Chapter 9

Summary and general discussion

Main objectives of this thesis

The main aim of this thesis was to elucidate the underlying neural correlates of motivational and cognitive processes in pathological gambling to better understand the aetiology and possible treatment targets for this disorder. Using hypotheses derived from models explaining the development and persistence of substance dependence, we tested the neural correlates of key elements from these models in pathological gambling comparing treatment seeking problematic gamblers (PRGs) with healthy controls (HCs). In addition, we investigated the specificity of these characteristics by comparing PRGs not only to HCs but also to subjects with a substance use disorder (e.g. alcohol dependent persons (ADs)). Finally, we explored attentional bias and response inhibition in computer and video gaming adolescents to test whether behavioural tendencies commonly related to addictive behaviours are also related to game addiction.

In this final chapter, we will summarize and discuss the main results of the studies presented (chapter 2-8). Finally, implications and recommendations for future research are provided.

Summary

Chapter 1 provides a short introduction to the theme of the thesis and a description of the chapters that follow.

In **Chapter 2** we present a literature review covering all relevant neurocognitive and neuroimaging studies in pathological gamblers from 2005 to 2010. The reviewed studies indicate that similar processes seem to be involved in pathological gambling and substance use disorders. First, increased reward seeking behaviour together with lowered reward sensitivity, characterized by diminished BOLD responses to monetary wins and losses in the ventral striatum and ventral medial prefrontal cortex was found in pathological gambling (de Ruiter et al., 2009; Goudriaan et al., 2005; Leiserson and Pihl, 2007; Reuter et al., 2005); corresponding to findings in substance dependence (Hommer et al., 2011; e.g., Park et al., 2010b; for a review see). Second, enhanced cue reactivity and attentional bias to gambling cues were reported in neuropsychological studies in pathological gambling (Zack and Poulos, 2004; Zack and Poulos, 2007). Neuroimaging studies on cue reactivity in pathological gambling showed increased brain activation in the parahippocampal gyrus, amygdala, occipital cortex and prefrontal areas in response to gambling-related stimuli (Crockford et al., 2005; Goudriaan et al., 2010), and thus indicate similarities in brain activity between pathological gambling and substance dependence to addictive cues. Neurocognitive studies on impulsivity showed that pathological gamblers have difficulties in filtering irrelevant information and inhibiting ongoing responses (Fuentes et al., 2006; Goudriaan et al., 2006a; Kertzman et al., 2006; Kertzman et al., 2008; Rodriguez-Jimenez et al., 2006). However, the one fMRI study investigating response inhibition only reported diminished ventral lateral prefrontal cortex activity in pathological gamblers during response inhibition (Potenza et al., 2003). Finally, studies using neurocognitive tasks showed that decision making and executive functions were compromised in pathological gambling (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 dependence (Bolla et al., 2003; Dom et al., 2006; Ratti et al., 2002; Zorko et al., 2004). The only fMRI study on this topic also found impaired decision making abilities in pathological gamblers (with co-morbid substance dependence) with attenuated activity in the ventral medial prefrontal cortex (Tanabe et al., 2007). The review ends with a framework for future studies, indicating the need for studies that investigate gambling-specific characteristics

such as reward expectancies in gamblers, and the inclusion of clinical control groups to facilitate direct comparisons between different addictive disorders.

In **Chapter 3** we describe the results of an fMRI study on reward expectancy in PRGs and HCs to gain insight into differences in reward expectancy prior to reward outcome between PRGs and HCs, because this may contribute to a better understanding of continued gambling despite incurring losses in PRGs. We employed an fMRI paradigm that allowed us to investigate the dissociable reward and loss related expectancies during different probabilities of winning or losing different amounts of money. Conclusions: PRGs show higher activity in the reward system during reward expectation than HCs, whereas we observed no difference between PRGs and HC in the loss value system. Furthermore, the negative relation between gambling severity and amygdala activation in gain expected value coding suggests that more severe PRGs are less likely to be risk aversive during gambling. Our study provides evidence that PRGs are characterized by abnormally increased reward expectancy coding, which may render them overoptimistic with regard to gambling outcomes.

In **Chapter 4** we report a study on the interaction between motor inhibition and salience attribution in PRGs and HCs. In most addiction models, loss of control over addictive behaviour (disinhibition) and enhanced salience of stimuli related to the addictive behaviour, combined with a decreased salience value for natural reinforcers, are thought to play a crucial role in the development and persistence of substance use disorders (Goldstein and Volkow, 2002). To date, neuroimaging evidence for the role of impaired inhibition and enhanced salience attribution in addiction has been investigated in separate designs, i.e. employing neutral Go/NoGo tasks in inhibition studies (Kaufman et al., 2003) and cue reactivity tasks to study salience attribution (e.g., Braus et al., 2001; Wrase et al., 2002). In pathological gambling studies, these functions have been studied separately as well (see chapter 2). However, functional MRI studies examining the interaction between cognitive control and salience attribution in addicted individuals were lacking. We therefore modified a standard Go/NoGo task by adding affective blocks (gambling, positive and negative) to the standard neutral block, in which subjects were requested to respond or withhold a response to specific types of pictures. This allowed us to study the interaction between motor inhibition and salience attribution in PRGs and HCs. In the neutral inhibition condition, PRGs were slower but similar in accuracy to HCs. However, PRGs did show more activation in areas responsible for cognitive control compared to HCs, suggesting less efficient task performance in PRGs. Interestingly, PRGs were better at response inhibition during gambling related and positive pictures than HCs, and showed lower activation of the ventrolateral, dorsolateral, and anterior cingulate cortex compared to HCs, suggesting more task efficiency in PRGs compared to HCs during gamble and positive pictures. Thus, unexpectedly, our findings suggest that motivational processes may improve cognitive functions in problem gamblers.

In **Chapter 5** we elaborate on the influence of affective stimuli on response inhibition in PRGs and HCs, by using a Psycho-Physiological Interaction (PPI) analysis. With this method we tested the modulatory effect of affective stimuli on the functional connectivity between dorsal “executive” and ventral “affective” processing systems. Studies in non-clinical samples indicate that interactions between dorsal executive and ventral affective processing systems are necessary to respond adequately in different affective situations (e.g., Pessoa, 2008; Pessoa, 2010). Congruent with previous studies in non-clinical samples showing the importance of these dorsal executive functions in response inhibition (Aron et al., 2007; Aron, 2007; for recent reviews see Chambers et al., 2009; Chen et al., 2009; Li et al., 2006; Picton et al., 2007), our study showed that accurate task performance during neutral inhibition trials was positively correlated with functional connectivity between different regions belonging to the dorsal executive system. Interestingly, during affective (gambling, positive and negative)

inhibition, task performance was positively correlated with functional connectivity between the dorsal executive and the ventral affective system. Group interactions on functional connectivity showed that during inhibition in the gambling and positive affective condition, PRGs compared to HCs showed greater functional connectivity between the right IFC and the dorsal executive system and between the left caudate and the dorsal executive system. Thus, our findings indicated that gambling-related and positive affective stimuli lead to enhanced functional connectivity between the ventral affective system and the dorsal executive system in PRGs compared to HCs, suggesting a facilitating bottom-up activation of the dorsal executive system, resulting in better task performance in PRGs in gambling and positive affective conditions.

In **Chapter 6**, we investigated the neural mechanisms of cognitive flexibility performance without the influence of incentive feedback in PRGs, ADs and HCs. Standard neuroimaging paradigms intended to investigate cognitive flexibility employ switch tasks that only implicitly indicate the need to switch, by providing some incentive feedback (e.g., money, points) to subjects' responses (e.g., de Ruiter et al., 2009; Nyhus and Barcelo, 2009). These switching paradigms with provision of incentive feedback are generally associated with brain areas crucial in the processing of reward and punishment and behavioural adaptations following changes in stimulus-reinforcement contingencies (Watanabe and Sakagami 2007). In fact these so-called cognitive flexibility tasks are affective flexibility tasks with monetary incentives acting as the main affective drive. Both substance use disorders and pathological gambling have been associated with impaired affective switching behaviour and diminished neural activity in reward and motivational systems during performance of these tasks (e.g., de Ruiter et al., 2009; Goudriaan et al., 2006a; Loeber et al., 2009a; Ratti et al., 2002). Thus, findings of impaired flexibility in these studies may also result from diminished feedback processing rather than from diminished switching ability (de Ruiter et al., 2009; Goudriaan et al., 2005; Goudriaan et al., 2006a; Grant et al., 2010). Our study therefore investigated the neural substrates of cognitive flexibility without (monetary) feedback in addictive behaviours. During a series of (purely cognitive) switch trials, PRGs showed slightly more activity in the left parahippocampal gyrus than HCs, and PRGs and HCs showed greater activity than ADs in the right anterior cingulate cortex. Behavioural performance was generally very similar for all groups. Our findings of similar behavioural performance in combination with only subtle differences in functional brain activity in PRGs and somewhat more extensive abnormalities in ADs during cognitive switching are different from previous studies using switching paradigms in which (monetary) feedback was provided and addictive groups showed clear impairments (e.g., de Ruiter et al., 2009; Goudriaan et al., 2006a; Loeber et al., 2009a; Ratti et al., 2002). Therefore, we concluded that future studies in addictive disorders should directly compare neural activation patterns of switch tasks with and without (monetary) feedback in different groups, in order to test whether (monetary) feedback further compromises cognitive flexibility in switch tasks with explicit rules.

In **Chapter 7** we used voxel based morphology (VBM) to investigate possible differences in regional grey matter (GM) volumes between PRGs, participants with an alcohol use disorder (AUDs; alcohol dependence and/or alcohol abuse) and HCs. An important difference between substance dependence, such as alcohol use disorders, and pathological gambling is the effect of toxic substances on the brain. It is well documented that long-term alcohol use disorder (alcohol abuse or alcohol dependence) is associated with cognitive impairments and gray matter brain reductions in cortical and subcortical brain regions (for a review see Sullivan et al., 2000; van Holst and Schilt, 2011). Although there is considerable overlap in the cognitive profile of subjects with an alcohol use disorder and PRGs, it has not yet been established whether pathological gambling, similar to alcohol use disorders, is

associated with abnormal gray matter (GM) volumes. Therefore, in **Chapter 7** we used a VBM study to compare GM volumes of PRGs, AUDs, and HCs. The study showed that problematic gambling behaviour is not associated with brain atrophy as was found in subjects with an alcohol use disorder in this study. Interestingly, the left OFC was found to be smaller across addicted participants (PRGs, AUDs, smoking HCs) compared to non-addicted participants (non-smoking HCs), irrespective of type of addiction. This suggests that the left OFC may be a pre-existing factor indicating an underlying vulnerability for addictive behaviours, including non-substance related addictive behaviours.

Finally, in **Chapter 8**, we tested the relation between self-reported levels of problem gaming and attentional bias and response inhibition in male adolescents gamers. Compared to classical gambling, gaming is a relatively new phenomenon with potential addictive tendencies (Charlton and Danforth, 2007; Fisher, 1994; Griffiths and Hunt, 1998). Adolescents with higher levels of self-reported game addiction displayed error-related attentional bias to game cues. Higher levels of game addiction were also related to impaired response inhibition, but only when game cues were presented. These findings are consistent with findings of attentional bias reported in officially recognized addictive disorders like substance dependence and pathological gambling (Boyer and Dickerson, 2003; Field and Cox, 2008) and suggest that similar underlying neural mechanisms are operating in substance use disorders, pathological gambling and excessive gaming.

Taken together, our findings indicate that there are many similarities between pathological gambling and substance dependence (see **Chapter 2**), especially with regard to functional impairments of the motivational system and enhanced activity during cue reactivity. However, there are also disorder specific differences between pathological gambling and substance dependent disorders, such as the absence of GM volume reductions in PRGs compared to AUDs and the more subtle differences in the neural correlates of cognitive flexibility in PRGs compared to ADs. Finally, findings in our game addiction study are in line with findings of attentional bias reported in other (officially recognized) addictive disorders like substance dependence and pathological gambling. Together, these findings contribute to the discussion on the proposed concept of 'Addiction and Related Disorders' (which may include non-substance related addictive behaviours) in the DSM-V.

General discussion

In this section, we will discuss our findings on neuroanatomical and functional MRI correlates in PRGs and ADs in more detail and we will try to answer the question to what extent these findings indicate similarities and differences between these disorders. Subsequently, we will discuss the findings of our studies investigating cognitive and affective response inhibition and reward expectation in pathological gambling. Finally, clinical implications of the presented studies and their limitations will be discussed, recommendations for future research will be addressed and game addiction as a new addictive disorder will be contemplated.

Similarities between pathological gambling and alcohol use disorders

Our review (**Chapter 2**) indicated several neuropsychological similarities between alcohol dependence and pathological gambling. First, impaired decision making abilities in pathological gamblers and alcohol dependent subjects have consistently been found (Cantrell et al., 2008; Cavedini et al., 2002; Goudriaan et al., 2005; Goudriaan et al., 2006a; Linnet et al., 2006; Miranda et al., 2009). However, because of the complexity of decision making tasks it is unclear which sub-process (i.e., reward sensitivity, punishment sensitivity, impulsivity, cognitive inflexibility) is responsible for these deficits and whether similar aberrant sub-processes lead to impaired decision making in pathological gambling and alcohol dependence.

Second, subjects with both disorders have shown to be more impulsive than HCs (Goudriaan et al., 2006a; Noel et al., 2007; for a review see; Verdejo-Garcia et al., 2008). Moreover, impulsivity has been found to be a vulnerability marker for the development of a substance dependent disorder or pathological gambling and has shown to be predictive of relapse in pathological gambling as well (Goudriaan et al., 2008; Verdejo-Garcia et al., 2008). Third, probably one of the most consistently reported similarities between pathological gambling and alcohol dependence is that they both show cue reactivity activation in reward and motivational brain areas during the presentation of addiction related stimuli (Braus et al., 2001; Crockford et al., 2005; Goudriaan et al., 2010; Myrick et al., 2008; Wrase et al., 2007). In addition, both disorders show attentional bias for addiction related words (Fadardi and Cox, 2006; Jones et al., 2006; Loeber et al., 2009b; Zack and Poulos, 2004). Congruently, in this thesis we also found evidence of enhanced cue reactivity in PRGs compared to HCs to gambling related pictures compared to neutral pictures (**Chapter 4**).

Differences between pathological gambling and alcohol use disorders

Despite the previously reported (mainly neuropsychological) similarities between PRGs and substance dependent populations reviewed in **Chapter 2**, in this thesis direct comparison of ADs with PRGs mainly yielded differences in neural correlates between these disorders.

Functional MRI results of our cognitive flexibility study indicated that whereas PRGs seemed to only differ subtly from HCs during task switching, ADs showed substantially less anterior cingulate cortex activation - an area responsible for task monitoring - during task switching compared to HCs and PRGs. Furthermore, ADs had to exert more executive control (higher activation in the superior frontal cortex and inferior frontal cortex) to perform adequately during repeat trials, the easiest trials in the switch task, than HCs. Thus overall, as compared to PRGs, ADs seemed to need compensatory recruitment of cognitive control areas to perform similar (although slower) to HCs.

We also found structural neurobiological differences i.e., gray matter volume differences between PRGs, AUDs and HCs in **Chapter 7**. Morphological brain abnormalities found in AUDs were not present in a behavioural addiction like pathological gambling. This is important because these findings show that the overlap in neuropsychological profile between AUDs and pathological gamblers cannot directly be related to gray matter reductions in pathological gambling, whereas there are studies that show correlation between GM volumes reductions and neuropsychological impairments in AUDs. Thus, gray matter abnormalities are not a prerequisite for neuropsychological impairments in addictive disorders. More subtle differences, such as differences in receptor density and neurotransmitter levels, or changes in functional connectivity between brain regions, therefore seem to be sufficient for abnormal neuropsychological functioning in behavioural addictions like pathological gambling or problematic gaming. It should be noted, however, that we did find a GM reduction of the orbitofrontal cortex in a conjunction analyses investigating common GM reductions in subjects with any addictive disorder (alcohol use disorder, problematic gambling or smoking) compared to non-smoking HCs. This is an interesting finding because the orbitofrontal cortex plays a pivotal role in addiction (Dom et al., 2005; Everitt et al., 2007; Koob and Volkow, 2010; Winstanley, 2007). Notably, abnormalities in orbitofrontal cortex functioning associated with diminished self-control have been found to be a pre-existing vulnerability factor for the development of an addiction (e.g., Bechara, 2005; Hill et al., 2009). Therefore we suggest that our finding of reduced left orbitofrontal cortex volume among subjects with various types of addictions may be a vulnerability marker for the acquisition of an addiction, although this interpretation is in need of empirical confirmation from prospective studies. Smaller orbitofrontal cortex volumes have also been found in psychiatric disorders such as

schizophrenia (Takayanagi et al., 2010) and obsessive compulsive disorder (Togao et al., 2010). Interestingly, as in addictive disorders, in these disorders abnormal salience processing is present (Figee et al., 2011; Heinz and Schlagenhauf, 2010). Because the orbitofrontal cortex is part of the circuits that modulate motivation and action, our finding of structural abnormalities of the orbitofrontal cortex may reflect disturbances in the feedback processing of the motivated action system, which may lead to dysfunctions of emotional and behavioural inhibition in a diversity of psychiatric disorders.

Taking these studies together, it could be that ADs showed a more aberrant brain activity during cognitive flexibility than PRGs because of structural gray matter volume reductions in brain areas associated with cognitive performance in AUDs (for a review see; Moselhy et al., 2001). However, more research is needed to further test this hypothesis. Future research should combine structural measures (VBM, but also diffusion tensor imaging (DTI) to measure white matter integrity) with functional MRI and neuropsychological test data to see whether structural brain differences between AUDs and PRGs are related to differences in cognitive function.

Neural correlates of cognitive and affective response inhibition in problem gamblers

In our studies comparing pathological gamblers to HCs we tested hypotheses derived from current neurobiological addiction models. In **Chapter 4** we tested the effects of salient cues on response inhibition in PRGs and HCs. Congruent with addiction models, PRGs showed increased responses in affective brain circuitry towards gambling stimuli and slower response inhibition performance in the neutral condition, in combination with higher prefrontal brain activation, indicating higher effort in PRGs compared to HCs during neutral inhibition. Unexpectedly, response inhibition was not affected by gambling related stimuli in PRGs, as was expected based on the Impaired Response Inhibition and Salience Attribution (I-RISA) model (Goldstein and Volkow, 2002), but instead response inhibition was strengthened in PRGs compared to HCs in the context of gambling related stimuli. This was also true for positive pictures. The fact that emotionally salient stimuli can capture attention and influence task performance can be explained by the interaction between motivational and cognitive functioning. Salient stimuli influence competition for processing resources both at the perceptual and executive level (Pessoa, 2008). For example, the spatial location of salient stimuli attracts extra attention, facilitating certain task performances, such as discrimination or response inhibition tasks. Indeed, results from the PPI-analyses in **Chapter** 5 showed that in PRGs during gamble and positive affective response inhibition, stronger functional connectivity between the ventral affective and dorsal cognitive system was associated with a more accurate task performance compared to HCs, suggesting an bottom-up enhancement of top-down cognitive control.

Reward processing in problem gamblers

Overall, we found that PRGs are not insensitive to positive and negative pictures (**Chapter 4 and Chapter 5**) and that PRGs are especially sensitive to gambling related stimuli (**Chapter 4**) and to the expectation of winning money (**Chapter 3**). Furthermore, in PRGs gambling related and positive pictures facilitated response inhibition compared to response inhibition performance when confronted with neutral pictures. This suggests that PRGs may be more responsive to potentially rewarding stimuli than HCs, leading to enhanced attention which in our task led to better task performance. It seems likely that dopamine function plays an important role in these findings. Salient stimuli enhance dopamine transmission in the mesolimbic system (Kienast et al., 2008; e.g., Schultz, 2006; Siessmeier et al., 2006) and dopamine is known to modulate prefrontal cortex functioning (Robbins and Arnsten, 2009).

Indeed, in humans, dopamine transmission has an effect on functional connectivity within the corticostriatal thalamic loops (Honey et al., 2003; Williams et al., 2002). One interesting study by Nagano-Saito and colleagues (2008) found that participants with normal dopamine levels showed significant frontal-striatal functional connectivity that was positively correlated with faster response times during the Wisconsin Card Sorting Task, suggesting that normal dopamine function supports both corticostriatal functional connectivity and efficient task performance. In addition, dopamine depletion in these participants resulted in impairment of frontal-striatal functional connectivity and less efficient task performance. Interestingly, during the neutral inhibition trials, PRGs showed less functional connectivity between regions belonging to the dorsal executive system than HCs, resembling the findings of dopamine depleted participants in the above-mentioned study. Indeed, problematic gamblers were found to have lower dopamine receptor density (Comings et al., 1997; Comings et al., 1999; Ibanez et al., 2003; Lobo et al., 2010) and less dopamine binding during gambling than healthy controls (Linnet et al., 2011b), suggesting a hypoactive dopamine system. Arguably, in our study in the gamble and positive condition, salient stimuli which are known to enhance DA transmission especially in the reward system (Horvitz, 2000; Schultz, 1998), could have transiently restored the normally hypoactive dopamine state of PRGs, facilitating functioning of the prefrontal cortex and functional connectivity between prefrontal brain regions during these conditions.

However, this enhanced salience to rewarding stimuli could also lead to impaired task performance. For example, when too much attention is allocated to salient stimuli, this can result in attenuated executive control recourses (Pessoa, 2008; Pessoa, 2010). Enhanced reward anticipation coding in PRGs, as was found in our study, could also lead to an overestimation of winning chances, and hence to disadvantageous decision making. Enhanced reward seeking behaviour and enhanced responsiveness to potential rewards could therefore be an important concept in understanding why especially on tasks with contingencies gamblers show diminished cognitive performance (Brand et al., 2005; e.g., de Ruiter et al., 2009; Goudriaan et al., 2005; Goudriaan et al., 2006b; Labudda et al., 2007; Tanabe et al., 2007).

Clinical implications

Based on previous neurocognitive and neuroimaging studies and our current findings we suggest that therapies for pathological gamblers should focus on the improvement of their dysfunctional reward and motivational system.

Current psychological treatments for problematic gambling, like cognitive behavioral therapy, focus on motivational, emotional, and cognitive interventions that are known to promote remission in a variety of addictions and are also shown to be effective in the treatment of pathological gambling (Petry et al. 2006; Petry 2006). These therapies are designed to enhance motivation to quit or stay abstinent from gambling, to strengthen coping strategies, and to develop strategies for handling personally identified risk situations, in order to avoid relapse. One element of effective psychotherapy appears unique for pathological gambling and has no direct parallel in treatment of substance use: cognitive therapy focusing on altering irrational gambling cognitions (Ladouceur et al. 2001; Ladouceur et al. 2003; Sylvain et al. 1997). However, about 50% of pathological gamblers who try to quit experience a relapse with seriously negative consequences (Hodgins and el-Guebaly, 2004), and other studies indicate frequent relapses in treatment-seeking pathological gamblers (Ledgerwood and Petry, 2006).

Several interventions targeted at the putative neurobiological mechanisms underlying pathological gambling may provide additional benefits. 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 these interventions, patients are trained to overcome their attentional bias by performing computer tasks, thereby aiming to reduce cue reactivity and to change habitual behaviours. A related intervention is retraining of automatic action tendencies, in which approach behaviour towards addiction related stimuli is retrained to avoidance behaviour (Schoenmakers et al., 2007; Wiers et al., 2006; Wiers et al., 2010). In alcohol dependence results from the suggested interventions are promising (Wiers et al., 2006; Wiers et al., 2010). However, these interventions have not yet been tested in pathological gambling and long-term effects of attentional and action tendency retraining are not yet available and need to be assessed in future research.

In addition, a number of promising pharmacological interventions for the treatment of pathological gambling have been reported (for a review see; van den Brink, 2011 submitted). Neurobiological findings indicate a pivotal role of the mesolimbic pathway, comprising the ventral striatum, and ventromedial prefrontal cortex (VMPFC) in pathological gambling. Because the VMPFC is a structure that mainly depends on dopamine (DA) projections that communicate with limbic structures to integrate information, dysfunctional DA transmission could be the underlying deficit causing the VMPFC dysfunctions in pathological gambling. 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 the opiate antagonists naltrexone and nalmefene, which are known to decrease dopamine release, have been found to reduce reward sensitivity and probably increase punishment sensitivity as well (Petrovic et al. 2008). Moreover, treatment with opiate antagonists has been shown to be effective in pathological gambling and to diminish gambling urges (Modesto-Lowe and Van 2002; Kim et al. 2001; Kim and Grant 2001; Grant et al. 2008).

While drugs and drug-associated stimuli may elicit dopamine release in the ventral striatum and thus reinforce drug intake during the acquisition of a substance use disorder, chronic drug intake is associated with neuroadaptation of glutamatergic neurotransmission in the ventral and dorsal striatum and limbic cortex (McFarland et al. 2003; Vorel et al. 2001). In addition, cue exposure has been found to depend on 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 human substance dependent persons (Rösner et al. 2008; Mann et al. 2008; Krupitsky et al. 2007). It is, therefore, promising that the first pilot studies with N-acetyl cysteine (Grant et al. 2007) and Memantine (Grant et al., 2010), modulating the glutamate system, have been successful in the treatment of pathological gambling.

Effects of medications to enhance decision-making and cognitive control 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. However, it can be argued that agents targeting these sub-processes may improve decision making and cognitive control over gambling. Cognitive enhancers such as modafinil may also have a beneficial effect on cognitive control functions in pathological gamblers, and consequently, on problem gambling behaviour (Killgore et al. 2008; Minzenberg and Carter 2008). Finally, although results from studies using selective serotonin reuptake inhibitors (SSRIs) show inconsistent results (van den Brink, 2011 submitted), treatment with high doses of SSRIs, similar as in OCD (Hollander et al., 2005; Marazziti and Consoli, 2010), may have a positive effect on pathological gambling as well (Hollander et al., 2005). SSRIs are known to improve cognitive flexibility in OCD and could help to restore these functions in pathological gamblers too. Higher doses of SSRIs probably do not have their effect directly via the serotonergic system

but indirectly via the dopaminergic and noradrenalin systems (Goodnick and Goldstein, 1998; Kitaichi et al., 2010).

Although pharmacological treatments are becoming more widely used in clinical trials with pathological gamblers, additional randomized controlled trials are needed to establish which pharmacological interventions are most promising (Leung and Cottler 2009).

Limitations and recommendations for future research

The main limitation of the studies presented in this thesis is that they were all cross-sectional. A cross-sectional design creates the possibility to study aspects of a disorder, but is not suitable for the study of causality or course. Prospective studies on the effects of gambling or drug use on neuropsychological functions could rule out the confounding role of pre-existing neuropsychological differences and provide a better insight into the causal direction of the neuropsychological decrements that are found within cross-sectional studies.

Another limitation might be that fact that many PRGs also smoke. Although we did account for the influence of smoking in our voxel based morphometry study, we did not control for smoking behaviour in our fMRI studies. Most ADs smoked (± 90%), more than half of the pathological gamblers smoked (± 60%), whereas the prevalence of smoking was lowest in our healthy control group (± 10%). However, including only non-smoking ADs or non-smoking pathological gamblers would have been highly impractical (because of the high co-occurrence) and would have resulted in rather atypical research groups and a serious limitation of the generalizability of the findings to the pathological gamblers population at large. Future research should try to more carefully match smoking and non-smoking participants or include smoking severity questionnaires as a covariate in statistical analyses to control for possible confounding effects of smoking behaviour.

Besides the high prevalence of smoking in pathological gamblers, higher levels of internalizing (anxiety and depression) and externalizing disorders (ADHD, conduct disorder and anti social personality disorder) are common in patients treated for addictive disorders. Excluding all ADs and PRGs with internalizing or externalising symptoms would therefore not be feasible, because these symptoms are very often related to, or part of the negative consequences of the addictive disorder (Petry et al., 2005; Romer et al., 2009; Winters and Kushner, 2003). However, blunted responses in reward and motivation brain systems to rewarding stimuli (e.g., money) have also been found in depressive disorders and ADHD (e.g., Carmona et al., 2009; Dichter et al., 2009; Gatzke-Kopp et al., 2009; Smoski et al., 2009). Future studies could benefit from inclusion of a comparison group with internalising or externalising disorders to test which aspects are specific to addiction and which aspects are shared by these other disorders.

Differentiating types of pathological gamblers on game preferences (slot machines vs. casino games) seems to be useful in studies because different pathological gambler groups show divergent neurocognitive results (Goudriaan et al., 2005), suggesting different neurobiological pathways to pathological gambling. For example, 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 (for a review see Sharpe 2002). In the studies in this thesis we did not differentiate problem gamblers according to preferred games because of the relatively small sample size. In addition, most of our PRGs indicated that they gambled on a variety of games (ranging from slot machines to roulette and poker), making a strict distinction in type of problematic gambling behaviour rather difficult. Moreover, subtyping of gamblers according to their favourite type of gambling may only provide a partial answer to the question about the role of typology in pathological gamblers. Additional or alternative sub-classifications of pathological gamblers based on age of onset or

some combination of clinical characteristics [e.g. Type 1 and Type 2 (Cloninger et al. 1981) or Type A and Type B (Babor et al. 1992) in alcohol dependence] could also be useful in order to develop more robust typologies for pathological gambling. Future research should focus on these aspects to better understand the different types of gamblers.

Finally, our studies only focused on male participants, and this raises concerns about the generalization of our findings to women. Sex differences in gambling behavior have been reported (Potenza, 2001) and examining those sex differences could reveal more about the underlying biology of pathological gambling in men and women.

Future directions for research

Imaging dopamine and other crucial neurotransmitters

Neuroimaging findings have indicated a pivotal role for the mesolimbic-frontal pathway, comprising the ventral striatum, and ventromedial prefrontal cortex in pathological gambling. 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 that communicate with limbic structures to integrate information, dysfunctional dopamine transmission could be the underlying deficit causing the VMPFC dysfunctions in pathological gambling, contributing to cognitive dysfunctions as well. Future research in pathological gambling could benefit from Positron Emission Tomography (PET) and single proton emission computed tomography (SPECT) studies, in which binding to dopamine receptors, dopamine transmission and dopamine receptor availability can be studied (for a review see; Volkow et al., 2003).

Recently, the research group of Linnet and colleagues have used PET studies with the tracer raclopride to measure dopamine D2 receptor (DRD2) a vailability in the ventral striatum during a non-gambling and gambling condition of the Iowa Gambling Task (IGT), a decision making task. They found a significant correlation between dopamine release and excitement level on this task in pathological gamblers, while no such interaction was found in HCs (Linnet et al., 2011a). Furthermore, dopamine release was associated with significantly higher IGT performance in HCs and significantly lower IGT performance in pathological gamblers (Linnet et al., 2011b). Finally, quite surprisingly, pathological gamblers who lost money had significantly increased dopamine release in the left ventral striatum compared with HCs. However, pathological gamblers and HCs who won money did not differ in dopamine release (Linnet et al., 2010b). Thus, these results indicate that that enhanced dopamine release is associated with excitement levels in pathological gambling and with maladaptive decision-making abilities in pathological gamblers. However, Linnet and colleagues did not find an overall difference in baseline binding potentials or a change in binding potentials between pathological gamblers and HCs (Linnet et al., 2011a). This is in contrast with the literature on substance dependence, where substance-dependent individuals have significantly lower DRD2 availability than healthy controls (Volkow et al., 2001), have a lower decrease in binding potential following drug taking (Volkow et al., 1997) and show a reduced hedonic response to drug taking (Volkow et al., 2002). These differences suggest that PGs do not suffer from the same down-regulation or 'blunting' of the dopamine system as seen in substance dependence, but instead have increased dopaminergic sensitivity towards gambling compared with healthy controls (Linnet et al., 2011a). These findings are in need of replication and could benefit from using less complex tasks, instead of the IGT, to have more insight about the specific relation between dopamine and certain neuropsychological functions that underlie decision making abilities. These kinds of studies could answer fundamental questions on what role dopamine has in pathological gambling and whether

dopamine dysfunction in pathological gambling is related to certain neuropsychological characteristics of pathological gambling.

In addition, Magnetic Resonance Spectroscopy (MRS) studies (Jissendi and Baleriaux, 2009) could provide a better insight in the role of the glutamatergic and GABAergic systems in pathological gambling and in the observed effects of glutamatergic drugs in the treatment of pathological gambling. Finally, PET studies looking at the opioid system (Frost, 1993) are crucial in a better understanding of the mechanisms underlying the positive effects of opioid antagonists in the treatment of pathological gambling.

The role of arousal in pathological gambling

Gambling is associated with robust changes in peripheral arousal. During several minutes of real blackjack or slot machine play, regular gamblers display significant elevations in a range of physiological parameters including heart rate, blood pressure, electrodermal activity, and cortisol (e.g., Anderson and Brown, 1984; Coventry, 2001; Meyer et al., 2000). However, the causal significance of these changes in arousal for the maintenance of gambling behaviour is poorly understood. It has been suggested that positively reinforcing properties of this arousal may be more important even than the monetary gains in the maintenance of gambling behaviour (Wulfert et al., 2005). Effectively, excitement may represent 'the gambler's drug' (Boyd, 1982). The findings of increased activity in the brain's reward circuitry in PRGs during anticipation of the outcome of winning money presented in **Chapter 3** seem to support and provide the neuronal mechanism behind this hypothesis.

In their addiction model, Koob and Volkow (2010) describe the role of stress and the hypothalamic-pituitary-adrenal axis (HPA-axis) in mediating the reinforcing effect of drugs and stress-induced relapse. Drugs acutely activate the HPA axis and dependence dysregulates the HPA axis (Piazza and Le Moal, 1996). The effect of glucocorticoids on the reinforcing effect of drugs is hypothesized to be attributable to activation of dopamine neurons in the ventral tegmental area and to increased dopamine release in the nucleus accumbens (Barrot et al., 2000; Barrot et al., 2001). Although the effect of gambling is not directly comparable with the ingestion of drugs of abuse, evidence of enhanced dopamine release in the ventral striatum during gambling is parallel to findings in drug use (Linnet et al., 2010a). Furthermore, individual differences in the responsivity of the HPA axis are associated with personality traits such as sensation-seeking and novelty seeking and with a higher propensity of self-administration of drugs, and this subsequently leads to dysregulation of the HPA axis (Piazza and Le, 1998). Higher levels of sensation and novelty seeking are often found in pathological gambling (Forbush et al., 2008; Goudriaan et al., 2006b; e.g., Petry, 2001), and gambling directly influences the HPA axis as evidenced by increased physiological parameters including heart rate, blood pressure, electrodermal activity, and cortisol (e.g., Anderson and Brown, 1984; Coventry, 2001; Meyer et al., 2000). These aspects could be especially important in the acquisition of pathological gambling and abnormal dopamine functioning in the nucleus accumbens as found in pathological gamblers. Therefore, neuroimaging studies investigating the complex relationship between arousal, HPA axis functioning and dopamine release in the development and course of pathological gambling seem to be a fruitful line of research to better understand the underlying mechanisms in pathological gambling.

Brain connectivity patterns

Functional neuroimaging studies have substantially contributed to our understanding of functional specialization of brain areas and their role in addictive behaviours. However, the brain functions by using distributed and coupled interactions between brain regions. In recent studies investigating psychiatric disorders, dysfunctional connectivity patterns between

specialized brain systems have been identified and these dysfunctional connectivity patterns seem to reflect an underlying neural mechanism contributing to disordered behaviour (Greicius, 2008; van den Heuvel and Hulshoff Pol, 2010).

Connectivity studies using methods such as Psycho-Physiological Interaction (PPI: Friston et al., 1997), structural equation modelling (SEM; McIntosh and Gonzalez-Lima, 1994) and/or dynamic casual modelling (DCM: Friston et al., 2003) provide an opportunity to test hypothesis of task dependent changes in connectivity patterns in the brain. Our study using the PPI method (**Chapter 6**) to further understand the influence of affective stimuli on cognitive functioning is one example of how these methods can improve our insight in the neural processes that are driving addictive behaviours.

Coherent spontaneous fluctuations in the fMRI signal, without task induced activations, can be measured with resting-state fMRI techniques. Resting state fMRI offers a means to directly quantify functional interactions between brain areas. Using this approach differences between functional connectivity networks in a variety of substance use disordered populations compared to controls have been reported (Cole et al., 2010; Gu et al., 2010; Kelly et al., 2011; Liu et al., 2009; Ma et al., 2011). For example, compared to controls, chronic heroin users were found to have increased functional connectivity between the nucleus accumbens and anterior cingulate cortex (ACC), between the nucleus accumbens and orbital frontal cortex (OFC), and between the amygdala and OFC. Furthermore, they were found to have a reduced functional connectivity between prefrontal cortex and OFC and between prefrontal cortex and ACC. These abnormal functional connectivity patterns in the addicted brain provides additional evidence supporting addiction theories that emphasize enhanced salience of a drug and its related cues and weakened cognitive control in addiction (Ma et al., 2011). Resting-state studies could therefore lead to a further understanding of functional connectivity patterns in the development and continuation of pathological gambling as well.

Finally, pattern classification methods can use fMRI data to learn and later classify multivariate data points based on statistical regularities in the data set (Formisano et al., 2008; Norman et al., 2006). This method could be used to detect disorder specific brain activity patterns and to ultimately discriminate between disorders in order to be used as a diagnostic tool to assess which disorder is present in a patient (Craddock et al., 2009; De Martino et al., 2008). This is especially interesting when trying to answer questions about which specific activity patterns overlap or differentiate pathological gamblers from ADs, for example. Overlapping patterns could suggest using similar therapy forms for pathological gamblers and for ADs, whereas differences in pattern classification could ideally lead to more tailored therapy targets in these disorders.

Testing and enhancing functions with neuromodulation techniques

Using state-of-the-art neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), research could be performed investigating whether neuromodulation could be used to change brain functions that are implicated in problem gamblers. For example, a key role for DLPFC functions in preventing relapse behaviour in smokers was supported by an rTMS study which demonstrated that high-frequency DLPFC stimulation in former smokers resulted in lower relapse rates and craving for smoking compared with former smokers who received sham rTMS (Amiaz et al., 2009). Similar results were found in alcohol dependent patients (and for a review see Barr et al., 2008; De Ridder et al., 2011), although long-term effects on relapse are less well-established. Using these and other neuromodulation techniques could inform us about brain functions critically involved in the course of addictive behaviours and may eventually offer new treatment options for pathological gambling.

Another interesting approach is the application of real-time fMRI neurofeedback in pathological gambling. By training individuals to change specific brain activity patterns, we could investigate whether such a strategy would enhance control over craving, or control over gambling behavior, and thus test how neurofeedback would affect gambling behaviour. This technique has already been tested in the treatment of chronic pain and could be effective in pathological gambling as well (deCharms 2008; deCharms et al. 2005). For example, studies have indicated blunted ventral striatal activity towards monetary cues in gamblers (de Ruiter et al., 2009; Reuter et al., 2005), and neurofeedback training could be focused on normalizing these activation patterns. Furthermore, by targeting focal prefrontal functions, executive functions may be trained, which may result in improved cognitive control and, hence, diminished likelihood of relapse when craving occurs.

A new addictive disorder: game addiction?

Recently, research on excessive computer or video gaming in adolescents and young adults has received increasing public attention. Whereas there are positive effects of computer games on learning in educational settings, excessive gaming shares characteristics with officially recognized addictive disorders, such as pathological gambling, e.g., craving, gaming in order to elevate a negative mood, loss of control over game playing and excessive time spent on video gaming resulting in serious negative psychosocial consequences (Charlton and Danforth, 2007; Fisher, 1994; Griffiths and Hunt, 1998). Neurobiological or behavioural studies about (computer or video) game addiction are still rare. The most frequently studied phenomenon in game addiction is cue reactivity (Han et al., 2010; Park et al., 2010a; Thalemann et al., 2007). Results from these studies are in concordance with the suggestion that game addiction is characterized and maintained through sensitization of the mesolimbic dopaminergic system along with increased incentive salience of addiction-associated cues (Robinson and Berridge, 2001). Our study findings are in line with previous findings, because we found that self-reported levels of problem gaming in adolescent gamers are associated with error-related attentional bias for game cues and diminished gaming related inhibition (**Chapter 8**). This indicates that behavioural patterns commonly associated with addictive disorders are also related to problem gaming. Thus, problem gaming has similarities to substance dependence and pathological gambling in underlying cognitive-motivational mechanisms. This finding could be used as an argument to discuss the classification of game addiction alongside pathological gambling. However, attentional bias similarities only provide evidence regarding one aspect relating to addictive disorders, and evidence from epidemiological, neuroimaging, and treatment studies should also be considered in this debate.

There are also some methodological issues that have to be resolved in game addiction studies such as the fact that there is no standardized screening list to assess gaming problems, making comparisons between studies difficult. In addition, more studies are needed to elucidate whether other aspects of game addiction, which are present in substance dependence and pathological gambling, are common to game addiction as well such as heightened impulsivity and disadvantage choice behaviour. Notably, research into game addiction should keep in mind that heavy gamers could also show better cognitive performance than sporadic gamers on measures of reaction time (as found in our study in **Chapter 8**) and attentional load, because of their extensive experience with speeded information processing during games. It is important to control these specific assets when using neuropsychological measures of impulsivity or salience that depend on reaction times.

In the coming years, new research on game addiction will answer the question whether game addiction should be categorized as an addictive behaviour, similar to pathological

gambling and substance dependent disorders, which are now united in the new DSM-V category “Addiction and Related disorder”.