Imaging studies in pathological gambling: similarities and differences with alcohol dependence
van Holst, R.J.

Citation for published version (APA):
van Holst, R. J. (2011). Imaging studies in pathological gambling: similarities and differences with alcohol dependence
Chapter 1

Introduction and outline of this thesis
Pathological gambling: a clinical example

Peter’s main problem is an uncontrollable urge to gamble on slot machines whenever he is alone and has access to money. Prior to gambling he feels tense, uneasy. Peter knows that this tension is relieved when gambling and that for a short time he will feel great. However, once his money has been lost, Peter feels guilty and angry with himself for gambling. Despite these negative consequences of gambling, he often returns the following day to “get even” for the money he lost. Peters says that the main internal cues to gamble are loneliness, depression and stressors in his life. However, external cues such as receiving bills, having money, and being in or near a gaming venue, also trigger his urge to gamble, although he was determined to quit gambling once and for all.

Pathological gambling: the disorder

In 1977, the World Health Organization was the first to include pathological gambling in one of the important classification systems; the 9th edition of the International Classification of Diseases (ICD-9; World Health Organization, 1977). In 1980, pathological gambling was also included in the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders as a disorder of “Impulse Control Not Elsewhere Classified” (American Psychiatric Association, 1980) which was updated in 1994 to the DSM-IV (American Psychiatric Association, 1994) and DSM-IV-R in 2000 (American Psychiatric Association, 2000).

In the current edition of the DSM, pathological gambling is still classified under the larger category of “Impulse-Control Disorders Not Elsewhere Classified,” along with compulsive stealing (kleptomania), fire starting (pyromania) and hair pulling (trichotillomania). According to DSM-IV-R, in order to be diagnosed with pathological gambling, a person needs to have five or more out of 10 possible symptoms (see Table 1). Examples of symptoms are a preoccupation with gambling; inability to control gambling behavior; lying to loved ones about gambling; and committing “illegal acts, such as forgery, fraud, theft or embezzlement to finance gambling.”

The American Psychiatric Association currently is in the process of updating the DSM to its fifth edition (DSM-V) and one of the working groups has proposed to move pathological gambling to a new category titled “Addiction and Related Disorders” and renaming pathological gambling “disordered gambling”. The “Addiction and Related Disorder” category will replace the current “Substance-Related Disorders” classification and will include all substance use disorders and disordered gambling (http://www.dsm5.org). Disordered gambling will be the sole “behavioural addiction” in the proposed “Substance-Related Disorders” classification (Holden, 2010), although some researchers have suggested to incorporate internet, game or sex addiction as well (for a review see; Frascella et al., 2010). These latter disorders might be included only in the future, as these potential addiction disorders need further study.

The rationale for this change of category for pathological gambling is that a growing body of scientific literature, especially epidemiological, neurobehavioral, and treatment research, has revealed many commonalities between pathological gambling, and substance use disorders (e.g., Goudriaan et al., 2004; Petry, 2006 and see Chapter 2).

Prevalence estimates for pathological gambling vary according to the threshold that is applied, but using the strict definition of ‘pathological gambling’ (where symptoms resemble those of DSM-III dependence) was reported to have a lifetime prevalence between 0.5% and 1.5% (Petry et al., 2005; Welte et al., 2002). However, the prevalence estimates are significantly higher when using the less strict definition of ‘problem gambling’ (based on social consequences, similar to DSM-III abuse) and can amount to 3.5% in the general population. In the Netherlands, the prevalence of ‘pathological gambling’ in the last year was
estimated between 0.1% to 0.6% of the population, whereas 0.8% to 2.2% would meet the
definition of ‘problem gambling’ in the last year (Schrijvers et al., 2010). Only a small
percentage of pathological gamblers (4-10%) seeks treatment for this disorder (Schrijvers et
al., 2010). However, with the liberalisation of gambling laws in many countries (including the
Netherlands) and the increase in gambling opportunities, for example via internet, the
prevalence of pathological gambling is expected to rise (Ladouceur et al., 1999; Schrijvers et
al., 2010).

Table 1: DSM-IV criteria
A. Persistent and recurrent maladaptive gambling behaviour as indicated by five (or more) of the following:
   • Is preoccupied with gambling (e.g. preoccupied with reliving past gambling experiences, handicapping
     or planning the next venture, or thinking of ways to get money with which to gamble)
   • needs to gamble with increasing amounts of money in order to achieve the desired excitement
   • has repeated unsuccessful efforts to control, cut back, or stop gambling
   • is restless or irritable when attempting to cut down or stop gambling
   • gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g. feelings of
     helplessness, guilt, anxiety, depression)
   • after losing money gambling, often returns another day to get even (“chasing” one’s losses)
   • lies to family members, therapist, or others to conceal the extent of involvement with gambling
   • has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling
   • has jeopardized or lost a significant relationship, job, or educational or career opportunity because of
     gambling
   • relies on others to provide money to relieve a desperate financial situation caused by gambling
B. The gambling behaviour is not better accounted for by a Manic Episode.

The neurobiology of pathological gambling
Unfortunately, knowledge about the aetiology of pathological gambling is limited and
treatment is effective only in a part of the pathological gamblers (e.g., Ledgerwood and Petry,
2006). Because of the considerable overlap in epidemiological and neurobehavioral aspects
between pathological gambling and substance dependence, neurobiological addiction models
seem to be a useful starting point to generate hypotheses and probe addiction relevant
neurobiological systems in pathological gambling to better understand the underling
mechanisms of this disorder.

Based on extensive animal and human research on substance dependence, multiple
models of addiction have been used to improve our understanding of the onset of addiction,
its course and possible treatment targets (Blum et al., 2000; Everitt and Robbins, 2005; e.g.,
Goldstein and Volkow, 2002; Koob and Volkow, 2010; Robinson and Berridge, 1993;
Volkow et al., 2004). Key elements of these models are (1) that drug intoxication is associated
with strong positive reinforcements or reward (by directly or indirectly enhancing dopamine
neurotransmission in the mesolimbic system), which induce stimulus response learning and heighten salience attribution to the drugs of abuse (e.g., Robinson and Berridge, 1993); (2) that repeated exposure to drugs or drug-related cues enhances the memory of the expected reward, resulting in overactivation of the reward and motivational circuits when confronted again with addiction related stimuli, also known as “cue reactivity” (Goldstein and Volkow, 2002); (3) that due to the changes in dopamine and glutamate functioning, salience of other reinforcers such as food, money or other pleasurable stimuli is decreased (Kalivas and Volkow, 2005); (4) that “self-control”, the ability to inhibit urges and control behaviour in a way to achieve goals, is thought to be compromised due to the repeated drug exposure and the resulting adaptations of mesolimbic-prefrontal glutamergic pathways in substance dependent individuals (Everitt and Robbins, 2005; Feil et al., 2010; Jentsch and Taylor, 1999; Koob and Volkow, 2010); and (5) the change from voluntary drug use to more habitual and compulsive drug use is thought to represent a transition at the neural level from prefrontal cortical to striatal control over drug seeking and drug taking behaviour as well as an progression form ventral to more dorsal parts of the striatum, known as habit formation (Everitt et al., 2008; 2005). Together, these processes are thought to contribute to an inability to inhibit the drive to seek and consume drugs and to relapse after periods of abstinence in substance dependence disorders.

These postulated key elements of addiction models can also be recognized in pathological gambling. Corresponding to the first key element in addiction models; evidence of the involvement of the mesolimbic dopamine circuit in pathological gambling has been provided by Positron Emission Tomography (PET) studies in pathological gamblers showing enhanced dopamine release in the ventral striatum (Linnet et al., 2011a), and enhanced glucose metabolism in mesocortical regions during gambling (Hollander et al., 2005). Moreover, enhanced saliency towards gambling cues (key element 2) has been reported using functional magnetic resonance imaging (fMRI) paradigms with movies or pictures of gambling as the main external cues (Crockford et al., 2005; Goudriaan et al., 2010; Miedl et al., 2010), similar to the heightened salience attribution to addictive substances in substance dependent disorders. In addition, diminished mesolimbic responses to natural rewarding stimuli (key element 3) are also found with fMRI studies in problematic gamblers (de Greck et al., 2010; de Ruiter et al., 2009; Reuter et al., 2005). Furthermore, impaired self-control functions (key element 4) are consistently reported in neuropsychological studies in pathological gambling (Goudriaan et al., 2004 and see Chapter 2). More specifically, pathological gamblers make more disadvantageous choices than healthy controls. However, there is a lack of imaging studies looking at the neural correlates of decision making in pathological gambling (just one; see Tanabe et al., 2007), and there are also some methodological issues to overcome (see Chapter 2). Similarly, impulse control functions have been found to be impaired on neuropsychological test in pathological gamblers. But again, only one fMRI study (Potenza et al., 2003a) has investigated the neurocorrelates of cognitive control in pathological gamblers. Finally, no data are currently available about the development of habit formation and compulsivity (key element 5) in pathological gambling.

Thus, although there is a multitude of neurocognitive studies indicating motivational and cognitive impairments in pathological gambling, neuroimaging studies in pathological gambling are scarce (van Holst et al., 2010 and see Chapter 2). However, the situation is rapidly changing: when we started this PhD project in 2007, only five fMRI studies (Crockford et al., 2005; Potenza et al., 2003a; Potenza et al., 2003b; Reuter et al., 2005; Tanabe et al., 2007) and one PET study (Hollander et al., 2005) were present investigating pathological gambling. Four years later, the number of neuroimaging studies has grown with six additional fMRI studies (Clark et al., 2009; Dannon et al., 2011; de Greck et al., 2010; de
Ruiter et al., 2009; Goudriaan et al., 2010; Miedl et al., 2010) and five additional PET studies (Hollander et al., 2008; Linnet et al., 2010; Linnet et al., 2011a; Linnet et al., 2011b; Pallanti et al., 2010).

Challenges that remain in understanding the underlying mechanisms of pathological gambling are manifold. First, methodological challenges such as controlling for psychiatric comorbidity in pathological gambling and inclusion of clinical control groups are aspects that need to be incorporated when aiming to elucidate the specific characteristic of pathological gambling. Notably, almost none (except from de Ruiter et al., 2009; Goudriaan et al., 2010; Potenza, 2008; Tanabe et al., 2007) of the neuroimaging studies have directly compared patients with substance use disorders with pathological gamblers and healthy controls, making direct inferences about which neurocognitive similarities and differences exist between substance use disorders and pathological gambling impossible.

Second, the main focus of neuroimaging studies so far has been on probing the reward and motivational system of pathological gamblers. These studies have consistently shown that the reward and motivational system in pathological gamblers show attenuated responses toward monetary wins and losses (e.g., de Ruiter et al., 2009; Reuter et al., 2005), comparable to these in substance dependent disorder (Kalivas and Volkow, 2005; Volkow et al., 2010; Wrase et al., 2007). However, testing the motivational system of pathological gamblers with monetary cues could be confounded by the fact that pathological gamblers are used to play with large amounts of money, which could also explain the attenuated response to winning and losing small amount of money. Thus the reward and motivational system should also be tested with other than monetary cues.

Third, studies on cognitive control functions in pathological gamblers are still rare, making firm conclusions about similarities in cognitive control functions in pathological gambling and substance dependence impossible. One should be cautious, however, to test cognitive functions with tasks that resemble gambling games or that provide (monetary) feedback, when aiming to investigate similar cognitive functions in substance dependent subjects and pathological gamblers. Pathological gamblers, of course, have far more experience with gambling games than substance dependent subjects or healthy controls. Furthermore cognitive tasks that resemble gambling games could also invoke “cue reactivity”, which could interact with cognitive functioning. Additionally, it should be kept in mind that cognitive performances could also be affected by abnormal functioning of the reward and motivational systems (as discussed above). For example, when feedback has to be incorporated to perform adequately on a cognitive task, performance can be negatively influenced when feedback is not efficiently used. Thus, studies probing cognitive functions need to use tasks measuring unitary constructs.

Fourth, there is still a lack of knowledge about the neural correlates of gambling specific characteristics. For example, overestimation of the probability to win is a common aspect in pathological gambling and should be investigated to understand how these specific behaviours contribute to the aetiology of pathological gambling. Thus, more research is needed focusing on gambling specific aspects that are dissimilar to substance dependence, to understand what makes pathological gambling a (unique) behavioural addiction.

Clarifying the neural correlates of pathological gambling
Clarifying the neural correlates in pathological gambling is vital for understanding the nosology and aetiology of pathological gambling and could lead to new treatment strategies for this disorder. The aim of our investigations into the neural correlates of pathological gambling is to better understand the similarities and differences in motivational and cognitive
processes between pathological gambling and substance use disorders. The attempts to reach this aim are described in this thesis.

We conducted (functional) MRI studies in treatment seeking gamblers, healthy controls, and made comparisons with a substance dependent group (treatment seeking alcohol dependent subjects). Because several psychopathological conditions are known to influence performance on neuropsychological tests and fMRI results, we excluded anyone having any psychiatric disorder other than the one we were interested in. Gamblers, alcohol dependent subjects and healthy controls with nicotine dependence and/or an elevated score on depression scales were, however, not excluded, because this would have led to the exclusion of most of our participants. We will refer to our treatment seeking gamblers as problematic gamblers because not all our recruited gamblers met full DSM-IV criteria for pathological gambling.

Due to the important role of self-control functions in addiction models and the scarcity of fMRI studies about these functions in pathological gambling, we used two paradigms to probe these functions in problematic gamblers. One cognitive flexibility paradigm was designed to investigate cognitive flexibility in problematic gamblers and alcohol dependent subjects to better understand the neuronal correlates of the frequently observed compulsive and inflexible behaviours seen in patients with these disorders. The second paradigm, an affective Go/NoGo task, was designed to study response inhibition in the context of varying affective stimuli. This paradigm was used to simultaneously test response inhibition abilities and reactions of the affective system towards different addiction and non-addiction related stimuli, and to test the interaction between cognitive and motivational systems and its effect on response inhibition abilities.

Furthermore, we wanted to study not only aspects of gambling that might be similar to substance dependent disorders, but we also wanted to better understand phenomena that distinguish pathological gambling from other addictions. For example, 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 very likely to result in a loss. Thus, the gamble in itself and the expectation of winning seem to be crucial elements in pathological gambling. Another crucial difference between substance dependent disorders and pathological gambling is that gambling does not result in toxic effects of exogenous substances on the brain. Although it is well established that alcohol abuse is associated with brain atrophy, brain morphology in pathological gambling has not yet been investigated. Therefore we conducted a voxel based morphometry study comparing gray matter volumes in alcohol dependent subjects, pathological gamblers and healthy controls.

Finally, in the light of the ongoing discussions about which disorders should be incorporated in the new ‘Behaviour Addictions” category of the DSM-V, we wanted to understand more about (computer and video) game addiction. Therefore, we investigated male adolescent computer and video gamers and tested whether commonly related behavioural tendencies in patients with addictive behaviours (i.e. attentional bias and response inhibition), would show a positive relation with high scores on a self reported (computer and video) game addiction questionnaire.

Outline of this thesis

First, we review all published neurocognitive and neuroimaging studies in pathological gamblers from 2005 to 2010 in order to have a clear overview of the state of neurobiological research in pathological gambling at that point. This review is presented in Chapter 2. It contains an overview of neurocognitive literature in pathological gambling, which is
Introduction and outline of this thesis

discussed in the light of important concepts in addiction models. Furthermore, aims for future research are discussed, including the aims for this PhD project.

As noted above, a difference between substance dependence disorders and pathological gambling seems to be the role of expectation. Having too optimistic expectations and overestimating the chances to win is a common phenomenon in pathological gambling. In order to understand more about the underlying pathology of this mindset, we conducted the fMRI study reported in Chapter 3, comparing monetary reward and loss anticipation in problematic gamblers with healthy controls.

In Chapter 4 we examine response inhibition in pathological gamblers and healthy controls. Loss of control or disinhibition over drug use and enhanced salience of drug use are thought to play an important role in the development and persistence of substance use disorders. To better understand response inhibition during affective stimuli (gambling related, positive and negative pictures) in problematic gamblers, we designed and applied an affective Go/NoGo task in pathological gamblers and healthy controls.

In Chapter 5 we further investigate the influence of affective stimuli on response inhibition in problematic gamblers and healthy controls using a psycho-physiological interaction (PPI) analysis. This method provides a better insight into the functional connectivity between brain areas and how this connectivity is modulated by task conditions.

In Chapter 6 we report about the neural correlates of cognitive flexibility in problematic gamblers, alcohol dependent subjects and healthy controls. Cognitive flexibility is relevant for goal-directed behaviour, which involves executive decisions on initiation and switching of behaviour. In clinical studies, cognitive flexibility is often tested with tasks providing direct feedback on the correctness of responses. These switching paradigms are dependent on behavioural adaptation following changes in stimulus-reinforcement contingencies. However, because impaired cognitive flexibility in pathological gamblers and alcohol dependent subjects may also result from diminished feedback processing rather than from diminished switching ability, we tested cognitive flexibility using a cognitive switch task without monetary feedback.

As described before, an important difference between substance dependent disorders, 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 (alcohol abuse or alcohol dependence) is associated with cognitive impairments and brain atrophy with smaller gray matter (GM) volumes in cortical and subcortical brain regions. Although there is considerable overlap in the cognitive profile of subjects with an alcohol use disorder and pathological gamblers (Goudriaan et al., 2005), it has not yet been established whether pathological gambling, similar to alcohol use disorders, is associated with abnormal GM volumes. To answer this question we performed a voxel based morphology study (Chapter 7) comparing regional GM volumes in pathological gamblers, problematic alcohol users, and healthy controls.

Finally, in light of the new update of the DSM-V and the new category of “Addictive Behaviours”, we examined whether behavioural tendencies commonly related to addictive behaviours are also related to the (computer and video) game addiction. Therefore, we tested attention bias and response inhibition in computer and video gaming adolescents. In a behavioural study reported in Chapter 8, we tested the relation between self-reported levels of game addiction and neurocognitive tasks measuring attentional bias and response inhibition in male adolescents.

In Chapter 9, our main findings and their clinical relevance are discussed and we conclude with limitations and recommendations for future research.
Reference List


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


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


