Boosting impulse control in addiction: Pharmacological neuroimaging studies
Schmaal, L.

Citation for published version (APA):

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PART I

CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
ADDICTION

Substance use disorders, also referred to as addiction, are characterized by compulsive drug-seeking and drug-taking behavior despite negative consequences and a loss of control over drug taking. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), substance dependence can be conceptualized as a cluster of symptoms including a strong desire to use, inability to control drug use, tolerance, withdrawal, preoccupation with the substance and continuation of use despite the negative consequences (American Psychiatry Association 1994). Although according to the DSM-IV dependence is specifically related to a substance, in recent years it has become clear that application of these criteria is not limited to dependence on a substance, but also applies for certain behavioral addictions such as pathological gambling (for a review see van Holst et al. 2010). Therefore, the upcoming DSM-V will substitute ‘Substance-Related Disorders’ by the new category ‘Addiction and Related Disorders’ including pathological gambling. For this reason, the term addiction is used interchangeably with the term substance dependence in this thesis.

Addiction has been linked to a huge burden of disease. In 2009, UNODC estimated that there were 15-39 million problem drug users globally (UN Office on Drugs and Crime 2011). With regard to alcohol, it is estimated that 3.2% of the world’s population meet criteria for an alcohol use disorder (Rehm et al. 2009). Drug and alcohol abuse have been associated with serious public health problems, public safety problems and economic damage. For example, smoking tobacco is the single most important cause of preventable disease and mortality. Given the tremendous negative consequences of problematic alcohol and drug use, addiction has been the subject of many scientific studies conducted over the last centuries.

The view on the concept of addiction has travelled a long road from constituting a weakness of the will in the 19th century, via representing symptoms of an underlying personality disorder (psychoanalytic model) or inappropriate learned behavior (behavioral model) in the mid 20th century to being regarded as a chronic and relapsing brain disorder in the late 20th century. Current brain disorder models emphasizes the importance of abnormal brain functioning in the development and continuation of addictive behaviors, influenced by both genetic and social/environmental factors (Leshner 1997). Recent advances in brain imaging techniques such as Positron Emission Tomography (PET), Single-photon Emission Computed Tomography (SPECT) and (functional) magnetic resonance imaging (MRI) have led to a rapid increase in the number of neuroimaging studies in substance dependent individuals, which have substantially advanced our understanding of the neurobiological underpinnings of addiction. The neurobiological mechanisms contributing to addiction will be discussed in more detail in the following section.
Evidence from both preclinical studies and neuroimaging studies in humans have substantially contributed to an enhanced insight into the neurobiology of addiction (for reviews see Everitt and Robbins 2005; Goldstein and Volkow 2011; Koob and Volkow 2010; Volkow et al. 2012). Several models have been proposed to explain continued drug use despite negative consequences as observed in substance dependent individuals. A key and common element in these models refers to a disrupted balance between an impulsive motivational system and a reflective cognitive control system (Bechara 2005; Koob and Volkow 2010; Wiers et al. 2007).

Chronic drug use has been associated with neuroadaptive changes in a motivational circuitry in the brain that processes reward and influences reward expectation, motivation, emotions and the feelings of pleasure. Therefore, this system is also referred to as the impulsive or motivational system (Bechara 2005; Wiers et al. 2007). Intake of a drug is associated with high, but brief, bursts in extracellular dopamine release in the motivational circuitry, primarily located in limbic brain regions including the nucleus accumbens located in the ventral striatum, which signals the occurrence of reward and positive reinforcement. Furthermore, the persistent abuse of an addictive substance induces conditioning and memory processes that link the drug and its environment to a pleasurable experience. The neuroanatomical substrates for consolidating this memory are likely to involve the amygdala and the hippocampus. As a consequence, these learned responses result in increased valuation of drug-related cues (such as certain drug paraphernalia, environmental contexts, habits or emotional states) relative to natural reward (reflected by increased salience, cue reactivity and automatic approach behavior to drug and drug-related stimuli) and increased attention for drug-associated stimuli (reflected by an attentional bias). These processes are mediated by limbic brain regions including the ventral striatum, in addition to the thalamo-orbitofrontal circuit, insular and anterior cingulate regions, and contribute to compulsive drug seeking, craving and relapse. Finally, frequent and persistent drug use can lead to habit formation and compulsive drug use even when the drug is no longer perceived as pleasurable, which also contributes to automatically generated responses to drug cues and is thought to be associated with a shift from ventral to more dorsal striatal region involvement (for reviews see Everitt and Robbins 2005; Goldstein and Volkow 2011; Koob and Volkow 2010; Volkow et al. 2012).

Normally, top-down control is exerted on the impulsive motivational system by a prefrontal cognitive control system (also termed the reflective system; Bechara 2005; Wiers et al. 2007) in order to control and inhibit the automatic prepotent responses initiated by the motivational system. However, diminished functioning of the prefrontal cognitive control system has been identified as another key factor involved in addiction.
(Goldstein and Volkow 2011; Mansouri et al. 2009). For instance, decreased activations of the dorsal anterior cingulate cortex, and dorsolateral and medial prefrontal cortex areas have been found in substance dependent individuals: areas that are related to diminished performance on tasks measuring higher order cognitive processing such as inhibitory control, conflict monitoring and decision making (Fu et al. 2008; Salo et al. 2009; Tanabe et al. 2007). Moreover, abnormal functional connectivity between the striatum and dorsolateral prefrontal cortex has been shown to predict impairments in adaptive decision making in alcohol dependent patients (Park et al. 2010). Taken together, the combination of a hyperactive “impulsive” motivational system tuned to immediate rewards (especially in the presence of drug-related cues) and a hypoactive cognitive control system necessary for the pursuit of long-term goals seems to be responsible for the chronic, relapsing nature of addiction.

With regard to neurotransmitter systems, the focus has been traditionally on the dopamine system. Especially in early stages of drug addiction, the brain’s mesolimbic dopamine system plays a pivotal role in the reinforcing properties of drugs. Intake of addictive drugs results in large and abrupt increases in dopamine release in the limbic reward system (either directly or indirectly), specifically in the nucleus accumbens. This dopamine release in the nucleus accumbens is associated with strong positive reinforcement or reward and contributes to salience attribution to the drugs of abuse (Volkow et al. 2004). Later exposure to the drug or drug-related cues can trigger dopamine release in the striatum (reward anticipation), which is associated with the subjective experience of craving (e.g. Volkow et al. 1999) and contributes to relapse into drug use. Chronic drug use has also been linked to decreased dopamine D2 receptor expression, which may in part be an adaptation to the chronic elevation in extracellular dopamine due to blockade of dopamine uptake by the drug (for a review see Nader and Czoty 2005). Decreased dopamine D2 receptor expression is thought to contribute to the anhedonia, i.e. decreased sensitivity to natural and drug rewards, observed during protracted abstinence (Volkow et al. 2004). Although dopamine seems to be the primary mechanism of the initiation of drug reinforcement, other neurotransmitters have been implicated indirectly in the acute reinforcing properties of substances of abuse, including gamma-aminobutyric acid (GABA), opioid peptides, serotonin, acetylcholine, endocannabinoids, and glutamate (for a review see Koob and Volkow 2010). Whereas dopaminergic neurotransmission plays a key role in initial stages of addiction because of its role in drug reward and reward anticipation, in addition to its role in the hedonic state observed in substance dependent individuals, recent preclinical research suggests that neuroadaptations of the glutamate system are crucial for the continuation of and relapse into drug use (Kalivas 2009). Glutamate neurotransmission plays a crucial role in synaptic plasticity associated with learning and memory. Synaptic changes in NMDA and AMPA receptors are part of the neuroadaptations involved in the conditioning and memory processes that take place during repeated drug
use, in which the reinforcing effects of the drug become associated with cues related to the drug (Lane et al. 2008). In addition, drug- and cue-induced reinstatement have been linked to glutamatergic pathways. Preclinical studies have revealed that glutamatergic projections from medial prefrontal areas as well as from the amygdala into the striatum, which are activated in response to drug cues and in turn trigger dopamine release, result in cue-induced reinstatement of drug-seeking behavior (Kalivas 2009). In humans, a few studies have investigated the role of glutamate in addiction using Proton Magnetic Resonance Spectroscopy (1H MRS) and revealed glutamate abnormalities in substance dependent individuals (Gallinat and Schubert 2007; Lee et al. 2007; Thoma et al. 2011; Umhau et al. 2010; Yang et al. 2009; Yucel et al. 2007).

**IMPULSIVITY AND ADDICTION**

Impulsivity can be broadly defined as “behavioral actions without adequate forethought” (Evenden 1999). According to dual-process models of impulsivity, (impulsive) behavior is the joint outcome of two types of cognitive processes: reflective (cognitive control) processes and impulsive (motivational) processes (Wiers et al. 2010). From this dual-process perspective, maladaptive levels of impulsivity are likely to result from an inability (or lack of motivation) to suppress automatic or reward-driven responses that are not appropriate given the current demands or that have long-term negative consequences. Defined in this way, impulsivity has clear relevance to addiction, since deficient inhibitory control over a response that provides immediate reinforcement is a key feature of substance use disorders. With regard to addiction, high levels of impulsivity may have been present prior to drug initiation, making an individual more vulnerable to develop a substance use disorder. In addition, impulsive behavior can be exacerbated by chronic drug use. Chronic use of certain drugs is associated with damaging effects on prefrontal functioning leading to diminished executive functioning, as well as with increased motivational impulses, especially in the presence of drug cues (i.e. overactive motivational system) (Verdejo-Garcia et al. 2008).

Impulsivity can be measured by various cognitive tasks such as the go-no go task, stop signal task, Stroop task and delay discounting paradigms. These different tasks are thought to measure distinct aspects of impulsivity such as response inhibition (i.e. impulsive action or motor impulsivity) and impulsive decision making (i.e. impulsive choice or cognitive impulsivity), however, detailed information on the nature of, and interaction between, different aspects of impulsivity is still scarce (see Chapter 2). Previous studies have revealed higher scores on self-report measures of impulsivity, increased impulsive action reflected by diminished performance on go-no go tasks and stop signal tasks, diminished cognitive control reflected by higher cognitive interference scores on the Stroop task, and increased
preference for (smaller) immediate over more beneficial delayed rewards in substance dependent individuals compared to healthy controls (for a review see Verdejo-Garcia et al. 2008).

Performance of neurocognitive tasks related to impulsivity depends on activity in prefrontal, striatal, cingulate, thalamic and (pre-) motor regions (Cardinal 2006; Chambers et al. 2009). Abnormalities in frontostriatal activation associated with heightened levels of impulsivity have been observed in substance dependent individuals (Goldstein and Volkow 2011). On a molecular level, impulsivity is mediated by various neurotransmitter systems (Pattij and Vanderschuren 2008). Historically, the focus has been on the role of serotonin underlying impulsive behavior. Especially diminished serotonin signalling has been assumed to underlie impulsive behavior (Chamberlain and Sahakian 2007). Evidence implicating an additional role for other neurotransmitter systems such as catecholamines (dopamine, noradrenaline) and glutamate has more recently started to accumulate. For example, a PET study by Lee et al. (2009) showed an association between low striatal dopamine D2 receptor availability and impulsivity. The proposed role of glutamate in impulsivity is mainly based on preclinical literature, because the availability of PET and SPECT tracers to image the glutamate system in humans is limited. Proton Magnetic Resonance Spectroscopy ($^1$H MRS) is a promising imaging technique to investigate the relationship between impulsivity and glutamate concentrations in the human brain. However, to date, evidence for such an association has come only from one study using MRS imaging in patients with borderline personality disorder (Hoerst et al. 2010). Therefore, the glutamatergic contribution to impulsivity observed in substance dependent individuals remains to be clarified.

**IMPULSIVITY AS A TREATMENT TARGET**

With the recognition of addiction as a major health problem, the demand for effective treatment strategies has increased. In the Netherlands, the demand for treatment related to alcohol or drug dependence has increased from 53,794 in 1994 to 76,295 in 2010 (Ouwehand et al. 2011). The proportion of alcohol related treatment demand has increased to almost 50% of the overall treatment demand over the past ten years (Ouwehand et al. 2011). Although a variety of interventions such as pharmacotherapy, cognitive behavioural therapy, motivational interviewing and relapse prevention is currently available to treat alcohol and drug dependent patients, many of the patients only show moderate response to the treatment or no response at all (Schippers and Broekman 2006). Furthermore, no approved pharmacotherapy for cocaine, methamphetamine and cannabis dependence exists at this time (van den Brink 2012). Therefore, there is a continued need for new and more efficient strategies to treat alcohol and drug dependence. To date, attenuation of
drug reward and craving has been the major focus of medication development in relation to addiction. However, since impulsivity is a core feature of addiction and has been shown to predict treatment outcome and relapse into substance use (Krishnan-Sarin et al. 2007; MacKillop and Kahler 2009; Streeter et al. 2008), improving impulse control could be an important new target for treatment.

The development of treatments targeting impulse control is likely to benefit from knowledge on the neurobiological mechanisms contributing to maladaptive impulsivity. The modulation of brain systems involved in impulse control could result in a reduction of impulsive behavior such as acting on the immediate rewarding properties of drinking alcohol or using drugs. Potential treatment strategies include pharmacotherapy aimed at restoring the imbalance between cognitive control and motivational drive by improving functioning of the cognitive control system and/or downregulating the motivational system. Several potential pharmacotherapies have been suggested for this purpose and N-acetylcysteine and modafinil are among the most promising compounds.

**N-ACTEYLICYSTEINE**

N-acetylcysteine (NAC) is used in the treatment of paracetamol overdose, prescribed for the management of COPD and sold over the counter as a mucolytic agent and nutritional supplement. It has received attention within the field of addiction because of its effects on glutamate neurotransmission. NAC is a precursor to the amino acid cystine, which regulates intra- and extracellular glutamate exchange through the cystine-glutamate antiporter. Cystine-glutamate antiporters, which are predominantly located on glial cells, exchange extracellular cystine for intracellular glutamate and thereby maintain optimal basal levels of extracellular glutamate. Extracellular glutamate stimulates inhibitory group II metabotropic glutamate (mGluR2/3) receptors, which in turn reduces synaptic glutamate release. Following previous preclinical studies indicating that cue-induced drug seeking behavior is associated with an increased firing rate of glutamatergic neurons projecting from the medial prefrontal cortex to the ventral striatum, in part the result of reduced basal levels of extracellular glutamate (i.e. reduced stimulation of inhibitory mGluR2/3 receptors; Baker et al. 2003a), studies using NAC to influence the glutamatergic system in drug-dependent animals have emerged in recent years. These studies have consistently shown that NAC administration restores abnormal basal levels of extracellular glutamate in the nucleus accumbens [thereby inhibiting synaptic glutamate release derived from prefrontal afferents (Kupchik et al. 2012)] and subsequently prevents relapse to drug-seeking behavior in rats previously treated with cocaine (Baker et al. 2003b; Madayag et al. 2007) and heroin (Zhou and Kalivas 2008). In humans, a few studies have examined the clinical effects of NAC in drug dependence (Amen et al. 2011; Grant et al. 2007; Grant
et al. 2010; Gray et al. 2010; Knackstedt et al. 2009; LaRowe et al. 2007; Mardikian et al. 2007). Overall, the results with regard to reduction of craving and drug use are promising. Nonetheless, these studies were mostly small clinical trials, non-randomized cohorts or case reports, so their results should be regarded as preliminary. In addition, the mechanism by which NAC improves clinical outcome remains to be elucidated. For instance, whether NAC exerts its effects through modulation of glutamate neurotransmission in the human brain has not been investigated as yet.

MODAFINIL

Whereas NAC appears to downregulate the motivational system by influencing the glutamatergically modulated reward-reinforcement, a potential pharmacotherapy to enhance cognitive control functions is modafinil. Modafinil is a vigilance and wakefulness promoting agent. It was first marketed in France in the 1990s. Currently, modafinil is approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for treatment of narcolepsy, sleep apnea, and shift work-induced sleep disorder. In addition, modafinil is widely used as a cognitive enhancer in healthy individuals (Repantis et al. 2010). Furthermore, modafinil has received great interest in the field of psychiatry as a treatment for cognitive dysfunctions implicated in many psychiatric disorders such as addiction (Dean et al. 2011; Hester et al. 2010; Vansickel et al. 2008; Zack and Poulos 2009), schizophrenia (Hunter et al. 2006; Pierre et al. 2007; Sevy et al. 2005; Spence et al. 2005; Turner et al. 2004b), attention deficit hyperactivity disorder (ADHD) (Taylor and Russo 2000; Turner et al. 2004a) and affective disorders (DeBattista et al. 2004). Specifically with regard to impulsivity, modafinil has been reported to improve impulse control in healthy individuals (Turner et al. 2003), patients with ADHD (Turner et al. 2004a), methamphetamine dependent patients (Dean et al. 2011) and pathological gamblers (Zack and Poulos 2009). However, a remarkable observation is that the effect of modafinil seems stronger when the window for improvement is larger. Several studies show a stronger improvement of modafinil in patients with a low baseline performance (Hunter et al. 2006; Zack and Poulos 2009), in sleep deprived subjects (Wesensten 2006), in more difficult tasks conditions (Marchant et al. 2009; Muller et al. 2004; Turner et al. 2003) and in patients with lower IQ (Randall et al. 2005). These results suggest that modafinil adjusts cognitive performance to an optimal level if necessary and compensates for cognitive deficiencies. However, the mechanism of action of modafinil is not yet fully understood. It appears to have an effect on multiple neurotransmitter systems in the brain including catecholamine, glutamate, GABA and serotonin neurotransmission. A few functional MRI (fMRI) studies have investigated the neural correlates of modafinil effects on cognitive functioning (Ellis et al. 1999; Ghahremani et al. 2011; Hunter et al. 2006; Minzenberg et al. 2011; Rasetti et al. 2010; Spence et al. 2005; Thomas and Kwong
2006). However, the neural substrates underlying modafinil mediated improvement in impulsivity remain to be elucidated. This is important to investigate, because it would not only enhance our understanding of the mechanism of action of modafinil in the treatment of addiction but also increase our knowledge on the neurobiological mechanisms of distorted impulse control. Finally, increased knowledge on the underlying mechanisms may help us to identify those patients most likely to benefit from modafinil treatment (personalized medicine).

AIMS AND OUTLINE OF THE THESIS

Distorted impulse control plays an important role in the aetiology and continuation of substance use disorders. Although in recent years knowledge on the concept and the neurobiological mechanisms of impulsivity has accumulated, there is still a pressing need for studies that further unravel the neurobiology of the various aspects of impulsivity. In addition, as can be inferred from the previous sections, promising new pharmacological treatment strategies such as NAC and modafinil have been proposed, however, relevant information on their neurobiological mechanisms of action is lacking. Therefore, the main objectives of this thesis are to further enhance our understanding of the neural mechanisms underlying impulsivity and to clarify the effects of NAC and modafinil on neural correlates of impulsivity in addiction. Because substance dependence and distorted impulse control are the result of an imbalance of interacting neural systems, the focus of most of the studies presented in this thesis is on neurobiological systems, such as the interaction between molecular and regional levels of brain functioning and connectivity between individual or large-scale networks of brain regions. The thesis is subdivided into five parts. Part I is this general introduction and outline of the thesis (Chapter 1). In Part II (Chapters 2 and 3), we focus on the concept and the neurobiology of impulsivity in healthy individuals. In Part III (Chapters 4 and 5), neurobiological and clinical effects of N-acetylcysteine in cocaine and nicotine dependence are investigated, respectively. In Part IV (Chapters 6, 7, 8 and 9), studies on the neural correlates of cognitive enhancing effects of modafinil in alcohol dependence are presented. In the final part, Part V (Chapter 10), the main findings and their clinical relevance are discussed.

PART II

In CHAPTER 2, a translational study is presented that focuses on the multidimensional construct of impulsivity. Animal models of impulsivity are important for clarifying the underlying neurobiology of impulsivity. However, whether different aspects can be dissected in a similar way in rodents and humans remains to be elucidated. This chapter presents translational data on the multidimensional construct of impulsivity in both a healthy rodent and a human population.
In **CHAPTER 3**, the neurobiology of impulsive decision making is further evaluated in healthy individuals. This study investigates whether individual variability in impulsive decision making can be predicted by intrinsic properties of brain functioning (under task-free conditions). In this chapter, the relationship between impulsive decision making and (the interaction between) resting state brain processes on several levels is discussed; on a molecular level in the form of glutamate concentrations and on a regional level of resting state activity in the form of spontaneous fluctuations in blood oxygen level-dependent (BOLD) activity (resting state functional connectivity).

**PART III**
**CHAPTER 4** focuses on the role of glutamate in cocaine dependent patients and investigates the effects of NAC on glutamate concentrations in the dorsal anterior cingulate cortex (dACC) in cocaine dependent patients and healthy controls in an open label design. Proton Magnetic Resonance Spectroscopy (1H MRS) is utilized in order to obtain a measure of glutamate concentration in the dACC. In addition, the association between dACC glutamate concentrations and baseline self-reported impulsivity is examined in this chapter.

In **CHAPTER 5**, in a pilot study, we further explore whether a short-term treatment with NAC modulates self-reported craving, withdrawal and the rewarding effects of smoking in heavy smokers.

**PART IV**
This section begins with a review in **CHAPTER 6**, which summarizes the findings of previous studies investigating the effects of modafinil on cognitive functioning in several psychiatric disorders such as addiction, ADHD, schizophrenia and affective disorders.

Next, **CHAPTER 7** aims to investigate the effects of a single dose of modafinil on neural correlates of one specific aspect of impulsivity, i.e. response inhibition, in alcohol dependent patients and healthy controls. A stop signal task is included to measure response inhibition and functional MRI images are obtained to investigate regional brain activation during successful response inhibition. In addition to examining the effects of modafinil on individual brain regions, the interaction between brain regions are studied by applying connectivity and mediation analyses.

Because impulsivity consists of several independent aspects (the reader is referred to Chapter 2), for the generalizability of the findings presented in Chapter 7 it is important to elucidate the effects of modafinil on neural substrates of other aspects of impulsivity, such as impulsive decision making. Therefore, **CHAPTER 8** presents a study that explores the effects of modafinil on brain activation during impulsive decision making in alcohol dependent patients and healthy controls using a delay discounting task. Again, communication between different brain regions is investigated using a connectivity analysis.
The final modafinil study presented in CHAPTER 9 focuses on modafinil effects on intrinsic functioning of the brain in the form of large-scale resting state networks. More specifically, the effects of modafinil on within- and between-network functional connectivity are discussed by using a combination of independent component and functional network connectivity analyses. Because the interaction between intrinsic task positive (executive) and task negative (default mode) networks have previously been shown to predict individual variability in cognitive performance, the relationship between modafinil-induced changes in network connectivity and changes in cognitive control measured by a Stroop task is explored.

PART V
Finally, CHAPTER 10 (English) and CHAPTER 11 (Dutch) summarizes and discusses the main findings of the studies included in this thesis. Limitations and recommendations for future research are also included in this chapter.