Boosting impulse control in addiction: Pharmacological neuroimaging studies
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PART V

CHAPTER 10

SUMMARY & GENERAL DISCUSSION
OBJECTIVES OF THE THESIS

The first objective of this study was to investigate the construct of impulsivity. We investigated whether different aspects of impulsivity and their translational value could be identified in a within-subjects cross-species translational design. In addition, the neurobiological substrates of impulsivity, specifically the role of glutamate and its interaction with resting-state functional connectivity in impulsive decision making, was studied. The second aim of this thesis was to elucidate the neurobiological mechanisms by which potential pharmacological treatments, i.e. N-acetylcysteine (NAC) and modafinil, exert their effects on impulsive behavior in substance dependent individuals. This second aim was studied by obtaining functional Magnetic Resonance Images (fMRI) during the performance of a variety of neurocognitive tasks assessing different aspects of impulsivity, as well as by focusing on more intrinsic properties of brain functioning using resting-state fMRI and Proton Magnetic Resonance Spectroscopy (¹H MRS). The studies were conducted in various populations, including healthy volunteers, cocaine dependent patients and alcohol dependent patients. In addition to the more fundamental neuroimaging studies, a pilot study was conducted investing the clinical effects of NAC in heavy smokers.

In this final chapter, we first summarize the main results of the studies presented (Chapter 2-9) and subsequently the findings of the studies are generally discussed according to the three main topics that were addressed in this thesis: impulsivity, N-acetylcysteine and Modafinil. Furthermore, some methodological limitations are considered. Finally, findings are integrated, and (clinical) implications of the results presented in this thesis and future directions for research are provided.

SUMMARY

The first part of the thesis (Chapter 1) provides a general framework for the work presented in this thesis. The second part (Chapters 2 and 3) consisted of studies aimed at further unravelling the construct and neurobiology of impulsivity in healthy volunteers. Whether different measures of impulsivity represent largely unrelated aspects or a unitary construct in both rodents and humans was addressed in Chapter 2. Using a within-subjects cross-species translational design, it was found that impulsive action, reflected by a failure to inhibit a prepotent response, and impulsive choice, reflected by an increased preference for immediate rewards over more beneficial delayed rewards, did not significantly correlate in both humans and rodents. In humans, a self-report measure of impulsivity represented an additional non-related aspect of impulsivity. In rodents, the within-subjects pharmacological effects of atomoxetine and amphetamine did not correlate between tasks, indicating the presence of distinct neural correlates.
underlying impulsive choice and impulsive action. These findings support the notion of
a non-unitary nature of impulsivity and are important to acknowledge when considering
the role of impulsivity in psychopathology characterised by maladaptive impulsivity and in
the development of treatments targeted at improving impulse control.

In Chapter 3, evidence from different neuroimaging techniques measuring intrinsic
properties of dorsal anterior cingulate cortex (dACC) functioning was combined to predict
individual differences in impulsive decision making assessed by a delay discounting task.
Proton MRS was used to measure glutamate concentrations in the dACC and resting-state
functional activity and connectivity of the dACC was assessed as a proxy measure of
spontaneous neuronal activation and communication. Individual differences in delay
discounting were associated with both dACC glutamate concentrations and resting state
functional connectivity of the dACC with a midbrain region including the ventral tegmental
area and substantia nigra. Moreover, a mediation model demonstrated that glutamate
concentrations in the dACC influenced impulsive decision making (at least partly) via
functional connectivity of the dACC with the midbrain. This is the first study showing an
important role for glutamate neurotransmission in human delay discounting and revealing
a possible neural pathway by which dACC glutamate concentrations affect impulsive
decision making. Given the critical role of impulsive decision making in addiction, our
results indicate that modulation of dACC glutamate concentrations could be an important
target for the treatment of substance dependent individuals.

In the third part of the thesis (Chapters 4 and 5), neurobiological and clinical effects
of NAC were investigated. Preclinical evidence indicates an important role for NAC in
restoring a disturbed glutamate homeostasis in rodents treated with cocaine (Baker et
al. 2003b; Madayag et al. 2007) or heroin (Zhou and Kalivas 2008). Therefore, glutamate
abnormalities and NAC effects on glutamate levels in the dACC, obtained using 1H MRS,
were studied in Chapter 4. We found increased basal glutamate concentrations in the
dACC in cocaine dependent patients compared to healthy controls. NAC normalized
glutamate concentrations in cocaine dependent patients, whereas it had no effect on
glutamate concentrations in healthy controls. Moreover, consistent with the observed
relationship between impulsivity and dACC glutamate concentrations in Chapter 3, higher
self-reported (cognitive) impulsivity was found to be predictive of basal and NAC-induced
changes in glutamate levels. The present study is the first to report findings of glutamate
modulating effects of NAC in the human brain and provides a neurobiochemical rationale
for implementing NAC as a treatment for cocaine dependence.

In Chapter 5, findings of a pilot study on the clinical effects of a 4-day treatment with NAC
in heavy smokers were reported. Beneficial effects of NAC on the rewarding sensation of
smoking and withdrawal symptoms were found. Together with one previous pilot study
investigating clinical effects of NAC in heavy smokers conducted by Knackstedt et al.
(2009), these results provide preliminary evidence for NAC as a promising pharmacological intervention for smoking cessation. The findings in Chapter 4 and Chapter 5 also suggest that glutamate neurotransmission is both associated with the cognitive control system (impulsivity; Chapter 4) and the motivational system (reward; Chapter 5) implicated in addiction.

The fourth part of the thesis (Chapters 6-9) consisted of studies that focused on the neural effects of modafinil on impulse control. Although modafinil has been proposed to enhance cognitive functioning and could therefore constitute a promising pharmacological agent for the treatment of cognitive dysfunctions in psychiatric disorders, the results of the review presented in Chapter 6 warrant further investigation before implementing modafinil as a treatment strategy. The number of placebo-controlled trials is limited and the results are rather inconsistent. However, despite methodological issues such as small sample sizes, short administration periods and the lack of placebo control conditions, there is some preliminary evidence for beneficial effects of modafinil in children with ADHD, patients with a depressive disorder and cocaine dependent patients.

The studies presented in Chapter 7, Chapter 8 and Chapter 9, aimed to investigate the neural substrates of modafinil-induced modulation of impulsivity in alcohol dependent (AD) patients. With regard to impulsive action, assessed with a stop signal task, modafinil improved response inhibition only in AD subjects who showed poor initial performance on the task, whereas a deterioration in response inhibition was observed in better performing AD subjects at baseline (Chapter 7). These differential effects of modafinil on behavior was also reflected by modafinil’s effects on brain activation during successful response inhibition: activation of the supplementary motor area (SMA) and the ventrolateral nucleus of the thalamus, key regions involved in successful response inhibition, was increased in AD subjects who improved their performance under modafinil, whereas response inhibition in AD subjects who worsened after modafinil administration was associated with a modafinil-induced decrease in activation in these same brain areas. This was supported by a mediation analysis revealing that activity changes within the SMA and thalamus were largely responsible for improvements and deteriorations observed in poor and better performing AD patients, respectively. In contrast, this differential effect of modafinil in low and high impulsive AD subjects was not observed on a measure of impulsive choice (delay discounting task; Chapter 8).

In Chapter 8, we found beneficial effects of modafinil on impulsive decision making in all AD patients, regardless of baseline performance. Importantly, this was accompanied by enhanced recruitment of frontoparietal brain regions, known to be involved in cognitive control, and decreased activation of the ventromedial prefrontal cortex, an area involved in the coding the subjective value of rewards and self-referential processes. Clearly, impulsivity is mediated by the interaction between the motivational system and the
cognitive control system and modafinil improves impulsive decision making by targeting both systems. These results not only stress the important differences between independent aspects of impulsivity (Chapter 2), they also fit the inverted u-shape relationship between catecholamine neurotransmission and cognitive performance (Cools and D’Esposito 2011) which proposes that distinct optimum levels of catecholamine neurotransmitters exist for different aspects of cognitive control. The modafinil effects on neural substrates of impulsivity presented in Chapter 7 and 8 were not limited to isolated brain regions. Instead, in both studies evidence was found that modafinil impacts the functional interaction between brain regions. Modafinil-induced improvement in response inhibition was accompanied by an increased functional coupling between the ventrolateral thalamus and the primary motor cortex, and enhanced connectivity between the superior frontal gyrus (SFG) and the ventral striatum was associated with reduced impulsive decision making after modafinil administration. These findings indicate that modafinil has a more general effect by affecting functional networks implicated in both the motivational system and the cognitive control system (and their interaction).

In Chapter 9, we took this a step further by examining modafinil effects on the intrinsic organization of brain functioning in AD patients. To do this, the effects of modafinil on interacting large-scale resting state networks including the default mode network (DMN), salience network (SN) and central executive network (CEN), and their association with cognitive control (measured using a Stroop task) were investigated. The results demonstrated that modafinil strengthens the negative functional coupling of the DMN with both the SN and CEN in AD. In addition, this increased anti-correlation between the DMN and SN and CEN was associated with modafinil-induced improvement in cognitive control in AD, indicating that modafinil modulates the functional organization and communication of the brain, which translates into enhanced cognitive control in AD.

Taken together, the results of the presented studies can be summarized in the following main findings: (a) Impulsivity is a complex multidimensional construct consisting of several independent aspects with different underlying neural mechanisms, which is important to acknowledge when studying impulsivity in psychiatric disorders and in the development of treatments targeted at reducing impulsive behavior. (b) In addition to the neurotransmitters traditionally implicated in addiction such as serotonin and dopamine, glutamate neurotransmission seems to play an important role in impulsivity and is disturbed in cocaine dependent patients. Therefore, glutamate is an important target for the treatment of addiction characterized by distorted impulse control. (c) NAC seems to be an effective and elegant agent to restore glutamate abnormalities in addiction, and these beneficial effects of NAC on glutamate abnormalities could underlie previous and current observations of beneficial clinical effects of NAC in substance dependent individuals. (d) Modafinil can enhance impulse control in alcohol dependent patients, however, the
effects of modafinil on neural substrates of various measures of impulsivity are rather complex which should be acknowledged when implementing modafinil as a treatment.

GENERAL DISCUSSION

IMPULSIVITY

Impulsivity can be broadly defined as “behavior that is performed with little or inadequate forethought” (Evenden 1999). Impulsivity can be functional in some situations, enabling us to seize opportunities and gain valuable new experiences. However, high levels of trait impulsivity are associated with negative consequences. For instance, impulsivity is associated with criminality and violence, physical harm to the self (such as suicide) and socially inappropriate behavior. Because maladaptive levels of impulsivity are observed in various psychiatric disorders it is important to enhance our understanding of the construct of impulsivity and its underlying neurobiology. From the limited number of human studies on the multidimensional nature of impulsivity employing a within-subjects design, there is consistent evidence that impulsivity is not a unitary construct, but rather is dissociable into different independent aspects such as impulsive action (motor impulsivity), impulsive choice (cognitive impulsivity) and self-reported impulsivity. In contrast, within the preclinical field, most evidence stems from between-group comparisons, which has the major limitation that potential findings of separable aspects can also be attributed to individual differences that might exist between (groups of) subjects. In addition, the very limited number of rodent studies that do use a within-subjects design show inconsistent results. Animal models are essential for unravelling the neurobiology of impulsivity; however, in order for these models to have translational value to human impulsivity, a consensus on the nature of the construct of impulsivity is required.

By assessing multiple aspects of impulsivity within the same subjects using parallel behavioral tasks in rodents and humans, our study revealed very similar results across species. Impulsive choice and impulsive action were found to constitute independent aspects of impulsivity. In addition to the findings of our translational study in healthy individuals, we also assessed different aspects of impulsivity in an alcohol dependent group (reported in Chapter 7-9). Performance on different behavioral measures of impulse control did not correlate within alcohol dependent subjects (stop signal task – delay discounting task: $r=-0.01$, $p=0.97$; stop signal task – Stroop task: $r=0.20$, $p=0.43$; delay discounting task – Stroop task: $r=0.13$, $p=0.62$). These results not only support the use of the currently available animal models to investigate the underlying neurobiological mechanisms of impulsivity, it also calls for caution when considering the contribution of impulsivity in psychiatric disorders such as addiction. For example, certain psychiatric disorders may be characterized by deficits in only one aspect of impulsivity. Severity
of antisocial personality disorder has been found to be associated with impairments in impulsive action, but not impulsive choice (Swann et al. 2009). Different aspects of impulsivity can also play distinct roles in clinical manifestations or stages of a disorder. For instance, in children with ADHD, impulsive choice was associated with a broad range of ADHD characteristics, but impulsive action showed only relationships with limited observations of impulsive behavior (Solanto et al. 2001). This is further emphasized by results from preclinical studies of our collaborators on a translational project investigating the role of impulsivity in addiction, showing that impulsive action and impulsive choice are distinctly involved in different stages of addiction. Whereas impulsive action seems to be more predictive of initial sensitivity to drugs and drug intake, impulsive choice may be more specifically involved in the persistence of and relapse into drug abuse (Broos et al. 2012; Diergaarde et al. 2008).

Furthermore, the observed behavioral distinction between impulsive choice and impulsive action seems to reflect dissociable underlying neural substrates. Neuroimaging studies using tasks tapping various aspects of impulsivity show both overlap and dissociation in brain regions activated during these tasks. Whereas the inferior frontal gyrus, motor regions [(pre-)supplementary motor cortex and primary motor cortex] and thalamic regions [subthalamic nucleus and thalamus] appear to be primarily involved in impulsive action (Aron 2011; Chambers et al. 2009), limbic regions such as the basolateral amygdala and hippocampus are dissociably engaged in memory processes and the evaluation of decision outcomes during impulsive choice (Cardinal 2006; Peters and Buchel 2011). In contrast, the (dorsal) anterior cingulate cortex, dorsolateral prefrontal cortex and striatum have been implicated in both forms of impulsivity. Moreover, certain parts of the brain’s default mode network, including the ventromedial prefrontal cortex, posterior cingulate cortex, precuneus and inferior parietal lobe, are involved in both impulsive action and impulsive choice. This anatomically and functionally interconnected brain system is thought to participate in internal modes of cognition, such as autobiographical memory retrieval, envisioning the future, and conceiving the perspectives of others (Buckner et al. 2008). During the performance of a stop signal or go no-go task, activation in these default network regions needs to be suppressed in order to successfully inhibit an inappropriate response (Zhang and Li 2012). Moreover, in delay discounting tasks greater activation within these areas is associated with increased impulsive decision making (Kable and Glimcher 2010; Sripada et al. 2011).

On a molecular level, there is both overlap and dissociation in the neurotransmitter systems modulating impulsive action and impulsive choice (for reviews see Dalley et al. 2008; Pattij and Vanderschuren 2008). For example, increasing dopamine transmission impairs impulsive action, but reduces delay discounting behavior, whereas enhancement of noradrenaline signalling seems to decrease both impulsive action and impulsive choice.
It should be noted, however, that our findings showed dissociative findings in response to the noradrenaline agonist atomoxetine in Chapter 2. In our current work, we also found differential effects of pharmacological compounds known to modulate dopamine and noradrenaline neurotransmission. Amphetamine decreased impulsive choice, whereas it increased impulsive action in the same rodents (Chapter 2). In contrast, atomoxetine showed the opposite pattern (Chapter 2). In addition, a single dose of modafinil significantly decreased impulsive decision making in AD patients (Chapter 8), whereas the effects of modafinil were less straightforward with regard to impulsive action, i.e. modafinil improved response inhibition in high impulsive AD patients, but performance deteriorated in low impulsive patients (Chapter 7). These findings further emphasize that impulsivity should be viewed as an umbrella term that covers subclasses of impulsive behavior with partly distinct underlying neural substrates.

More recently, accumulating evidence for a role of glutamate in impulsivity has emerged. NMDA receptor antagonists have consistently shown to increase impulsive action in rodents (Higgins et al. 2003; Mirjana et al. 2004). In addition, metabotrophic glutamate receptors (mGluRs; in particular mGluR1) have been observed to modulate impulsive behavior in animal models of impulsivity (Sukhotina et al. 2008). In humans, the number of studies investigating the role of glutamate in impulsivity is small, partly because of a limited availability of PET and SPECT tracers to image the glutamate system. Our studies, using $^1$H MRS to obtain measures of glutamate levels, are among the first (see also Hoerst et al. 2010 and a very recently published study by Falkenberg et al. 2012) to show a direct relationship between glutamate concentrations and impulsivity in healthy volunteers (Chapter 3) and in cocaine dependent patients (Chapter 4). Higher dACC glutamate levels were associated with higher levels of impulsivity, with cocaine dependent patients showing increased levels of both impulsivity and glutamate levels compared to healthy controls. In addition, our results indicated a functional pathway by which dACC glutamate concentrations influence individual differences in impulsive decision making; glutamate concentrations translate into behavioral manifestations of delay discounting through their effects on the functional connectivity between the dACC and a midbrain region containing the VTA and substantia nigra.

Because a growing interest in the role of the glutamate system in modulating impulsive behavior has only recently emerged, many questions remain to be answered. For instance, the findings in humans are at present limited to glutamate concentrations in the dACC. The dACC represents a core region involved in cognitive control processes (Kouneiher et al. 2009), has strong connections to frontoparietal and frontostriatal cognitive control networks (Margulies et al. 2007) and is rich in glutamatergic innervation (Palomero-Gallagher et al. 2009), rendering it a prime candidate for investigating the association between glutamate concentrations and impulse control. However, future
studies investigating the association between impulsivity and glutamate concentrations in other brain regions that are implicated in impulsivity are warranted. In addition, it remains to be elucidated whether glutamate neurotransmission is differentially involved in distinct aspects of impulsivity. In our current work, we found an association of dACC glutamate levels with both self-reported impulsivity and delay discounting, but not with performance on a classical Stroop task (unpublished data). Furthermore, mGluR1 receptor blockade has been shown to reduce impulsive choice while facilitating impulsive action (Sukhotina et al. 2008). Given the importance of the non-unitary nature of impulsivity in clinical manifestations or different stages of psychiatric disorders, research is required that further addresses the specific involvement of glutamate signalling in different aspects of impulsivity in order to develop more tailored glutamatergic pharmacotherapies for reducing specific aspects of impulsivity.

N-ACETYLCYSTEINE

Historically, most pharmacological strategies to treat addiction were aimed at targeting monoaminergic (dopamine, noradrenaline, serotonin) or opioid neurotransmitter systems. However, to date, these medications have only shown moderate success (van den Brink 2012). Because of the accumulating evidence that glutamate neurotransmission plays a critical role in the persistence of and relapse into drug abuse (Kalivas 2009), in addition to its emerging role in maladaptive impulsivity (Chapter 3 and Hoerst et al. 2010), which is a key characteristic of addiction (Verdejo-Garcia et al. 2008), the glutamatergic system is a promising target for treating substance use disorders. In this respect, medications such as acamprosate and topiramate, which are currently used for the treatment of alcohol dependence, target glutamate neurotransmission by restoring the balance between excitatory and inhibitory neurotransmission and antagonizing AMPA receptors, respectively. These medications have shown moderate success in the treatment of alcohol dependence (van den Brink 2012). Because glutamate is the major excitatory neurotransmitter in the brain, mediating as much as 70% of synaptic transmission within the central nervous system, this calls for a pharmacological strategy that influences aberrant glutamate signalling, but at the same time leaves normal glutamatergic transmission unimpaired. NAC has been suggested as a promising new candidate agent for this purpose, because of its regulatory function on extracellular glutamate homeostasis. NAC is an effective and easy way to deliver cystine to the brain, where it binds to cystine/glutamate antiporters exchanging extracellular cystine for intracellular glutamate. These antiporters are of key importance for maintaining optimal levels of extracellular glutamate. Extracellular glutamate stimulates mGluR2/3 receptors, which in turn regulate synaptic glutamate release. This suggests that the effects of providing cystine to the brain by NAC administration are regulatory, leading to restoration of the natural balance rather than simply acting as a direct glutamatergic agonist. Indeed, it has been observed that NAC only affects glutamate signaling when glutamate homeostasis is
disturbed. For instance, NAC has been shown to normalize altered extracellular glutamate levels in rodents chronically treated with cocaine (Baker et al. 2003b; Madayag et al. 2007) or heroin (Zhou and Kalivas 2008), whereas it had no effect in healthy control animals. Restoring glutamate homeostasis by NAC subsequently prevented cue-induced relapse into drug seeking behavior in these rodents (Baker et al. 2003b; Madayag et al. 2007; Zhou and Kalivas 2008). Consistent with these preclinical findings, our study showed that NAC was able to normalize glutamate concentrations in the dACC of cocaine dependent humans, which were found to be increased compared to healthy controls (Chapter 4). The lack of effect of NAC on dACC glutamate levels in our healthy control group corroborates the notion that NAC has a regulatory effect on glutamate transmission.

NAC-induced changes in glutamate concentrations as found in our cocaine dependent group could underlie the beneficial effects of NAC observed in clinical studies in substance dependent individuals (Grant et al. 2007; Grant et al. 2010; Gray et al. 2010; Knackstedt et al. 2009; LaRowe et al. 2007). Unfortunately, we did not include clinical measures such as ratings of craving or withdrawal symptoms in our study investigating the effects of NAC on glutamate concentrations in cocaine dependent patients. However, in a pilot study in heavy smokers attempting to quit, we did observe some beneficial effects of NAC on withdrawal symptoms and the rewarding effects of smoking a cigarette (Chapter 5). In line with previous findings indicating that stimulation of mGluR2/3 receptors (implicated as one of the mechanisms by which NAC exerts its effects on glutamate transmission) diminishes the rewarding effects of nicotine (Liechti et al. 2007), one could speculate that the currently observed reduction in nicotine reward is a result of NAC’s effects on glutamate levels. However, more research is needed that incorporates both clinical measures and measures of glutamate concentrations (and preferably also measures of regional brain functioning such as fMRI) to elucidate the neurobiological pathway by which NAC affects clinical outcome in patients with different substance use disorders.

It is noteworthy that although we did not find an association between duration of abstinence and glutamate concentrations in the brain, results from other studies indicate that glutamate levels change as a function of abstinence duration (Ernst and Chang 2008; Mon et al. 2012). Especially during early withdrawal, alterations in glutamate concentrations are found in substance dependent individuals, whereas they tend to normalize over time. This might implicate that NAC is most effective during early abstinence when glutamate abnormalities are more pronounced, because a persistent rise in the glutamate level contributes to craving and relapse in alcoholism, as has been commonly hypothesized. In contrast, we found a trend towards a negative correlation between cocaine use in the last six months and dACC glutamate concentrations (Chapter 4). Clearly, the relationship between glutamate levels and substance dependence is rather complex, depending on multiple facets of drug use characteristics, which needs further investigation.
Given our findings of an important role of dACC glutamate levels in impulsivity (Chapter 3) and higher levels of both glutamate and impulsivity in cocaine dependent patients compared to healthy controls (Chapter 4), it can be expected that NAC-induced normalization of glutamate levels will also affect impulsive behavior. Moreover, one may speculate that impulsivity mediates the relation between NAC-induced glutamate changes and beneficial clinical effects such as the prevention of relapse. The mGluR2/3 receptor antagonist LY341495 has been shown to reduce high levels of impulsivity, indicating that impulsive behavior is in part regulated by mGluR2/3 activation (Wischhof et al. 2011). Therefore, it can be expected that by influencing mGluR2/3, NAC may also affect impulsivity. Furthermore, in a study of Knackstedt et al. (2009), a downregulation of cystine/glutamate antiporters has been observed in the VTA in rats that had self-administered nicotine. In turn, this downregulation of cystine/glutamate antiporters has been associated with a reduction in basal glutamate levels observed after chronic cocaine use (Baker et al. 2003a). As our results showed that dACC glutamate concentrations affect connectivity of the dACC with the midbrain including the VTA, which underlies individual differences in impulsive choice, normalizing glutamate concentrations in the dACC is likely to affect VTA functioning, which could in turn lead to changes in impulsive behavior. In addition, besides substance use disorders, NAC has shown beneficial effects in other disorders characterized by distorted impulsivity, such as pathological gambling (Grant et al. 2007), trichotillomania (Grant et al. 2009; Odlaug and Grant 2007), pathological nail biting (Berk et al. 2009) and pathological skin picking (Odlaug and Grant 2007). Clearly, since only indirect evidence exists for a relationship between NAC effects on impulsivity, future research is required to further delineate the potential beneficial effects of NAC on impulsive behavior.

MODAFINIL
The presented studies on the effects of modafinil on neural correlates of impulse control in alcohol dependence revealed rather general effects by affecting multiple brain systems. Modafinil did not affect some specific brain regions, but instead targeted activity and connectivity in areas specifically associated with the successful performance on each individual task employed. For instance, modafinil-induced improvements in performance on the stop signal task was associated with activity changes in the SMA and thalamus, and connectivity changes between the thalamus and M1 (Chapter 7). In contrast, modafinil seemed to primarily modulate connectivity between the SFG and the ventral striatum in the delay discounting task, which was associated with a reduction in impulsive decision making (Chapter 8). This suggests that modafinil has widespread effects as a cognitive enhancer, an observation that was supported by the findings of modafinil-induced changes in the interaction between large-scale brain systems (Chapter 9). Moreover, this also seems to match the effects of modafinil on a broad range of neurotransmitters in the brain. Although the exact working mechanism has not yet been elucidated, modafinil has
been observed to impact signalling of dopamine, noradrenaline, glutamate, serotonin and GABA (Minzenberg and Carter 2008).

Interestingly, modafinil demonstrated distinct effects on different aspects of impulsivity, both on a behavioral and on a neurobiological level. Whereas modafinil improved performance on the stop signal task through enhanced brain activation and connectivity only in AD patients with initial poor performance, modafinil administration reduced delay discounting in all AD patients. Moreover, modafinil actually diminished stop signal task performance (and brain activation and connectivity) in patients with adequate levels of baseline response inhibition. These findings of differential modafinil effects depending on baseline performance are in line with previous studies showing similar results with modafinil on response inhibition (Eagle et al. 2007; Zack and Poulos 2009; Joos et al. in press) and other domains of cognitive functioning (Finke et al. 2010; Hunter et al. 2006; Kalechstein et al. 2010; Spence et al. 2005). Moreover, these differential effects of modafinil are similar to findings of differential effects of amphetamine and atomoxetine on distinct forms of impulsivity (i.e. impulsive action and impulsive choice) observed in our translational study (Chapter 2) and other preclinical studies (Baarendse and Vanderschuren 2012; Sun et al. 2012), suggesting a role for dopamine and noradrenaline neurotransmission underlying these differential modafinil effects. The distinct effects of modafinil on different cognitive tasks fit the inverted U-shaped relationship between catecholamine neurotransmitter (including dopamine and noradrenaline) levels in the PFC and cognitive performance (Cools and D'Esposito 2011; Levy 2009). This inverted U-shaped curve implies that there is an optimum for catecholamine neurotransmitter levels to efficiently execute cognitive tasks, in which both excessive and deficient levels impair cognitive performance. Moreover, these optimum levels can be different for different cognitive tasks; i.e. some tasks benefit from increasing catecholamine signalling (green curve in Figure 1), while at the same time can have detrimental effects in other tasks (red curve in Figure 1). This explains the often observed differential effects of drugs influencing catecholamine transmission across different individuals that perform the same task or within the same individual across different tasks (current work and Cools et al. 2001; Cools et al. 2003; Mehta et al. 2004).

Previous studies show that baseline levels of cognitive performance are dependent on basal levels of prefrontal dopamine (Ko et al. 2012; Okubo et al. 1997; Phillips et al. 2004), which in turn may be attributed to genetic variation across individuals. For instance, the Val^{158}Met polymorphism in the catechol-O-methyltransferase (COMT) gene, an enzyme that breaks down dopamine that is released in the synaptic cleft primarily in the PFC, has been associated with both impulsivity (Boettiger et al. 2007; Congdon et al. 2009; Gianotti et al. 2012; Paloyelis et al. 2010; Shehzad et al. 2012) and the differential effects of dopamine-modulating drugs on cognitive performance (Bodenmann et al. 2009;
Hamidovic et al. 2010). Individuals carrying a Val-allele have relatively high COMT activity, and hence low dopamine levels, compared to Met-allele carriers. Individuals with the Val-allele have been observed to respond more impulsively in response inhibition and delay discounting tasks, accompanied by altered frontoparietal brain activation (Boettiger et al. 2007; Congdon et al. 2009; Hamidovic et al. 2012; Shehzad et al. 2012). To date, a few studies have examined the interaction between COMT genotype and modafinil effects. Modafinil improved vigor and maintained baseline performance with respect to executive functioning and attention in Val-allele carriers, but was hardly effective in Met-allele carriers (Bodenmann et al. 2009). Moreover, the optimal daily dose of modafinil was approximately 100 mg higher in narcoleptics carrying a Val-allele of the COMT gene (Dauvilliers et al. 2002). These lines of evidence suggest that modafinil may alter impulsivity differentially as a function of underlying genotype. Interestingly, the COMT gene has also been implicated to play a role in the development of addiction (Schellekens et al. 2012, but see also Tammimaki and Mannisto 2010). Therefore, future studies investigating the effects of modafinil treatment in substance dependent individuals could benefit from taking into account genetic variation in catecholamine genes and baseline levels of catecholamine neurotransmitters. Taken together, the current work indicates that modafinil affects different tasks by modulating distinct cortico-thalamo-striatal loops with distinct optimal catecholamine levels and provides a neurobiological account of within-subject variability in modafinil effects across different tasks related to impulsivity. In that respect, the current work provides additional information on modafinil’s mechanisms of action, which is of critical importance to the future introduction of modafinil in the treatment of several psychiatric disorders.

The main aim of the studies conducted with modafinil was to further elucidate its neurobiological effects on impulse control in alcohol dependent patients. We chose to include only a single dose, because previous studies have found effects with only a single dose of modafinil on cognition and related brain activation as measured using fMRI. However, this design did not allow thorough investigation of (long-term) modafinil effects on clinical outcome. We did show that a single dose of modafinil acutely reduced self-reported craving, but only when AD patients with positive urine tests for benzodiazepines and cannabis were excluded (Chapter 8). This interaction between recent drug use and modafinil-induced changes in self-reported craving could be of particular interest to the clinical field and therefore warrants further investigation in clinical trials.
The relationship between cognitive performance and dopamine levels follows an inverted U-shaped function, in which both too little and too much dopamine impairs performance. How likely it is that a drug will cause beneficial or detrimental effects depends partly on basal DA levels. A single curve is insufficient to predict performance: some tasks benefit from increasing DA (green), although performance on other tasks is disrupted by increasing DA (red). The black arrow represents the DA-enhancing effect of a hypothetical drug, leading to a detrimental effect on task A (red) but a beneficial effect on task B (green). Figure taken with permission from Cools and D’Esposito (2011).

METHODOLOGICAL CONSIDERATIONS

The findings of the studies presented in this thesis need to be viewed in light of some methodological limitations. Perhaps the main limitation of the current work refers to the relatively small sample sizes employed in the studies. Especially given the evidence for an important role of individual differences in the display of impulsivity and the response to acute pharmacological treatment, a small sample size creates major limitations. For example, in Chapter 3 we describe the neurobiological basis of delay discounting; however, with only 14 healthy volunteers the full range of individual differences in impulsive decision making cannot be captured. Moreover, as alcohol dependence is a heterogeneous disorder and individual differences are observed in response to modafinil administration, a larger sample size would have allowed the formation of subgroups of adequate sizes. With regard to fMRI analyses, the limited sample sizes yielded not enough power to detect significant changes in brain activation at a whole brain corrected statistical threshold. As a workaround for this issue, regions of interests (ROIs), based on findings in previous studies, were used in the current analyses. Although this is standard practice in
imaging research, different researchers are likely to select slightly different ROIs, limiting the generalizability of findings. Clearly, the current findings need to be replicated in future studies using larger sample sizes. Since it is difficult for individual research groups to collect large amounts of data among patient groups, effective data sharing across research groups might prove to be critical for this. In addition, the current studies on the effects of pharmacological agents on measures of brain functioning were all conducted in a randomized cross-over design. The advantages of a cross-over design include the fact that each subject serves as its own control, thereby reducing the variability and allowing for smaller sample sizes compared to parallel designs because of this statistical efficiency. A major disadvantage of such a design is the lack of an adequate baseline measure (for some subjects placebo was administered during the second session), limiting the possibility of investigating treatment response in subgroups based on baseline characteristics and rendering possible regression towards the mean effects when doing so (see the discussion in Chapter 7).

Another limitation is that, although patients with different types of addictive disorders were assessed, the specific effects of the pharmacological agents were not tested in multiple substance use disorders. NAC’s effects on glutamate concentrations were examined in cocaine dependent individuals, whereas its clinical effects were assessed in heavy smokers. Moreover, the effects of modafinil on neural correlates of impulse control were only investigated in alcohol dependent patients (but see our paper on modafinil effects on cue reactivity in cocaine dependent patients: Goudriaan et al. 2012). Although there is considerable overlap in the neurobiological mechanisms underlying various classes of substance use disorders, different types of drugs of abuse may interact with different neurotransmitters, or with the same neurotransmitters albeit by targeting different receptors or transporters (Badiani et al. 2011; Gass and Olive 2008; Sulzer 2011). To date, there are no other studies that have investigated the effects of NAC on glutamate concentrations in addiction and only one other study has examined the modafinil effects on neural substrates of cognitive functioning in addiction (i.e. methamphetamine dependence; Ghahremani et al. 2011). Therefore, the pharmacological effects of NAC and modafinil remain to be elucidated in types of addiction other than those under investigation in the current studies. In addition, merely comparing one patient group to a healthy control group limits inferences on the specificity of the findings. Observed differences between patients and healthy controls could stem from psychopathology not specifically related to the type of addiction under investigation. For example, the substance dependent groups reported higher levels of depressive symptoms and included a higher number of cigarette smokers compared to the control groups. However, as affective disorders and substance use disorders are highly comorbid (Boschloo et al. 2011) and polydrug use is the rule rather than the exception in addiction (Ouwehand et al. 2011), these characteristics may also be regarded as an inseparable part of the disorder.
Remarkably, despite a considerable amount of evidence of impaired impulse control related to alcohol dependence, we did not observe pronounced differences between patients and healthy controls in terms of baseline (placebo) neurocognitive functioning and brain activation and connectivity. Nonetheless, modafinil only affected cognitive performance (with the exception of performance on the Stroop task), and brain activation and connectivity in AD patients, but not in healthy controls. The absence of baseline differences in cognitive performance might in part be explained by some specific characteristics of the AD patients included in the current studies. Diminished cognitive functioning has been more consistently reported in stimulant addictions such as cocaine dependence than in alcohol dependence (Kirby and Petry 2004; van der Plas et al. 2009). With regard to alcohol dependence, high levels of impulsivity are more frequently observed in AD patients with polysubstance use and comorbid psychopathology (Dom et al. 2006a, 2006b) and are associated with an early age of onset of the disorder (Dom et al. 2006c, 2006d; Joos et al. in press). In the current study, the presence of comorbid psychiatric disorders was an exclusion criterion and, although we did not have a valid measure of age of onset, there was a considerable variation in age in the AD group. This could have contributed to the findings of no overall differences in impulse control between AD patients and healthy controls at baseline, whereas within the AD group there may have been more individuals with greater room for improvement.

In addition to limitations specifically related to the currently performed studies, there are some methodological challenges to the application of neuroimaging techniques in general, and fMRI in particular. One obvious challenge relates to the question of what we are actually measuring with fMRI, i.e. how the BOLD signal, as measured using fMRI, is coupled to the underlying neurophysiology. Functional MRI provides a powerful tool to spatially identify the neural underpinnings of cognitive functions; however, it is a measure of haemodynamic changes and therefore does not allow direct inferences on ‘neural activity’. For example, BOLD imaging cannot distinguish between inhibitory and excitatory neural processes. Moreover, in contrast to other neuroimaging techniques such as electroencephalography (EEG) and magnetoencephalography (MEG), functional MRI has a low temporal resolution, and therefore cannot record very rapid neuronal firing. Combining imaging approaches such as fMRI, EEG/MEG and MRS could enhance our insight into the relationships between cognitive processes, neural activity and the BOLD-fMRI signal. For instance, by performing an experiment while simultaneously recording fMRI and EEG or MEG, one could examine which electrophysiological signals (which are more closely related to neural activity) seem to match the BOLD response. Moreover, information on inhibitory and excitatory neurotransmission (i.e. GABA and glutamate neurotransmission) could shed more light on the underlying nature of the BOLD signal. In this respect, MRS could provide a valuable tool. Indeed, evidence based on correlational analyses between MRS and fMRI measures indicate that the BOLD
response magnitude is inversely correlated with GABA concentrations (Donahue et al. 2010; Muthukumaraswamy et al. 2009; Muthukumaraswamy et al. 2012; Northoff et al. 2007). Interestingly, glutamate concentrations as measured using 1H MRS appear not to be associated with low frequency spontaneous fluctuations in the BOLD response in the measured region itself, but do predict BOLD responses in connected brain regions (Chapter 3 and Duncan et al. 2011; Falkenberg et al. 2012). However, these correlations between neurotransmitter concentrations obtained by MRS and the fMRI BOLD signal are in turn also difficult to interpret, because of the drawbacks associated with MRS imaging. For instance, 1H MRS is not able to distinguish between extracellular and intracellular, and between neurotransmitter and metabolic pools of neurotransmitters such as glutamate and GABA. Clearly, although the currently used neuroimaging techniques can greatly contribute to an increased knowledge on the neural underpinnings of cognitive processes including impulsivity and of abnormal brain functioning as observed in addiction, we should realize that the interpretation of such findings must be done with great caution. Although the parameters obtained by these techniques relate to underlying neural mechanisms, they may still be a considerable number of biological steps removed from directly measuring neural function.

**IMPLICATIONS AND FUTURE DIRECTIONS**

**IMPULSIVITY**

Despite a substantial amount of evidence of high levels of impulsivity in patients with substance use disorders, the clinical implications of these observations have received limited attention. The lack of success of currently available psychosocial treatments may in part be the result of cognitive impairments associated with chronic drug abuse, as diminished impulse control predicts treatment outcome and relapse (Krishnan-Sarin et al. 2007; MacKillop and Kahler 2009; Streeter et al. 2008). Several studies have suggested that these cognitive deficits are not reversible but persist during abstinence (Clark et al. 2006). Therefore, improving impulse control may be an important (adjunct) strategy to enhance the effectiveness of psychosocial treatments. However, impulsivity is a broad construct consisting of various, independent aspects which are thought to be involved in different stages or clinical manifestations of psychiatric disorders. The efficiency of treatment strategies to reduce maladaptive levels of impulsivity could be improved if they would target more specific aspects of impulsivity. For example, given the preclinical observations that impulsive action seems to be more predictive of initial sensitivity to drugs and that impulsive choice may be more specifically involved in the persistence of and relapse into drug abuse (Diergaarde et al. 2008), targeting impulsive action might be more important for prevention strategies, while the development of relapse prevention strategies could benefit from focusing on impulsive choice. However, it is worth noting
that pharmacologically induced changes in trait impulsive choice failed to show favourable outcomes on relapse measures in cocaine treated animals (Broos et al. 2012). This lack of an association between changes in delay discounting and treatment outcome has also recently been observed in opioid dependent individuals (Landes et al. 2012), which questions the efficacy of modulating impulsive decision making on clinical outcome. In the current work we also found no association between modafinil-induced changes in delay discounting and the observed reductions in craving (Chapter 8), although we only used a single dose administration precluding inferences on long-term clinical outcome. As these results are preliminary, further research is required to elucidate whether improving impulsive decision making, and perhaps executive functioning in general, can lead to improved clinical outcomes (but see also a discussion on this below).

Translational study designs, combining clinical and preclinical data, are particularly suited to further delineate the role of impulsivity in mediating drug abuse and for developing effective treatments. Laboratory animals have the advantage of being in an environment that is easier to control and to manipulate. In addition, a substantial body of evidence for impulsivity as a vulnerability factor to substance abuse, and not merely as a consequence of substance abuse stems from animal research (for a review see Winstanley et al. 2010). Whereas in humans it takes years to investigate cause-and-effect relationships between impulsivity and addiction, preclinical models have the advantage that animals can be selected based on their initial (baseline) trait impulsivity and subsequently be compared during various stages of addiction. Nonetheless, preclinical models can never fully model complex psychiatric disorders such as addiction. Therefore, additional, carefully controlled longitudinal clinical studies are required to disentangle the associations between impaired impulse control and the development of an addiction.

N-ACETYLCYSTEINE

In the current work, two potential pharmacotherapeutics that are known to influence top-down and bottom-up processes implicated in addiction were investigated. Together with previous clinical research, the current studies indicate that NAC constitutes a promising pharmacological agent for the treatment of stimulant addictions. Because of its elegant regulatory working mechanism by affecting glutamate transmission only when glutamate homeostasis is disturbed, the very limited amount of side effects reported and the fact that it is sold over the counter, NAC seems a safe, inexpensive and readily available treatment option. However, to date, most clinical studies with NAC have been conducted using a pilot design, emphasizing the need for large double-blind placebo controlled trials in order for NAC to be approved as a standard treatment. In addition, most studies have investigated clinical effects of NAC in stimulant addictions and no data is currently available on the effects of NAC in for example alcohol dependence. Since glutamate abnormalities have also been observed in alcohol dependent patients (Thoma et al. 2011; Umhau et al.
2010), clinical trials assessing the effects of NAC in substance use disorders other than stimulant dependence are required. Furthermore, the precise dose of NAC remains to be established. Whereas the tolerability profile of NAC appears to be favorable, it needs to be stressed that there is no extensive evidence on the (adverse) effects of longer-term use. Finally, because NAC seems to affect glutamate only when glutamate signalling is disturbed, and was found to be most effective in patients with high initial dACC glutamate levels, assessing baseline glutamate concentrations by means of a pre-treatment 1H MRS scan could aid in providing a patient with optimal care (personalized medicine).

Notably, in addition to its regulating effects on the glutamatergic system, NAC has also received interest in the field of psychiatry for its participation in antioxidant activities. Cystine combines with glutamate and glycine, all of which are precursors in the production of glutathione. Glutathione is the primary endogenous antioxidant, acting as a free radical scavenger. Because oxidative stress has been implicated in a variety of psychiatric disorders, including schizophrenia, major depression, bipolar disorder and anxiety disorder (Ng et al. 2008), NAC has been tested in a number of clinical studies (in most studies as an augmentation strategy). Beneficial effects in the form of symptom reductions have been observed in patients with schizophrenia (Berk et al. 2008) and bipolar disorder (Berk et al. 2008; Berk et al. 2011; Magalhaes et al. 2011). In a glutathione-deficient mouse model of schizophrenia, treatment with NAC normalized glutathione levels in the ACC that were initially found to be elevated (das Neves Duarte et al. 2012). Furthermore, several studies have reported that chronic alcohol consumption is associated with markers of oxidative stress (Lee et al. 2012; Seiva et al. 2009) and that NAC significantly improved antioxidant defences in alcohol treated rats (Seiva et al. 2009). This suggests that besides its restoring effect on glutamate homeostasis, NAC could also be implemented to treat the toxic effects associated with chronic substance use. Therefore, future studies investigating the neurobiological effects of NAC would benefit from taking into account information on both glutamate and glutathione concentrations. Fortunately, recent advances in MRS techniques allow imaging of both glutamate and glutathione concentrations in the human brain.

MODAFINIL

The effects of modafinil on neural substrates of impulse control were less straightforward. Although beneficial effects were observed on measures of delay discounting and Stroop task performance in AD patients, accompanied by normalizing effects on brain activation and connectivity, detrimental effects were also observed with respect to stop signal task performance depending on initial levels of response inhibition. This latter finding suggests that modafinil administration could lead to iatrogenic deterioration, as diminished response inhibition is associated with relapse (Goudriaan et al. 2008; Powell et al. 2010). Our findings were recently supported by a clinical trial with modafinil in AD patients
conducted by our collaborators (Joos et al. in press). Their 10-week trial with modafinil yielded similar results; whereas beneficial effects were observed in patients with initial poor response inhibition in terms of abstinence, even larger negative effects with a faster decline in the percentage abstinent days and a steeper increase in percentage heavy drinking days were observed in patients with good response inhibition at baseline. Therefore, caution is warranted with the prescription of modafinil to non-selected samples of AD patients.

The observation that a pharmacotherapy may constitute a useful adjunct therapy for some substance dependent individuals but not for others is not new to the field. Substance dependence is a heterogeneous disorder with many contributing factors, which vary from person to person and are known to contribute to individual differences in treatment response. The current observation of ‘one size does not fit all’ is consistent with results obtained using other pharmacotherapeutics and it stresses the importance of personalized medicine. Personalized medicine emphasizes that baseline characteristics should be considered in order to identify patients with a specific profile that are likely to benefit from treatment with a pharmacotherapy such as modafinil. Although clinical and sociodemographic characteristics have been found to predict treatment response in general (Adamson et al. 2009; Reske and Paulus 2008), these characteristics do not relate to underlying pathogenetic mechanisms of addiction, and hence can not fully capture inter-individual differences in the response to a treatment. The identification of predictors for treatment response could benefit from taking into account trait-like characteristics associated with the pathogenesis of addiction, for example in the form of biomarkers. In this respect, pharmacogenetic studies, in which genetic variations that give rise to differential responses to drugs are investigated, could be of particular interest. For example, naltrexone has been shown to be more likely to increase abstinence in alcohol dependent patients carrying a G-allele compared with A-allele carriers of the mu-opiod receptor gene (Chamorro et al. 2012). As mentioned above, the COMT gene might be of particular interest to investigate in relation to modafinil effects in substance dependent individuals. In addition to genetic variation, endophenotypes, such as neuroimaging and cognitive measures, may provide an intermediate step less distal to the clinical phenotype compared to genotypes. For instance, it would be of interest to examine whether baseline levels of dopamine transmission, obtained by SPECT or PET imaging, could predict the effects of modafinil on measures of impulsivity. Furthermore, given the observation that the enhancing effects of modafinil on brain activation and connectivity were associated with improved response inhibition, and likewise that modafinil-induced deactivation was associated with a deterioration in performance in the stop signal task, pretreatment levels of activation within these areas or networks could constitute useful biomarkers that may be used to identify those patients that will benefit from treatment with modafinil.
However, perhaps the biggest challenge in the field of human brain mapping is its application to the treatment of individual patients. Neuroimaging techniques have greatly contributed to an enhanced understanding of the neurobiology of disorders such as addiction and to the acknowledgement of addiction as a brain disorder. They have led to the identification of biomarkers associated with addiction and treatment response, however, these biomarkers have only been reliably observed at a group level (which ignores individual differences), and thus extrapolation to individual diagnostic assessment and therapy monitoring is not yet straightforward. Multivariate pattern-recognition algorithms are promising analytical techniques to analyse MRI data, which allows the classification of individual observations into distinct groups or classes based on high-dimensional data such as fMRI (Vapnik 1995). These techniques allow for deriving a single value representing the degree to which a disease-specific spatial pattern of brain structure or function is present in a single individual. The application of such techniques received most attention in the scientific field of gerontology for diagnosing Alzheimer Disease or for predicting the conversion from mild cognitive impairment to Alzheimer Disease (Orru et al. 2012). In addition, these algorithms may be used to identify biomarkers that predict treatment response in an individual instead of merely at a group level. For instance, the application of pattern recognition algorithms to structural MRI scans has demonstrated to predict response to treatment in patients with major depression with a classification accuracy of up to 90% (Costafreda et al. 2009; Gong et al. 2011). Nonetheless, the application of multivariate pattern recognition algorithms as an aid for clinical decisions is still in its infancy and a considerable amount of work needs to be done in the validation of classification results by applying classifiers obtained in one particular study to large, independent samples. Moreover, whether these techniques can be successfully applied in the field of addiction remains to be investigated.

It is worth noting that, given its effects on dopamine neurotransmission, modafinil may have the potential for abuse. Currently, the jury is still out on the stimulant properties of modafinil because of conflicting evidence. Although earlier studies found no evidence for abuse potential (Myrick et al. 2004; O'Brien et al. 2006), recent neuroimaging and animal studies indicate that modafinil increases dopamine in the nucleus accumbens and produces pronounced locomotor sensitization, both indicators of abuse liability (Andersen et al. 2010; Paterson et al. 2010; Volkow et al. 2009). In contrast, a recent study by Loland et al. (2012) showed that although modafinil binds to dopamine transporters and increases extracellular dopamine concentrations, these effects are less potent and efficient, and has a longer duration of action compared to cocaine. These observations could account for the lower behavioral stimulation from modafinil compared to other stimulants (Jasinski 2000) and the cocaine-euphoria reducing effects of modafinil (Dackis et al. 2003; Malcolm et al. 2006) found in clinical studies. Nevertheless, these observations indicate that prescription of modafinil needs to be done with caution. Treatment of substance
use disorders might benefit from pharmacological agents selectively targeting dopamine transmission in the PFC (and thereby improving cognitive control), while at the same time not affecting dopamine in the nucleus accumbens. For example, atomoxetine, a selective noradrenaline transporter inhibitor, selectively increases dopamine and noradrenaline in the PFC (Swanson et al. 2006), probably due to the contribution of noradrenaline transporters in the clearance of extracellular dopamine in the PFC (Carboni et al. 1990). Atomoxetine has been found to improve response inhibition in healthy individuals and patients with ADHD (Chamberlain et al. 2007; Chamberlain et al. 2009; Faraone et al. 2005; Nandam et al. 2011), however, this compound remains to be evaluated in clinical trials for addiction.

GENERAL IMPLICATIONS AND FUTURE DIRECTIONS
Clearly, although the above-mentioned effects of acute administration of pharmacological agents do not resemble the effects of chronic administration used in clinical treatment, study designs with a single dose administration (in animals as well as in humans) enhance our insight into the neurobiology of impulsivity and allow the identification of neurobiological targets to reduce impulsive behavior. Treatment strategies targeting specific neurotransmitter systems or neural circuitries in the brain could involve pharmacotherapeutics, but may also include neuromodulation techniques such as transcranial magnetic stimulation, transcranial direct-current stimulation or - even more direct but also more invasive - deep brain stimulation to improve impulse control. In addition, strategies involving active participation of the patients to increase cognitive functioning and/or reduce craving might be useful in the treatment of addiction. For example, real-time fMRI (rt-fMRI) provides patients direct, online feedback on his/her regional brain activity (based on blood oxygenation level dependent or BOLD response) within one target area or a network of target areas. Using this feedback, participants can train themselves in order to gain control over brain activity and thereby change their affective or cognitive states. It has been observed that heavy smokers were able to modulate the BOLD signal in the ACC during the presentation of smoking-related cues, thereby reducing their craving sensations (Li et al. 2012). Furthermore, behavioral strategies such as cognitive rehabilitation or cognitive bias modification (CBM) training may prove useful. Cognitive rehabilitation typically involves repeated practice of cognitive tasks. For instance, Bickel and colleagues (2011) demonstrated that training on a working memory task resulted in reductions of delay discounting among stimulant users. In addition, working memory training has also been associated with a reduction in alcohol intake in problem drinkers (Houben et al. 2011). In contrast to improving executive functioning, CBM training is specifically developed to target the more automatically processes involved in addiction such as attentional bias (exaggerated attention to drug cues; Field and Cox 2008) and approach bias (the tendency to automatically approach drug cues; Wiers et al. 2010). This CBM training has been shown to improve treatment
outcome in alcohol dependent patients (Schoenmakers et al. 2010; Wiers et al. 2011). Clearly, promising new strategies have been developed to improve top-down cognitive control or to down-regulate the more automatic impulsive system and combining these different therapies might prove to be more effective than single approaches.

In addition to implications for clinical practice, results of the current studies also highlight that future research is required to further elucidate the neurobiological mechanisms underlying the different aspects of impulsivity, addiction, and their interaction. Although animal models continue to play a crucial role in unravelling the exact neurobiological mechanisms underlying addiction, in delineating the cause and effect of impulsivity in addiction and in drug discovery for the treatment of addiction, the use of neuroimaging techniques allows for further delineation of the pathophysiology in humans. Moreover, neuroimaging markers can bridge the gap between drug discovery in preclinical studies to clinical studies in patients or healthy volunteers by providing translational markers of a drug’s effect in animals and humans. Future research on this topic is likely to benefit from investigating (the interaction between) brain networks, because one may be missing a significant part of the picture when only the mean activation of individual brain regions is analyzed. On a functional level, resting state functional connectivity methods may be of particular interest in this respect. The brain consumes about 20% of the body’s energy and most of this is used to support ongoing neuronal signalling. Task-related increases in neuronal metabolism are usually small (less than 5%) when compared to this large resting energy consumption (Ames 2000; Raichle and Mintun 2006). Therefore, we can learn a lot when taking into account spontaneous neuronal activity, which is the component that consumes most of the brain’s energy. Resting-state networks are highly consistent across individuals, can also be identified during the performance of tasks and resemble structural connectivity, supporting their functional relevance. Using resting-state fMRI to investigate the influence of substance abuse and/or medication on the brain has clear advantages over task-related fMRI, because no complicated experimental design is required and researchers will be conducting their experiments in the same way (contributing to effective data sharing), although task-related fMRI might be the preferred method when one is interested in brain activation and/or connectivity associated with specific cognitive processes.

Furthermore, by combining different neuroimaging techniques, one can go a step beyond merely identifying separate brain processes that are dysfunctional in psychiatric disorders such as addiction. Since the underlying pathophysiology of addiction is complex and likely results from brain dysfunction on multiple interacting levels, combining neuroimaging techniques measuring different characteristics including brain structure (e.g. Diffusion Tensor Imaging, structural MRI) and brain function (e.g. on a regional level: task-related and resting-state functional MRI, and on a molecular level MRS, PET and SPECT) could
greatly contribute to the identification of neural pathways towards disorders. Moreover, adding genetic information into this equation will allow identification of genetic risk factors for addiction and examining full models of genotype-endophenotype-phenotype pathways. Assuming there is a long road between genes and clinical phenotypes, neuroimaging techniques measuring functional and structural integrity of neural circuits that are more directly affected by genes through molecular and cellular mechanisms could provide important tools for unravelling the causal pathway from genetic variation to distal diseases such as addiction. Moreover, research integrating information on the level of genes with information on an intermediate level including neuroimaging data and information on cognitive functioning could help to identify those patients most likely to benefit from specific treatments and thereby contribute to better patient-treatment matching.