studies to date have involved small samples of predominantly or exclusively men, raising concerns regarding the generalizability of the findings, particularly to women. Sex differences in gambling behaviours have been reported both with respect to types of gambling problematic for women as compared to men as well as for patterns of development of gambling problems (Potenza *et al.* 2001). For example, the 'telescoping' phenomenon, a process referring to the foreshortened time frame between initiation and problematic levels of behavioural engagement, was first described for alcoholism, more recently for DD, and most recently for problem and PG (Potenza *et al.* 2001). Given such clinically relevant differences, examinations into the underlying biology of PG should consider potential influences of sex. Similarly, different stages of gambling pathology should be considered in biological investigations, given the data suggesting differential involvements of neurocircuitry (e.g. ventral versus dorsal striatum) as behaviours progress from more novel or impulsive to habitual or compulsive (Everitt & Robbins 2005; Chambers *et al.* 2007; Belin & Everitt 2008; Brewer & Potenza 2008). Additional considerations include the nature of impulsivity and its relationship to ICDs and substance addictions. That is, it is possible that substance use may lead to more gambling, more gambling may lead to substance use, or that common factors like impulsivity may contribute to excessive engagement in each domain. Clarifying these possibilities in animal and real-life settings represents a clinically and scientifically relevant goal (Dalley *et al.* 2007). Given that impulsivity is a complex multifaceted construct (Moeller *et al.* 2001), understanding how specific aspects relate to pathophysiologies of and treatments for PG and drug addictions is important. Finally, PG is arguably the best studied of a group of ICDs that are currently categorized together in diagnostic manuals. Additional research is needed into other ICDs and their neurobiology, prevention and treatment, particularly as these



disorders are associated with markers of greater psychopathology and appear currently to go frequently undiagnosed in clinical settings (Grant *et al.* 2005).

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