Imaging studies in pathological gambling: similarities and differences with alcohol dependence
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Chapter 2

Why gamblers fail to win; a review of cognitive and neuroimaging findings in pathological gambling

Chapter 2

Abstract
The purpose of this review is to gain more insight in the neuropathology of pathological gambling and problem gambling, and to discuss challenges in this research area.

Results from the reviewed PG studies show that PG is more than just an impulse control disorder. PG seems to fit very well with recent theoretical models of addiction, which stress the involvement of the ventral tegmental-orbito frontal cortex. Differentiating types of PG on game preferences (slot machines vs. casino games) seems to be useful because different PG groups show divergent results, suggesting different neurobiological pathways to PG.

A framework for future studies is suggested, indicating the need for hypothesis driven pharmacological and functional imaging studies in PG and integration of knowledge from different research areas to further elucidate the neurobiological underpinnings of this disorder.
**Introduction**

Pathological gambling (PG) is characterized by persistent, uncontrolled gambling leading to deleterious psychosocial consequences (American Psychiatric Association, 1994). Unfortunately, knowledge about the aetiology of this disorder is limited and treatment is effective only in part of the PG population (Grant et al., 2008; Ledgerwood and Petry, 2006b; Petry et al., 2006; Petry et al., 2007).

Several models have been developed to explain PG behaviour (Blaszczynski and Nower, 2002; Sharpe, 2002). The ‘biopsychosocial model’ (Sharpe, 2002) suggests that genetic predispositions such as changes in neurotransmitter systems or impulsive personality traits are likely to contribute to the vulnerability to develop gambling problems. In the biopsychosocial model (Sharpe, 2002) and in the ‘pathways model’ (Blaszczynski and Nower, 2002), it is stated that gambling behaviour is influenced by classical and operant conditioning leading to increased participation and the development of habitual patterns of gambling. Moreover, it is hypothesized that once gamblers begin to use gambling as a coping mechanism, patterns of gambling behaviour will become entrenched and maladaptive (Sharpe, 2002). Urges for gambling will develop over time, weakening the capacity for behavioural self-control in spite of increasing negative consequences as a result of gambling. This is thought to create a vicious cycle and to perpetuate gambling problems.

In addition, two groups of gamblers are identified in the ‘biopsychosocial model’ that differ in gambling motives. One group, mainly slot machine players, is thought to gamble in order to escape stressful situations. A second group, mainly horse race and/or casino gamblers, gambles to resolve feelings of boredom and to replace low levels of arousal with high levels of arousal (Ledgerwood and Petry, 2006a; Wulfert et al., 2005). These subgroups are also identified in the ‘pathways model of pathological gambling’ (Blaszczynski and Nower, 2002). This model additionally includes a third group that is behaviourally conditioned to gambling, displays minimal levels of psychopathology and is thought to be on the less severe end of pathological gambling.

Studies investigating the heritability and genetic contribution of PG have found allelic variants of dopamine and serotonin receptors in neurotransmitter systems (Eisen et al., 2001; Ibanez et al., 2003). These vulnerabilities were also found to be higher in groups with antisocial personality disorder (ASPD), depression and substance use dependence (SUD) (Eisen et al., 2001; Ibanez et al., 2003). Considering the similarities and resemblances in symptoms in PG and SUD, such as tolerance and craving, recent studies have suggested that PG may be considered a behavioural addiction (Goudriaan et al., 2004; Petry, 2007; Potenza, 2006; Tamminga and Nestler, 2006).

During the past few years, interest has grown in the neurobiological basis of PG. In 2004, Goudriaan et al. published a comprehensive review on all biobehavioral studies concerning PG conducted until 2004. The authors concluded that the findings of the reviewed articles were difficult to interpret and the conclusions sometimes speculative, because of methodological shortcomings, such as lack of clinical control groups, small sample sizes, and heterogeneity with regard to comorbidity in the PG groups. It was advised to improve methodology and to combine different research methods to gain more knowledge about the aetiology of PG.

Now, after five years, we consider it timely to provide an update on studies published since 2004, focusing on cognitive and neurobiological functions implicated in the development and persistence of PG. Thus, we aim to provide an updated overview of research findings and challenges regarding the neuropathology of PG.

Four important cognitive-emotional processes can be identified, which play an important role in PG. Behavioural conditioning is the first process involved in the
development of gambling behaviour (Blaszczynski and Nower, 2002; Sharpe, 2002), because gambling operates on a variable intermittent pattern of reinforcement (Redish et al., 2007). Differences in behavioural conditioning depend on underlying reward and punishment sensitivity, and therefore the first process discussed in this review is reward and punishment processing. The second process discussed in this review is the increased salience of, and responding to, gambling cues that often results in strong urges or craving for gambling. The third process included in this review is impulsivity, because it has been implicated both as a vulnerability trait for acquiring PG and as a consequence of gambling problems. The fourth process is impaired executive functioning and decision making, because pathological gamblers continue gambling in the face of severe negative consequences.

This paper reviews studies that focus on these four processes and how they relate to the aetiology and neuropathology of PG. Because of the considerable overlap between SUD and PG (Potenza, 2006; Tamminga and Nestler, 2006), neurocognitive similarities or differences between these disorders are discussed where appropriate. Furthermore, studies comparing subgroups of gamblers are reviewed because it has been suggested that subgroups of pathological gamblers may differ in the neurobiological nature of this disorder (Blaszczynski and Nower, 2002; Goudriaan et al., 2005; Ledgerwood and Petry, 2006a).

Each section starts with a short description of the concept at hand and how this relates to PG. This description is followed by a review of neuropsychological and neuroimaging studies in PG concerning the concept. Each neuroimaging section is preceded by an introduction on neuroimaging findings in healthy subjects in order to provide a background for interpretation of the findings in PG. Each section ends with a conclusion and discussion of the research findings. This review concludes with a general discussion of the reviewed studies, their relation to addiction theories, clinical implications, and future challenges and directions for gambling research.

Methods

A comprehensive literature search was conducted in PUBMED and PsychINFO with key search terms, including wildcards (*): neuropsychol*, reward, punishment, (f)MRI, neuroimaging, neurocogn*, decision making, attentional bias, craving, cue reactivity, and impulsivity, in combination with the key word gambl*. Selection criteria for studies were inclusion of a cognitive task, presence of a control group, and English language. Cross-references were searched in the selected articles. Groups diagnosed with PG through DSM-IV or ICD-10 assessment are referred to as “pathological gambling groups” (PG groups). Groups defined by gambling problems, measured with problem gambling questionnaires, are referred to as “problem gamblers” throughout this paper. When information is provided in the reviewed article regarding game preference of the participants in the gamblers group, we explicitly report this.

Because Goudriaan et al. (2004) published a comprehensive review on bio-behavioural PG studies until 2004, only studies published from December 2003 until December 2008 are reviewed. Results from earlier studies are summarized at the beginning of each section.

A total of 1437 hits were retrieved in PUBMED and PsychINFO using the search terms. Abstracts of these articles were examined to select only those articles that included neuropsychological or neuroimaging studies on PG. After this selection, 77 papers remained that included PG or problem gambling groups. A total of 26 studies fulfilled all the above mentioned criteria and were included in this review (see Table 1 in supplementary data at the end of this chapter). The remaining 51 articles were excluded because no control group was
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included in the study (n=20), articles were already included in the review by Goudriaan et al (n=20), it concerned review articles (n=9), or because no cognitive task was included (n=2).

Reward and punishment processing

Concept
The initial process common to all gamblers refers to the influence of classical and operant conditioning, leading to increased participation and the development of habitual patterns of gambling (Blaszczynski and Nower, 2002; Redish et al., 2007; Sharpe, 2002). Operant conditioning occurs during gambling when intermittent rewards are delivered according to a variable-ratio schedule, and produce states of arousal often described as equivalent to a ‘drug-induced-high’ (Blaszczynski and Nower, 2002). By repeating this stimulus-response pairing, ‘winning’ arousal also becomes classically conditioned to stimuli associated with the gambling environment. In addition, a history of early wins during gambling may predict longer continuation of gambling during a gambling episode (Coventry, 2001). Gamblers who are winning money have more frequent erroneous estimates of their winning chances and irrational beliefs about the gambling game than gamblers who are losing money (Monaghan et al., 2009). Irrational beliefs are thought to contribute to the initiation and prolongation of gambling sessions and eventually to the emergence of problem gambling behaviour.

On a neurobiological level, studies investigating dopamine receptor density in SUD populations have found that people with lower dopamine (DA) receptor density need more dopamine release to experience the same high than people with higher DA receptor density (Thanos et al., 2001; Volkow et al., 2002). Subsequently, it is thought that being neurobiologically less reward sensitive (i.e., people with lower DA transmission) will make someone more likely to engage in reward seeking behaviour than someone with greater neurobiological sensitivity for rewards. Sensitivity to rewards, therefore, seems to be a factor in the susceptibility to continued gambling behaviour, i.e. having a low neurobiological reward sensitivity will make it less likely for a person to experience ‘winning-highs’. Therefore, larger rewards or longer gambling periods are needed to establish the same rewarding experience in someone with a neurobiologically underactive reward system compared to someone with high neurobiological reward sensitivity. Gambling can also reduce aversive states, such as anxiety and/or depression and can, therefore, act as a negative reinforcer (Blaszczynski and Nower, 2002; Sharpe, 2002). This may further increase the probability of continued and/or excessive gambling.

Few studies have investigated the role of punishment (or negative consequences of behaviour) in the development and course of PG. However, some studies have suggested that subjects at risk for addiction display diminished punishment sensitivity, as is found in subjects with ASPD, a disorder which is genetically related to PG (Eisen et al., 2001) and is highly co-morbid with addictive behaviours (Blair, 2006; Dom et al., 2006). It is thought that diminished punishment sensitivity leads to suboptimal use of feedback and hence disadvantageous choices.

Heightened neurobiological reward sensitivity and diminished punishment sensitivity may explain why some people become problem or pathological gamblers. Although rewards and losses are present in many of the cognitive tasks discussed below, they are mostly discussed in relation to reward processing only. Whenever possible, we will also discuss aspects of punishment sensitivity as addressed in these studies.

Cognitive Behavioural findings regarding reward and punishment processing in PG
Studies investigating reward and punishment processing in PG were reviewed by Goudriaan et al (2004). Summarizing the findings from the three studies published at that time, the
authors concluded that problem gambling was characterized by increased reward seeking behaviour and/or increased insensitivity to loss based on behavioural tasks (Cavedini et al., 2002; Petry, 2001b; Vitaro et al., 1999). Because these studies used complex tasks covering both reward and punishment sensitivity, Goudriaan et al. recommended the development of tasks which tap specific sub-processes of reward and loss to discern whether abnormal reward, abnormal loss, or a combination of abnormal reward and loss sensitivity is present in PG. Further recommendations were to assess the preferred type of gambling and comorbidity in PG. Because various types of gambling differ in, for example, height of stakes involved or odds, and because there is evidence that different types of problem gamblers differ in levels of anxiety and preferred level of arousal (Cocco et al., 1995), this could point to different neuropsychological pathways to PG.

Since December 2003, four new neuropsychological studies on reward and punishment sensitivity, including control groups were published and are reviewed below.

Goudriaan and colleagues (2005) employed the Card Playing Task in a group of 48 pathological gamblers (40 males) recruited from an outpatient treatment facility without comorbid disorders and 49 healthy controls (HCs; 34 males). In this computerized task, a win or a loss is presented after playing a card from a deck, and the subject has to choose whether (s)he wants to play another card or to quit the task. Early in the task the majority of cards are reward cards, but this balance gradually shifts towards a majority of loss cards at the end of the task. Behavioural results on the Card Playing Task showed a worse performance for the pathological gamblers compared to the HC group due to more subjects continuing to play cards despite the increasing proportion of loss cards, indicating increased reward seeking behaviour or diminished punishment sensitivity in pathological gamblers. In addition, a differentiation among type of gambling preference and task performance was found: slot machine gamblers (n=23) showed a conservative response style with a lower amount gained due to early discontinuation of the task, suggesting increased sensitivity for punishment, whereas casino gamblers (n=18) showed a more perseverative strategy for reward, suggesting increased reward seeking behaviour and/or diminished punishment sensitivity in this group.

A study by Leiserson and Pihl (2007) focused on different components of perseverative chasing behaviour in problem gamblers, at-risk gamblers and HCs, all male, by investigating reward sensitivity dominance, deficient inhibition of reward-seeking behaviour, and working memory deficits. A total of 14 problem gamblers (SOGS >5; Lesieur, 1987), 28 at-risk gamblers (SOGS 1-4), and 23 control subjects (SOGS = 0) were recruited from a student population through newspaper advertisements. Reward-sensitivity was operationalized as extraversion, which was measured with the Eysenck Personality Questionnaire (EPQ; Eysenck, 1975), and reward-seeking behaviour was assessed with the sensation seeking scale (SSS-V; Zuckerman et al., 1978). A reward-punishment GO/NO-GO task was administered to investigate reward seeking inhibition deficiencies. Working memory tasks were also performed. The groups did not significantly differ on self-reported extraversion (reward sensitivity) and sensation seeking. Also, no group differences were found for inhibition of reward seeking behaviour. However, problem gamblers and at-risk gamblers did differ from the control group on multiple working memory tasks, indicating worse memory performance in both problem gamblers and at risk gamblers. A more elaborate discussion of these findings of diminished memory performance can be found in the section regarding decision making and executive functioning in PG (see page 30).

Notably, Leiserson and Phil (2007) did not find any differences between their PG group and HC on self-report questionnaires on reward and punishment sensitivity, which is in agreement with findings by Goudriaan et al. (2005), who used the Behavioural inhibition scale and the Behavioural activation scale (BIS/BAS scale; Carver and White, 1994; Putman
et al., 2004) to investigate self-reported punishment and reward sensitivity in combination with physiological measures. No differences between BIS and BAS score were found between PG and HC groups.

**Neuroimaging reward and punishment processing in PG**

The use of neuroimaging techniques has given much greater insights into the neural substrates of human reward processing in the past several years (for a review see McClure et al., 2004). Although specific brain areas activated during processing of rewarding events have varied with the behavioural task, rewarding events have consistently been found to increase the blood-oxygen-level dependent signal (BOLD) response in a common set of neural structures that include the orbitofrontal cortex (OFC), amygdale, and ventral striatum/nucleus accumbens (Hampton et al., 2007; Knutson and Cooper, 2005; Yacubian et al., 2006). The OFC has been implicated to store reward contingencies of different situations and it thereby facilitates context-appropriate behaviour (Rolls, 2004). The amygdala is involved in learning associations between stimuli and subsequent reward or punishment, operating in connection with the OFC (Hampton et al., 2007). The ventral striatum has been associated with increased BOLD signal in fMRI studies when reward magnitude increased and decreased activity when expected rewards are obtained (Knutson et al., 2001; Knutson et al., 2003; Wrase et al., 2007a; Yacubian et al., 2006; Yacubian et al., 2007).

In their 2004 review, Goudriaan et al. included only one neuroimaging study on reward/punishment in PG. This PET study focused on monetary reward processing in PG (Hollander et al., 2005a). Hollander et al. concluded that gambling for money was associated with a higher metabolic rate in the primary visual cortex, the cingulate gyrus, the putamen and the prefrontal areas. Unfortunately, no control group was included in this study, and therefore the significance of these findings for the neuropathology of PG is unclear.

More recently, Reuter et al. (2005) compared fMRI BOLD responses associated with reward and punishment events in 12 male pathological gamblers with preference for slot machine gambling and 12 matched healthy men using a guessing paradigm. Subjects had to choose between two playing cards, and received or lost $1 when playing a card, with a probability of about 50%. A direct comparison between pathological gamblers and controls showed lower ventral striatal and ventromedial prefrontal cortex (VMPFC) activity in pathological gamblers when receiving monetary gains compared to controls, confirming the hypothesis of a less sensitive reward system in PG. In addition, Reuter et al. (2005) found a negative correlation between ventral striatal activity and severity of gambling problems. These findings are compatible with theories postulating reduced reward sensitivity in pathological gamblers. However, an alternative interpretation may be that reduced activity of the ventral striatum and the VMPFC results from lower salience of monetary rewards for pathological gamblers, who are used to winning and losing large amounts of money while gambling. A further limitation of this study is that main effects of winning and losing could not be studied separately. Therefore, it is possible that lower regional brain activity in pathological gamblers was not the result of lower reward sensitivity but of higher punishment sensitivity (Reuter et al., 2005).

A recent fMRI study by de Ruiter et al. (2009) did make a clear distinction between reward and loss trials. They used an affective switching paradigm to investigate the effects of reward and punishment on subsequent behaviour. Subjects were 19 male pathological gamblers recruited from an outpatient treatment centre, 19 male HCs and 19 nicotine dependent men (NDs) recruited through newspaper advertisements. During each trial, two stimuli were presented simultaneously and the subject had to respond to one of the stimuli. Upon a correct response, positive or negative feedback based on an 8:2 ratio was directly
given in the form of monetary loss (negative feedback) or gain (positive feedback) on each trial. On the affective switching paradigm, pathological gamblers performed less well than NDs, and NDs performed worse than HCs. Imaging results from monetary gain conditions showed an activation pattern in the right ventrolateral prefrontal cortex (VLPFC), frontal operculum, right parietal and occipital cortex, including the bilateral caudate nucleus and the subthalamic region. Compared to HCs, pathological gamblers showed lower VLPFC activation to monetary gain. Monetary loss was associated with activation of the right frontal operculum and insular cortex, as well as the sub-thalamic region. Pathological gamblers and NDs showed less VLPFC activation relative to HCs during loss.

In order to exclude executive dysfunction in PG as a possible confounder, de Ruiter et al. (2009) also administered the Tower of London task. There were no differences in performance on the Tower of London between the groups. However, problem gamblers did show less posterior parietal activation during increased planning difficulty, compared to HCs, with intact behavioral performance. These results suggest that problem gamblers are actually more efficient at planning than controls and therefore the posterior parietal cortex is recruited to a lesser extent.

Low responsiveness of the VLPFC to monetary gains in pathological gamblers is consistent with the findings of hypoactivation of the ventral prefrontal cortex in pathological gamblers in response to monetary gain (Reuter et al., 2005) and suggest a lower sensitivity for reward. Lower VLPFC activity during monetary loss is consistent with diminished punishment sensitivity (Goudriaan et al., 2005).

Conclusion reward and punishment processing studies in PG
Since 2004, the number of studies on reward and punishment processing in PG has grown from three to seven. One of the two behavioural studies conducted during the last 5 years showed a differentiation between groups of gamblers on reward and loss processing: slot machine gamblers display heightened punishment sensitivity on a card playing task, whereas casino gamblers display lowered punishment sensitivity in combination with heightened reward seeking behaviour. The heightened punishment sensitivity that was found in the slot machine gamblers could be explained by higher risk avoidance in this group. For example, slot machine players are often thought to gamble in order to escape stressful situations (Blaszczynski and Nower, 2002; Ledgerwood and Petry, 2006a).

Results from neuroimaging studies in pathological gamblers show diminished ventral striatum and VMPFC/VLPFC activation during non-specific rewarding and punishing events in pathological gamblers compared to normal controls (de Ruiter et al., 2009; Reuter et al., 2005), implicating a blunted neurophysiological response to rewards as well as to losses in pathological gamblers.

The reported diminished ventral striatum activation found by Reuter et al. (2005) is in accordance with theories stating drug users and gamblers are characterized by decreased basal ganglia dopaminergic transmission, which predates the development of addictive behaviour, and that repeated drug use or repeated gambling results in a further reduction of DA transmission, leading to a further reduction of reward sensitivity to rewarding stimuli, including drug-related and gambling related stimuli (Goldstein and Volkow, 2002; Volkow et al., 2004; Volkow et al., 2009). Pathological gamblers are therefore likely to seek more rewarding events to compensate for a pre-existing anhedonic state (Berridge and Robinson, 1998; Nader et al., 2006; Robinson and Berridge, 2008). However, from the existing data on PG it is not yet clear whether this diminished reward and punishment sensitivity is a consequence or precursor of addictive behaviours. Animal studies suggest that diminished reward sensitivity is both a cause and a consequence of drug use (Nader et al., 2006).
Lowered punishment sensitivity, which was found in the behavioural study of Goudriaan et al. (2005) and the diminished VLPFC activity during loss trials in the fMRI study by de Ruiter et al. (2009), may imply a need for powerful negative cues to enable adequate responding to negative feedback or loss events in pathological gamblers. This could also contribute to preservation of gambling behaviour in pathological gamblers. Hence, abnormal feedback processing is likely to result in maladaptive behaviour in pathological gamblers. However, lower punishment sensitivity, which is behaviourally operationalized as reward seeking perseveration, could also be explained as heightened reward sensitivity driving the subject to try to obtain more rewards despite greater losses. Interestingly, opioid antagonists (e.g. naltrexone, nalmefene) that are effective in the treatment of PG (Leung and Cottler, 2009) probably exert their action by attenuating reward sensitivity while also increasing punishment sensitivity (Petrovic et al., 2008).

Notably, reward and punishment sensitivity has been extensively investigated in ADHD, and subjects with ADHD have consistently been characterized by higher behavioural reward sensitivity and, albeit less clearly, by lower punishment sensitivity (Luman et al., 2005). Given the high comorbidity between ADHD and PG, the presence and the (confounding) effect of ADHD need to be considered when assessing reward and punishment sensitivity in addicted groups.

Interestingly, a growing number of studies have reported the development of PG during treatment of Parkinson’s Disease (PD). PD is characterized by cell loss of dopaminergic neurons in the mesolimbic and mesocortical networks, and treatment with dopamine agonists has been associated with reward seeking compulsive or impulsive behaviours, such as PG, compulsive shopping and disinhibition (Torta and Castelli, 2008). These behaviours likely reflect modulation of reward circuitry function by dopaminergic drugs. Neuroimaging studies have indeed reported decreased activation in the mesolimbic pathway during monetary gains in PD (Keitz et al., 2008; Thiel et al., 2003), similar to findings in PG and other addictions. In addition, lower D2/D3 binding was found in a PET study in PD with comorbid PG compared to a control group with PD only (Steeves et al., 2009). These observations are consistent with a ‘reward deficiency syndrome’, in which a chronic hypo-dopaminergic state is hypothesized to render individuals vulnerable to addictions by triggering a drive for rewarding substances or behaviours, in order to increase low dopaminergic activity in the brain reward circuitry. It remains unclear, however, why only a subset of PD patients will develop addictive disorders such as PG. Future research investigating dopaminergic dysregulation in PD patients with and without PG may contribute to our understanding of neurophysiological factors predisposing to addictive behaviours.

Finally, the behavioural differentiations between subgroups of gamblers highlight the importance of studying PG subgroups on the basis of preferred gambling activities and subject characteristics. In addition, the need for carefully designed paradigms for disentangling reward and loss processing is warranted. Prospective studies should aim to clarify whether diminished sensitivity for reward or loss leads to a vulnerability for developing PG and/or is the result of PG.

Attentional bias and cue reactivity

Concept
Exposure to situations and stimuli associated with addictive behaviours may promote relapse among individuals with a history of SUD (Carter and Tiffany, 1999; Grusser et al., 2004; Heinz et al., 2007; Wrase et al., 2002). Cue reactivity refers to the enhanced responsiveness to addiction related cues. It has been associated with concepts such as craving and attentional bias to addiction related stimuli, and is considered a central characteristic of SUD and PG.
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(Goldstein and Volkow, 2002; Kalivas and Volkow, 2005; Potenza, 2008; Robbins and Ehrman, 2004).

Cue reactivity and craving have been defined as a strong physiological reaction and subjective desire to use drugs in substance dependent subjects respectively, and have been extensively studied in SUD populations using neuroimaging techniques (Fregni et al., 2008; Garavan et al., 2000; Heinz et al., 2004; Risinger et al., 2005; Wang et al., 2007; Wrase et al., 2007b).

Attentional bias, on the other hand, has been studied mainly with the aid of neurocognitive tasks. Attentional bias is defined by higher attention for addiction related stimuli compared to non-related stimuli, often operationalized as an increase or decrease in reaction time (RT) in tasks involving such stimuli. For example, an increase in RT to substance-related words in an addiction Stroop (Cox et al., 2006) consisting of substance-related and neutral words, is thought to indicate attentional bias. Participants are instructed to name as quickly and accurately as possible the colour in which each word is presented while ignoring the semantic content of the word. Attentional bias is indexed as the difference between participants' mean colour-naming reaction time on trials with substance-related and those with neutral words. Slower colour naming on trials with the substance-related words indicates automatic processing of the semantic content of the words, which interferes with and impairs colour naming. In contrast, shorter reaction times are thought to indicate attentional bias in the visual probe task (e.g. Ehrman et al., 2002). In this task, a substance-related and a matched control stimulus are simultaneously presented. When the stimuli disappear, a visual probe appears at the place that was once occupied by one of the stimuli. The reaction times to probes that replace substance-related stimuli are compared with those that replace neutral stimuli. Because participants generally respond faster to probes that appear in attended vs. non-attended regions of a visual display (Posner et al., 1980), attentional bias is inferred when participants respond faster to probes that replace substance-related stimuli than those that replace control stimuli.

Biased attention toward addiction-related cues may have an important role in addiction because it is likely to contribute to ongoing gambling, or relapse following treatment, by turning attention of individuals to addiction-related cues (Franken, 2003; Franken et al., 2005). In addition, attention towards gambling related events may generate expectancy of future gambling and thereby motivate instrumental gambling behaviour (Field and Cox, 2008).

Cognitive behavioural findings regarding attentional bias in PG

Studies in PG on cue reactivity and attentional bias have been scarce. Whereas Goudriaan et al. did not include such studies in their 2004 review; we were able to identify two studies that used cognitive tasks addressing this issue. In the first, Zack and Poulos (2004) investigated whether a psychostimulant drug could prime motivation to gamble in problem gamblers, since previous research suggested that modest doses of addictive drugs can prime motivation for the use of drugs with similar properties. Ten (seven male) problem gamblers (SOGS>5), six (four male) drinking problem gamblers, eight (five male) problem drinkers and twelve (nine male) controls were given D-amphetamine (AMPH) and were tested with visual analogue scales for addictive motivation and subjective effects of the drug. Questionnaires measuring the desire for gambling and alcohol use were administered to assess the effects of AMPH. AMPH increased the desire to gamble in the problem gamblers group and increased desire for alcohol in the drinking problem gamblers but not in the other groups. A rapid reading task designed to assess the effect of medication on reading speed of words from motivationally relevant (gambling) and irrelevant semantic words was also assessed. On the reading task, AMPH
produced an improvement of reading speed for all words in the non gambling groups. In the problem gambler group, an increase in reaction time to gambling words and a decrease in neutral words under AMPH were found, whereas these effects were not found in the problem drinkers. In addition, during the placebo condition no group differences were found on reading speed, indicating the absence of attentional bias to gambling words during the placebo condition. The authors concluded that psychostimulant (Eisen et al., 2001; Ibanez et al., 2003) activation can increase attentional bias and motivation for gambling.

More recently, Zack and Poulos (2007) investigated the role of DA during reinforcement processes in pathological gambling using haloperidol, a selective DA D2 antagonist. Twenty (17 male) pathological gamblers with mixed preferences of gambling games and eighteen (14 male) non-gamblers were given a single dose of 3 mg haloperidol and were tested using subjective drug and mood effects questionnaires, and had to perform a similar rapid reading task as used in their previous study (Zack and Poulos, 2004). In addition, participants were asked to gamble on a slot machine and report pleasurable effects of the game. The results showed no differential effects of haloperidol on the subjective drug and mood effects questionnaires. Unexpectedly, haloperidol enhanced the salience of gambling words relative to neutral words in problem gamblers, as evidenced by faster responses during the rapid reading task. In addition, haloperidol increased the desire to gamble during the slot machine game, but did not influence the pre-game desire to gamble in problem gamblers. Unfortunately, differences in reading speed between groups during the placebo conditions were not reported, precluding firm conclusions with regard to the saliency of gambling words compared to neutral words in pathological gamblers without drug manipulation. The finding that partial D2 blockade enhanced the rewarding effects of gambling in pathological gamblers are inconsistent with studies showing that D2 blockade consistently decreases the reinforcing efficacy (Bari and Pierce, 2005; Caine et al., 2002) and cue reactivity of psycho stimulant drugs in substance dependent subjects (Franken et al., 2004). However, the authors (Zack and Poulos, 2007) argue that low D2 receptor availability (either induces by dopamine antagonists or genetic variants) are indeed associated with greater subjective rewarding effects of drugs and interpret their findings as indicative of a role of the D2 substrate in pathological gambling.

Neuroimaging cue reactivity in PG
The most frequently used cue reactivity paradigms applied in neuroimaging studies are those in which participants view addiction related and neutral stimuli (i.e. pictures or movies) while functional MRI scans are being acquired. Using such paradigms, several brain regions associated with cue-induced craving in SUD populations have been identified. Specifically, addicted subjects who viewed addiction related cues versus neutral cues compared to healthy controls were found to have greater activity in the amygdala, anterior cingulate cortex, OFC, and VPFC. These effects have been consistently found in patients with alcohol, heroine, cocaine, and nicotine dependence (Braus et al., 2001; George et al., 2001; Grusser et al., 2004; Heinz et al., 2004; Tapert et al., 2004; Wrase et al., 2002).

The first fMRI study on gambling urges was published in 2003 (Potenza et al., 2003b) and reviewed by Goudriaan et al (2004). When viewing a gambling tape which was designed to evoke emotional and motivational predecessors to gambling (e.g. actors who mimicked emotional situations), the PG group showed less activation in the cingulate gyrus, (orbito) frontal cortex, caudate, basal ganglia and thalamic areas compared to the HC group. The authors argue that these findings are consistent with diminished impulse control similar to findings in other disorders characterized by poor impulse control.
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Recently, Potenza and colleagues (2008) re-analyzed their 2003 data to determine whether motivational processes of the pathological gamblers and cocaine users were different from recreational gamblers and cocaine non-users. Regions of the ventral and dorsal anterior cingulate and right inferior parietal lobule were activated more during the viewing of addiction compared to neutral scenarios, with relatively decreased activity in pathological gamblers as compared to the control group and increase of activity in the cocaine users compared to the control group. The authors suggest that decreased activity in the cingulate gyrus, frontal cortex, caudate and basal ganglia in PG during the cue reactivity task were consistent with decreased brain activity found during reward processing tasks. However, one might question whether watching gambling movies should be seen as a rewarding event. In addition, the gambling movies used in Potenza’s studies were complex because actors were used to mimic emotional and motivational feelings associated with gambling events. This is dissimilar to general used movies created for cue exposure experiments which show scenes or pictures of drug related scenes. Results of these studies are therefore hard to interpret in the light of cue reactivity in response to gambling cues.

Another fMRI cue reactivity study that included 10 pathological gamblers with mixed preferences of gambling games and 11 controls, all male, also employed a gambling movie paradigm (Crockford et al., 2005). A stronger BOLD response was found in the right DLPFC, right inferior frontal gyrus, medial frontal gyrus, left parahippocampal region, and left occipital cortex in response to gambling stimuli in pathological gamblers compared to HCs. In addition, the dorsal visual processing stream was activated in pathological gamblers when viewing gambling movies, whereas the ventral visual stream was activated in controls when viewing these movies. The authors argued that brain regions activated in pathological gamblers compared to controls predominantly involved regions associated with the DLPFC network. Visual gambling cues activated brain areas in pathological gamblers that were associated with attention, reward expectancy, and behavioural planning for attaining rewards. These activity patterns found during gambling cues are inconsistent with findings reported in SUD studies. In cue-exposure studies in SUD increased activity is usually reported in the ventral stream, limbic circuit and prefrontal cortex (Braus et al., 2001; George et al., 2001; Grusser et al., 2004; Heinz et al., 2004; Tapert et al., 2004; Wrase et al., 2002). Therefore, it can not be excluded that the movies elicited a conditioned response rather than cue reactivity or craving. This could explain the increased activity in the dorsal network because conditional responses are associated with activity in the dorsal striatum and DLPFC (Everitt and Robbins, 2005).

Conclusion attentional bias and cue reactivity in PG

Whereas cue reactivity and attentional bias have been studied extensively in patients with SUDs, only two studies in PG and problem gambling are available (Zack and Poulos, 2004; Zack and Poulos, 2007). Both studies found attentional bias to gambling related words during DA D2 receptor manipulation in PG. A DA agonist enhanced the saliency of gambling related words and motivation for gambling, while a DA D2 partial antagonist increased the rewarding effects of gambling in pathological gamblers. The similar results of a DA D2 agonist and antagonist on the rewarding and motivational effects of gambling seem surprising and hard to interpret in light of earlier research, which shows that D2 blockade consistently decreases the reinforcing effects of drugs. Future research needs to clarify the role of the dopamine system in cue reactivity in PG.

The studies investigating cue reactivity in PG showed conflicting results. While the studies of Potenza and colleagues (2003b; 2008) reported decreased activity in VMPFC and limbic circuit, Crockford et al (2005) found increased activity in the DLPFC network. These
findings are all inconsistent with results for SUD studies with increases in activity in the limbic circuit and VMPFC. The neuroimaging studies (Potenza et al., 2003b; 2008) investigating cue reactivity in PG used very complex gambling movies to elicit gambling urges and this makes the interpretations of these findings speculative. Unfortunately, Potenza et al. (2003b; 2008) did not report PG severity or duration, so that comparisons with the Crockford et al. (2005) study are problematic. The importance of such factors has been demonstrated by Volkow et al. (2006), who showed that cue reactivity was associated with addiction severity. Also, Wilson et al (2004) reported increased prefrontal cortex activity during cue exposure only in subjects who were not in treatment for their substance dependence.

Future cognitive-behavioural studies on craving and attentional bias need to include both pathological gamblers and healthy controls, reports of severity and duration of disorder, valid tests, such as an addiction Stroop or dot probe task to measure attentional bias. Functional MRI studies investigating cue reactivity will need clear addiction related stimuli such as used in studies on cue reactivity in SUD populations (Braus et al., 2001; George et al., 2001; Grusser et al., 2004; Heinz et al., 2004; Tapert et al., 2004; Wrase et al., 2002), in order to obtain more knowledge about these concepts in PG.

**Impulsivity**

**Concept**

Pathological gambling is classified among impulse control disorders in the DSM-IV-TR (American Psychiatric Association, 1994), and higher impulsivity in PG has consistently been reported (Verdejo-Garcia et al., 2008). Some longitudinal studies have reported that poor inhibition in children may predict the development of gambling problems later in life (Vitaro et al., 1999).

A recent review by Verdejo-Garcia et al. (2008) addressed the role of impulsivity in substance abuse, and concluded that impulsivity is an endophenotype of individuals at risk for SUD and PG.

In the field of cognitive neuroscience, impulsivity is often equated with ‘disinhibition’, thought to represent a state during which top-down control mechanisms that ordinarily suppress automatic or reward-driven responses are inadequate to meet current demands (Aron, 2007). In order to investigate cognitive and behavioural models of impulsivity, objective tests have been developed that measure performance in terms of accuracy and reaction time.

Three broad classes of neurocognitive tests used to measure impulsivity can be distinguished: (i) measures of response inhibition based on the suppression of an automatic (prepotent) response, such as the GO/NO-GO test, the Stop Signal test, the Stroop test, and measures of commission errors during Continuous Performance Tests (CPTs; Boronat and Logan, 1997); (ii) measures of delay discounting, which define impulsivity in terms of choice preference for a small reward available immediately (or after a short delay) over a larger reward available at some point in the future (Reynolds, 2006); and (iii) measures of cognitive impulsivity, a broad term that refers to impulsive behaviour in the domain of decision-making, including measures such as the Iowa Gambling Task (IGT; Bechara et al., 1994), the Cambridge Gamble Task (CGT; Manes et al., 2002), and the Risky Decision Making Task (RDMT; Rogers et al., 1999). However, performance deficits on decision making tasks are not necessarily indicative of impulsivity (Busemeyer and Stout, 2002), and therefore we will discuss decision making separately.

**Cognitive behavioural findings regarding impulsivity in PG**
Five studies on impulsivity in PG, published between 1989 and 2004, were reviewed in Goudriaan et al. (2004). In general, it was concluded that PG is associated with increased impulsiveness indicated by higher delay discounting curves, higher scores on impulsivity questionnaires and more impulsive choices on inhibition tasks. However, due to the high comorbidity in the PG groups in the studies reviewed, these findings could not easily be generalized to pathological gamblers.

More recently, Fuentes and colleagues (2006) studied pathological gamblers, 50% female, with co-morbid psychiatric disorders (CPG: n=162: PG + depressive disorder (62 %), PG + anxiety, panic and/or phobia (74 %) and PG + substance dependence other than nicotine (21 %), pathological gamblers without psychiatric co-morbidity (HCPG; n = 52), and healthy controls (HC; n = 82) using a self-report measure of impulsivity (Barratt Impulsivity Scale; BIS-11; Patton et al., 1995), a Simple Choice Auditory Reaction (SCA) test and a Simple Visual Reaction test (SVR). During the SCA test, subjects had to press a button when hearing a high tone and had to refrain from responding to low tone stimuli. On the SCV test, subjects had to respond to yellow squares and not respond to blue rectangles. In both tests, direct feedback was given, i.e. presenting a positive or negative sound or a happy or sad face, respectively. Pathological gamblers with co-morbid disorders were more impulsive on the BIS-11 than pathological gamblers without psychiatric comorbidity, who were much more impulsive than normal controls. In addition, the HCPG and CPG groups made more incorrect responses during the SCA and SCV tests to non-target stimuli than the HC group, whereas reaction times did not differ between the groups. In a logistic model, both BIS-11 scores and number of incorrect responses on the SCA and the SCV test added independently to the discrimination between the PG and HC group. It should be noted, however, that SCA and SVR tests are known to measure a broader construct than merely impulsivity, such as selective attention and stimulus response processing. Therefore, the authors concluded that due to the lack of reaction time differences between groups, errors were presumably not due to motor impulsivity, but rather reflected impaired information integration and processing in the PG groups.

In a study investigating the role of childhood ADHD on impulsivity in male pathological gamblers, sixteen pathological gamblers with a history of ADHD (PG-ADHD), 39 pathological gamblers without such a history (PG-non-ADHD), and 40 HCs were examined (Rodriguez-Jimenez et al., 2006). In addition to the BIS-11, a stop signal task, a CPT task and a Differential Reinforcement of Low Rate Responding tasks (DRL) were administered. On the DRL (Gordon and Mettelman, 1988), participants were instructed to attain the highest amount of points possible by responding within a time interval that was unknown to them. In order to win points, the delay time had to be six seconds or more. Results showed that patients in the PG-ADHD group exhibited a significantly lower capacity to delay gratification than those in the PG-non-ADHD and control groups, and lower inhibitory control on the stop signal task than those in the PG-non-ADHD group. Self-report questionnaires such as the BIS-11 yielded similar results: PG-ADHD patients scored higher on impulsivity than PG-non-ADHD patients and control subjects. However, no differences were found between groups on the CPT. Therefore, this study provides evidence that gamblers with childhood ADHD have greater deficits in inhibitory control than pathological gamblers without ADHD, and emphasises the necessity of assessing ADHD in impulsivity research. The authors suggest that the deficits in inhibitory control in PG-ADHD may be attributed to VMPFC dysfunction rather than DLPFC, which has been associated with planning and working memory.

Goudriaan et al. (2006) assessed impulsivity in pathological gamblers (PG group; n=46, 40 male), alcohol dependent subjects (AD group: N=48, 40 male), subjects with
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Tourette’s syndrome (TS group; N=46, 32 male) and healthy controls (HC group; N=49, 34 male), using a stop-signal task, a circle tracking task, and a Stroop task. On the circle tracing task, the PG group and the TS group traced the circle faster than the HC group, showing poor inhibition of an ongoing response. On the Stroop Colour–Word Test, the clinical groups revealed greater interference effects, and had more difficulty inhibiting responses to incongruent stimuli than the HC group. Slower Stop Signal reaction times were found the clinical groups compared to the HC group, indicating poor inhibition of a response in the clinical groups. Impaired inhibition on the stop task was predictive of relapse in this PG group at one year follow up (Goudriaan et al., 2007).

Kertzman et al. (2006) also used the Stroop task to measure inhibition in 62 (44 male) PG group and 83 (58 male) HCs, with, however, less consistent findings. Performance was found to be significantly slower and less accurate in pathological gamblers compared to HCs. Paradoxically, pathological gamblers performed slower during the congruent condition than the incongruent condition, resulting in a negative interference effect. The authors speculated that this effect might have resulted from the greater percentage of dyslexia and other reading disabilities in the PG group compared to the HC group. Therefore, the results from this study are difficult to interpret as indicative for higher impulsivity in PG compared to HC.

Kertzman et al. (2008), measured impulsivity in 83 (44 male) pathological gamblers without co-morbidity and 84 (58 male) HCs using a CPT and a GO/NO-GO task. Unexpectedly, the PG group showed an overall longer response time compared to HCs. The PG group, however, did show more commission errors than controls, indicative of higher impulsivity in pathological gamblers. In addition, a higher rate of omissions was found in the PG group compared to the HCs. Pathological gamblers had more difficulties in switching between tasks than controls, suggesting executive dysfunction. Moreover, a positive correlation between the number of commission errors and response time in the PG group was found. This is remarkable because this correlation is generally negative in healthy controls. The authors explain these findings as a possible result of deficits in the organisation of stimulus-response schemata (see also Carter and van Veen, 2007).

A study by MacKillop and colleagues (2006) investigated the validity of measures of cognitive distortions, impulsivity and time perspective in predominantly male (75.5 %) pathological gamblers, problem gamblers and HCs, based on SOGS (Lesieur, 1987) scores. Two behavioural tasks were included, i.e. a delay discounting task and a future time perspectives task. The self report measures and the delay discounting task were shown to discriminate reliably between groups. Pathological gamblers displayed a higher delay discounting rate than problem gamblers and problem gamblers displayed higher delay discounting rates than HC. These findings are consistent with earlier findings of Petry et al. (2001a) and Dixon et al. (2003), and also with findings in SUD (e.g. Kirby and Petry, 2004; Monterosso et al., 2007; Petry and Casarella, 1999; Reynolds, 2006).

In summary, seven new neurocognitive studies have been added to the older five studies reported by Goudriaan et al (2004). Further evidence has been provided that PG is associated with impaired performance on neurocognitive measures of response inhibition, including the domains of motor inhibition and delay discounting. Deficiencies in these domains have also consistently been found in SUD populations (Bolla et al., 2004; Fillmore and Rush, 2002; Hester and Garavan, 2004; Hoffman et al., 2006; Kirby and Petry, 2004; Monterosso et al., 2005). It should be noted that high comorbidity in PG groups was present in some of the studies reviewed above (Fuentes et al., 2006; Kertzman et al., 2006) and comorbid ADHD was not always assessed (Rodriguez-Jimenez et al., 2006). The two studies with pathological gamblers without comorbidity, however, also reported increased impulsivity in PG (Goudriaan et al., 2006; Kertzman et al., 2008).
Chapter 2

Neuroimaging Impulsivity in PG

Several neuroimaging paradigms have been used to uncover the brain mechanism(s) underlying inhibition in healthy subjects. GO/NO-GO tasks and Stroop tasks are known to activate bilateral DLPFC extending into the right inferior frontal gyrus (IFG), insula, supplementary motor area (SMA) and ACC (Egner and Hirsch, 2005; Roberts and Hall, 2008; Wager et al., 2005). However, neuroimaging studies investigating the neural correlates of impulsivity in PG have been rare, with the exception of (Potenza et al., 2003a), which was not included in the Goudriaan et al. (2004) review. In this study, 13 pathological gamblers and 11 HC, all male, performed a Stroop colour-word task in- and outside the scanner by silently naming congruent or incongruent stimuli. Performance and reaction times were obtained after scanning. No behavioural differences were found between pathological gamblers and HCs. Imaging results across groups showed increased activity in dorsal ACC, bilateral IFG, right insula, and right thalamus, and decreased activation in ventral ACC in the incongruent versus congruent trials. Pathological gamblers and HCs could only be differentiated by the activation pattern of the left VLPFC: pathological gamblers showed lower activation in left middle and superior frontal gyri, bordering the superior frontal sulcus laterally and the OFC ventrally compared to the HC group. The lack of performance differences in the Potenza et al. (2003a) study is inconsistent with the literature on impaired Stroop performance in PG (Goudriaan et al., 2006; Regard et al., 2003; Rugle and Melamed, 1993) and may be due to the fact that Stroop performance was assessed after scanning, i.e. after extensive familiarizing and training of the subjects. There was, however, no indication of ceiling effects. Also, because of the assessment afterwards, no information on behavioural performance of the subjects during scanning was present, complicating the interpretation of the imaging data.

Conclusion Impulsivity in PG

In summary, neurocognitive studies in PG have found slower stop-signal reaction time performance as well as more commission errors and greater Stroop interference effects compared to controls. Taken together, these findings indicate that pathological gamblers have difficulty inhibiting irrelevant behaviours and ignoring irrelevant information. In addition, higher delay discounting rates were found in PG. However, the reviewed studies also show the need to asses and better control for comorbidity in PG studies, especially ADHD, to further elucidate the role of impulsivity in PG.

The only neuroimaging study on inhibition in PG (Potenza et al., 2003b) indicated lower activation in the VLPFC in pathological gamblers versus HC using a colour-word Stroop task in the scanner. Due to the complexity of this study the findings are difficult to interpret and additional neuroimaging studies are needed before final conclusions can be made.

Although a vast amount of literature exists of impulsivity measures in PG, more fMRI studies with larger populations and assessment of a variety of impulsivity measures in PG are warranted to gain more insight into the role of impulsivity and associated brain functions in the development and continuation of gambling problems.

Decision making and executive function

Concept

Pathological gamblers and SUD patients exhibit a pattern of decision-making that repeatedly ignores long-term negative consequences in order to obtain immediate gratification or relief from uncomfortable states associated with their addiction (Yechiam et al., 2005).
The Iowa Gambling Task (IGT) is a widely used instrument to assess decision making and is an ecologically valid task because it mimics real life decision making situations, with factors as uncertainty and reward and punishment (Bechara et al., 1994). In the IGT, subjects have to choose cards from four decks of cards. At the start of the task the subject is ignorant of the different payout and loss magnitudes of the decks. Two decks give low payouts and occasionally low penalties, which make them advantageous in the long run. The other two decks give high payouts, but also higher penalties and are disadvantageous in the long run. The participants are encouraged to gain as much money as possible and have to discover which decks are advantageous in the long run and learn to choose the advantageous decks instead of the more risky, disadvantageous decks. Hence, the key feature of this task is that participants have to forgo short term benefits for long term benefits.

Performance on the IGT has been shown to be a sensitive measure of impaired decision making in a diversity of neurological and psychiatric conditions (Bechara et al., 1994). Patients with frontal lesions, subgroups of SUD individuals, and pathological gamblers have demonstrated a preference for short term gains despite larger net losses while performing the IGT (Bechara et al., 1994; Bechara et al., 2000; Cavedini et al., 2002; Manes et al., 2002; Petry, 2001a).

A variety of cognitive and emotional processes influence decision making. Risk taking, experiencing and evaluating immediate versus delayed wins and losses, and impulsivity have been found to constitute the multi-faceted concept of decision-making (Krawczyk, 2002). In addition, executive dysfunction, mainly diminished cognitive flexibility, have been associated with impairments in decision making (Clark et al., 2004; Dretsch and Tipples, 2008; Hinson et al., 2002; Jameson et al., 2004). In this section, therefore, we will review studies assessing decision making and executive functioning in pathological gamblers.

**Cognitive findings of decision making and executive functioning in PG studies**

In a former review of decision making in PG, two decision making studies (Cavedini et al., 2002; Petry, 2001b) published prior to 2004 were discussed (Goudriaan et al., 2004), and it was concluded that pathological gamblers displayed disadvantageous choice behaviour compared to HCs. However, both studies involved pathological gamblers with comorbid substance abuse, and therefore the interpretation of the results on the IGT for pathological gamblers was hindered. In addition, an important methodological issue was noted with regard to the IGT: impaired task performance could be the consequence of abnormal reward or loss processing, or aberrant cognitive processes. Executive functions in pathological gamblers were found to be impaired in two (Regard et al., 2003; Rugle and Melamed, 1993) of the three (Cavedini et al., 2002) studies reviewed by Goudriaan et al. (2004).

More recently, Goudriaan et al. (2006) compared 48 (40 male) pathological gamblers with 46 (36 male) alcohol dependent subjects (AD), 47 (32 male) patients with Tourette syndrome (TS), and 49 (34 male) HCs using the IGT. Performance of the PG group did not differ from the AD group, and both groups chose fewer cards from the advantageous decks than the HC group. Pathological gamblers displayed less knowledge of the advantageous decks, showed a higher response speed and less response shifting after losses compared to the controls. Interestingly, Goudriaan et al. (2006) found a difference in decision making strategies between slot machine gamblers and casino gamblers (engaged mainly in strategic card games), with the former performing worse than the latter, and the latter not different from HCs. This finding emphasizes the need for studies to take into account within-group differences based on gambling preferences (For an overview of findings concerning heterogeneity in PG based on gambling preferences see Ledgerwood and Petry, 2006a).
In another recent study, disadvantageous decision making strategies on the IGT were found in a group of 61 (54 male) pathological gamblers compared to 39 (11 male) normal controls from a first year student population (Linnet et al., 2006). The study focused on quantifiable within-session gambling behaviour, and hypothesized that “chasing one’s losses”, defined as sequences of persistent choices from disadvantageous decks leading to losses, would be more prominent in the PG group than in the HC group. Chasing was operationalized as a minimum of five consecutive choices from disadvantageous decks minus five consecutive choices from advantageous decks. The PG group exhibited more chasing behaviour than the HC group, and this finding was affected by gender: male pathological gamblers chased more compared to male controls, but female pathological gamblers did not chase more than female controls. However, these findings should be interpreted with caution given the differences in age, educational level and gender between the pathological gamblers and HCs.

Whereas Linnet and colleagues interpreted these findings as increased chasing behaviour in pathological gamblers, other researchers have found similar deviant choice behaviour in pathological gamblers and interpreted this as a sign of cognitive inflexibility, as is often displayed in SUD (Goudriaan et al., 2005). The hypothesis of cognitive inflexibility in PG is congruent with reported findings (Barry and Petry, 2008; Clark et al., 2004; Fellows and Farah, 2005; Linnet et al., 2006; Verdejo-Garcia et al., 2004) and seems a more parsimonious explanation for this deviant choice behaviour. To elucidate whether chasing behaviour encompasses more than cognitive inflexibility, interviewing participants for their motives when displaying this ‘chasing’ behaviour, and including tests of cognitive flexibility would be necessary.

A study by Lakey et al. (2006) employed the Georgian Gambling Task (GGT), the IGT, and the self-reported Diagnostic Interview for Gambling Severity (DIGS) in a student population of frequent card players (N=221, 166 male). Based on the DIGS, students were classified as non-problem gamblers (DIGS 0-2), problem gamblers (DIGS 3-4) or pathological gamblers (DIGS >4). The GGT was designed to measure both overconfidence and risk taking by first letting participants answer two-choice general knowledge questions and then assessing their confidence in each answer. In the next phase of the GGT, the measure of risk taking, participants either accepted or rejected a bet on each answer. The original IGT was also included and, consistent with earlier research, pathological gamblers displayed more disadvantageous choice behaviour than the non-pathological players (Lakey et al., 2006). Performance on the GGT and IGT was used in a regression analysis to predict gambling pathology based on the DIGS. Overconfidence and acceptance of bets on the GGT, and disadvantageous decision making on the IGT, significantly predicted gambling related pathology. Unfortunately, the groups studied by Lakey et al. (2006) can not be viewed as representative for the general problem gambling population because their participants were students with a card game preference.

A study with a small group of pathological gamblers from a casino hall was done by Roca et al. (2008). They assed general cognitive functions, decision making abilities (IGT), and inhibition (Go/NoGo) in 11 pathological gamblers and 11 HCs. In terms of their background neuropsychological functioning, the PG group had worse performance in word fluency and memory compared to HC. Also on the IGT and Go/NoGo task a worse performance was displayed by the PG group compared to the HC group. There were no significant correlations between Go/NoGo commission errors and IGT performance. There was, however, a significant correlation between diminished reaction time on the Go/NoGo task and the SOGS severity score, indicating higher impulsivity in more severe gamblers.
Kalechstein and colleagues (2007) investigated EFs in ten (nine male) pathological gamblers, 25 (18 male) abstinent methamphetamine dependent subjects, and nineteen (15 male) controls matched on education, premorbid IQ and depression scores. Pathological gamblers and methamphetamine dependent subjects performed less well than control subjects on the Ruff Figural Fluency Test (original version) and The Trail Making Task part B, two cognitive flexibility tasks, and on the Stroop task, measuring cognitive interference. The performance on these tasks was worse for pathological gamblers than for methamphetamine dependent subjects. These findings indicate that pathological gambling is characterized by diminished cognitive flexibility and enhanced impulsivity; tasks associated with frontal lobe dysfunction.

Forbush et al. (2008) administered a large battery of EF tests to 25 (14 male) pathological gamblers and 34 (nine male) controls. Three tasks to measure cognitive flexibility were the WCST, Controlled Oral Word Association Test and the Trail making task A and B. To measure aphasia, the Diagnostic Aphasia Examination Animal Naming test was included. Working memory and inhibition were assessed using the Wechsler adult intelligence scale (WAIS) letter-number sequencing and the Stroop test. In addition, the IGT and two self-report questionnaires (BIS and Temperament and Character Inventory) were used. Since the groups differed with regard to gender and years of education, results were corrected for differences in pre-morbid IQ. Accept from the Trail making task performance, The PG group performed significantly worse on all tasks compared to the HC group.

Another study focusing on EF in PG was conducted by Marazziti et al (2008). They administered the WCST and verbal associative fluency test (FAS) to assess cognitive flexibility, and the Wechsler memory scale revised (WMS-R) to measure working memory in 20 (15 male) pathological gamblers. The results were compared to normative data of matched HCs. The only group difference was found for the WCST: pathological gamblers had more difficulty finding alternative methods for problem solving compared to HCs. Because this study included gamblers with comorbid psychiatric disorders such as bipolar disorder, obsessive compulsive disorder and substance abuse, caution is warranted in generalizing these results to gamblers without these comorbid disorders. However, these findings are in agreement with the literature showing higher rates of perseveration in PG and less ability to switch between different options (Forbush et al., 2008; Kertzman et al., 2008).

Brand et al.(2005) examined decision making in 25 male pathological gamblers and 25 male HCs in a gambling task with explicit rules, the Game of Dice. This task differs from the IGT because it employs explicit and stable rules for gains and losses as opposed to the implicit IGT rules. The subject is asked to maximize his/her starting capital within 18 dice throws. One virtual single die and a shaker are displayed on a computer screen, and on each trial the subject has to guess which number will occur in the next throw. Subjects can choose between different single numbers, two numbers, three numbers, or four numbers (winning probability 1/6, 2/6, 3/6, and 4/6, respectively). Each choice is associated with a specific gain or loss, and is clearly depicted on the computer screen so that the win and loss probabilities with each choice are easily understood. Brand et al (2005) predicted that decision making ability would be correlated with performance on EF tasks and therefore also administered tasks measuring set-shifting and cognitive flexibility (The Modified Card Sorting Test; MCST, (Lineweaver et al., 1999; Nelson, 1976), interference susceptibility (Stroop) and overall cognitive function (DemTect: Kessler et al., 2000). Although performance of the PG group on the EF tasks was within the normal range, EF task scores correlated positively with the frequency of disadvantageous decision making on the Game of Dice. Consistent with other PG studies using the IGT, Brand et al. (2005) showed that pathological gamblers had a significant preference for disadvantageous choices compared to controls. In addition, Brand et
al (2005) analyzed the effects of providing negative feedback on subsequent decision making, observing that pathological gamblers shifted 33% of their choices after negative feedback compared to 75% in the HC group. This latter finding is consistent with Goudriaan et al. (Goudriaan et al., 2005) and may indicate insensitivity to loss or punishment in PG.

The Game of Dice was also used in a study in 22 male pathological gamblers to investigate the association between decision making strategies and neuroendocrine responses, measured by salivary cortisol and alpha-amylase concentrations (sAA) before and during task performance (Labudda et al., 2007). Pathological gamblers were found to have decision making deficits compared to 19 controls, while displaying comparable neuroendocrine responses to HCs. Labudda and colleagues concluded that the task did not induce enough stress to produce an endocrine response. According to the authors, post hoc analyses revealed that only those patients who showed less disadvantageous decision-making patterns had an increase of sAA during the task. Therefore, the increase of sAA – as an indirect marker of sympathetic nervous system activity – in those patients with less severe decision-making deficits might reflect the role of somatic markers biasing the decision-making process. The somatic maker hypothesis (Damasio, 1996) proposes a mechanism by which physiological processes can guide (or bias) behaviour, particularly decision-making, a model which has been subject of frequent debate because empirical findings have often been contradictory. For a critical reading on the somatic marker theory see Dunn et al. (2006).

Lastly, working memory deficits were reported in the study by Leiserson and Pihl (2007) discussed earlier in the section on cognitive behavioural findings regarding reward and punishment processing (see page 8-9). These authors tested whether problem gamblers (n=14) and at-risk gamblers (n=28) differed from healthy controls (n=23) on multiple working memory tasks such as the Self-Ordered Pointing Task (SOP), and Spatial and Non-Spatial Conditional Association Task (CAT). Impaired memory performance on the CAT in both problem gamblers and at risk gamblers compared to controls was observed, but no differences were reported on the SOP. The authors suggested that memory impairments were related to perseveration and were associated with deficient functioning of the dorsolateral prefrontal cortex (Leiserson and Pihl, 2007). A number of other studies reported evidence for working memory problems (Forbush et al., 2008; Goudriaan et al., 2006; Marazziti et al., 2008). Some studies have found diminished cognitive flexibility in PG (Goudriaan et al., 2006; Marazziti et al., 2008; Rugle and Melamed, 1993), associated with perseveration, whereas others did not find any cognitive flexibility abnormalities (Cavedini et al., 2002).

In summary, PG is characterized by less advantageous decision making abilities and diminished switching behaviour after punishment trials compared to HC. In addition, executive dysfunction, evidenced by impaired cognitive flexibility and working memory problems, was also found in PG.

While the IGT provides information on decision making under uncertain reward and loss contingencies, interpretation of task performance is somewhat hindered by the complexity of the task. For example, the decks in the IGT not only differ in terms of long-term outcome (Lin et al., 2007), but also in terms of punishment frequency: each pair of advantageous and disadvantageous decks consists of one deck which results in small frequent losses and one deck which results in high but infrequent losses. Recent studies have reported that these differences in frequency of punishment may be more important for choice behaviour in healthy subjects than the focus on long term profits as suggested by Bechara and colleagues (Chiu and Lin, 2007; Lin et al., 2007). In addition, performance of pathological gamblers on decision making tasks has been found to be correlated with cognitive flexibility as measured by standard neuropsychological tasks (Brand et al., 2005), and with emotion processing indices (Verdejo-Garcia and Bechara, 2009). A similar relation between cognitive
flexibility and decision making has also been found in substance dependent groups (Barry and Petry, 2008).

**Neuroimaging findings of decision making and executive functioning in PG**

Although research paradigms have varied considerably, a consistent view has arisen regarding the involvement of various brain areas linked through an integrated network to perform decision making behaviour in healthy subjects. This network is thought to involve the OFC, medial PFC, DLPFC, anterior cingulate cortex (ACC), insula and inferior parietal cortex (Brand et al., 2007; Hampton and O'doherty, 2007; Krawczyk, 2002). Regions in the medial and lateral OFC and adjacent mPFC have been consistently found to encode expectancy values as well as the rewarding value of outcomes in decision making tasks and in other paradigms investigating reward processing (Hampton and O'doherty, 2007; Knutson et al., 2005; Knutson and Cooper, 2005; Knutson and Wimmer, 2007; Krawczyk, 2002). The dorsal ACC mediates action selection in situations involving conflict between competing responses and action selection between responses with different reward contingencies (Brown and Braver, 2007; Carter and van Veen, 2007). The insula has been found to respond during uncertainty in action choice and in situations involving risk or ambiguity (Roberts and Hall, 2008). Finally, the inferior parietal cortex has been implicated in attentional processes necessary for task execution or cognitively demanding tasks (Chong et al., 2008; Kihara et al., 2007; Krueger et al., 2007).

Until now, neuroimaging studies focusing on decision making processes in PG have not been published. However, one fMRI study included participants with substance dependence with and without co-morbid gambling problems (Tanabe et al., 2007). Results from this study are of interest because a neurocognitive behavioural study by Petry (2001a) found that pathological gamblers with substance dependence (SDPG) performed worse on the IGT than participants with a diagnosis of substance dependence alone (SD), suggesting an additive effect of pathological gambling in persons with substance dependence.

Tanabe et al. (2007) used a modified version of the IGT to investigate decision making performance in sixteen (five male) healthy controls, twenty (10 male) individuals with SD and twenty (12 male) substance dependent persons with co-morbid gambling problems (SDPG). The task was modified so that the computer selected the decks and the subjects had to confirm “playing” the card or “passing” the card. This ensured that differences in search strategy across the decks, such as perseverative behaviour in addicted groups, were controlled for. The other modification was that instead of receiving a constant reward and an occasional punishment like in the original IGT, the subjects received a single monetary outcome (gain or loss) on all trials in which a card was chosen dependent on which deck they choose. Although SDPG tended to perform better than SD and HC, these differences were not statistically significant. SD and SDPG individuals showed lowered VMPFC activity compared to controls when performing the IGT. Furthermore, the SD group showed less right PFC activity during decision making than the SDPG and HC groups. The authors concluded that larger right prefrontal activity in SDPG compared to SD may reflect hypersensitivity to gambling cues since the IGT resembles a gambling game. Another possibility is that the higher right prefrontal activity reflects better stimulus-reinforcement learning by the SDPG group. In fact, similar to controls, SDPG subjects learned to differentiate the advantageous and the disadvantageous decks slightly faster than non-gambling SD persons. A third possible explanation for the difference among substance users is that the prefrontal cortex responses on basis of previously experienced rewards and punishments (Frank and Claus, 2006). The finding that prefrontal activity was lowest in the SD group suggests that this group is less able
to maintain reward and/or punishment information from trial to trial, and thus may be less sensitive to motivational feedback during decision making.

Unfortunately, the study by Tanabe (2007) did not focus on decision making deficits in a pure PG group, but in a group with co-morbid substance dependence and problem gambling. Their results suggest that co-morbid PG does not result in an added impairment in decision making in SD; a finding inconsistent with Petry et al. (2001a). These inconsistent findings could be explained by the fact that Tanabe (2007) used a modified version of the IGT that prevented perseveration on a specific deck. This could have facilitated correct choices in the SD groups by eliminating the cognitive flexibility element that is found to be aberrant in PG (Brand et al., 2005; Clark et al., 2004; Fellows and Farah, 2005).

**Conclusion decision making and executive functioning in PG**

Behavioural decision making studies have yielded a consistent view of disadvantageous decision making and less efficient EFs in PG. However, it remains unclear which underlying processes contribute to the aberrant choice behaviour displayed on decision making tasks.

In neuroimaging studies investigating decision making abilities in substance dependent subjects, lower activation in VMPFC and DLPFC has been reported compared to controls (Bolla et al., 2005; Paulus et al., 2003; Paulus et al., 2005). However, two studies using PET found higher OFC activation coupled with lower DLPFC activation during the IGT in substance abusers (Bolla et al., 2003; Ersche et al., 2005). Interestingly, cocaine users who did not show a clear behavioural deficit on the IGT displayed higher activation in the OFC, which was positively correlated with task performance (Bolla et al., 2003), which may suggest a compensatory mechanism.

Unfortunately, less is known on the brain activation patterns underlying deficient decision making in PG, because the only study including pathological gamblers focused on substance dependent persons with co-morbid gambling pathology (Tanabe et al., 2007). Nevertheless, Tanabe did find diminished VMPFC activation in substance dependent groups with and without gambling problems.

The IGT may not be the most suitable task to be used in a neuroimaging paradigm investigating decision making abilities. In healthy volunteers, the IGT, as mentioned earlier, activates a large part of the prefrontal cortex (Ernst et al., 2002). This can be explained by the complexity of the task, involving stimulus reinforcement, reversal learning and working memory, as well as decision making (Clark et al., 2004; Fellows and Farah, 2005). The complexity of the IGT makes it difficult to distinguish differences in brain mechanisms between healthy and addicted groups that are associated with disadvantageous decision making. For example, Clark et al. (2004) found that reversal learning, which depends on DLPFC activity, is crucial for performance on the IGT. Therefore, deficits of each of these sub-processes could be related to a diminished IGT performance. As a consequence, abnormalities in brain functions responsible for these sub-processes could explain the diminished prefrontal brain activity in neuroimaging studies in PG and other addictive behaviours. Future neuroimaging research in PG should therefore simultaneously focus on tasks that tap into complex decision making functions and in sub-processes that are necessary for intact decision making, thereby unravelling the underlying neurobiological processes of diminished decision making and its sub-processes in PG.

**General discussion**

In this review, the results of biobehavioral PG studies published between December 2003 and December 2008 were located through a comprehensive literature search using the search engines PubMed and PsycINFO, were summarized and discussed. This provides an overview
Cognitive and neuroimaging findings in pathological gambling

of the research published in the past five years on the neuropsychology of PG. In this general discussion, theoretical models of addiction and PG are discussed in the light of the results from the studies reviewed.

In the last few years PG has been increasingly regarded as a behavioural addiction instead of an ‘impulse control disorder’, as in the DSM-IV (American Psychiatric Association, 1994) (Goudriaan et al., 2004; Petry, 2006; Petry, 2007; Tamminga and Nestler, 2006). Many of the diagnostic criteria for PG share features with those for substance dependence, and similarities extend to phenomenological, epidemiological, clinical, genetic and other biological domains (Goudriaan et al., 2004; Petenza, 2006; 2008) and raise the question whether PG should be characterized as a ‘non-chemical’ or ‘behavioural’ addiction.

Core components of substance use disorders have been proposed including (i) increased salience of drug related stimuli compared to general rewarding stimuli, (ii) craving for drug related stimuli, (iii) diminished control over behaviour or impulsivity, and (iv) continued engagement in behaviour despite adverse consequences (Goldstein and Volkow, 2002; Kalivas and Volkow, 2005).

The reviewed studies indeed indicate that PG is not exclusively characterized by impulsive regulation deficiencies and that similar processes are involved in PG as in substance use disorders. First, increased reward seeking behaviour together with lowered reward sensitivity, characterized by diminished BOLD responses to natural rewarding stimuli in the ventral striatum and VMPC in PG (de Ruiter et al., 2009; Goudriaan et al., 2005; Leiserson and Pihl, 2007; Reuter et al., 2005), is consistent with current addiction models. Moreover, lower punishment sensitivity was found in neuroimaging studies and behavioural studies as well (de Ruiter et al., 2009; Goudriaan et al., 2005). Second, enhanced cue reactivity and attentional bias to gambling cues have been reported in neuropsychological studies in PG (Zack and Poulos, 2004; 2007). However, one of the only two neuroimaging studies on cue reactivity in PG showed increased brain activation to gambling-related stimuli (Crockford et al., 2005), whereas the other study, which reported diminished brain activation in a cue reactivity paradigm, was methodologically problematic (Potenza et al., 2003b). The neurobiological mechanisms of cue reactivity in PG are therefore not yet clear, but the similarity between PG and SUDs at this level seems convincing. Third, neurocognitive studies on impulsivity have shown that pathological gamblers have difficulty filtering irrelevant information and inhibiting ongoing responses (Fuentes et al., 2006; Goudriaan et al., 2006; Kertzman et al., 2006; Kertzman et al., 2008; Rodriguez-Jimenez et al., 2006). Finally, decision making and executive functions have been shown to be compromised in PG (Alessi and Petry, 2003; Brand et al., 2005; Forbush et al., 2008; Goudriaan et al., 2005; Kalechstein et al., 2007; Labudda et al., 2007; Lakey et al., 2006; Marazziti et al., 2008), which is consistent with findings in substance dependency (Bolla et al., 2003; Dom et al., 2006; Ratti et al., 2002; Zorko et al., 2004).

Addiction models describe the vicious cycle from initial drug use to the loss of control over this behaviour, emphasizing the role of the meso-limbic-prefrontal cortex circuit in the process of developing substance dependence. Sporadic and controlled drug use enhance, directly or indirectly, dopamine neurotransmission in the meso-limbic system, including the ventral tegmental area and nucleus accumbens (Volkow et al., 2009). In addition, drug intoxication is associated with strong reinforcement effects, which induce stimulus response learning and heighten salience attribution to the drugs of abuse. When substance abuse arises, characterized by excessive, uncontrolled substance use, cognitive control functions over drug use diminish (prefrontal cortex, PFC; dorsal anterior cingulate gyrus, dACC; e.g. Goldstein et al., 2007; Volkow et al., 2004). Furthermore, as a consequence of continued drug use, the salience of drug-related stimuli increases and drug craving emerges, mediated by changed
dopamine and glutamate functioning, at the expense of salience of other reinforcers (Kalivas and Volkow, 2005). This ‘hijacking’ of the reward system by drug-related stimuli is supported by results from fMRI studies that report decreased ventral striatal, OFC, and VMPFC activity during monetary reward and increased activity in these regions during cue reactivity paradigms in substance dependent subjects compared to controls (Braus et al., 2001; Grusser et al., 2004; Heinz et al., 2004; Wrase et al., 2007b). Repeated exposure to drugs or drug-related cues enhances the memory of the expected reward, resulting in overactivation of the reward and motivational circuits (OFC) while decreasing the influence of the cognitive control circuit (dPFC, dACC) over this motivational circuit. On a cellular level, repeated drug exposure will lead to adaptations of mesolimbic-prefrontal glutamergic pathways, reflected in a transition from prefrontal cortical to dorsal striatal control over drug seeking and drug taking behaviours, as well as a progression from ventral to more dorsal parts of the striatum (Everitt et al., 2008; 2005) These processes contribute to an inability to inhibit the drive to seek and consume drugs in substance dependence.

The process of cellular adaptations of the mesolimbic-prefrontal glutamergic pathways in SUD also seems to play a role in the development of PG. Firstly, the acquisition of gambling behaviour is thought to be similar to SUD because gambling behaviour is influenced by classical and operant conditioning (Blaszczynski and Nower, 2002; Redish et al., 2007; Sharpe, 2002). Although direct evidence of enhanced DA neurotransmission during gambling has not yet been provided, enhanced dopamine blood levels were found in persons during gambling episodes (Meyer et al., 2004). In addition, gamblers report euphoric feelings during a gambling episode, comparable to the “high” experienced by drug users – thus making them more prone to continued gambling. Secondly, by continued gambling, the salience attribution to gambling is strengthened and induces cue reactivity which can result in subjective craving, and potentially further enhancement of DA neurotransmission. Continued gambling and subsequently altered DA neurotransmission could lead to cellular adaptations of mesolimbic-prefrontal glutamergic pathways. In this sense, continued gambling and the development of PG resemble the dynamic process found in SUDs. The proposed cellular adaptations are however speculative because, to our knowledge, no studies exist that describe the cellular adaptations during the acquisition of PG. Therefore, future research should look into the neurophysiological and neuropsychological changes during the development of PG, in order to understand which processes are affected at specific stages of the development of PG and how these relate to developmental processes in SUDs.

These similarities between PG and substance use disorders are interesting and seem to point to a common vulnerability to addictive disorders. Furthermore, these similarities provide a rationale to change the classification of PG as an ‘impulse control disorder’ to a new classification of PG as a ‘behavioural addiction’ in DSM-V.

However, two crucial differences between PG and SUD exist. Firstly, gambling does not result in toxic effects of exogenous substances on the brain. Therefore, it has been suggested that PG might be a useful model to investigate the effects of addictive behaviour on the brain without having to deal with possible confounds due to toxic effects of excessive substance use (Verdejo-Garcia et al., 2008). Secondly, the expectancy of drug use for a dependent person differs from the expectation of gambling for a pathological gambler. The rewarding effect of drugs is guaranteed while a gamble need not result in winning, but in fact is likely to result in a loss. The gamble in itself and the expectation of winning are crucial elements in gambling. Risky decision making and expectancies of gamblers seem therefore to be a potentially fruitful line of research when trying to delineate differences between pathological gamblers and substance dependent subjects.
Clinical implications

Psychological treatments, focusing on motivational, emotional, and cognitive interventions are known to promote remission in a variety of addictions and are also shown to be effective in the treatment of PG (Petry et al., 2006; Petry, 2006). These therapies are designed to enhance motivation to quit or stay abstinent from gambling, to strengthen coping strategies for negative life events, and to provide useful coping strategies for handling risk situations, in order to avoid relapse. One element of psychotherapy appears unique for pathological gambling and has no direct parallel in treatment of substance use: Cognitive therapy focused on altering irrational gambling cognitions has shown potential efficacy (Ladouceur et al., 2001; Ladouceur et al., 2003; Sylvain et al., 1997).

Several interventions targeted at the putative neurobiological mechanisms underlying PG, as reviewed in this study, could prove to be beneficial when treating PG. Starting with non-pharmacological interventions, cue reactivity and attentional bias to gambling cues could be targeted by ‘attentional retraining’ (MacLeod et al., 2002; Wiers et al., 2006). During this type of intervention patients are trained to overcome their attentional bias by performing computer tasks, thereby aiming to reduce cue reactivity and change behaviour. Although the direct effects of this intervention on attentional bias in heavy alcohol drinkers are promising (Field and Eastwood, 2005), the influence of reduced attentional bias on drinking behaviour is less clear. In addition, this intervention has not yet been tested in PG and long-term effects of attentional retraining have to be assessed in future research.

Diminished executive functioning and heightened impulsivity, as found in PG, could be targeted with the aid of neurocognitive training programs. These programs, which are used during treatment of learning disabilities and ADHD, focus on improving attentional skills by teaching and training these abilities. For example, through the use of reinforcement strategies such as token payments and the training of inhibition skills with computer tasks, more adaptive behaviour is learned. In ADHD these programs have shown to enhance a variety of attentional functions and some were associated with improvements in classroom performance (DuPaul et al., 1992; Rapport et al., 1996; Shalev et al., 2007). However, generalisation of these results to more ecological settings appears to be limited (Riccio and French, 2004).

In general, existing therapies could be improved by adapting interventions to cognitive impairments as found in PG, thereby increasing treatment adherence. In addition, frequent rehearsal of coping strategies, and aiding pathological gamblers in identifying subject-specific risk situations from general examples provided in treatment materials may improve the results of treatment interventions in those with neurocognitive impairments.

Furthermore, a number of promising pharmacotherapeutical interventions for treatment of PG have been reported. Neurobiological findings indicate a pivotal role of the mesolimbic pathway, comprising the ventral striatum, amygdalae, ventral striatum, and ventromedial prefrontal cortex in PG. Functional MRI studies have consistently shown diminished activity in these areas, which are thought to play an important role in integrating behavioural consequences and emotional processing in healthy subjects. Because the VMPFC is a structure that depends on DA projections which communicate with limbic structures to integrate information, dysfunctional DA transmission could be the underlying deficit causing the VMPFC dysfunctions in PG. However, numerous other neurotransmitter systems are probably also engaged and may interact during processing positive and negative feedback. For example, opiates are known to increase dopamine release in the reward pathway, and opiate antagonists, naltrexone and nalmefene, which are known to decrease dopamine release, have been found to reduce reward sensitivity and probably heighten the punishment sensitivity as well (Petrovic et al., 2008). Moreover, these treatments have shown to be
effective in PG by diminishing gambling urges (Grant et al., 2008; Kim et al., 2001; Kim and Grant, 2001; Modesto-Lowe and Van, 2002).

While drugs and drug-associated stimuli may elicit dopamine release in the ventral striatum and thus reinforce drug intake during the acquisition of dependence behaviour, chronic drug intake is associated with neuroadaptation of glutamatergic neurotransmission in the ventral striatum and limbic cortex (McFarland et al., 2003; Vorel et al., 2001). In addition, cue exposure has been found to depend on strong projections of glutamatergic neurons from the prefrontal cortex to the nucleus accumbens (LaLumiere and Kalivas, 2008). Blocking the release of glutamate has prevented drug seeking behaviour in animals as well as in SUD (Krupitsky et al., 2007; Mann et al., 2008; Rosner et al., 2008). The first study with N-acetyl cysteine (Keith et al., 1974), modulating the glutamate system, has also been successful in diminishing gambling problems in PG (Grant et al., 2007).

Impulsivity and impaired impulse control have been targeted by selective serotonin reuptake inhibitors (SSRIs) in impulse-control disorders (Hollander et al., 2005b). In PG, mixed results have been found, with some studies demonstrating a benefit distinct from placebo. However, the presence or absence of a co-morbid condition may often determine the effectiveness of medication used to treat PG. While SSRIs such as fluvoxamine may be efficient in treating PG with a comorbid obsessive-compulsive spectrum disorder or OCD features, SSRIs may not be the treatment of choice in PG with co-morbid ADHD.

Medications to enhance decision-making and EF abilities are less well known because of the complexity of these functions, which comprise different sub-processes such as reward and punishment sensitivity and impulsivity, as discussed earlier. However, it can be argued that agents targeting these subprocesses may improve decision making as well. In addition, cognitive enhancers such as modafinil might also have beneficial effects (Killgore et al., 2008; Minzenberg and Carter, 2008).

As was concluded in the review by Goudriaan et al (2004), and is supported by recent neurocognitive and behavioural studies presented in this review, it would be clinically relevant to investigate subgroups of gamblers based on gambling preferences. Horse race/casino gamblers are often described as seeking excitement and arousal, whereas slot machine gamblers seem to seek escape from dysphoric mood and a reduction of arousal (Sharpe, 2002). Arguably, casino gamblers could benefit more by taking natrexone or nalmefene, diminishing their reward seeking behaviour, while slot machine gamblers could benefit more form SSRIs targeting their compulsive symptoms. Moreover, Zack and Poulos (Zack and Poulos, 2009) observed differential drug effects in two PG groups based on high and low impulsiveness scores. Modafinil decreased motivation to gamble, salience of gambling words, risky decision making, and improved inhibitory control in high impulsivity subjects. Interestingly, modafinil had opposite effects on these indices in low impulsivity subjects. Investigations in specific subgroups, therefore, are expected to give more insight into the pathology of these groups and perhaps lead to more tailored and efficient therapies in PG.

Although pharmacological interventions in PG are starting to become more widely used, additional standardized randomized controlled trials are needed to establish which pharmacological interventions are most promising (Leung and Cottler, 2009).

**Future directions**

New neurobiological PG research should include matched controls, account for co-morbidities in PG groups, differentiate between gambling preferences and use single domain cognitive tasks. So far, neuroimaging studies investigating PG are scarce, restricted to very small groups, and mainly focused on male gamblers. This raises concerns about the
generalization of findings, particularly to women. Sex differences in gambling behaviour have been reported (Potenza, 2001) and examining those sex differences could reveal more about underlying biology of PG. It is, therefore, expected that future studies accounting for these shortcomings, will reveal more insight in the underlying mechanisms of PG.

Furthermore, future research could profit from pharmacological challenges in combination with neuroimaging techniques to unravel the neurobiological mechanisms of PG. For example, manipulating the opiate system with placebo and naltrexone in an fMRI study designed to investigate the effects of naltrexone on reward and punishment sensitivity, cue reactivity and craving in response to general positive and specific gambling-related pictures.

In addition, studying the relation between cue reactivity, impulsivity, decision making and relapse could provide insight in the underlying mechanisms and lead to the development of new interventions to diminish relapse in PG.

Based on addiction theories, predictions can be made about the relation between cue reactivity and loss of behavioural control. For example, addiction theories predict that when pathological gamblers display a strong activation of brain areas associated with expectancy and behavioural planning during presentation of gambling-related cues, this will diminish behavioural control and will enhance the probability of relapse. However, gamblers without strong cue reactivity and perhaps better behavioural control functions will show a smaller probability to display relapse behaviour. Such a hypothetical pathway could be examined by presenting addiction related cues and simultaneously measuring behavioural control, such as inhibition during a Go/NoGo task in an fMRI experiment to investigate the role of cue reactivity on behavioural control. Secondly, with use of a follow up design it could be investigated which neuropsychological functions are predictors for relapse behaviour.

Recently, more detailed theories are investigated and paradigms have been developed to disentangle a variety of sub-domains in decision making behaviour. One of these sub-domains is prediction error (Sutton and Barto, 1998) which is the difference between predicted and obtained rewards, and is essential for reward-driven learning (Tobler et al., 2007). A second sub-domain is the expected value of an outcome, defined as the product of reward magnitude and reward probability/expectancies (Machina, 1987). Risk or expectancy representation in the brain is of great interest when trying to decipher choice behaviour because it relates to the planning successful behaviour and seems to go awry in people with gambling problems (Brand et al., 2005; Goudriaan et al., 2005).

Studies focusing on expectancy values in PG are interesting because abnormalities found in reward and punishment sensitivity could be related to aberrant expectations of reward and loss. For example, correct coding of the chance of reward or loss guides people to make more advantageous choices, however, when people are too optimistic about their winning chances, this could lead to the continuation of disadvantageous PG behaviour. Thus, when negative expectancies are less well coded in PG, this will make pathological gamblers less aware of the risk of certain behaviours, and hence less punishment sensitive. In addition, expectancy could be influenced by cognitive distortions which play a significant role in gambling problems. Cognitive distortions are evident in pathological gamblers by erroneous beliefs about the probability of chance or the idea that the person can influence their chances, although their chances are fixed (Joukhador et al., 2003; Toneatto et al., 1997).

In addition, gambling games are thought to foster certain characteristics that exaggerate confidence of one’s chances of winning, thereby stimulating gambling propensity. In a recent fMRI study, Clark et al. (2009) investigated two of these characteristics, namely personal control over the game and the ‘near miss’ event in healthy controls. ‘Near miss’ events are events where unsuccessful outcomes are proximal to the jackpot, such as when two cherries are displayed on the slot machine pay line. Their findings showed that ‘near miss’
events increased desire to play when the subject had personal control over arranging their
gamble, but without personal control this effect was absent. Interestingly, ‘near miss’
outcomes recruited ventral striatal and insula circuitries that also responded to monetary wins.
These findings provide insights into the underlying mechanisms responsible for the
continuation of gambling behaviour in spite of the notion that one will lose money over time.
Future research should elaborate these findings to further understand the transition of
gambling to problem gambling and the addictive potential of certain game characteristics.

A final area for future development is the subject of resilience to the development of
addictive behaviours. Blaszczynski and Nower (2002) described a group of frequent gamblers
without co-morbidities and minimal pathology. This less severe gambling group is also
known to overcome their gambling episode without therapeutic interventions. This group is
interesting to further understand which neuropsychological functions are protective for the
progression of gambling behaviour in PG, and/or which functions are predictive for relapse
behaviour. Understanding these phenomena is very important because this could ultimately
lead to targeted prevention measures.

In conclusion, pathological gamblers suffer from similar neurobiological abnormalities
that are also present in other addictions. Most consistently reported are abnormal reward and
punishment sensitivity, disadvantageous decision making, and diminished inhibition. Less
consistent information is present on cue reactivity and attentional bias. Biobehavioral studies
in PG still have some methodological difficulties to overcome, and more knowledge about the
neurobiological functions underlying the above mentioned abnormalities in PG is needed.
With the use of sound methodology, hypothesis driven studies based on current
neurobiological theories of PG and SUD, and in combination with neuroimaging techniques,
biobehavioral research can be expected to further develop and implement efficient therapies
for PG treatment.
## Cognitive and neuroimaging findings in pathological gambling

### Supplementary Material

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Chapter 2
Cognitive and neuroimaging findings in pathological gambling

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<tr>
<td>Kertzman et al 2008</td>
<td>PG = 83, 56 male&lt;br&gt;HC = 84, 56 male</td>
<td>diagnose</td>
<td>-Continues performance task&lt;br&gt;-Go/No-Go task&lt;br&gt;-Switch between the tasks</td>
<td>-RT on tasks: PG &lt; HC&lt;br&gt;-Commission errors: PG &gt; HC&lt;br&gt;-Ommision errors: PG &gt; HC&lt;br&gt;-Switch errors between tasks: PG &gt; HC</td>
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<tr>
<td>Labudda et al 2007</td>
<td>PG = 22 male&lt;br&gt;HC = 19 male</td>
<td>DSM diagnosis</td>
<td>-GDT&lt;br&gt;-Salivary samples for cortisol and sAA concentration analyzes</td>
<td>-GDT: PG &lt; HC&lt;br&gt;-cortisol differences during the task: PG = HC&lt;br&gt;-The number of disadvantageous choices correlated with the delta score of sAA alterations within PG.</td>
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<td>Lakey et al 2006</td>
<td>HC = 57, 48 male&lt;br&gt;PPG = 85, 63 male&lt;br&gt;PG = 79, 55 male</td>
<td>DIGS; 0-2</td>
<td>-GGT (overconfidence measures)&lt;br&gt;-Original IGT</td>
<td>-Overconfidence and bed acceptance on the GGT and disadvantageous choices on IGT predicted gambling related pathology.</td>
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<tr>
<td>Leiserson and Pihl, 2007</td>
<td>PG = 14 men&lt;br&gt;PPG = 28 men&lt;br&gt;HC = 23 men</td>
<td>9.4 (3.20)&lt;br&gt;2.3 (1.12)&lt;br&gt;0</td>
<td>-Wechsler memory scale-revised (WMS-r)&lt;br&gt;-Self order pointing task (SOP)&lt;br&gt;-Spatial and Non spatial conditional association tasks (CAT)&lt;br&gt;-Go/No-Go: reward –punishment version&lt;br&gt;Self report&lt;br&gt;-Extraversian (EPQ questionnaire&lt;br&gt;-Sensation seeking</td>
<td>-Working memory: HC, PPG &lt; PG&lt;br&gt;-SOP: HC, PPG = PG&lt;br&gt;-CAT: HC, PPG &lt; PG&lt;br&gt;-Go/No-Go: HC, PPG = PG&lt;br&gt;-extraversion (EPQ) questionnaire: HC = PPG &gt; PG&lt;br&gt;-sensation seeking questionnaire: HC = PPG = PPG</td>
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<tr>
<td>Linnet et al 2006</td>
<td>PG = 61, 54 male&lt;br&gt;HC = 39, 11 male</td>
<td>8.93 (1.86)</td>
<td>-IGT (children version with cheese)&lt;br&gt;Self report&lt;br&gt;-Sensation seeking scale Zuckerman</td>
<td>-IGT: PG &lt; HC&lt;br&gt;-Switching behaviour after negative feedback: PG &lt; HC&lt;br&gt;Sensation seeking was correlated with disadvantageous and particularly advantageous players of the IGT.</td>
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<tr>
<td>MacKillop et al 2006</td>
<td>PG = 24&lt;br&gt;PPG = 40</td>
<td>7.7 (2.8)&lt;br&gt;1.85 (1)</td>
<td>-Delay discounting task&lt;br&gt;-Future time perspectives&lt;br&gt;Self report&lt;br&gt;-Gamblers belief questionnaire,</td>
<td>-delay discounting: PG &gt; PPG &gt; HC&lt;br&gt;-future time perspective: PG = PPG = HC&lt;br&gt;-Gambling belief, luck/perseverance and illusion of control: PG &gt;</td>
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<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Diagnosis</td>
<td>Tasks/Measures</td>
<td>Findings</td>
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</tbody>
</table>
| Marazziti et al 2008 | PG= 20, 15 male | HC=41 | DSM diagnosis | the gambling passion scale, Eysenck impulsivity questionnaire, Stanford time perspective inventory | PPG > HC  
-Gambling passion scale: PG> PPG = HC  
-Eysenck Impulsivity questionnaire subset impulsivity: PG > PPG = HC  
-Stanford time perspective: PG= PPG =HC |
| Potenza et al 2003 | PG= 10 men, HC=11 men | DSM diagnosis | -Wisconsin card sorting task (WCST)  
-WMS-r  
-FAS | -PCST: PG< HC  
-WMS-R and FAS: PG=HC  
-Gambling urges: PG > HCs  
- HC > PG bilateral cingulate gyrus, precuneus, right inferior parietal lobule, right superior frontal gyrus, OFC, caudate, basal ganglia, and thalamus |
| Potenza 2008     | PG= 10 men, HCforPG = 11 men, CD= 9 men, HCforCD= 6 men | DSM diagnose | -Cue reactivity task (as described in Potenza 2003) | -HCforPG < PG in right inferior parietal lobule, bilateral dorsal and ventral anterior cingulate  
-HCforCD > CD in right inferior parietal lobule, bilateral dorsal and ventral anterior cingulate  
-No common activation patterns were found between the addicted groups. |
| Reuter et al 2005 | PG= 12 men, HC=12 men | DSM diagnose | -Guessing paradigm in fMRI.  
-Choosing one of two cards and receiving feedback of win or lose. | -PG < HC in ventral striatum activity (winning vs losing)  
-HC > PG in VMPF (winning vs losing)  
-Severity of gambling problems in PG showed a negative correlation in right ventral striatum. |
| Roca et al 2008  | PG= 11, HC= 11 Unknown ratio male/female | DSM diagnose | -IGT  
-Go/No-Go  
-Addenbrooke’s cognitive Examination; short screen for general cognitive functions. | -IGT: HC> PG  
-commission errors Go/No-Go task: HC< PG  
-general cognitive functions; word fluency and memory: HC> PG |
| Rodriguez-Jimenez et al 2006 | PG= 39 men, PG-ADHD=16 men, HC=40 men | DSM diagnosis | -Stop signal task  
-Low rate responding task (delay gratification)  
-Continues performance task(sustained attention) | -delay gratification and Stop signal task: PG-ADHD< PG, HC  
-continued performance task: PG-ADHD= PG= HC |
| De Ruiter        | PG= 19 men | 9.6 (2.6) | -Probabilistic reversal learning task, reversal learning: PG< HC | -Probabilistic reversal learning task, reversal learning: PG< HC |
### Cognitive and neuroimaging findings in pathological gambling

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Design</th>
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<th>Findings</th>
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<tbody>
<tr>
<td>Tanabe et al 2007</td>
<td>SD = 14, 10 male SD+PG= 14, 12 male HC= 18, 5 male</td>
<td>IGT modified version</td>
<td>-GT: SD = SD+PG = HC -Decision making vs control condition: OFC, ventral medial dorsal, ventrolateral/anterior insula, ACC, ventral striatum, parietal en occipital lobes in all groups. -SD&lt; HC= SD+PG in VMPFC and right anterior PFC activity.</td>
</tr>
<tr>
<td>Zack and Poulos 2004</td>
<td>PG= 10, 7 male PG+AD= 6, 4 male AD=8, 5 male HC=12, 9 male</td>
<td>&lt;5</td>
<td>-AMPH D2 agonist and placebo -Desire for gambling -Rapid reading task</td>
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<tr>
<td>Zack and Poulos 2007</td>
<td>PG=20, 17 male HC=18, 14 male</td>
<td>DSM diagnosis</td>
<td>-Haloperidol augmented pleasurable effects if gambling: HC&lt; PG -Haloperidol enhanced salience for gambling word reading speed: HC&lt; PG -Haloperidol increased blood pressure during gambling HC=PG</td>
</tr>
</tbody>
</table>

**Table 1:** HC= healthy controls, PG= Pathological gamblers, PPG= problem gambler, SD= substance dependent, AD= alcohol dependent, CD= cocaine dependent, TS = Tourette syndrome, AMPH= D-amphetamine, ADHD: attention deficit hyperactivity disorder DA: dopamine, HR= Heart rate, SCR=skin conductance response, IGT= Iowa Gambling Task, GDT= Game of Dice task.

VLPFC= ventral lateral prefrontal cortex, VMPFC= ventral medial prefrontal cortex, OFC = orbito frontal cortex, ACC= anterior cingulate cortex.
Reference List


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Petry, N.M., 2006. Should the scope of addictive behaviors be broadened to include pathological gambling? Addiction 101 Suppl 1, 152-160.


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