Neurocognitive Insights in Nicotine Addiction

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Chapter One

General introduction

In the Netherlands, 27% of the population is currently smoking. Nicotine is among the most addictive substances of abuse. Thirty-two percent of the people who tried smoking develop nicotine dependence within ten year. This percentage is higher for nicotine than for other substances of abuse (e.g., 23 for heroin: Anthony, et al. 1994). Eighty percent of the smokers intend to quit smoking in the future while only 25% actually attempt to quit every year. Most of these quit attempts fail as 88-95% of the quitters smoke again in the year following the quit attempt (International Tobacco Control Policy Evaluation Project 2011). Although smoking rates are decreasing since 1970, the decline in smoking rates is less distinct in populations with a lower social economic status. Youngsters with lower educational levels start smoking more often and it could be that those with lower social economic status have more difficulties giving up smoking. Nicotine dependence is currently included in the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR) as a 'substance use disorder'. Examples of diagnostic criteria are tolerance, withdrawal, smoking more than one intended, and the continuation of smoking despite knowledge of adverse consequences. Although nicotine dependence is included in the DSM-IV, nicotine dependence is rarely diagnosed. In addition, many smokers do not meet the diagnostic criteria, although they do experience problems giving up smoking (Schmitz, et al. 2003) and have increased risks for serious health problems. All these characteristics of smoking imply that smoking is a serious and chronic condition that occurs in a substantial part of the population.

Neurocognitive processes in smokers

Several theories of addiction suggest an imbalance in cognitive processing in addicted individuals (Field, et al. 2008; Franken 2003; Goldstein, et al. 2011; Volkow, et al. 2004; Wiers, et al. 2007). These models explain substance dependence as a consequence of an overactive motivational brain circuit in combination with insufficient control due to an ineffective cognitive control circuit. This ineffective cognitive control circuit may be one of the reasons why addicted individuals are characterized by the inability to adequately control behavior related to substance use such as abstaining from substances of abuse. Adequate cognitive control is of key importance when habitual and rigid behavioral patterns should be changed. The ability to guide our behavior according to our long-term goals, such as giving up smoking, requires the inhibition of automatic behavior and the monitoring of ongoing behavior, with both these functions being implemented by cognitive control circuits in our brain. Inhibitory control and error-processing are two core components of cognitive control (Ridderinkhof, et al. 2004a) that are associated with addictive behaviors.

Inhibitory control refers to the ability to suppress behaviors (such as smoking) that are automatic, inappropriate, unsafe or no longer required (Chambers, et al. 2007). Error-processing, on the other hand, refers to the monitoring and evaluation of ongoing behavior in order to be able to continue and optimize future behavior (Ridderinkhof, et al. 2004a). Chapter 2 introduces the concept of cognitive control in more detail. The sub-processes inhibitory control and error-processing are further explained, task paradigms to measure these cognitive processes are described, and the neural networks and event-related potentials associated with these processes are explained. Chapter 2 also includes an overview of the studies investigating cognitive control in addiction. At the moment this thesis project was started (2008), studies in opiate and cocaine dependent patients showed reduced inhibitory control and error-processing and associated hypoactivation in prefrontal regions such as the anterior cingulate cortex and dorsolateral prefrontal cortex (Franken, et al. 2007; Fu, et al. 2008; Hester, et al. 2004b; Kaufman, et al. 2003). However, it was unclear whether smokers are also characterized by reduced inhibitory control and error-processing. Another ongoing scientific endeavor with regard to inhibitory control is the underlying pharmacology. Recent studies in humans have shown that inhibitory control may be modulated by dopamine levels (Nandam, et al. 2011), although these studies are still scarce. It is important to gain more knowledge on how dopamine affects neural networks underlying inhibitory control to better understand disorders such as addiction, known to be characterized by dysfunctional dopamine systems (Balfour 2009; Berkman, et al. 2011; Diekhof, et al. 2008; Franken, et al. 2005; Koob, et al. 1997; Volkow, et al. 2009). Possibly, the alterations in dopaminergic functioning in addiction may lie at the basis of observed deficits in inhibitory control as well as hypoactivation in associated prefrontal regions.

Addicted individuals are also characterized by an overactive motivational and reward related network (i.e., the mesocorticolimbic system) when they are confronted with substance-related cues (Kuhn, et al. 2011). It has been suggested that enhanced attention allocation to substance-related cues is one of the cognitive processes that may contribute to the overactive motivational brain system in addicted individuals (Franken 2003; Robinson, et al. 2003). This attention allocation to substance-related cues is also referred to as attentional bias and is defined as the tendency of addicted individuals to automatically and involuntarily turn their attention to and maintain their focus on conditioned substance-related cues. Attentional bias has consistently been found in various types of addiction (Field, et al. 2008; Franken 2003; Robbins, et al. 2004) utilizing a wide range of experimental paradigms including attentional tasks such as the emotional Stroop and visual probe task. Smokers, for example, are slower in

naming the color of smoking-related words when compared to neutral words during the smoking Stroop tasks (Munafo, et al. 2003), and they are faster in responding to probes replacing smoking pictures than to probes replacing non-smoking pictures (Bradley, et al. 2004; Ehrman, et al. 2002; Mogg, et al. 2005) during the visual probe task. Eye-tracking studies (Field, et al. 2004; Mogg, et al. 2003) have also indicated enhanced attentional processing of drug cues in smokers. As predicted by theoretical models, attentional bias is associated with current craving, the strong subjective urge to consume a substance of abuse (Field, et al. 2009; Franken 2003). Recently, attentional bias has been associated with clinically relevant aspects such as the temptation to use substances (Waters, et al. 2012), treatment outcome (Carpenter, et al. 2006; Cox, et al. 2002) and relapse rates (Marissen, et al. 2006; Waters, et al. 2003). Further, preliminary evidence has suggested that attentional bias extinction training reduces conditioned cigarette craving in smoking males (Attwood, et al. 2008) and drinking behavior in alcohol dependent patients (Fadardi, et al. 2009; Schoenmakers, et al. 2010). However, research into attentional bias extinction training is still in its infancy and it seems that a single training session is not sufficient to reduce smoking behavior (Attwood, et al. 2008; Field, et al. 2009; McHugh, et al. 2010b). Theoretical models further suggest that attentional bias is a consequence of a dopamine signal that triggers attention to substance-related cues whenever they are encountered by substance dependent patients (Franken 2003; Robinson, et al. 2003). There is general consensus that the dopaminergic system, with projections from the ventral tegmental area (VTA) to the striatum, the anterior cingulate cortex (ACC) and other prefrontal brain regions, is responsible for reinforcement learning and experiencing reward (Schultz, et al. 1997). After repeated drug intake, substance-related cues become conditioned cues and elicit dopaminergic activity (Volkow, et al. 2006; Wong, et al. 2006; Zijlstra, et al. 2008) thereby signaling the expectation of a future reward (i.e., the intake of the substance of abuse). Gradually, the dopaminergic system becomes sensitized to substance-related cues so that they become extremely salient, the focus of attention, and elicit behaviors like drug seeking and consumption (Phillips, et al. 2003; Robinson, et al. 2008). Although attentional bias theories (Franken 2003; Robinson, et al. 1993) explain attentional bias in terms of neurobiological processes, neuroimaging studies in humans investigating the neurobiology of attentional bias are scarce. Two event-related potentials (ERPs), the P300 and Late Positive Potential (LPP), measured using electroencephalography (EEG), represent the allocation of enhanced attentional resources to motivationally relevant stimuli. A recent meta-analysis showed that both the P300 and LPP are consistently enhanced in addicted individuals for substance-related cues (Littel, et al. in press) indicating increased neural

processing of these cues. However, due to limited spatial resolution, ERP studies cannot provide information concerning the role of specific brain regions in attentional bias. Functional magnetic resonance imaging (fMRI) can provide this information; however, fMRI studies using attentional bias paradigms in addicted individuals are rare, therefore empirical evidence concerning the role of specific brain regions in attentional bias is as yet lacking.

Research objectives and relevance

The main objective of this thesis is to gain more knowledge about the neurocognitive processes involved in smoking behavior. This is achieved by investigating brain functions associated with cognitive control and attentional bias in smokers and healthy controls. Greater insight into the malfunction of neural networks associated with cognitive control and attentional bias in smokers could provide valuable information to understand the low success rates for giving up smoking. In addition, it can eventually contribute to the development of new strategies to support quit attempts in smokers. At the start of the current PhD project it was not yet clear whether smokers are characterized by reduced inhibitory control and ineffective prefrontal brain activation. At that moment, a few studies investigated inhibitory control in smokers by means of behavioral paradigms, without measuring accompanied brain activation. Results of these studies in smokers were inconsistent. That is, some studies have found response inhibition to be impaired in smokers relative to controls (e.g., Spinella 2002) whereas other studies could not confirm this (Dinn, et al. 2004; Monterosso, et al. 2005; Reynolds, et al. 2007). Therefore, the aim of the current thesis was to investigate inhibitory control and associated brain activation in smokers. An additional aim was to gather more detailed information concerning the underlying mechanisms for problems with inhibitory control in addiction. Addiction models suggest that problems with inhibitory control arise when rewarding stimuli, such as substance-related cues or stimuli associated with immediate reward, are to be suppressed (Dawe, et al. 2004a; Goldstein, et al. 2002; Jentsch, et al. 1999). This is, however, not explicitly tested in studies manipulating the type of stimuli to be suppressed. Therefore, we examined whether the presence of smoking-related cues could hamper inhibitory control and whether inhibitory control in smokers is impaired when previously rewarding stimuli need to be inhibited in order to obtain a larger delayed reward. Furthermore, the pharmacology of inhibitory control is largely unknown so our aim was to clarify the role of dopamine in inhibitory control, as more knowledge concerning the pharmacology of inhibitory control could eventually contribute to the development of pharmacotherapy for addiction. Error-processing, the ability to detect and monitor performance errors

in order to continue ongoing behavior (Ridderinkhof, et al. 2004a), is also critically depending on optimal activation in the prefrontal cognitive control system, especially the ACC. In the last few years, error-processing is emerging as an important concept in addiction. Therefore, it was evaluated whether smokers sufficiently process and monitor their errors in ongoing behavior.

A second major objective of this thesis was to investigate the motivational brain system in smokers by elucidating the neural mechanisms associated with attentional bias. More specifically, we wanted provide empirical evidence for theoretical models stating that attentional bias is the result of enhanced brain activation when smokers are confronted with smoking-related cues due to dopaminergic activity evoked by these cues. Consequently, both the neuroanatomical substrate of attentional bias in smokers was investigated, as well as the effect of a dopaminergic challenge on brain activation associated with attentional bias. Understanding the neuroanatomical correlates of attentional bias as well as the pharmacology of attentional bias could provide vital information for future research with the aim to reduce attentional bias in smokers.

Neuroimaging techniques

In order to investigate the neural correlates of cognitive processing in smokers we need neuroimaging techniques to measure ongoing brain activation. Technical advances in the past decades have made it possible to study brain activation in a non-invasive way. Brain activation associated with cognitive processes (e.g., inhibitory control, error-processing or attentional bias) is evoked by specific task paradigms that evoke brain activation associated with the cognitive process under investigation. Neuroimaging methods used in this thesis are event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI). In addition, a pharmacological challenge is used in combination with fMRI to clarify the role of dopamine in inhibitory control and attentional bias.

For the studies described in chapter 3 and chapter 4 we have used ERPs to measure brain activation. ERPs are acquired by means of the recording electroencephalographic (EEG) activity. EEG is the electrical activity along the scalp reflecting the summation of the synchronous activity of thousands or millions of neurons that have similar spatial orientation (Fabiani, et al. 2000). ERPs are electrical brain potentials that are averaged and time-locked to the occurrence of specific events such as the onset of a particular stimulus in a cognitive task. ERPs provide sensitive indices of the temporal aspects of neural processes representing cognitive functions evoked by the cognitive task. This is

because ERPs have temporal resolution in the order of milliseconds and because previous ERP research has shown that each ERP indexes a specific cognitive process. For example, for error-processing two ERP components have been identified. The error-related negativity (ERN) and the error-positivity (Pe) and it is known that the ERN is associated with fast initial error detection while the Pe is associated with the more conscious evaluation of an error (Overbeek, et al. 2005).

For the studies described in chapter 5, 6, 7, and 8 we have used fMRI to measure brain activation. FMRI has a high spatial resolution and is therefore suitable to detect brain activation in specific brain regions that are involved in the cognitive process under investigation. fMRI does not provide an absolute measure of brain activation, but provides a reliable measure of changes in brain activation depending on the supply of oxygen to an active region. The so-called Blood Oxygenation Level-Dependent (BOLD) contrast is the most commonly measured contrast for fMRI. A wealth of research has provided evidence that the BOLD response is tightly linked to neuronal activity (Logothetis, et al. 2001). Changes in BOLD signal that are correlated in time with the cognitive performance on the task paradigm are interpreted as an indication that this specific brain region is activated due to task performance. Cognitive paradigms developed for fMRI research usually involve an experimental and a control condition. Brain activation associated with the control condition is used to isolate the activation associated with the cognitive process under investigation. fMRI can also be used in combination with a pharmacological challenge. It is then referred to as pharmacological fMRI (phMRI). As phMRI can also be applied to cognitive task paradigms, it is a very suitable method to measure the effects of a pharmacological challenge on cognitive processes (Honey, et al. 2004; Stein 2001). To elucidate the effects of the pharmacological challenge, task related brain activation after the pharmacological challenge must be compared to a measurement of baseline task related activation obtained after administration of placebo. To answer the research questions concerning the role of dopamine in inhibitory control and attentional bias the dopamine system was challenged using a single administration of a dopamine antagonist combined with phMRI measurements.

The above-mentioned characteristics make ERP and fMRI techniques very suitable to study neurobiological correlates of cognitive dysfunctions present in substance dependence. A combined evaluation of ERP and fMRI research may provide valuable and complementary insights in both the temporal and spatial properties of the neural substrate of the cognitive processes involved in nicotine dependence.

Outline of the current thesis

This thesis describes a series of seven studies (chapter 2 to 8). In six of these studies smokers were compared to matched non-smoking controls while brain activation was measured and a cognitive task paradigm was developed with the aim to measure the cognitive process under consideration. **Chapter 2** is an introductory chapter in which the concept of cognitive control is explained in more detail. The sub-processes inhibitory control and error-processing are defined, task paradigms to measure these cognitive processes are described and the neural networks and event-related potentials associated with these processes are explained. Most importantly, this chapter provides an overview of the neuroimaging research in substance dependent individuals. Similarities and differences between the substances of abuse are described. In light of the new update of the DSM-V, which will include a section 'Substance Use and Addictive Disorders', studies in pathological gamblers and excessive internet users are also included in the overview. This chapter also provides treatment implications and future research suggestions.

In the study described in **chapter 3**, cognitive control in smokers was evaluated by focusing on error-processing. Deficits in error-processing in smokers were evaluated under challenging conditions, as the Flanker paradigm developed for this study included exposure to smoking-related cues. It was hypothesized that during smoking cue exposure limited capacity may be available to monitor ongoing performance. As a consequence, smokers would show reduced error-processing compared to non-smoking controls. Additionally, the nature of error-processing deficits was investigated in more detail by investigating their associations with trait impulsivity, severity of nicotine dependence and cigarette craving.

In **chapter 4**, a study is described in which we investigated whether decreased inhibitory control is evident in smokers. In line with theories suggesting that inhibitory control is more severely impaired in substance dependent individuals in the presence of substance-related cues it was also investigated whether deficits in inhibitory control in smokers are more distinct during smoking cue exposure. In this study behavioral accuracy on a Go/NoGo task as well as event-related potentials associated with inhibitory control were evaluated in smokers and non-smokers. It was expected that smokers showed reduced inhibitory control both on the behavioral and electrophysiological level as compared to non-smoking controls. Furthermore, it was expected that these effects were more evident during smoking cue exposure.

The study described in **chapter 5** investigated the neural basis to inhibit an immediately rewarding stimulus in order to obtain a larger delayed reward in smokers. It was also investigated whether punishment insensitivity could be another factor contributing to inefficient inhibitory control over addictive behaviors. To examine the effects of reward and punishment on brain activation associated with inhibitory control, a modified version of the Go/NoGo response-inhibition paradigm was designed that allowed the examination of neural activity during inhibitory control over rewarding NoGo stimuli. In the punishment condition failure to inhibit resulted in immediate money loss. In line with contemporary theories on addiction, we presumed that smokers would have significantly more difficulty inhibiting their response to a rewarding stimulus when compared to matched control participants. With regard to punishment sensitivity, it was expected that smokers are less sensitive to the effects of punishment to guide control over rewarding stimuli. More specifically, we expected that non-smoking controls would adopt a more cautious responding style when failed inhibition resulted in an immediate punishment, while this was not expected to influence behavior to the same extent in smokers.

In the study described in **chapter 6**, the association between dopamine and inhibitory control was examined. Currently, the pharmacology of inhibitory control is still largely unknown. Theorists suggest that optimal dopamine levels are needed in order to efficiently implement inhibitory control (Cools, et al. 2011). This implies that deficiencies in dopaminergic functioning that have been observed in substance dependent individuals including smokers may contribute to problems in inhibitory control in these populations. A pharmacological fMRI study in which dopamine levels were manipulated in smokers and non-smoking controls is described in this chapter. Haloperidol (2mg), a selective D2/D3 dopamine antagonist, or placebo was orally administered our hours before each scanning session in a double-blind randomized cross-over design in smokers and non-smoking controls. It was assumed that a reduction in dopamine levels after the administration of haloperidol reduces inhibitory control and associated brain activation. In addition, based on baseline differences in dopaminergic functioning between smokers and non-smoking controls it was expected that haloperidol will have differential effects on brain activation associated with inhibitory control in smokers and non-smokers.

In **chapter 7** the neural substrate of attentional bias and associated subjective craving in smokers was investigated. For this aim a pictorial attentional bias task was developed (the attentional bias line counting task) and smokers and non-smoking controls performed this task while we measured brain

activation using fMRI. It was expected that the dorsal zone of the ACC (dACC) would be overactive in smokers during the attentional bias paradigm. This dACC activity will contribute to focused attention on the primary task, as smokers will be highly distracted by the conditioned smoking cues. In line with other brain regions involved in salience attribution and top-down attention, we expected the ventral ACC, orbitofrontal cortex, ventral striatum, amygdala, superior parietal and dorsolateral frontal cortex to be similarly hyperactive.

It has been suggested that attentional bias emerges as a consequence of dopaminergic activity evoked by substance-related cues (Franken 2003; Robinson, et al. 1993). The pharmacological fMRI study described in **chapter 8** employed a dopaminergic challenge in order to test the hypothesis that brain activation associated with attentional bias in smokers can be modulated by a dopamine antagonist. To manipulate dopamine levels the same procedures were used as in chapter 6. Again, the pictorial attentional bias line counting task was used to measure brain activation associated with attentional bias to be able to replicate and compare findings to those in chapter 7. It was expected that administration of a dopamine antagonist normalized brain activation associated with attentional bias in smokers.

In **chapter 9**, our main findings will be summarized and evaluated in light of current theories on addiction. Limitations of the current studies are discussed. In addition, future research suggestions and clinical implications are provided.

Chapter Two

Deficits in cognitive control in substance dependence and behavioral addictions: A systematic review of ERP and fMRI studies on inhibitory control and error-processing

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Abstract

Several theories of addiction stress the role of reduced cognitive control. The current review evaluates neural deficits in the domains of inhibitory control and error-processing in substance dependent individuals and in individuals showing excessive addiction-like behaviors. Event-related potential (ERP) and functional magnetic resonance imaging (fMRI) studies were selected based on a Pubmed/Embase search. The approach in the current review of combined evaluation of ERP and fMRI findings offers unique information regarding neural deficits in cognitive control in addicted individuals. In line with recent theories, the most consistent findings in addicted individuals were reduced N2 and error-related negativity amplitudes as well as hypoactivation in the anterior cingulate cortex, inferior frontal gyrus and dorsolateral prefrontal cortex. Some differences between the major classes of substances of abuse were identified and preliminary support for similar neural deficits in excessive addiction-like behaviors and substance dependent individuals is provided. Future research suggestions include the need for a shift in neuroscience research to clinically relevant research.

Introduction

Cognitive control has been described as a multifactorial construct that implies cognitive operations to allow individuals to optimize goal-directed behavior and to adapt behavior accordingly (Botvinick, et al. 2001; Ridderinkhof, et al. 2004a). The role of cognitive control in substance dependence is emphasized in several contemporary theoretical models of substance dependence (Dawe, et al. 2004a; Goldstein, et al. 2011; Jentsch, et al. 1999; Lubman, et al. 2004; Verdejo-Garcia, et al. 2008). Substance dependent individuals are characterized by the inability to adequately control behavior related to substance use such as abstaining from substances of abuse. In addition, the reduced ability to perform goal directed behavior in substance dependent individuals is often accompanied by an apparent failure to adaptively learn from previous harmful behavior (Franken, et al. 2007). The ability to guide our behavior in accordance with our long-term goals requires inhibition of automatic behavior and the monitoring of ongoing behavior, with both these functions being implemented by cognitive control circuits in our brain. More specifically, inhibitory control and error-processing are two core components of cognitive control that are associated with specific neural networks; the former to implement the inhibition of inappropriate behavior and the latter to monitor performance errors in order to prevent future mistakes (Ridderinkhof, et al. 2004a). Adequate cognitive control is of key importance when habitual and rigid behavioral patterns should be changed, such as when substance dependent individuals try to control or withhold using the substance of abuse. Given the important role of cognitive control in substance dependence, greater insight into the malfunction of neural networks in substance dependent individuals could provide valuable information for understanding the problems associated with controlling substance use. Consequently, a rapidly increasing number of studies have examined inhibitory control and error-processing in substance dependent individuals by using neuroimaging techniques such as event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI). ERPs are electrical brain potentials associated with the occurrence of specific events such as the onset of a particular stimulus or event in a cognitive task. ERPs are acquired via the recording of electroencephalographic (EEG) activity, and provide sensitive indices of the temporal aspects of neural processes underlying cognitive functions. FMRI, on the other hand, has a high spatial resolution and is suitable for localizing activation in the brain. Advances in fMRI technology in the last decades have dramatically increased our knowledge of the neurobiological basis of cognitive control. By means of advanced experimental designs, knowledge has been increased on the contribution of each brain region to

cognitive control. The above-mentioned characteristics make ERP and fMRI techniques very suitable to study neurobiological correlates of cognitive dysfunctions present in substance dependence. A combined evaluation of ERP and fMRI research in this domain may provide valuable and complementary insights in both the temporal and spatial properties of the neural substrate of cognitive control in substance dependence. Therefore, the main goal of this review is to evaluate fMRI and ERP studies in the domains of inhibitory control and error-processing in order to evaluate the consistency of the findings across neuroimaging studies in the major classes of substance dependent populations.

A second goal of this review is to contribute to the ongoing discussion concerning the differences and similarities between substance dependence and other excessive behaviors that have been proposed to have addictive characteristics but do not involve the ingestion of substances (Grant, et al. 2010). For example, pathological gambling is listed as an impulse control disorders in the diagnostic and statistical manual of mental disorders (i.e., DSM-IV TR: American Psychiatric Association 2000) and is characterized by unsuccessful efforts to control, cut back or stop gambling, similar to the problems with controlling substance related behaviors. Based on these and other similarities between substance abuse and gambling (for reviews see: Potenza 2006; Van Holst, et al. 2010), pathological gambling may be listed under the heading 'substance use and addictive disorders' in the upcoming fifth edition of the diagnostic and statistical manual of mental disorders (DSM-5). Other suggested excessive addiction-like behaviors such as excessive computer game playing or internet use (Grant, et al. 2010) are not proposed as diagnostic categories in DSM-5 and no clear diagnostic criteria have been formulated. Currently individuals showing these excessive addiction-like behaviors are identified based on questionnaires examining the compulsivity of the behavior under investigation (Beard, et al. 2001; Meerkerk, et al. 2009) or based on the amount of time they invest in their excessive addiction-like behaviors. Obviously, clear diagnostic criteria for these behaviors will contribute to their identification and will improve quality of research into these behaviors. However according to the American Psychiatric Association, excessive internet use and gaming will not be included in DSM-5 because of a current lack of sufficient scientific research to justify their inclusion. Therefore, we will include neuroimaging studies that have investigated inhibitory control and error-processing in excessive gamers, excessive internet users and pathological gamblers in order to compare results to those obtained in substance dependent individuals. Throughout the paper, the term 'addiction' will refer both to substance dependence and the proposed behavioral addictions.

This review starts with an overview of experimental task paradigms that have been employed to measure inhibitory control and error-processing. In addition, the neural correlates of inhibitory control and error-processing are discussed in order to provide a framework for the evaluation of empirical studies. Although most substance users use multiple substances of abuse (Smith, et al. 2011), many studies have recruited participants based on their primary substance of abuse. Consequently, the literature review will be organized according to subjects' primary substance of abuse (i.e., stimulants including cocaine and (meth) amphetamine, opioids, cannabis, alcohol, and nicotine). Studies that have investigated inhibitory control and error-processing in excessive addiction-like behaviors will be discussed separately. This review will conclude with a discussion of the findings as well as clinical implications and guidance for future research directions.

Experimental measures of inhibitory control

The Go/NoGo and Stop Signal task are the most commonly used paradigms to measure inhibitory control (Chambers, et al. 2009; Dalley, et al. 2011; Verbruggen, et al. 2008). In the Go/NoGo task, participants respond as quickly as possible to frequent 'Go' stimuli, and inhibit responses to infrequent 'NoGo' stimuli which requires inhibitory control in order to overcome execution of an automatic response. The proportion of correctly inhibited NoGo trials reflects the ability to inhibit automatic behavior. The Stop Signal paradigm (Logan, et al. 1984) measures the ability to exert inhibitory control over a response that has already been initiated by asking participants to respond as quickly as possible to a continuous stream of Go stimuli. In a minority of the trials, a stop signal is presented after the onset of the primary stimulus indicating that the response to this stimulus should be canceled. The ability to inhibit already initiated behavior is indexed by the stop signal reaction time (SSRT), which is the time needed to cancel 50% of the Stop trials, relative to mean reaction time for Go stimuli. Larger SSRTs represent worse inhibitory control. Most Stop Signal paradigms use a staircase method in which that the amount of errors in the task are deliberately kept constant. Both the Go/NoGo and the Stop Signal task require the activation of a common inhibitory brake. The major difference between these tasks being that the Go/NoGo task requires (non) response selection and inhibition, whereas the Stop Signal task requires inhibition of an already initiated response (Dalley, et al. 2011). In order to place high demand on inhibitory control, NoGo and Stop trials should be both infrequent (e.g., 25% or less) and unpredictable. Besides the Go/NoGo and Stop Signal task, other cognitive paradigms such as the Stroop (Stroop 1992) and Eriksen-Flanker (Eriksen, et al.

1974) tasks are argued to measure inhibitory capacities. However, these tasks also measure other processes such as conflict resolution, response selection and attention (Nigg 2000; Ridderinkhof, et al. 2004b). In order to keep the current review focused and to be able to make straightforward comparisons of results, only studies utilizing Go/NoGo or Stop Signal paradigms will be included.

ERP measures of inhibitory control

Two major ERP components have been reported to reflect changes in brain activity related to inhibitory control (Kok, et al. 2004). The first of these ERP-components is the N2, which is a negative-going wave emerging approximately 200-300 ms after stimulus presentation. The neural generators of the N2 appear to be the anterior cingulate cortex (ACC, Huster, et al. 2010; Kok, et al. 2004; Nieuwenhuis, et al. 2003) and the right inferior frontal gyrus (IFG, Lavric, et al. 2004). The N2 is believed to index a top-down mechanism needed to inhibit the automatic tendency to respond (Falkenstein 2006; Kaiser, et al. 2006) and corresponds to behavioral outcomes of inhibitory control (Dimoska, et al. 2006; Falkenstein, et al. 1999; Van Boxtel, et al. 2001). In addition, the N2 component has been associated with conflict detection during early stages of the inhibition process (Falkenstein 2006; Nieuwenhuis, et al. 2003). Consequently, the N2 can be interpreted as an index for early cognitive processes necessary to implement inhibitory control rather than the actual inhibitory brake. The second ERP component that is associated with inhibitory control is the P3 (P300), which is a positive-going wave emerging 300-500 ms after stimulus onset. Recent research shows that the P3 is associated with the efficiency of inhibitory control (Kok, et al. 2004). More specifically, the P3 appears to represent the urgent inhibitory brake (Dimoska, et al. 2006). The source of the P3 has been found to be close to motor and pre-motor cortices (Huster, et al. 2010; Kok, et al. 2004; Ramautar, et al. 2006). Hence, P3 amplitudes appear to reflect a later stage of the inhibitory process that is closely related to the actual inhibition of the motor system in the premotor cortex (Band, et al. 1999; Dimoska, et al. 2006; Kok, et al. 2004). Together, accumulating research shows that the N2 and P3 reflect functionally distinct processes associated with inhibitory control. Accordingly, reduced N2 or P3 amplitudes in addicted populations can be considered markers for deficits in inhibitory control.

fMRI measures of inhibitory control

Inhibitory control in healthy individuals is associated with a mainly right lateralized network including the inferior frontal gyrus (IFG), the ACC/ pre-

supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC), as well as parietal and subcortical areas including the thalamus and basal ganglia (Chambers, et al. 2009; Garavan, et al. 2006; Simmonds, et al. 2008). Experimental studies have provided information on the specific contribution of these regions to implement inhibitory control. A recent hypothesis for the role of the right IFG in inhibitory control is that it detects behaviorally relevant stimuli (e.g., NoGo or Stop Signal stimuli) in cooperation with inferior parietal lobe (IPL) and temporoparietal junction through its effects on stimulus driven attention (Corbetta, et al. 2002; Li, et al. 2006). Given the proximity of the pre-SMA/ dorsal ACC (dACC) to the motor areas, the function of this region may be related to response selection and updating of motor plans (Mostofsky, et al. 2008). In addition to frontal and parietal regions, the involvement of subcortical basal ganglia and thalamic regions in inhibitory control is well established through feedback loops that connect these regions with prefrontal and motor areas (Chambers, et al. 2009; Garavan, et al. 2006; Li, et al. 2008b) such that activation in the subcortical areas modulates response execution via connections with motor areas.

Experimental measures of error-processing

All tasks that have been used to measure error-processing are speeded reaction time tasks. The most commonly used paradigms are the Eriksen-Flanker and the Go/NoGo task (Overbeek, et al. 2005; Shiels, et al. 2010). In a typical version of the Eriksen-Flanker task (Eriksen & Eriksen, 1974), participants are exposed to series of stimulus arrays either being letters or arrows. In the congruent condition version of the task five equal letters are presented (i.e., HHHHH/ SSSSS), while in the incongruent condition the middle letter differs from the other letters (i.e., SSHSS/HHSHH). In both conditions, participants are asked to identify the middle letter via a button response. Because of high stimulus conflict in the incongruent condition and the emphasis on response speed participants usually commit a sufficient amount of errors to analyze the processing of these performance errors. For the current review, studies employing the Flanker paradigm are only included for the evaluation of performance errors and not for the measurement of conflict evoked by the incongruent trials. In Go/NoGo or Stop Signal paradigms, false positive reactions for NoGo or Stop trials result in an erroneous motor response that are subsequently used to evaluate error-processing. Regardless of task paradigm, reaction times on trials after performance errors are usually longer compared to reaction times on trials following correct responses, which is referred to as post-error slowing. Post-error slowing is regarded as a behavioral index for error monitoring and is

argued to reflect cautious post-error behavior aimed at preventing future mistakes (Danielmeier, et al. 2011; Rabbitt 1966a).

ERP measures of error-processing

ERP investigations of error-processing have revealed two error-related brain waves that consistently emerge after performance errors, i.e., the error-related negativity (ERN) and the error-positivity (Pe). The ERN and Pe appear to be independent as they are differentially sensitive to experimental manipulations, individual differences in task performance and both reflect different stages of error-processing (Hewig, et al. 2011; Nieuwenhuis, et al. 2001; Overbeek, et al. 2005). The ERN arises 50-80 milliseconds after making an error and is known to reflect initial and automatic error detection (Bernstein, et al. 1995) thereby incorporating perceptual and proprioceptive evidence (Wessel, et al. 2011). Converging evidence indicates that the ACC is the neural generator of the ERN (Gehring, et al. 2000; Herrmann, et al. 2004; Miltner, et al. 2003a; Ridderinkhof, et al. 2004a; Van Veen, et al. 2002). The ERN is usually followed by a positive deflection in the electroencephalography, the Pe, emerging approximately 300 ms after incorrect responses (Falkenstein, et al. 2000). Research to identify the neural origin of the Pe has provided rather heterogeneous results (Wessel, et al. 2011). Whereas the ERN signals the initial error detection, the Pe appears to be associated with the more conscious evaluation of errors as well as error-awareness (Overbeek, et al. 2005; Wessel, et al. 2011). In addition, the Pe appears to the associated with the motivational significance that is attributed to an error (Ridderinkhof, et al. 2009). In line with these accounts, it may be concluded that the Pe reflects the conscious evaluation of the motivational significance of the error. Together, the ERN and Pe evaluate the correctness of ongoing behavior (i.e., a specific outcome or behavior was worse or better than expected), which is then used to guide future behavior (Holroyd, et al. 2009).

fMRI measures of error-processing

The suggested crucial role for the ACC in error-processing by ERP studies has been confirmed in fMRI studies. More specifically, Ridderinkhof and colleagues (2004b) suggest that a sub-region of the ACC, called the rostral cingulate zone (RCZ), that is located at the border of the dACC and the SMA, is consistently activated during monitoring of ongoing behavior. Some researchers suggest that the ACC monitors response conflict or the likelihood of errors (Brown, et al. 2005; Magno, et al. 2006) rather than error-processing per se. Two independent meta-analyses have shown that both response conflict and response error

activate approximately the same region within the ACC (i.e., the RCZ: Hester, et al. 2004a; Ridderinkhof, et al. 2004a) suggesting that the RCZ may be involved in both these functions or that activation emerging in the RCZ as a result of response conflict and response error may actually reflect two sides of the same coin. FMRI studies investigating error-processing further show that a large neural network coactivates with the RCZ including the bilateral insula, the DLPFC, the thalamus and right IPL (IPL, Hester, et al. 2004a; Menon, et al. 2001). Functional interactions between these regions have been reported as well, especially between the RCZ and the DLPFC. A study by Kerns et al. (2004) showed that the close interaction of the DLPFC and the RCZ is responsible for the implementation of adjustments in activation to prevent future mistakes. To conclude, performance errors in the human brain are processed by a neural circuit that extends beyond the RCZ, and includes the insula, the DLPFC, thalamus as well as parietal regions. This error-processing circuit collectively monitors and adjusts behavior when necessary.

Literature Review

Selection of studies

A comprehensive literature search was conducted in PUBMED and Embase including search terms for substance dependent populations and populations with a behavioral addiction: ‘substance related disorders (MeSH Term)’, ‘alcohol related disorders (MeSH Term)’, ‘amphetamine related disorders (MeSH Term)’, ‘cocaine related disorders (MeSH Term)’, ‘Marijuana Abuse (MeSH Term)’, ‘opioid related disorders (MeSH Term)’, ‘smokers’, ‘gambling (MeSH Term)’, ‘gaming’, ‘gamers’ or ‘internet’. The key search terms for various addicted populations had to co-occur in combination with the following search terms concerning inhibitory control and error-processing or related task paradigms: ‘cognitive control’, ‘inhibitory control’, ‘response inhibition’, ‘error-processing’, ‘error monitoring’, ‘Go NoGo’, ‘Stop Signal’ or ‘Flanker’ and in combination with the following search terms for neuroimaging methods and measures: ‘Magnetic Resonance Imaging (MeSH Term)’, ‘evoked potentials (MeSH Term)’, ‘error-related negativity’, ‘error-positivity’, ‘N200’, ‘N2’, ‘P300’, ‘P3’. The search was limited to research performed in humans and articles written in English. All included articles were required to be published in peer-reviewed journals and had to be included in Pubmed or Embase before October 2011. A total of 147 hits were retrieved. Abstracts of these articles were examined to select articles

that fulfilled the following criteria: a) participants included a group of addicted individuals (i.e., substance dependent patients for cocaine, (meth) amphetamine, opioids, cannabis, alcohol and nicotine, or individuals showing excessive addiction-like behaviors such as gambling, gaming or internet use). Social drinkers and recreational drug users were excluded; b) the inclusion of a control group such that decreased or increased brain activation as well behavioral deficits described in this review are always relative to healthy controls (to emphasize the clinical relevance of cognitive control, studies without a control group were included if they either evaluated the effect of treatment outcome or a pharmacological intervention within the addicted group); b) the number of participants was at least 10 in each group; c) participants performed the Go/NoGo, Stop Signal or Eriksen Flanker task to measure inhibitory control or error-processing (i.e., see sections on experimental task paradigms for inclusion of task paradigms); d) the use of fMRI or ERPs as neuroimaging tools. A total of 27 studies fulfilled our criteria. Cross-references in those 27 articles were searched which yielded another 5 studies that met our inclusion criteria. In total, 32 articles were included in this review. Six of these studies evaluated both inhibitory control and error-processing. Results of all studies are summarized in table 1 and table 2, and discussed below. In order to keep the current review concise we refer to the tables for study details such as the number of participants. In addition, we refer to the tables for a complete overview of fMRI results as we will only discuss fMRI findings in key regions involved in inhibitory control and error-processing as described in this review.

Table 1

Overview of ERP and fMRI studies investigating inhibitory control in substance dependence and behavioral addictions

Study	Participants	Measures	Main results -behavioral	Main results - Imaging
Opiate dependence				
Yang et al. (2009)	14 ODI 14 HC	- ERPs - Go/NoGo task	No group differences	NoGo N2: no group differences Go N2: ODI > HC at midline cluster P3: No group differences
Fu et al. (2008)	30 ODI 18 HC	- fMRI - Blocked Go/NoGo task	RTs: ODI > HC	Contrast: Go/NoGo block minus Go Block ODI < HC: bil-medPFC, bil-ACC, bil-FG, l-MFC, l-insula, l-uncus, PHG, r- precuneus, r-SPL, r-MTG
Stimulant dependence				
Sokhadze et al. (2008)*	19 CoDI 15 HC	- ERPS - Combined Flanker & Go/NoGo task	RTs: CoDI > HC ACCU: CoDI < HC in the congruent Flanker condition	N2 NoGo minus Go: CoDI < HC for incongruent trials at frontal cluster P3 NoGo minus Go: CoDI < HC at frontal cluste
Hester & Garavan (2004)	15 CoDI 15 HC	- fMRI - Go/NoGo task with varying WM demands	ACCU: CoDI < HC	Contrast: NoGo C versus baseline CoDI < HC: r-SFG, r-pre-SMA, l-ACC
Kaufman et al. (2003)*	13 CoDI 14 HC	- fMRI - Go/NoGo task	ACCU: CoDI < HC	Contrast: NoGo C versus baseline CoDI < HC: r-dACC, r-insula
Leland et al. (2008)	17 MDI 19 HC	- fMRI - Go/NoGo task with warning cues	ACCU after warning > ACCU without warning in CoDI and not in HC	Contrast: NoGo C minus Go No group differences Contrast: Warning GO cues > Go cues MDI > HC: vACC, dACC
Li et al. (2008)	15 CoDI 15 HC	- fMRI - Stop Signal Task	No group differences	Contrast: Stop C minus Stop E CoDI < HC: ACC, r-SPL, l-SPL, l-IOG
Li et al. (2010)	10 CoDI	- fMRI - Stop Signal Task - after placebo and single dose of MP	SSRT MP < PL	Contrast: Stop C minus Stop E MP > PL: bil-striatum, bil-thalamus, r-cerebellum PL < MP: STG SSRT MP < SSRT PL pos corr: l-MFG, neg corr.: r-VMPFC

Table 1

Continued

Study	Participants	Measures	Main results -behavioral	Main results - Imaging
Alcohol dependence				
Cohen et al. (1997)	17 ADI 30 HC	- ERPs - Go/NoGo task with selection of response hand	RTs ADI > HC	N2: not investigated NoGo P3: ADI < HC, whole brain Go P3: ADI < HC, whole brain Go versus NoGo P3: not different in ADI. In HC Go > NoGo in central, parietal and temporal clusters
Colrain et al. (2011)	10 ADI 25 HC	- ERPs - Combined Oddball & Go/NoGo task	No behavioral data reported	N2: not investigated NoGo P3: ADI < HC at CZ Go P3: No group differences
Fallgatter et al. (1998)	20 ADI 20 HC	- ERPs - Go/NoGo task with warning cues	No group differences	N2: not investigated P3: Location of Go P3 more posterior in ADI. The more anterior the NoGo P3 the lower the sensation seeking score in ADI
Kamarajan et al. (2005)	30 ADI 30 HC	- ERPs - Go/NoGo task with reward properties	ACCU: ADI < HC	N2: not investigated NoGo P3: ADI < HC in frontal and central clusters. Go P3: ADI < HC for Go in parietal cluster Go versus NoGo P3 Go > NoGo in parietal and occipital clusters
Karch et al. (2007)**	16 ADI 8 ANX+, 8 ANX-16 HC	- ERPs - Go/NoGo task with warning cues	No group differences	N2: not investigated P3: No group differences No differences between ANX+ and ANX-
Pfefferbaum et al. (1987)	42 ADI 66 HC	- ERPs - Go/NoGo task with varying Go/NoGo probabilities	No group differences	N2: not investigated NoGo P3: No group differences Go P3: ADI < HC at Cz and Pz
Karch et al. (2008)**	16 ADI 8 ANX+, 8 ANX-16 HC	- fMRI - Go/NoGo task with warning cues	No group differences	Contrast: NoGo versus baseline No Group differences ANX+ > ANX-: l-MFG, bil-SFG, bil-MTG, r-IFG, bil-IPL,bil-precuneus, r-PCC, l-thalamus ANX+ < ANX-: r-SFG, r-PCG, l-STG, bil-IPL
Li et al. (2009)*	24 ADI 24 HC	- fMRI - Stop Signal Task	RTs: ADI > HC ACCU: ADI > HC	Contrast: Stop C minus Stop E ADI < HC: l-DLPFC

Table 1

Continued

Study	Participants	Measures	Main results -behavioral	Main results - Imaging
Cannabis dependence				
Hester et al. (2009)*	16 CaDI 16 HC	- fMRI - Go/NoGo task	No group differences	Contrast: NoGo C versus baseline CaDI > HC: r-IPL, r-putamen, r-pre-SMA
Tapert et al. (2007)	16 CaDI (adolescents) 17 HC (adolescents)	- fMRI Go/NoGo task	No group differences	Contrast: NoGo versus baseline CaDI > HC: bil-SFG, bil-MFG, r-insula, bil-medFG, bil-IPL, bil-SPL, r-lingual, r-MOG Contrast: Go versus baseline CaDI > HC: r-IFG, r-insula, r-SFG, r-SPL , r-IPL, r-precuneus
Nicotine dependence				
Evans et al. (2009)	49 NDI 22 HC	- ERPs - Go/NoGo task	No group differences	N2: not investigated P3 NoGo minus Go: NDI < HC in central and parietal clusters
Luijten et al. (2011)	19 NDI 20 HC	- ERPs - Go/NoGo task with smoking and neutral pictures	ACCU: NCI < HC	NoGo N2: NDI < HC for both smoking and neutral pictures at frontocentral cluster Go N2: no group differences Go and NoGo P3: no group differences
Berkman et al. (2011)	27 NDI	- fMRI - Go/NoGo task	n/a	Contrast: NoGo C minus Go The higher the activatin in bil-IFG, bil-SMA, bil-putamen and l-caudate the lower the correlation between craving and smoking after a quit attempt. This moderation effect was opposite for r-amygdala
de Ruiter et al. (2011)*+	18 NDI 17 HC	- fMRI - Stop Signal Task	No group differences	Contrast: Stop C minus control NDI < HC: r-dACC
Galvan et al. (2011)	25 NDI (adolescents) 25 NDI (adolescents)	- fMRI - Stop Signal task	No group differences	Contrast: Stop C minus Go No group differences Neg corr within NDI group with heaviness of smoking in bil-MFG, ACC, SMA, l-OFC, r-SFG, l-IFG
Nestor et al. (2011)*	13 NDI 10 ex-NDI 13 HC	- fMRI - Go/No Go task	RTs: NDI & HC < ex-NDI ACCU: NDI < ex-NDI & HC	Contrast: NoGo C versus baseline NDI < HC: r-SFG, l-MFG, r-ACC, bil-IPL NDI & ex-NDI < HC: l-IFG, bil-PCG, r-STG, r-MTG, bil-insula, l-PHG NDI < ex-NDI & HC: l-MTG NDI < ex-NDI: l-ACC

Table 1

Continued

Study	Participants	Measures	Main results -behavioral	Main results - Imaging
Excessive addiction-like behaviors				
Dong et al. (2010)	12 EIU 12 HC	- ERPs - Go/NoGo task	No Group differences	NoGo N2: EIU < HC at frontal, central and parietal clusters Go N2: No group differences NoGo P3: EIU > HC at frontal, central and parietal clusters Go P3: No group differences
Zhou et al. (2010)	26 EIU 26 HC	- ERPs - Go/NoGo task with reward properties	ACCU: EIU < HC	NoGo N2: EIU < HC at frontal and central clusters. Go N2: not analyzed P3: not investigated
de Ruiter et al. (2011)*+	18 PG 17 HC	- fMRI - Stop Signal Task	No group differences	Contrast: Stop C minus control PG < HC: r-dACC

Note table 1 ** Study is also included in the error-processing section, ** These articles are based on data from the same participants, + This study includes a NDI, PG and HC group and therefore is included in NDI and behavioral addiction sections. Abbreviations: CoDi: cocaine dependent individuals; MDI: methamphetamine dependent individuals; ODI: opioid dependent individuals; ADI: alcohol dependent individuals; CaDi: cannabis dependent individuals; NDI: nicotine dependent individuals; PG: Pathological gamblers; EIU: excessive internet users; HC: healthy controls; NoGo C: NoGo Correct; Stop C: NoGo Correct; Stop E: NoGo Error; r-: right, l-: left, bil-: bilateral, RTs: reaction times, ACCU: accuracy, ANX+: high levels of anxiety, ANX-: low levels of anxiety, n/a: not applicable, MP: methylphenidate, PL: placebo, pos corr: positive correlation, neg corr: negative correlation, Cz, Pz: names of EEG electrodes referring to the location of the electrode.*

Inhibitory control in opiate dependence

Currently one ERP study investigated inhibitory control in opiate dependent individuals. No differences between groups on NoGo accuracy or N2 and P3 amplitudes were found in this study (Yang, et al. 2009), suggesting that inhibitory control was not impaired in this sample of opiate dependent individuals. It should be noticed, however, that inhibitory requirements in this task were low given the high probability of NoGo trials (i.e., 50% of the trials were NoGo trials), so that the task may have been too easy to reveal differences in inhibitory control between opiate dependent individuals and healthy controls.

Using fMRI and a Go/NoGo task in which accuracy levels were deliberately kept constant across individuals, abstinent opiate dependent individuals were found to have slower Go reaction times and reduced brain activation in the key regions implicated in inhibitory control such as the ACC, the IFG and the left insula (Fu, et al. 2008). However, Go and NoGo stimuli were presented in blocks in this study, such that inhibitory requirements in this study were low. Findings in this study should therefore be replicated in a design with stronger inhibitory requirements and currently provide only preliminary evidence that possible deficits in inhibitory control could be the result of hypoactivation in the ACC, IFG in opiate dependent individuals. Generally, studies investigating inhibitory control in opiate dependent individuals are scarce and future studies could benefit from improvements in task design.

Inhibitory control in stimulant dependence

N2 and P3 amplitudes in a Flanker task that incorporated NoGo trials were evaluated in current cocaine dependent individuals (Sokhadze, et al. 2008). It was found that the enhancement of NoGo N2 and P3 amplitudes relative to Go amplitudes was less pronounced in cocaine dependent individuals compared to healthy controls. However, behavior findings did not show decreased accuracy for NoGo trials among cocaine dependent individuals such that ERP results should be interpreted cautiously.

Using fMRI, Hester and Garavan (2004b) and Kaufman et al. (2003) both found reduced accuracy in Go/NoGo tasks in cocaine dependent individuals accompanied by reduced activation in the ACC/preSMA. Reduced activation was also found in the right superior frontal gyrus (SFG, Hester, et al. 2004b) and the right insula (Kaufman, et al. 2003). The Go/NoGo task in the Hester et al. study involved different levels of working memory load in order to mimic high working memory demands that are usually present during exposure

to drug-related cues. The hypoactivation associated with inhibitory control in the ACC was most pronounced when working memory load was high, suggesting that inhibitory control is most compromised in situations requiring high working memory loads. Li et al. (2008) confirmed hypoactivation associated with inhibitory control in the ACC in cocaine dependent individuals using a stop-signal task, which was extended to the bilateral superior parietal lobe (SPL). However, no differences were found between groups regarding SSRTs. A later study from the same group investigated the role of dopamine in inhibitory control by administration of a single dose of methylphenidate (Li, et al. 2010). It was found that methylphenidate enhanced inhibitory control in cocaine dependent individuals (i.e., the SSRT was shorter after methylphenidate). Furthermore, methylphenidate-induced decreases in SSRT were positively correlated with activation in left middle frontal cortex (MFC) and negatively with activation in the right ventromedial prefrontal cortex (VMPFC), suggesting that these regions may constitute a biomarker for the dopamine induced increase in inhibitory control. Another study in abstinent stimulant dependent individuals with methamphetamine as their primary drug of choice showed an alternative strategy to improve inhibitory control (Leland, et al. 2008). This study, employing a Go/NoGo task, did not find evidence for deviant performance or brain activation associated with inhibitory control in methamphetamine dependent individuals. Nevertheless, it was found that accuracy for NoGo trials was enhanced in methamphetamine dependent individuals (and not in healthy controls) when NoGo trials were preceded by an explicit warning cue that signaled the need for inhibition on the next trial. In addition, methamphetamine dependent individuals showed increased activation in the ACC for warning cues which was positively correlated with improved accuracy due to the warning cues. These findings imply that inhibitory control can be improved by explicit environmental cues that predict the need for inhibitory control via pre-activation of the ACC. Alternatively, methamphetamine dependent individuals may benefit from exogenous cues by boosting attention to NoGo stimuli.

Several conclusions can be drawn from the neuroimaging studies in stimulant dependent individuals. First, the single ERP study in cocaine dependent individuals suggests that neural deficits may be present in cocaine dependent individuals both in early and late stages of the inhibition process, however, it is unclear whether this may be associated with behavioral deficits. Second, hypoactivation in the ACC during inhibitory control in cocaine dependent individuals was found in multiple studies, however, this was not always associated with impaired task performance making interpretation of hypoactivation difficult (see discussion section for an in-depth discussion

concerning the interpretation of differences in behavioral performance and brain activation). Third, both explicit external cues as well as methylphenidate may improve inhibitory control, both via increasing activation associated with inhibitory control in the medial prefrontal cortex.

Inhibitory control in alcohol dependence

Six ERP studies were identified that investigated inhibitory control in alcohol dependent individuals (Cohen, et al. 1997; Colrain, et al. 2011; Fallgatter, et al. 1998; Kamarajan, et al. 2005; Karch, et al. 2007; Pfefferbaum, et al. 1987). Remarkably, none of these studies investigated N2 amplitudes so we cannot evaluate whether early cognitive processes contributing to inhibitory control are affected in alcohol dependent individuals. The study by Kamarajan et al. (2005) found a reduction in accuracy in alcohol dependent individuals whereas all other studies did not observe accuracy differences between alcohol dependent individuals and healthy controls. Reduced accuracy in the Kamarajan et al. study was accompanied by smaller NoGo P3 amplitudes in alcohol dependent individuals. Reduced P3 amplitudes for NoGo trials were replicated by Colrain et al. (2011). However, several other studies (Cohen, et al. 1997; Fallgatter, et al. 1998; Pfefferbaum, et al. 1987) found reduced P3 amplitudes in alcohol dependent individuals for both Go and NoGo trials. A general reduction in P3 amplitudes suggest that group differences in these studies do not merely reflect differences in inhibitory capacities but may be related to more overall deficits in attention, or, alternatively may reflect the use of different strategies during task performance. Karch et al. (2007) on the other hand, did not find deficits in alcohol dependent individuals on either Go or NoGo P3 amplitudes. Comparisons of results and interpretation of the conclusions for some of these studies are hampered due to considerable methodological differences and drawbacks. First, task paradigms differ greatly between the studies, in some studies Go and NoGo probabilities varied across blocks (Pfefferbaum, et al. 1987) or NoGo probabilities were high resulting in low inhibitory requirements (Fallgatter, et al. 1998; Kamarajan, et al. 2005). In addition, some task paradigms involved reward evaluation (Kamarajan, et al. 2005) or cueing for NoGo trials (Fallgatter, et al. 1998). Second, data analyses in some studies were not focused on regions in which NoGo amplitudes usually peak (Cohen, et al. 1997), or were focused on P3 localization rather than amplitudes (Fallgatter, et al. 1998). Altogether, evidence for neural deficits in the later stages of inhibitory control is mixed, most likely as a result of large methodological differences. However, one of the more carefully designed studies (Colrain, et al. 2011) did find a reduction of NoGo P3 amplitudes in

alcohol dependent individuals suggesting that these deficits can be revealed if task design and analyses are optimal.

Notably, ERPs in the study by Karch et al. (2007) were recorded while brain activation was simultaneously measured with fMRI (Karch, et al. 2008). The fMRI findings confirm ERP findings of comparable brain activation levels for alcohol dependent individuals and healthy controls (Karch, et al. 2008). This combined ERP and fMRI study further investigated differences between high and low anxious alcohol dependent individuals. It was found that P3 amplitudes in high and low anxious alcohol dependent individuals were comparable. However, high anxious alcohol dependent individuals show enhanced activation in prefrontal regions (including SFG, MFG and IFG) and the IPL as compared to low anxious alcohol dependent individuals. These findings raise the possibility that elevated anxiety levels in alcohol dependent individuals may be associated with increased activation levels when inhibitory control is executed. Another fMRI study investigating inhibitory control in alcohol dependent individuals (Li, et al. 2009) showed reduced activation in the left DLPFC in alcohol dependent individuals compared to healthy controls, while SSRTs were intact.

Altogether, neuroimaging and behavioral evidence for neural deficits associated with inhibitory control is weak, most likely due to large methodological differences between studies and general study limitations. For example, N2 amplitudes were not evaluated in any of the ERP studies. However, a reduction in NoGo P3 amplitudes in alcohol dependent individuals was found when task design and analyses were optimal, suggesting that the last minute inhibitory brake concerning the motor-response may be suboptimal in alcohol dependent individuals. The two discussed fMRI studies did not show convincing inhibitory control deficits yet, although tentative evidence suggests that brain activation associated with inhibitory control in the DLPFC may be dysfunctional in alcohol dependent individuals.

Inhibitory control in cannabis dependence

Currently, no ERP studies in cannabis dependent individuals have been published that evaluated N2 or P3 amplitudes in the context of inhibitory control, while two fMRI studies have been published (Hester, et al. 2009b; Tapert, et al. 2007). Both studies did not find behavioral deficits in cannabis dependent individuals in Go/NoGo tasks. However, active cannabis dependent individuals showed increased activation during inhibitory control in the AAC/pre-SMA, right IPL and putamen (Hester, et al. 2009b). These findings can be interpreted

as a compensatory mechanism given that cannabis dependent individuals did not show behavioral deficits. The finding of increased neural effort was also found in abstinent adolescent cannabis dependent individuals, as they showed increased activation associated with inhibitory control in a large network of brain regions involving the right SFG and left medial frontal gyrus (medFG) as well as the right IPL and SPL (Tapert, et al. 2007). Clearly, more research is needed in order to confirm these findings. In addition, the time course of the neural deficits in cannabis dependent individuals should be investigated by measuring N2 and P3 amplitudes in order to obtain information about the time frame of possible decrements in cannabis dependent individuals in inhibitory control.

Inhibitory control in nicotine dependence

Evens et al. (2009) investigated inhibitory control in nicotine dependent individuals and healthy controls who did smoke in the past but never became regular smokers by evaluating P3 (but not N2) amplitudes in a Go/NoGo task. While NoGo P3 amplitudes were reduced in nicotine dependent individuals, no differences between groups were found for behavioral performance. Additional findings in this study show that reduced NoGo P3 amplitudes in nicotine dependent individuals may not be a static process but may vary across nicotine dependent individuals depending on variations in genotypes coding for dopamine receptors, smoking withdrawal and mood states. Luijten et al. (2011a) investigated whether inhibitory control in nicotine dependent individuals was influenced by the presence of smoking cues. Nicotine dependent individuals showed reduced accuracy on the Go/NoGo task accompanied by reduced NoGo N2 amplitudes. P3 amplitudes did not differ between groups. Interestingly, NoGo accuracy and N2 amplitudes were reduced both when neutral and smoking pictures were presented at the background, suggesting that the observed deficit in inhibitory control reflects a general inhibition problem that is not further impaired when smoking cues are present.

Four fMRI studies in smokers in the domain of inhibitory control were included in the current review. The study performed by De Ruiter et al. (2012) showed reduced BOLD activation associated with inhibitory control in the dACC in nicotine dependent individuals on a Stop-Signal task, while SSRTs were not impaired. Nestor et al. (2011) found reduced accuracy on a Go/NoGo task in nicotine dependent individuals compared to both healthy controls and ex-smokers. Reduced brain activation associated with inhibitory control in nicotine dependent individuals in the ACC was confirmed in this study and extended to

the right SFG, left MFG and bilateral IPL. In addition, nicotine dependent individuals and ex-smokers both showed reduced activation in the left IFG and the bilateral insula compared to healthy controls. The comparison of nicotine dependent individuals and ex-smokers is interesting, because it provides information on the reversibility of deficits in inhibitory control. The results of the Nestor et al. study suggest that behavioral and activation deficits in nicotine dependent individuals may be reversible to some extent, while hypoactivation in other regions persist even after prolonged periods of giving up smoking. An alternative interpretation for the findings that NoGo accuracy and neural activation differs between nicotine dependent individuals and ex-smokers may be that more heavy dependent smokers show more pronounced behavioral and neural deficits and that they are the ones who fail to give up smoking. The idea that more heavy nicotine dependent individuals show more pronounced hypoactivation is supported by findings in adolescent nicotine dependent individuals (Galvan, et al. 2011). While adolescent nicotine dependent individuals and healthy controls had similar accuracy rates and brain activation, it was found that heaviness of smoking within nicotine dependent individuals was associated with reduced activation in those regions critically involved in inhibitory control, i.e., ACC, SMA, left IFG, bilateral MFG, and right SFG.

Importantly, a study by Berkman et al. (2011) investigated the link between brain activation during inhibitory control on a Go/NoGo task and real world inhibition of craving. Nicotine dependent individuals reported craving and the number of smoked cigarettes at several times during the day in the first three weeks after a quit attempt. It was found that higher activation levels in the bilateral IFG, SMA, putamen and left caudate during task performance attenuated the association between craving and real world smoking. Two important conclusions can be drawn from this study. First, brain activation in an abstract laboratory task to measure inhibitory control is associated with inhibition of feelings of craving in daily life. Secondly, lower brain activation in those regions critical for inhibitory control is actually disadvantageous because it is associated with a strong coupling between craving and smoking.

To summarize, ERP findings suggest that N2 as well as P3 amplitudes are reduced in nicotine dependent individuals. Later inhibitory processes, as reflected in P3 amplitudes, appear to be co-dependent on genetic variability, smoking status and mood states. fMRI studies consistently show hypoactivation in the inhibitory neural network which is associated with heaviness of smoking and may be partly reversible after giving up smoking. Hypoactivation during inhibitory control has also been shown to be disadvantageous for daily life

smoking behavior as it was associated with increased coupling between craving and smoking after a quit attempt. Again, decreased brain activation associated with inhibitory control was not always accompanied by behavioral deficits, thereby hampering the interpretation of some of the observed findings.

Inhibitory control in excessive addiction-like behaviors

Two ERP studies investigating inhibitory control in excessive addiction-like behaviors were included in the current literature review. The ERP study performed by Zhou and colleagues (2010) in excessive internet users showed reduced NoGo N2 amplitudes along with reduced accuracy in excessive internet users compared to casual internet users. P3 amplitudes were not evaluated in this study. Dong et al. (2010) confirmed reduced NoGo N2 amplitudes in male excessive internet users compared to casual internet users, while P3 amplitudes in excessive internet users were enhanced. No differences in behavioral performance were found in the latter study. It may be that enhanced activation in the final stage of inhibitory control in this group of excessive internet users served as a compensation for the reduced early inhibitory mechanisms in excessive internet users in order to obtain behavioral performance levels equal to casual internet users.

An fMRI study in pathological gamblers found reduced activation in the dACC for successful stops in a Stop Signal task (De Ruiter, et al. 2012). Although SSRTs were not impaired in pathological gamblers, this finding suggests similar hypoactivation in the dACC as found in substance dependent individuals. FMRI studies in excessive gamers and excessive internet users should be performed in order to see whether this also holds for other behavioral addictions.

Table 2

Overview of ERP and fMRI studies investigating error processing in substance dependence and behavioral addictions

Study	Participants	Measures	Main results -behavioral	Main results - Imaging
Opiate dependence				
Forman et al. (2004)	13 ODI 13 HC	- fMRI - Go/NoGo task	RTs: ODI > HC ERRORS: ODI > HC	Contrast: NoGo E versus baseline ODI < HC: r-ACC
Stimulant dependence				
Franken et al. (2007)	14 CoDI 13 HC	- ERPs - Flanker task	ERRORS: CoDI > HC Repeated ERRORS: CoDI > HC	ERN error: CoDI < HC at Fz, FCz, Cz ERN correct: No group differences Pe error: CoDI < HC at Fz, FCz, Cz Pe correct: No Group differences
Sokhadze et al. (2008)*	6 CoDI 6 HC	- ERPs - Combined Flanker & Go/NoGo task	RTs: CoDI > HC ERRORS: CoDI > HC	ERN error: CoDI < HC at frontal cluster ERN correct: No Group differences Pe: not investigated
Kaufman et al. (2003)*	13 CoDI 14 HC	- fMRI - Go/NoGo task	ERRORS: CoDI > HC	Contrast: NoGo E versus baseline CoDI < HC: r-medFG, l-IFG, r-dACC, l-insula
Alcohol dependence				
Padilla et al. (2011)	14 ADI 14 HC	- ERPs - Flanker task with high and low conflict and stimuli and response	No group differences	ERN error: ADI > HC at FCz ERN correct: ADI > HC at FCz Pe: not investigated
Schellekens et al. (2010)	29 ADI 8 with and 21 without anxiety disorder 15 HC	- ERPs - Flanker task	RTs: ADI > HC ERRORS: ADI > HC	ERN error: ADI > HC at FCz ERN correct: not investigated ERN error: ADI ANX+ > ADI ANX- at FCz Pe: not investigated
Li et al. (2009)*	24 ADI 24 HC	- fMRI - Stop Signal Task	No group differences	Contrast: Stop E minus Stop C ADI > HC: bil-MTG, bil-SPL, bil-SFG, bil-MFG, r-CS, l-ACC, r-SOG, r-MOG corr. Post-Error RTs ADI < HC: r-DLPFC
Cannabis dependence				
Hester et al. (2009)*	16 CaDI 16 HC	- fMRI - Go/NoGo task with aware and unaware errors	ERROR awareness: CaDI < HC	Contrast: NoGo E aware versus baseline CaDI > HC: bil-precuneus, l-putamen, left caudate, left hippocampus Contrast: NoGo E unaware versus baseline CaDI (and not HC) hypoactivation in r-ACC, r-putamen, r-IPL, bil -MFG

Table 2

Continued

Study	Participants	Measures	Main results -behavioral	Main results - Imaging
Nicotine dependence				
Franken et al. (2010)	23 NDI 28 HC	- ERPs - Flanker task	No group differences	ERN: no group differences Pe error: NDI < HC at Fz, Cz, Pz Pe correct: No group differences
Luijten et al. (2011)	13 NDI 14 HC	- ERPs - Flanker task with smoking and neutral pictures	RTs: HC (and not NDI) show post-error slowing	ERN error: NDI < HC at FCz, Cz, CPz ERN correct: No group differences Pe error: NDI < HC at FCz, Cz, CPz Pe correct: No group differences
de Ruiter et al. (2011)*+	18 NDI 17 HC	- fMRI - Stop Signal Task	No group differences	Contrast: Stop E minus control NDI < HC: r-dACC NDI > HC: r-DMPFC
Nestor et al. (2011)*	13 NDI 10 ex-NDI 13 HC	- fMRI - Go/NoGo task	RTs: NDI & HC < ex-NDI ERRORs: NDI > ex-NDI & HC	Contrast: NoGo E versus baseline NDI < HC: r-SFG, l-STG NDI < ex-NDI: r-SFG, l-ACC, l-PCC, l-MTG, l-cerebellum NDI & HC < Ex-NDI: bil-SFG, r-MFG, l-MTG, bil-PHG, l-cerebellum Ex-NDI > HC : l-SFG, r-MFG, l-insula, bil-STG
Excessive addiction-like behaviors				
de Ruiter et al. (2011)*+	18 PG 17 HC	- fMRI - Stop Signal Task	No group differences	Contrast: Stop E minus control PG < HC: r-dACC

Note table 2 ** Study is also included in the inhibitory control section, + This study includes a NDI, PG and HC group and therefore is both included in NDI and behavioral addiction sections. Abbreviations: CoDi: cocaine dependent individuals; ODI: opioid dependent individuals; ADI: alcohol dependent individuals; CaDi: cannabis dependent individuals; NDI: nicotine dependent individuals; PG: Pathological gamblers; HC: healthy controls; NoGo E: NoGo Error; Stop E: NoGo Error; Stop C: NoGo Correct; r-: right, l-: left, bil-: bilateral, RTs: reaction times, ANX+: high levels of anxiety, ANX-: low levels of anxiety, corr: correlation, Fz, FCz, Cz, CPz, Pz: names of EEG electrodes referring to the location of the electrode.*

Error-processing in opiate dependence

At present, only one study was identified that has investigated error-processing in opiate dependent individuals (Forman, et al. 2004). Brain activation associated with performance errors on a Go/NoGo task in opiate dependent individuals was compared to brain activation in healthy controls. It was found that opiate dependent individuals made more errors and that error-related activation in the ACC was reduced. Furthermore, an associated between ACC activation and behavioral performance in opiate dependent individuals was lacking, whereas this brain-behavior correlation was present in healthy controls. Obviously, the finding of reduced ACC activation for error-processing in opiate dependent individuals should be replicated. Furthermore ERP studies should be performed to evaluate whether possible deficits in error-processing in opiate dependent patients are due to reduced initial error detection, as reflected in decreased ERN amplitudes, due to more conscious evaluation of errors, as reflected in decreased Pe amplitudes, or as a consequence of both reduced initial and elaborative processing of errors.

Error-processing in stimulant dependence

Two ERP studies investigated error-processing in active cocaine dependent individuals (Franken, et al. 2007; Sokhadze, et al. 2008). Participants in Franken et al. (2007) performed a Flanker task. ERP findings showed that both the initial automatic processing of errors and the later more conscious processing of errors is reduced in cocaine dependent individuals since both ERN and Pe amplitudes were attenuated. Furthermore, cocaine dependent individuals committed more errors. More specifically, they committed more errors following an error on the previous trial which suggests that behavioral adaptation is suboptimal. Sokhadze et al. (2008) confirmed both reduced task performance as well as reduced ERN amplitudes in active cocaine dependent individuals compared to controls in a combined Flanker & Go/NoGo task. Pe amplitudes were not investigated in this study. One fMRI study in cocaine dependent individuals investigated brain activation associated with error-processing employing a Go/NoGo task (Kaufman, et al. 2003). Reduced error-related brain activation in cocaine dependent individuals compared to healthy controls was found in the ACC, right medFG, left insula and left IFG. In addition, cocaine dependent individuals committed more errors during task performance.

To conclude, both ERP and fMRI studies show reduced error-processing in cocaine dependent individuals. Decreased activation after performance errors in regions critical for optimal error-processing such as the ACC, insula

and IFG was found in cocaine dependent individuals. Reduced ERN and Pe amplitudes in cocaine dependent individuals suggest that problems with error-processing may emerge both as a consequence of deficits in initial error detection as well as from deficits in the more conscious evaluation of performance errors.

Error-processing in alcohol dependence

A remarkably different pattern of error-processing was found in alcohol dependent individuals. Padilla et al. (2011) and Schellekens et al. (2010) investigated ERN (and not Pe) amplitudes in abstinent alcohol dependent individuals evoked by errors on a Flanker task. Alcohol dependent individuals in Padilla et al. (2011) performed the task as accurately as controls but showed increased ERN amplitudes suggesting enhanced monitoring of performance errors. However, enhanced monitoring of behavior may not be specific for errors since the alcohol dependent individuals in this study also showed increased amplitudes for correct trials. Another ERP study in alcohol dependent individuals confirmed increased ERN amplitudes specific for errors (Schellekens, et al. 2010). In addition, these alcohol dependent individuals showed increased error rates for congruent trials. Interestingly, when alcohol dependent individuals with comorbid anxiety disorder were compared to alcohol dependent individuals without anxiety disorder, it was found that ERN amplitudes were larger in the high anxious group. Enhanced ERN amplitudes in high anxious individuals is in line with theories suggesting that internalizing psychopathology is associated with enhanced monitoring of behavior such as performance errors (Olvet, et al. 2008). In line with ERP findings, an fMRI study performed by Li and colleagues (2009) showed increased error-related brain activation in alcohol dependent individuals in a Stop Signal task in the right ACC, and bilateral MFG and SFG, as well as in parietal and occipital brain regions (see table 2 for a complete overview).

To summarize, it appears that the processing of errors is enhanced in alcohol dependent individuals as it was found that ERN amplitudes and ACC activation was increased. Currently, none of the ERP studies evaluated Pe amplitudes, therefore no information is available concerning more conscious processing of errors in alcohol dependent individuals. These findings suggest that alcohol dependent individuals are a specific sub-population in substance dependent individuals regarding error-processing, maybe because of differences between substance dependent populations such as elevated levels of internalizing psychopathology in alcohol dependent individuals.

Error-processing in cannabis dependence

Research investigating error-processing in cannabis dependent individuals is scarce. No ERP studies were identified for in the current review that have investigated error-processing in cannabis dependent individuals, and only one fMRI study was identified (Hester, et al. 2009b). In this study, participants were asked to press a button in a Go/NoGo task whenever they were aware that they made a mistake such that aware and unaware errors could be evaluated separately. For aware errors, activation in regions critical for error processing was similar in cannabis dependent individuals and controls (see table 2 for group differences in other regions). The proportion of errors in cannabis dependent individuals was not increased, however, cannabis dependent individuals showed reduced error-awareness. In addition, cannabis dependent individuals showed less activation in the right ACC, and bilateral MFG for unaware errors compared to aware errors, while controls did not show a difference between unaware and aware errors in these regions. The difference in activation in the ACC for aware relative to unaware errors was positively associated with reduced error-awareness suggesting that the failure of the ACC to activate for unaware errors may underlie the poor awareness for errors in cannabis dependent individuals. More fMRI studies should be performed to confirm reduced error processing and accompanied hypoactivation in the ACC in cannabis dependent individuals. Also, ERP studies should evaluate whether the initial automatic stage of error-processing is reduced and should replicate reduced error-awareness in cannabis dependent individuals by evaluating Pe amplitudes.

Error-processing in nicotine dependence

Several ERP and fMRI studies have addressed the investigation of error-processing in nicotine dependent individuals. Utilizing a Flanker task, Franken et al. (2010) found that task performance as well as ERN amplitudes for incorrect trials were not impaired in nicotine dependent individuals. However, Pe amplitudes were reduced in nicotine dependent individuals. These findings may indicate that initial error detection in nicotine dependent individuals is intact but that more conscious evaluation of errors may be reduced. Luijten et al. (2011b) investigated whether error-processing is altered in nicotine dependent individuals when smoking cues are presented during task performance using an adapted Flanker task. Nicotine dependent individuals were not impaired on task performance, but nicotine dependent individuals did not adapt their behavior after an error (i.e., post-error slowing was not observed in nicotine dependent individuals). Furthermore, both ERN and Pe amplitudes were reduced in nicotine

dependent individuals. Results of this study, combined with results of Franken et al. (2010) suggest that initial error detection may be specifically compromised in nicotine dependent individuals when limited cognitive resources are available for error-monitoring such as during exposure to smoking cues. On the other hand, the more conscious processing of errors may be generally reduced in nicotine dependent individuals.

An fMRI study in which participants performed a Stop-Signal task showed reduced activation after an error in nicotine dependent individuals in the dorsal ACC coupled with increased activation in a more anterior region of the dorsomedial prefrontal cortex (DMPFC, De Ruiter, et al. 2012). Using a Go/NoGo task, Nestor et al. (2011) found that nicotine dependent individuals made more errors accompanied by reduced brain activation in the right SFG, whereas no activation deficits were found in the ACC or insula. This study also included a group of ex-smokers who showed enhanced error-related activity in the ACC, bilateral SFG and right MFG. These findings suggest that more elaborate neural monitoring of errors may increase chances to quit smoking or that the deficits in nicotine dependent individuals are reversible.

In conclusion, results from ERP studies suggest that initial error detection may be reduced in nicotine dependent individuals during more cognitive challenging situations, whereas the more conscious evaluation of errors may also be reduced in affectively neutral conditions. Hypoactivation in the ACC reaction to an error was found in one of the two fMRI studies in nicotine dependent individuals. Further research should clarify under which conditions neural deficits associated with error-processing are present in nicotine dependent individuals.

Error-processing in excessive addiction-like behaviors

No ERP studies that addressed error-processing in subjects with excessive addition-like behaviors were identified. In an fMRI study by De Ruiter and colleagues (2012) error processing was investigated in the context of behavioral addiction. It was found that error-related brain activation in the dACC on the Stop Signal task was reduced in pathological gamblers, while task performance was intact. This finding suggests reduced monitoring of errors in pathological gamblers in the most important region for error-processing. This result resembles findings in substance dependent individuals. More fMRI and ERP studies are needed to be able to compare excessive addition-like behaviors with substance dependence in terms of brain activation associated with error-processing.

Discussion

The current review provides an overview of ERP and fMRI studies that have addressed inhibitory control and error-processing in substance dependent individuals and in individuals showing excessive addiction-like behaviors. Results of included studies are summarized in table 1 and 2 and were discussed in the text. This discussion provides a summary and critical review of major results in light of current addiction theories as well as suggestions for future research and treatment implications.

ERP studies of inhibitory control, as operationalized using Go/NoGo and Stop Signal paradigms, have found deficits in addicted individuals both on N2 and P3 amplitudes. Among the studies that evaluated N2 amplitudes, several studies showed reduced N2 amplitudes in substance dependent individuals as well as in excessive internet users. Reduced N2 amplitudes suggest that deficits in inhibitory control in addiction may be due to problems with early cognitive processes such as conflict detection that are necessary to execute inhibitory control. Results regarding P3 amplitudes are less consistent with some studies showing no deficits in addicted individuals, some showing reduced and others increased P3 amplitudes. Reduced versus enhanced P3 components in addicted individuals imply hypoactivation versus compensatory activation during the late urgent inhibitory brake. Complementary to reduced N2 amplitudes, several fMRI studies showed hypoactivation associated with inhibitory control in addicted individuals mainly in the ACC, IFG and DLPFC but also in inferior and superior parietal gyri (see figure 1 for summary of fMRI findings for inhibitory control in the ACC). From these findings, it can be concluded that substantial parts of the network underlying inhibitory control are dysfunctional in addicted individuals.

Reduced error-related brain activation in addicted individuals in the ACC, the most critical area for error-processing, was found in several fMRI studies (see figure 2 for summary of fMRI findings for error-processing in the ACC). Additionally, reduced activity in other regions such as superior and inferior frontal gyri and the insula was reported. ERP findings both confirm and complement fMRI findings. Reduced ERN amplitudes were found in substance dependent individuals confirming reduced initial error detection in addicted individuals. Given that the ACC is the neural generator of the ERN (Herrmann, et al. 2004; Ridderinkhof, et al. 2004a; Van Veen, et al. 2002), both ERN and fMRI findings suggest that ACC dysfunction could be a biomarker for reduced error-processing in addicted individuals. Pe findings complement fMRI findings by providing information on the timeframe of error-processing deficits. Reduced Pe

amplitudes in substance dependent individuals suggest that, besides the initial error detection, more conscious processing of errors is reduced in addicted individuals.

Two findings in the current review constitute an exception to the above mentioned conclusions. First, fMRI findings in cannabis users with regard to inhibitory control show hyper- instead of hypo- activation in several brain regions including the pre-SMA, DLPFC, insula and IPG. The enhanced activation in cannabis users can be interpreted as increased neural effort in order to reach control sample levels of behavior performance (i.e., no behavioral deficits were found in cannabis users). This hyperactivation could also be problematic in more challenging or real world situations when the brain may no longer be able to compensate, which is illustrated by findings in cocaine dependent individuals who showed more pronounced deficits in inhibitory control under high working memory loads (Hester, et al. 2004b). Another explanation for hyperactivation in cannabis users is the relatively young age of cannabis users in both fMRI studies relative to other studies in substance dependent individuals (Hester, et al. 2009b; Tapert, et al. 2007). In addition, participants in Tapert et al. (2007) were abstinent from cannabis for 28 days, which is longer than in most other studies, suggesting that brain activation may change as a function of abstinence duration (Schweinsburg, et al. 2010).

ERP and fMRI findings regarding error-processing in alcohol dependence constitute the second exception on the generally observed hypoactivation in addicted individuals. In contrast to other addicted individuals, alcohol dependent individuals show enhanced processing of errors as reflected by enlarged ERN amplitudes and increased error-related activation in the ACC. Findings in the study by Schellekens et al. (2010) provide a plausible explanation for these findings as ERN amplitudes in high anxious alcohol dependent individuals were larger than in low anxious alcohol dependent individuals. These findings of increased ERN amplitudes in high anxious alcohol dependent individuals suggest that the often observed comorbid internalizing psychopathology (i.e., anxiety-related disorders) in alcohol dependent individuals (Bacon, et al. 2010; Baillie, et al. 2010) may be responsible for the increase in error-processing. An overview of ERN findings in both internalizing and externalizing psychopathology confirms that internalizing psychopathology is associated with enhanced ERN amplitudes while externalizing psychopathology is associated with reduced ERN amplitudes (Olvet, et al. 2008). The effects of anxiety in alcohol dependent individuals on error-related brain activation suggest that comorbidity with internalizing psychopathology

may be a confounding factor in studies in substance dependent individuals. It would be interesting if future studies report comorbidity and investigate individual differences within substance dependent individuals.

A secondary goal of this review was the evaluation of possible neural deficits associated with cognitive control in individuals showing excessive addiction-like behaviors such as pathological gambling, excessive internet use and excessive gaming. If observed deficits are similar to those in substance dependent individuals, this could be interpreted as an argument for the classification of these behaviors as an 'addictive disorder' which may have important consequences for diagnoses and treatment programs. Indeed,

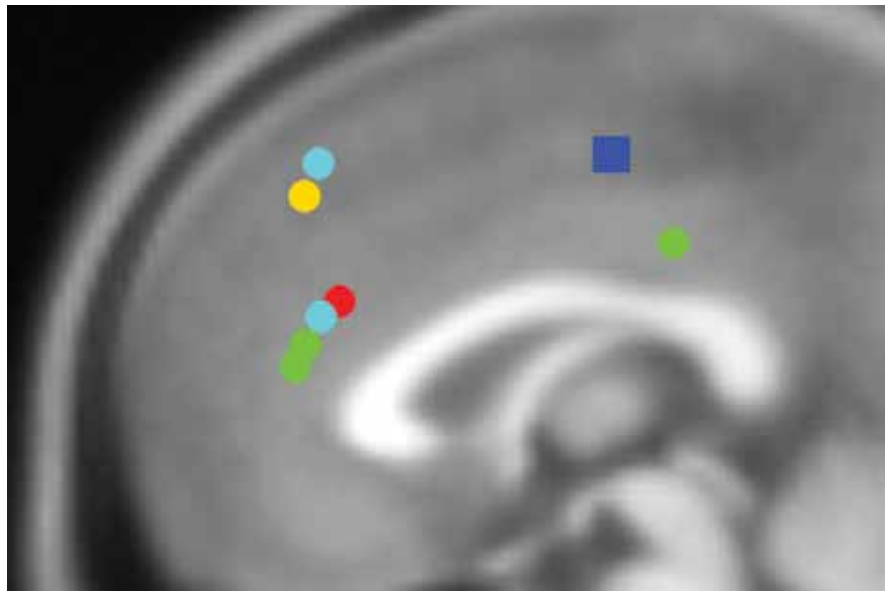

Figure 1
Summary of Anterior Cingulate dysfunction in addicted individuals for inhibitory control

Note figure 1 *Circles represent hypoactivation and squares hyperactivation for inhibitory control in addicted individuals relative to healthy controls. Red: opioid dependent individuals; Green: cocaine dependent individuals; Dark blue: cannabis dependent individuals; Cyan: nicotine dependent individuals; Yellow: pathological gamblers. Locations are based on reported Talairach or MNI coordinates in studies reporting group differences included for this review. Talairach coordinates were converted to MNI using the GingerALE toolbox. Foci of activation were projected onto the midline for ease of viewing.*

studies showed similar findings in excessive internet users and pathological gamblers to those observed in substance dependent individuals. More specifically, reduced N2 amplitudes reflecting early cognitive processes associated with inhibitory control have been found in excessive internet users (Dong, et al. 2010; Zhou, et al. 2010). In addition, reduced activity in the ACC for both inhibitory control and error-processing has been found in pathological gamblers (De Ruiter, et al. 2012), which is among the most often observed findings in substance dependent individuals. It appears that neural deficits in behavioral addictions are not the result of comorbid substance use or dependence, as this was an exclusion criterion in two of the reviewed studies (De Ruiter, et al. 2012; Zhou, et al. 2010). Since neuroimaging studies in the

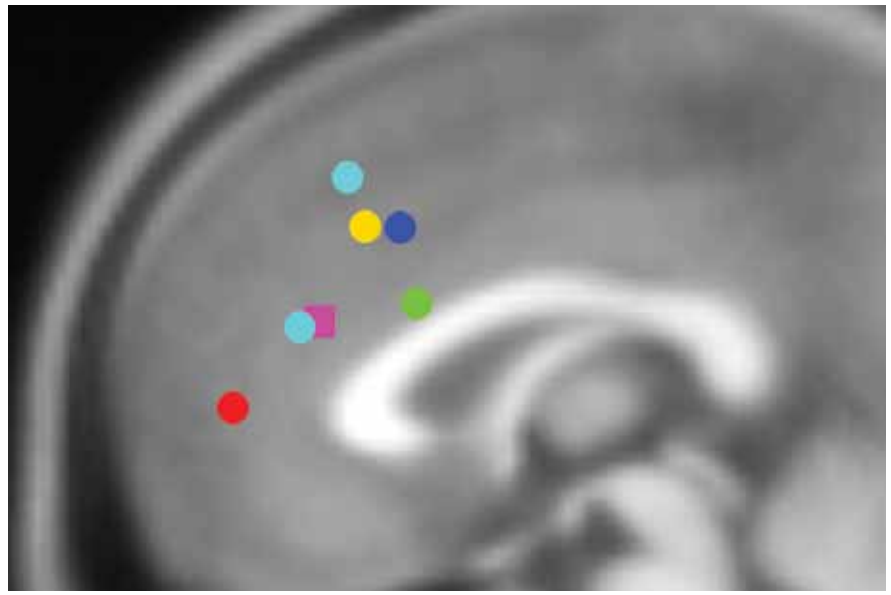

Figure 2
Summary of Anterior Cingulate dysfunction in addicted individuals for error processing

Note figure 2 *Circles represent hypoactivation and squares hyperactivation for error processing in addicted individuals relative to healthy controls. Red: opioid dependent individuals; Green: cocaine dependent individuals; Purple: alcohol dependent individuals; Dark blue: cannabis dependent individuals; Cyan: nicotine dependent individuals; Yellow: pathological gamblers. Locations are based on reported Talairach or MNI coordinates in studies reporting group differences included for this review. Talairach coordinates were converted to MNI using the GingerALE toolbox. Foci of activation were projected onto the midline for ease of viewing.*

domain of cognitive control in individuals showing excessive addiction-like behaviors are still scarce, we conclude that current findings in those individuals provide only preliminary support for similar neurocognitive deficits as substance dependent individuals. Clearly, more studies addressing other critical aspects of addictive behaviors than cognitive control (craving, desire to reduce addictive behavior, failure to fulfill obligations etc.) are needed in order to provide solid evidence to list these excessive behaviors under 'substance use and addictive disorders' in the upcoming DSM editions.

Overall, the results of this review point to a reduction in the function of the neural circuits underlying inhibitory control and error-processing in both substance dependent individuals and individuals showing excessive addition-like behaviors, which is in line with several theoretical and animal models of addiction. These models explain substance dependence as a consequence of insufficient control applied by the hypoactive cognitive control circuit in the brain over the overactive reward and motivational brain circuit (Goldstein, et al. 2002; Jentsch, et al. 1999; Volkow, et al. 2010). Insufficient functioning of the cognitive control brain circuit may arise from both the overwhelming effect of the motivational circuit (enhanced "drive") due to repeated substance intake and from individual differences in the strength of cognitive control circuits that renders an individual vulnerable to develop substance dependence (George, et al. 2010; Kirisci, et al. 2006; Tarter, et al. 2003; Verdejo-Garcia, et al. 2008). The findings in the current review provide empirical support for reduced functioning of the control circuits in the brain both when it comes to the inhibition of inappropriate behavior and behavior monitoring. The correspondence of the preliminary findings in behavioral addictions with those in substance dependent individuals is in line with theoretical accounts that pathological gambling and other proposed behavioral addictions share common underlying mechanisms with substance dependence (Grant, et al. 2010; Potenza 2006; Van Holst, et al. 2010).

Combined evaluation of ERP and fMRI studies

The combined evaluation of ERP and fMRI studies in this review is unique and offers information regarding neural deficits in cognitive control in addicted individuals with a high temporal and spatial resolution. Several findings in the current review provide examples for complementary insights when ERP and fMRI findings are compared. First, given the neural generators of the N2 and P3 components (i.e., ACC and right IFG versus motor cortices respectively) the observed hypoactivation in addicted individuals in fMRI studies in the ACC and right IFG for inhibitory control may be linked to reduced N2 rather than P3

amplitudes. Although speculative, such a comparison between fMRI and ERP results suggest that fMRI findings in these regions are linked to the early processes associated with inhibitory control such as conflict detection and resolution.

Another illustration of the added value of ERP findings for fMRI research are findings in excessive internet users. Reduced N2 amplitudes accompanied by increased P3 amplitudes were found in excessive internet users when behavioral performance is intact (Dong, et al. 2010; Zhou, et al. 2010). Enhanced P3 amplitudes point to a late compensation mechanism for the observed deficits in early inhibitory processes (i.e., reduced N2 amplitudes). Combined hypo-and hyperactivation is often found in fMRI studies, however, given the limited temporal resolution of fMRI it is not possible to draw inferences on hyperactivation as compensation in the final stage of inhibitory control. ERP findings such as those observed in excessive internet users provide clues on the exact role of hyperactivation coupled with hypoactivation. A final illustration of complementary insights from fMRI and ERP are the findings regarding error-processing in smokers. FMRI studies in smokers show reduced activation in the dorsal ACC after a performance error (De Ruiter, et al. 2012; Nestor, et al. 2011). Additionally, results from ERP studies provide details on the time frame of deficits in error-processing. In fact, ERP findings suggest that initial error detection is reduced in smokers only during cognitively challenging situations, whereas the more conscious evaluation of errors is generally reduced in smokers (Franken, et al. 2010; Luijten, et al. 2011b).

Unfortunately, not all ERP studies investigating error-processing or inhibitory control evaluated both ERN and Pe, or N2 and P3 amplitudes, respectively. The evaluation of only one ERP component limits the unique possibility of ERP research to provide information regarding the timeframe of cognitive control deficits. Therefore, it is recommended that future studies evaluate both ERN and Pe or N2 and P3 amplitudes. In addition, the neuroimaging field could make a step forward if they take advantage of current technological advances to simultaneously acquire ERP and fMRI data. By doing this, rich data sets with both high temporal and spatial resolution can be obtained and comparison of ERP and fMRI data will become more straightforward.

Limitations and strengths

Although consistent results in addicted individuals regarding neural deficits underlying cognitive control were identified, inconsistencies have been reported as well. For example, addicted individuals in some studies showed hyper-

instead of hypo-activation associated with cognitive control. Generally, the interpretation of hypo-versus hyperactivation in ERP and fMRI studies in clinical populations relative to healthy controls remains equivocal. Behavioral findings such as reduced accuracy or reaction time differences are crucial to guide the interpretation of hypo- or hyperactivation. Hypoactivation in combination with reduced accuracy is relatively straightforward and most likely signals reduced neural capacities leading to behavioral deficits. Although often observed in both ERP and fMRI studies, hypoactivation without behavioral deficits is less straightforward. One possible explanation for hypoactivation without behavioral deficits is that brain activation is a more sensitive measure to detect abnormalities in addicted individuals, which is suggested by Goldstein and Volkow (Goldstein, et al. 2011). In this context it would be interesting to investigate associations between the amount of substance use or the level of dependency on one hand and the extent of hypoactivation on the other hand. For example, accuracy on a Go/NoGo task was the same for smokers and non-smokers in the study by Galvan et al. (2011), while the level of nicotine dependence in smokers was found to be associated with hypoactivation in several prefrontal brain regions. These findings imply that hypoactivation without a behavioral deficit is indeed associated with addictive behaviors. Finally, hyperactivation coupled with intact behavioral performance is often interpreted as increased neural effort or the use of alternative cognitive strategies to reach normal levels of behavioral performance. In line with this notion, literature in the field of aging shows that initial cognitive decline is characterized by a combination of increased frontal engagement and intact behavioral performance (for review see: Goh, et al. 2009). Results in the current review should be interpreted with these considerations in mind.

Inconsistencies in results are probably due to differences in methodology, participant selection, data acquisition and analyses techniques. A strength of the current review is that we strictly selected task paradigms to measure inhibitory control and error-processing, thereby reducing variability in results due different cognitive processes evoked by different task designs. For example, studies employing the Stroop task were excluded because it is known to evoke cognitive processes such as conflict resolution, response selection and attention (Nigg 2000; Ridderinkhof, et al. 2004b), consequently ERPs in Stroop paradigms differ from those in Go/NoGo and Stop Signal paradigms (i.e., N250 and conlfict slow waves versus N2 and P3: Atkinson, et al. 2003; Chen, et al. 2011; Larson, et al. 2009). Additionally, the Stroop task employed in several fMRI studies often involved drug-related words (Ersche, et al. 2010; Goldstein, et al. 2009a; Goldstein, et al. 2010) which is known to reflect attentional bias

rather than cognitive control (Field, et al. 2008; Franken 2003). However, some findings in fMRI and PET studies employing the classic color-word Stroop task are in line with the current findings by showing reduced activation in addicted individuals in the ACC and DLPFC (Bolla, et al. 2004; Potenza, et al. 2003; Salo, et al. 2009). Despite the strict selection of task paradigms, variance within Go/NoGo and Stop Signal paradigms may still explain some of the inconsistencies in results for inhibitory control. For example, brain activation associated with inhibitory control has been found to be linearly depending on the frequency of NoGo trials (De Zubicaray, et al. 2000; Nieuwenhuis, et al. 2003). Also, Go/NoGo tasks in which NoGo trials are rather frequent (e.g., 40% or more) may reduce cognitive requirements to a level at which differences between addicted individuals and healthy controls are strongly attenuated. The same is true for task designs in which NoGo trials are predictable (e.g., in a block design). Differences in analysis techniques further contribute to inconsistencies in results. For fMRI studies, whole brain versus regions of interest analysis is a major source of variance as well as the use of different contrasts for analyses (i.e., Stop Correct minus Go versus Stop Correct minus Stop Error) and different methods to correct for multiple comparisons. Finally, anatomical localization of fMRI activation may be influenced by different naming conventions and anatomical atlases. A related issue exists in ERP studies, in which the selection of electrodes contributes to variance in results. Ideally, task design and analysis techniques should become much more standardized such that results of future studies are better comparable and may become more consistent.

Treatment implications and future research directions

Contemporary effective treatments for addiction involve pharmacotherapy, cognitive-behavior therapy and contingency management (McHugh, et al. 2010a; Rawson, et al. 2006; Van den Brink, et al. 2003). Nevertheless, relapse rates are still high so there is ample room for improvement. Several treatment targets based on the findings in this review merit further investigations. First, cognitive control capacities and underlying neural networks could be trained to increase cognitive control. It has been shown that explicit training of inhibition of drinking cues via pairing with NoGo trials is associated with a reduction in drinking behavior in social drinking (Houben, et al. 2011). Another possibility to increase inhibitory control is the direct training of hypoactive brain regions such as the ACC, IFG and DLPFC via neurofeedback techniques (see deCharms 2008 for an overview of clinical applications of real time neurofeedback). Previous research has shown that participants can regulate their ACC activation by providing them with real-time feedback on ACC activation (deCharms, et al.

2005). Another potential treatment method for addiction with the brain as a direct target is transcranial magnetic stimulation (TMS, for reviews see: Barr, et al. 2008; Feil, et al. 2010b). Repetitive stimulation of the DLPFC in depressive individuals reduced Hamilton Depression Rating Scale scores (Wassermann, et al. 2012). It would be interesting to see whether repetitive TMS can be effective in addicted individuals by improving cognitive control via stimulation of the prefrontal cortices. Specific medications with the aim to enhance cognitive functions (i.e., cognitive enhancers such as modafinil) may be another possible treatment intervention to increases cognitive functioning via its effects on catecholaminergic systems (for review see: Brady, et al. 2011). For example, modafinil improved inhibitory control in methamphetamine dependent individuals on a Go/NoGo task (Dean, et al. 2011). Generally, investigating the role of neurotransmitters in cognitive control could provide valuable insights concerning the biochemistry of cognitive control deficits. For example, cognitive control has been found to be depending on prefrontal dopamine levels (Cools, et al. 2011). The association between dopamine and cognitive control could have important implications for cognitive control deficits in addicted individuals, as it is known that substance dependence is characterized by dysfunctional dopamine systems (Volkow, et al. 2009). It is therefore possible that reduced cognitive control in addicted individuals result as a consequence of disturbances in the dopamine system. Knowledge concerning the role of neurotransmitters in cognitive control may eventually contribute to the development of new pharmacotherapies. More research into these clinical applications is needed to explore which of these potential treatment strategies may eventually be effective in the reduction of addictive behaviors.

Cognitive control capacities can also be used in clinical practice to guide treatment plans according to individual needs. It has been shown that deficits in cognitive control are associated with the reduced capacity to recognize problems with substance abuse and lower motivation to enter treatment (Severtson, et al. 2010). Furthermore, an increasing number of studies indicate that substance dependent individuals with reduced cognitive control tend to drop out in treatment programs more often (Ersche, et al. 2007). The Berkman et al. (2011) study showed that individual differences in activation in the inhibitory control network are linked to the ability to inhibit craving in daily life in order to prevent smoking. This study provides a good illustration on how neuroimaging research can develop to become valuable for clinical practice. A related line of future research is the prediction of relapse based on neuroimaging data. Furthermore, the systematic evaluation of harmful or protective effects from individual differences within the population of addicted individuals could

provide profiles of addicted individuals who suffer from or are protected against problems arising from reduced cognitive control. The findings that high levels of anxiety in alcohol dependent individuals are associated with enhanced error-processing (Schellekens, et al. 2010) imply that differences exist within addicted populations regarding cognitive control capacities. These differences may point to differential treatment options for high and low anxiety subjects. Altogether, recent findings regarding cognitive control in addicted individuals highlight the need to monitor cognitive deficits during treatment programs and suggest that cognitive capacities may be used as an indication to identify addicted individuals who are more vulnerable to relapse. It should be noted, however, that more information on how to improve reliability of neuroimaging measures is necessary for both fMRI and ERP measures to increase the applicability of neuroimaging research for clinical practice.

Besides a shift to more directly clinically relevant research, several other future research directions are important. First, the literature search for the current review paper revealed that opiate and cannabis dependent individuals have been under researched. Also, more studies in individuals showing excessive addiction-like behaviors are needed in order to provide a definite answer regarding the classification of these disorders as addictive disorders. Second, one of the most important remaining questions is the question on causality. It is not yet known whether neural deficits associated with cognitive control in addiction predispose individuals to substance use or whether they are a consequence of substance use. While it cannot be excluded that continuously repeating excessive addiction-like behaviors may cause changes in neural circuits underlying cognitive control, the correspondence of the neural deficits in behavioral addictions to those observed in substance dependent individuals suggest that substance intake alone is not sufficient to cause these neural deficits. In addition, it has been shown in animal studies that individual differences in prefrontal brain function in rats is predictive for the transition to excessive drug intake, although these kind of animal studies are still scarce (for review see: George, et al. 2010). Two types of research should be performed in order to find out whether neural deficits underlying reduced cognitive control are causes or consequences of addictions. First, neural performance associated with cognitive control in at risk populations, such as children of substance dependent parents, should be investigated. For example, a recent meta-analysis (Euser, et al. 2012) showed that the P300, which is an ERP reflecting allocation of attention resources in oddball paradigms, is reduced in offspring of substance dependent individuals, suggesting that a reduced P300 is a vulnerability marker for the development of addiction. It remains to be seen whether this is also true for

neural correlates of reduced cognitive control. Most importantly, longitudinal population based neuroimaging studies should be performed in order to see whether neural correlates of cognitive control can differentiate between individuals who will develop addiction later in life from those who do not. Finally, another relevant research questions that has not yet been investigated concerns the role of cognitive control during exposure to environmental cues associated with the addiction. Theoretically, it is expected that impairments in cognitive control are more pronounced during cue-exposure (Dawe, et al. 2004a; Goldstein, et al. 2002). However, the only study included in this review that evaluated whether the presence of drug-related cues have a negative influence on inhibitory control in smokers did not support this theory (Luijten, et al. 2011a). More studies are needed in order to clarify this issue.

Conclusions

This review is the first one that systematically evaluated ERP and fMRI findings concerning inhibitory control and error-processing in substance dependent individuals as well as in excessive addiction-like behaviors. The combined evaluation of ERP and fMRI in the current review offers new insights and future research directions. Overall, results show that substance dependence is characterized by neural deficits associated with inhibitory control and error-processing. The most consistent findings being reduced N2 and ERN amplitudes and hypoactivation in the ACC, IFG and DLPFC. In addition, preliminary evidence has been found to support the idea that excessive addiction-like behaviors are characterized by similar neural deficits as those observed in substance dependent individuals. Notably, neuroimaging research in the domain of cognitive control should use much more standardized methods in order to improve comparability between studies and to be able to contribute to the development and evaluation of treatment programs.

Chapter Three

Diminished error-processing in smokers during smoking cue exposure

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Abstract

Deficits in error-processing may contribute to the continuation of impulsive behaviors such as smoking. Previous studies show deficits in error-processing among substance abuse patients. However, these studies were all conducted during affectively neutral conditions. Deficits in error-processing in smokers may become more pronounced under affectively challenging conditions, such as during smoking cue exposure. The aim of the present study was to investigate whether smokers showed initial error-processing deficits, as measured with the error-related negativity (ERN), and decreased motivational significance attributed to an error, as measured with the error positivity (Pe) when exposed to smoking cues. Additionally, we examined the nature of the ERN and Pe amplitudes in more detail by investigating their associations with trait impulsivity, nicotine dependence levels and cigarette craving. Event-related potentials were measured during a modified Erikson flanker task in both smokers and non-smoking controls. Smokers showed reduced ERN and Pe amplitudes after making an error, accompanied by diminished post-error slowing of reaction times. These results suggest that initial error-processing and decreased motivational significance attributed to an error are affected in smokers during smoking cue exposure. Furthermore, individual variation in impulsivity and nicotine dependence were associated with reduced ERN amplitudes.

Introduction

Substance abuse is characterized by a variety of impulsive behaviors including diminished inhibitory control and the preference of immediate rewards over delayed larger rewards (Dawe, et al. 2004a; Li, et al. 2008a; Reynolds 2006; Verdejo-Garcia, et al. 2008). A common behavioral pattern that accompanies these processes is an apparent failure to learn from harmful behavior for self or others (Franken, et al. 2007). The ability to monitor ongoing performance is a crucial function of the human brain in order to adapt behavior appropriately to situational demands and to continue goal directed behavior (Ridderinkhof, et al. 2004b). Deficits in error-processing may, therefore, contribute to the continuation of impulsive behaviors (such as drug use) despite negative consequences. Hypothetically, the impulsivity observed in substance abuse patients may result from the fact that errors are processed in a limited way and are therefore not detected optimally.

The processing of errors can be measured both at behavioral and physiological levels. On the electrophysiological level, at least two different error-related brain waves can be distinguished in the Event-Related Potential (ERPs: Falkenstein, et al. 2000; Herrmann, et al. 2004). The Error-Related Negativity (ERN) arises after 50-80 milliseconds after making an error in speeded response tasks and is followed by the ongoing error positivity (Pe) potential. The ERN and the Pe are regarded as two independent components of error-processing (Herrmann, et al. 2004; Overbeek, et al. 2005). The ERN is a fast and automatic response reflecting initial error detection (Bernstein, et al. 1995). A growing body of evidence supports the notion that the ERN is modulated by dopaminergic brain systems (Holroyd, et al. 2002). Haloperidol, a dopamine (DA) antagonist, significantly attenuated ERN amplitudes to self-detected errors during a flanker task (Zirnheld, et al. 2004). In contrast, the indirect DA agonist d-amphetamine leads to an enlargement of ERN amplitudes (De Bruijn, et al. 2004). The reinforcement learning theory predicts that a disruption of the mesencephalic dopamine system should affect the ERN (Holroyd, et al. 2002; Holroyd, et al. 2009). This theory further suggests that the ERN arises from a dopaminergic midbrain learning signal that is conveyed to the anterior cingulate cortex. Converging evidence indeed indicates that the anterior cingulate cortex is the neural generator of the ERN (Gehring, et al. 2000; Herrmann, et al. 2004; Mathalon, et al. 2003; Miltner, et al. 2003b; Ridderinkhof, et al. 2004a; Stemmer, et al. 2004; Van Veen, et al. 2002).

The Pe has been linked with the motivational significance attributed to an error (Falkenstein, et al. 2000) and the more conscious reflection on an error (Overbeek, et al. 2005). Recent research confirmed that the Pe covaried with the stimulus locked P3 that is known to be involved in conscious processing of motivationally significant events (Ridderinkhof, et al. 2009).

Very few ERP studies investigated error-processing in substance dependence (Franken, et al. 2007; Franken, et al. 2010; Sokhadze, et al. 2008). Results of studies among cocaine dependent patients suggest a disruption in the brain's error-processing system as indicated by reduced ERN (Franken, et al. 2007; Sokhadze, et al. 2008) and Pe amplitudes (Franken, et al. 2007). In a study among smokers, Franken et al. (2010) did not show reduced ERN amplitudes, but did show reduced Pe amplitude as compared to controls, suggesting that initial error-processing seems to be intact, while the motivational significance attributed to errors might be compromised. Interestingly, these findings of affected error-processing are not specific to substance abusers. Reduced error-processing has also been observed in ADHD patients (Liotti, et al. 2005; Van Meel, et al. 2007; Zhang, et al. 2009), in psychopaths (Brazil, et al. 2009; Munro, et al. 2007) and in borderline personality disorder patients (Ruchsow, et al. 2006). Results of these studies are in line with a recent theory proposing that patients with externalizing psychopathology share the inability to monitor performance errors (Hall, et al. 2007; Olvet, et al. 2008). These similarities in error-processing among clinical populations may be the result of shared personality traits in externalizing psychopathology including sensitivity to reward and enhanced impulsivity levels. Reduced ERN components in high impulsive people in the normal population provide further support for the idea that reduced error-processing may be related to personality traits (Potts, et al. 2006; Ruchsow, et al. 2005).

Although Franken et al. (2010) suggest that initial error-processing is intact in smokers, possible error-processing deficits may remain undetected unless the smoker is tested in more challenging environments, such as during smoking cue exposure. A possible mechanism for enhanced cognitive deficits during cue exposure is that through the course of developing nicotine addiction, increased incentive salience has been assigned to smoking-related cues, which results in increased attentional priority given to these cues (Field, et al. 2008; Franken 2003; Littel, et al. 2007; Robinson, et al. 2008). This attentional bias for smoking-related cues might reduce the overall cognitive resources available to monitor ongoing behavior resulting in reduced ERN and Pe amplitudes. The possibility that cue exposure may interfere with error-processing is further supported by the idea that both cue exposure and error-processing are depending

on dopamine release in the ventral striatum (Brody, et al. 2004; Holroyd, et al. 2002) suggesting that cue exposure may change the ERN by changing the underlying dopaminergic system. A previous study among psychopaths indeed showed a reduced ERN during an emotion recognition task, but not during an affective neutral task (Munro, et al. 2007), suggesting that error-processing is indeed dependent on the presence of environmental, motivational relevant, stimuli. Therefore, the current study investigated error-processing in smokers and non-smoking controls while being exposed to smoking cues. For this purpose, the Erikson Flanker task was adapted by adding smoking-related pictures. It is expected that error-processing will be reduced in smokers as compared to controls while being exposed to these smoking-related cues. More specifically, we expect to find reduced post-error slowing of reaction times on the behavioral level and reduced ERN and Pe components at the physiological level. Additionally, we examined the nature of the ERN and Pe amplitudes in more detail by investigating their associations with trait impulsivity, severity of nicotine dependence and cigarette craving.

Materials and Methods

Participants

Nineteen smokers and 20 non-smoking controls participated in this study. Exclusion criteria for both groups were (a) drug abuse other than nicotine and alcohol, and (b) indications of current physical or psychological illness. Six smokers and 6 non-smokers were excluded from analyses because they had less than ten artifact free error-related EEG epochs (due to too few errors, n = 5, or too much artifacts, n = 7). The final group consisted of 13 smokers (mean age = 20.7 years, *SD* = 1.3, 9 male) and 14 non-smokers (mean age = 21.4 years, *SD* = 2.6, 10 male). The mean age (*t* = .96, ns) and gender ratio (chi-square = .02; ns) of the smoker and non-smoker groups did not differ. Smokers smoked at least 10 cigarettes a day (mean = 16.8 cigarettes per day, range = 10-25) for a duration of at least two years (mean = 4.6 years, range = 2-7). The Fagerström test for nicotine dependence (FTND) served as a measure of nicotine dependence in smokers (mean score = 5.0, range = 0-8) and suggested medium levels of nicotine dependence (Heatherton, et al. 1991; Vink, et al. 2005). Non-smokers had smoked ten or less cigarettes lifetime (mean = 1.6 cigarettes lifetime, range = 0-10). Participants consisted of undergraduate psychology students, who received course credit or a small financial compensation for participation. The

study was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written informed consent of the subjects. The ethics committee of the Institute of Psychology of the Erasmus University Rotterdam approved the study.

Instruments

Breath carbon monoxide concentration was measured using a Micro+ Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) to objectively define smokers and non-smokers. The impulsiveness subscale of the Dutch version of the I7 questionnaire (Lijffijt, et al. 2005) was used to measure trait impulsivity. Several questionnaires were used in order to investigate possible confounders. Alcohol consumption, both quantity and frequency, was measured using a QF-index (Lemmens, et al. 1992). The positive affect negative affect scale (PANAS: Watson, et al. 1988) and the Snaith-Hamilton Pleasure Scale (SHAPS: Snaith, et al. 1995) were used to measure mood state and anhedonia. In addition, smokers completed the FTND to measure nicotine dependence and the Questionnaire of Smoking Urges (QSU: Cox, et al. 2001) to indicate their subjective craving for a cigarette.

Task paradigm

A modified version of the Erikson Flanker Task was developed for the purpose of the current study (see figure 1). Participants had to indicate the direction of the middle arrow with a button press using left and right index fingers. To increase the amount of errors, participants were instructed to respond as fast as possible. In the beginning of each trial participants saw a warning sign (^) for a random duration between 300 and 500ms, after which two rows of five horizontal flanker arrows appeared. The middle arrow in both rows was either congruent or incongruent with the direction of the flanker arrows. The proportion of congruent and incongruent trials was equal. Pictures with smoking-related content or non smoking-related content were semi-randomly presented in between the five flanker arrows. Arrows and pictures remained on the screen until the button press. A blank screen appeared with a randomly varying duration between 600 and 800ms before a feedback symbol (a green plus sign for correct trials or a red minus sign for incorrect trials) was presented for 400ms. Seventy-five smoking-related pictures and 75 non-smoking pictures were each presented six times during the total of 900 trials. Sixteen practice trials were presented before the start of the task and four rest periods were included during task presentation. Smoking-related pictures showed people engaged in smoking behavior or

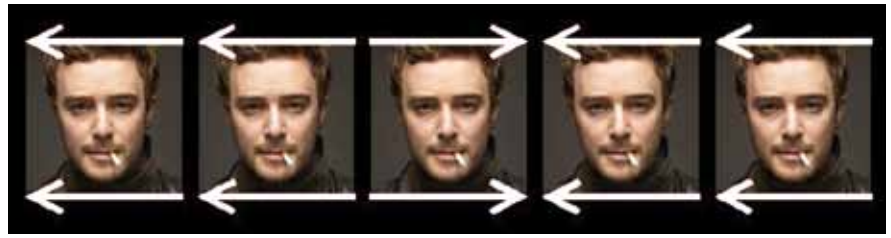

Figure 1

Example of an incongruent trial combined with a smoking cue picture during the modified affective Flanker task

smoking-related objects, whereas non-smoking pictures showed people engaged in non-smoking behavior or neutral objects. The proportion of smoking and non-smoking pictures displaying persons versus objects was equal for both picture categories. In addition, smoking and non-smoking pictures where matched on gender of the displayed persons and visual complexity (e.g., number of objects on the picture).

Procedure

Smokers were instructed to abstain from smoking for at least one hour before the experiment. This short period of smoking deprivation was introduced in order to reduce the acute effects of nicotine on ERP amplitudes (Houlihan, et al. 1996; Houlihan, et al. 2001) without introducing strong withdrawal effects. After arrival, participants approved participation by signing informed consent. The CO breath sample was taken and the questionnaires were completed. Subsequently, participants were seated in a comfortable EEG chair in a light and sound-attenuated room. Electrodes were attached and task instructions were explained, after which the smoking Flanker task was started. Smokers completed the QSU again after completing the task.

EEG recording and data reduction

The EEG was recorded using the Biosemi Active-Two amplifier system from 34 scalp sites (10-10 system, and two additional electrodes at FCz and CPz) mounted in an elastic cap. Six additional electrodes were attached to left and right mastoids, two outer canthi of both eyes (HEOG), and infraorbital and supraorbital regions of the right eye (VEOG). All signals were digitalized with a sample rate of 512 Hz and 24-bit A/D conversion with a bandpass of 0-134 Hz.

Data were off-line re-referenced to computed mastoids. Off-line, EEG and EOG activity was filtered with a bandpass of 0.10-30 Hz (phase shift-free Butterworth filters; 24dB/octave slope). Data were segmented in epochs of 1 second (200ms before and 800ms after response or stimulus presentations). After ocular correction (Gratton, et al. 1983) epochs including an EEG signal exceeding ± 75 μV were excluded from the average. The mean 200 ms pre-response or pre-stimulus period served as baseline. After baseline correction, average ERP waves were calculated for artifact-free trials at each scalp site for correct and incorrect responses separately. The ERN was defined as the mean value in the 25-75 ms time segment after onset of the response. The Pe was defined as the mean value in the 250-350 ms time segment after onset of the response. Both the ERN and Pe were studied at the midline electrodes, FCz, Cz and CPz. The chosen time windows include ERN and Pe peaks at these midline electrodes as observed in many studies (Overbeek, et al. 2005). In addition, stimulus locked ERP's were calculated by the mean ERP activity between 200 and 300 ms for the N2, 300 and 500 ms for the P3 and 500 and 800 ms for the slow wave at the same midline electrodes.

Statistical analyses

Group differences on demographics and questionnaire data were analyzed using independent sample t-tests. The difference in self-reported craving before and after task performance was analyzed by means of a paired sample t-test. Repeated measures (RM) ANOVA's were used to analyze task performance and ERP data with Greenhouse-Geisser adjusted p-values. Group (smokers versus non-smokers) was used as a two-level between subjects factor in all RM-ANOVA's. Post-hoc tests for interactions were performed only for interactions including the between subject factor Group. For all analyses, the .05 level of significance was employed and a Bonferroni correction was applied in post-hoc analyses.

The current task design resulted in the following two-level within subject factors of interest (a) Congruency (congruent versus incongruent arrow direction); (b) Picture (smoking versus neutral pictures); (c) Correctness (correct versus incorrect trials) and (d) Post-correctness (reaction times on post-correct versus post-incorrect trials; a commonly used measure for between group comparisons on post-error slowing; Brazil, et al. 2009; Franken, et al. 2007; Franken, et al. 2010; Jonkman, et al. 2007; Munro, et al. 2007; Potts, et al. 2006; Rabbitt 1966a; Rabbitt 1966b; Van Meel, et al. 2007). For the behavioral accuracy (percentage of errors) we employed a Group x Congruency x Picture RM-ANOVA. Three RM-ANOVA's were employed for mean reaction time (RT) data: (1) Group x Congruency x Picture, (2) Group x Correctness and (3) Group x Post-correctness. Electrode (FCz, Cz, CPz) was included as a three-level within subject factor in all ERP analyses. The number of analyzable ERN and Pe epochs did not differ between smokers (mean = 23.8, *SD* = 10.3) and controls (mean = 20.1, *SD* = 11.3), $t(25) = 0.46$, ns. However, the number of epochs was too small (i.e., resulted in too few segments for each category) to include the Picture within subject factor in the ERN and Pe analyses. Therefore a Group x Electrode x Correctness RM-ANOVA was conducted for the ERN and Pe. To further investigate the nature of the ERN and Pe peaks we calculated Spearman's rho correlation coefficients with trait impulsivity across groups and with nicotine dependence and the increase in self-reported craving in smokers only. These correlations were performed separately for correct and incorrect trials and with FCz, Fz and CPz averaged together in order to avoid multiple comparisons. For each stimulus locked ERP (N2, P3, slow wave) a Group x Electrode x Congruency x Picture RM-ANOVA was conducted.

Results

Breath CO levels and questionnaires

As expected, smokers showed higher carbon monoxide (CO) parts per million concentration (mean CO = 11.6, *SD* = 6.4) than non-smoking controls (mean CO = 1.1, *SD* = 1.2), $t(25) = 6.1$, $p < 0.001$. Smokers and controls did not differ on positive and negative affect as measured by the PANAS, on anhedonia as measured by the SHAPS, and on habitual alcohol drinking patterns, that is alcohol drinking quantity and frequency. However, smokers scored higher (mean = 10.1, *SD* = 4.4) than controls (mean = 6.4, *SD* = 4.3) on the impulsiveness subscale of the Dutch version of the I7 questionnaire, $t(25) = 2.3$, $p < .05$, which indicates that smokers reported higher trait impulsivity levels than non-smokers. Subjective craving in smokers was significantly increased after task performance, $t(12) = 4.7$, $p = .001$.

Behavioral data

Table 1 shows the percentages of errors and reaction times for both groups on the affective flanker task. A robust main effect for congruency, $F(1,25) = 34.0$, $p < .001$, $\eta^2 = 0.58$ showed that more errors were made on incongruent than on

congruent trials (mean difference = 2.7%). No main effect of Picture was observed. There was no overall effect of Group on percentage of errors, neither an interaction effect including Group, suggesting similar percentage of errors between smokers and non-smokers regardless of Congruency and Picture type.

A main effect for Congruency, $F(1,25) = 67.3$, $p < .001$, $\eta^2 = 0.73$ on reaction times, showed the expected effect that reaction times to incongruent trials were longer than to congruent trials (mean difference 13.23 ms). No main effect of Picture was observed. Also as expected, a main effect of Correctness showed that reaction times to incorrect trials were faster than reaction times to incorrect trials, $F(1,25) = 42.0$, $p < .001$, $\eta^2 = 0.63$ (mean difference 66.65 ms). Furthermore, a main effect for Post-correctness, $F(1,25) = 17.6$, $p < .001$, $\eta^2 = 0.41$ showed that reaction times to trials following an incorrect trial were longer than reaction times to trials that followed a correct trial (mean difference 22.93 ms). No main effect for Group was observed nor interactions between group and one or more of the within-factors Congruency, Picture and Correctness.

Table 1

Percentage errors and reaction times in milliseconds on the affective flanker task. Standard deviations are displayed in brackets

	Non-Smokers	Smokers
Percentage errors smoke incongruent	6.2 (2.6)	5.7 (4.0)
Percentage errors smoke congruent	3.8 (3.2)	4.0 (2.8)
Percentage errors neutral incongruent	5.7 (3.9)	7.2 (4.2)
Percentage errors neutral congruent	3.0 (1.9)	3.4 (2.9)
Reaction time smoke incongruent	390 (54)	376 (40)
Reaction time smoke congruent	381 (52)	362 (35)
Reaction time neutral incongruent	394 (53)	376 (42)
Reaction time neutral congruent	378 (52)	364 (35)
Reaction time correct trials	389 (57)	374 (37)
Reaction time incorrect trials	328 (55)	302 (51)
Reaction time post-correct trials	384 (52)	370 (37)
Reaction time post-incorrect trials	418 (62)	381 (44)

However, a significant interaction effect of Group x Post-correctness, $F(1,25) = 4.4$, $p < .05$, $\eta^2 = 0.15$ was found. Post-hoc tests showed that the difference between post-incorrect and post-correct was significant for non-smokers, $t(13) = 4.7$, $p < .001$, but not for smokers. These results indicate that non-smokers adjusted their behavior after making an error by slowing down reaction times, whereas smokers did not. In addition, a negative correlation, $r = -.40$, $p < 0.05$, between post error slowing (defined as the difference between averaged reaction times for post error trials versus post correct trials) and the overall percentage of errors showed that post error slowing is related to more accurate task performance.

Event-related potentials

ERN

ERN and Pe amplitudes at the midline electrodes on correct and incorrect trials are displayed in figure 2. As expected, a significant main effect was found for Correctness $F(1,25) = 120.14$, $p < .001$, $\eta^2 = 0.83$ on the ERN at the midline electrodes showing that ERN amplitudes were larger for incorrect trials than for correct trials. We also found a significant main effect for Electrode, $F(2,50) = 56.10$, $p < .001$, $\eta^2 = 0.69$. No main effect was found for Group. The Group x Correctness x Electrode interaction was not significant $F(2,50) = 1.74$, ns. The interaction effect for Electrode x Correctness was significant $F(2,50) = 11.81$, $p = 0.001$, $\eta^2 = 0.32$ and, most importantly, an interaction effect for Group x Correctness was found $F(1,25) = 7.83$, $p = .01$, $\eta^2 = 0.24$. Post-hoc analysis indicated that the ERN to incorrect trials was significantly reduced in smokers as compared to non-smokers $t(25) = 2.09$, $p < .05$. Smokers and non-smokers did not differ on correct trials.

Pe

As expected, a main effect for Correctness was found $F(1,25) = 15.02$, $p = .001$, $\eta^2 = 0.38$ on the Pe amplitude, being larger for incorrect trials than for correct trials. No significant main effect was found for Electrode. A significant main effect of Group was found, $F(1,25) = 8.82$, $p < .01$, $\eta^2 = 0.26$ which showed that smokers have overall lower Pe amplitudes. The Group x Correctness x Electrode interaction was not significant. Furthermore, the interaction effect for Electrode x Correctness was non significant. Importantly, the interaction effect for Group x Correctness was significant $F(1,25) = 5.07$, $p < .05$, $\eta^2 = 0.17$. Post-hoc analysis indicated that the Pe to incorrect trials was significantly reduced in smokers as compared to non-smokers $t(25) = 3.00$, $p < .01$. Smokers and non-smokers did not differ on correct trials.

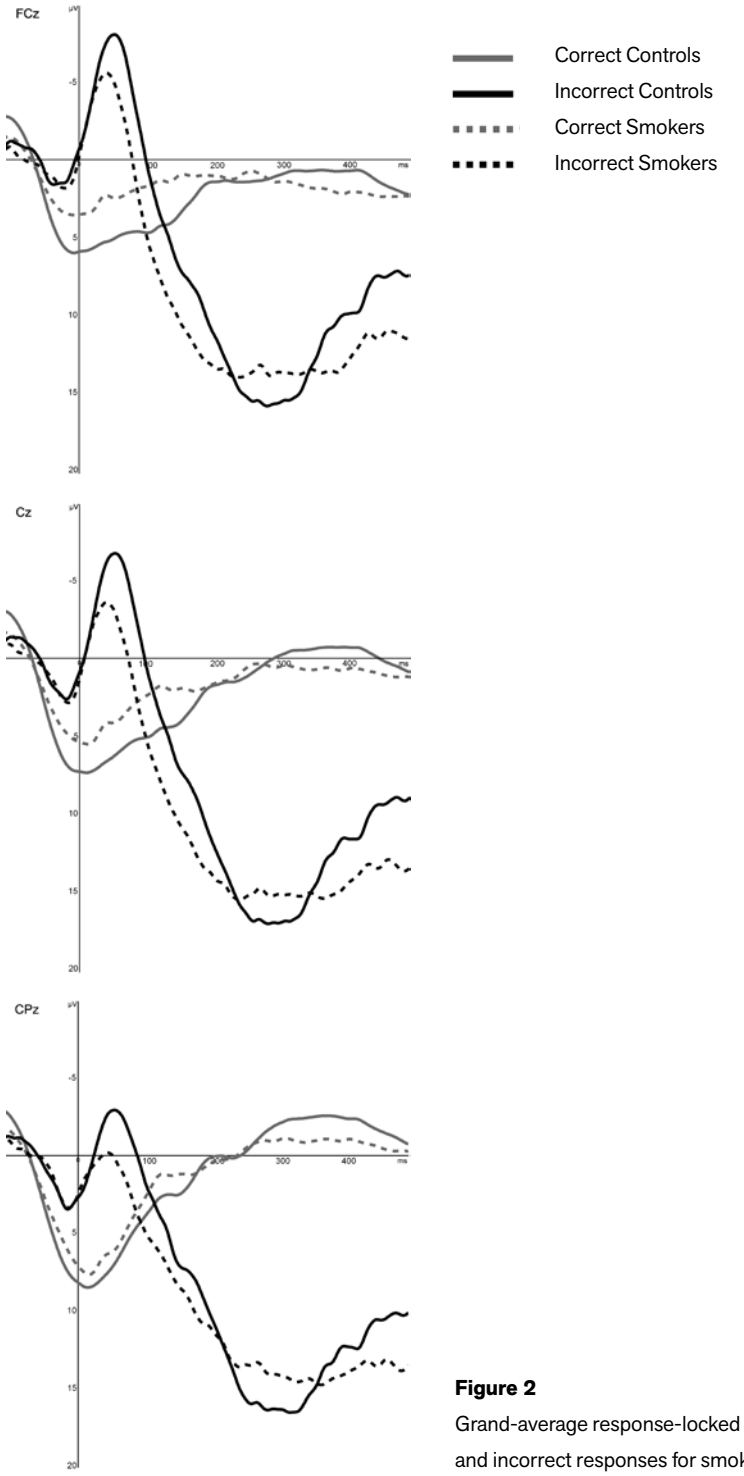

Figure 2

Grand-average response-locked waveforms at FCz, Cz, CPz of correct and incorrect responses for smokers and non-smoking controls

Table 2

Correlations between Impulsiveness, Nicotine dependence, Craving and mean ERN and Pe responses over FCz, Cz and CPz (collapsed)

	ERN incorrect trials	ERN correct trials	Pe incorrect trials	Pe correct trials
Impulsiveness[a]	*r* = .44[c]	*r* = .04	*r* = -.09	*r* = 0.20
Nicotine Dependence[b]	*r* = .69[d]	*r* = - .20	*r* = .19	*r* = .09
Craving[b]	*r* = .14	*r* = .23	*r* = -.03	*r* = .00

Note table 2 *[a] Correlations includes smokers and non-smokers, [b] Correlations includes smokers only, [c] significant at the .05 level, [d] significant at the .01 level.*

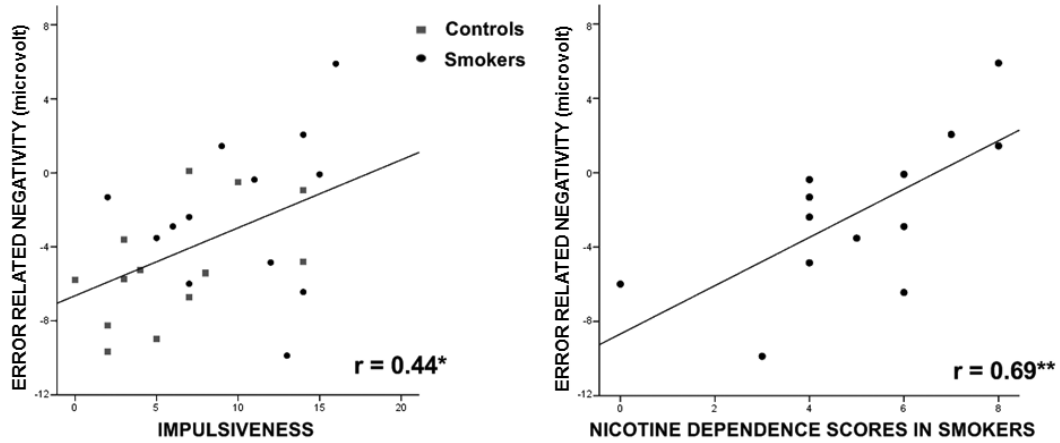

Figure 3

Correlation between the mean amplitude of the Error Related Negativity for incorrect responses and self-reported trait impulsivity (left panel) and nicotine dependence levels (right panel).

Note figure 3 ** significant at the .05 level, ** significant at the .01 level.*

Correlations

Correlations between ERN and Pe components with trait impulsivity, FTND scores and self-reported craving are displayed in table 2 and figure 3. Results show that reduced ERN amplitudes on incorrect trials across groups are associated with higher levels of impulsiveness, $r = .44$, $p < .05$, just like stronger nicotine dependence in smokers, $r = .69$, $p < .01$. Higher self-reported craving is not related to magnitude of ERN response. No significant correlations were found on Pe amplitudes.

Stimulus locked ERPs

Data analysis did not reveal any significant main effect of Group, or interaction effects including Group on stimulus locked ERP components including the N2, P3 and slow wave.

Discussion

The current study showed behavioral and physiological evidence of reduced error-processing in smokers during a task in which participants were exposed to smoking cues. More specifically, this study showed reduced ERN and Pe amplitudes following incorrect responses and accompanied diminished post-error slowing in smokers as compared to non-smoking controls. In addition, self-reported levels of impulsivity, which were higher in smokers, were associated with a reduced ERN across smokers and non-smokers. Moreover, higher nicotine dependence levels among smokers were also associated with smaller ERN responses. On the behavioral level, smokers showed less post-error slowing than non-smoking controls suggesting that also behavioral adaptation (e.g., slowing down after an incorrect response in order prevent another error) is reduced in smokers. However, it must be noted that smokers and non-smokers made comparable numbers of errors. Both groups made more errors on incongruent trials and were faster to respond on error trials. Analyses of stimulus locked ERP waves further suggest that the findings of reduced error-processing in smokers are not influenced by an overall reduced cognitive ability that may arise as a result of possible withdrawal effects, as no differences between smokers and non-smokers were found on the stimulus locked ERPs.

Reduced error-processing in smokers is in line with previous ERP studies in cocaine users (Franken, et al. 2007; Franken, et al. 2010; Sokhadze, et al. 2008) and smokers (Franken, et al. 2010). Furthermore, several functional imaging studies show reduced activation in the ACC related to error-processing in various substance use disorder patients including opiate (Forman, et al. 2004), cocaine (Kaufman, et al. 2003), cannabis (Hester, et al. 2009b), and methamphetamine (London, et al. 2005) abusers. As expected, we did find a reduced ERN in smokers, in contrast to a previous study of our lab (Franken, et al. 2010). A plausible explanation for this discrepancy is the exposure to smoking-related cues during task performance in the current study. Unfortunately, this hypothesis could not directly been tested because participants made not enough errors to analyze error trials for smoking and neutral pictures separately. However, the idea that smoking cues influence the cognitive state of smokers is supported by the significant increase in craving for cigarettes following task performance. The current results, in combination with those of Franken et al. (2010), therefore suggest that fast and automatic error-processing may be specifically compromised in smokers when limited cognitive resources are available for error monitoring such as during exposure to smoking cues. Munro et al. (2007) found similar results related to psychopathy. Violent offenders showed reduced ERN amplitudes only during emotion recognition and not during a neutral task paradigm. However, findings of a study of Wiswede et al. (2009) offer an alternative explanation for the reduced ERN in smokers. Wiswede et al. found that ERN amplitudes in healthy controls are enlarged after viewing unpleasant pictures. It may be that the current sample of non-smoking controls considers the smoking pictures as unpleasant and consequently had larger ERN amplitudes than the smokers.

The reduced Pe in smokers confirms the Franken et al. (2010) finding that the motivational significance attributed to an error may be diminished in smokers. It appears that smokers not only process their errors less intensely, they seem to be less worried by their mistakes. However, self-report studies are needed to confirm this finding. Furthermore, the Pe in the current study is, in contrast to the ERN, not correlated with trait impulsivity or nicotine dependence levels, which is in line with the idea that the Pe and ERN reflect independent processes (Overbeek, et al. 2005; Ridderinkhof, et al. 2009).

The finding in the current study that higher levels of self-reported trait impulsivity across groups are related to lower ERN amplitudes provides further evidence for the idea that personality traits may be associated with reduced error-processing. Ruchsow et al. (2006) demonstrated similar results in

borderline personality disorder patients. They showed reduced ERN amplitudes in borderline personality disorder patients and correlations with enhanced impulsivity and reduced ERN components. Studies performed in the normal population also confirm that high levels of impulsivity are related to lower ERN amplitudes (Potts, et al. 2006; Ruchsow, et al. 2005). These studies, together with the findings of the current study, provide evidence for the idea that impulsivity may explain reduced error-processing in smokers. Note, however, that enhanced impulsivity in smokers was found on self-reported trait impulsivity, while smokers did not show diminished impulse control on behavioral performance indices of the adapted Flanker task. This clearly suggests that although self-reported trait impulsivity and behavioral errors both reflect impulsivity, they tap different aspects of impulsivity (Alderson, et al. 2007; Van Mourik, et al. 2005). More research is needed to elucidate the discrepancy between self-reported and behavioral impulsivity. Furthermore, the current study design does not allow drawing conclusions on causality. It may be that impulsivity and reduced error-processing are a predisposition to start smoking, or that impulsive behavior, including smoking, contributes to diminished error-processing. However, since the ERN in smokers in the current study also varied with the degree of nicotine dependence, an impulsive predisposition cannot fully explain diminished error-processing. Other characteristics specific for nicotine dependence may have a complementary effect on the deficit in error-processing. A possible explanation for the association between the level of nicotine dependence and reduced ERN amplitudes is the compromised function of the dopaminergic system in the ventral striatum in addiction (Volkow, et al. 2009). In either case, reduced error-processing undermines the ability to monitor ongoing behavior and may be related to the continuation of addiction-related behaviors.

A limitation of the current study is the relatively small size of the samples, such that replication of the current results in larger groups of participants is essential. In addition, it must be kept in mind that the present smokers are relative young smokers in an early stage of smoking dependence. Although generalization to other categories of smokers is limited, the current sample of smokers can be considered heavy smokers within the student population of smokers (Berg, et al. 2010), which is further supported by moderate levels of FTND scores (Heatherton, et al. 1991).

To conclude, results of the current study showed reduced error-processing in smokers both at the behavioral and physiological level. Decreased ERN and Pe amplitudes in smokers were accompanied by reduced post-error

slowing. Furthermore, self-reported impulsivity levels were associated with reduced ERN amplitudes in smokers and non-smokers and nicotine dependence was associated with lower ERN amplitudes in smokers specifically. Together, these results suggest that both personality traits and specific nicotine dependent characteristics, such as a disturbed dopamine system, are associated with diminished error-processing. Since adequate error-processing is required to adapt behavior properly, reduced error-processing may contribute to the development and maintenance of addictive behaviors.

Acknowledgements

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Chapter Four

Deficits in inhibitory control in smokers during a Go/NoGo task: An investigation using event-related brain potentials

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Abstract

Introduction The role of inhibitory control in addictive behaviors is highlighted in several models of addictive behaviors. Although reduced inhibitory control has been observed in addictive behaviors, it is inconclusive whether this is evident in smokers. Furthermore, it has been proposed that drug abuse individuals with poor response inhibition may experience greater difficulties not consuming substances in the presence of drug cues. The major aim of the current study was to provide electrophysiological evidence for reduced inhibitory control in smokers and to investigate whether this is more pronounced during smoking cue exposure.
Methods Participants (19 smokers and 20 non-smoking controls) performed a smoking Go/NoGo task. Behavioral accuracy and amplitudes of the N2 and P3 event-related potential (ERP), both reflecting aspects of response inhibition, were the main variables of interest.
Results Reduced NoGo N2 amplitudes in smokers relative to controls were accompanied by decreased task performance, whereas no differences between groups were found in P3 amplitudes. This was found to represent a general lack of inhibition in smokers, and not dependent on the presence of smoking cues.
Conclusions The current results suggest that smokers have difficulties with response inhibition, which is an important finding that eventually can be implemented in smoking cessation programs. More research is needed to clarify the exact role of cue exposure on response inhibition.

Introduction

Several contemporary models of addiction highlight the role of impulsivity and executive functioning in the development and maintenance of addiction (Dawe, et al. 2004a; Feil, et al. 2010a; Field, et al. 2008; Goldstein, et al. 2002; Jentsch, et al. 1999; Olmstead 2006; Verdejo-Garcia, et al. 2008; Wiers, et al. 2007). A core component of executive functioning is response inhibition which is generally defined as the ability to adaptively suppress behavior when environmental contingences demand this (Groman, et al. 2009). It has been proposed that poor response inhibition in substance-dependent individuals is associated with difficulties to resist the consumption of a substance especially when exposed to highly salient substance-related cues (e.g., Dawe, et al. 2004a).

Reduced response inhibition has been observed in several substances dependent patient populations including alcohol (Rubio, et al. 2008), cocaine (Fillmore, et al. 2002), and opioid (Fu, et al. 2008) dependent patients. Some studies have also investigated response inhibition in smokers. In these studies, inhibitory control was generally assessed by means of behavioral paradigms, such as Go/NoGo tasks. In the Go/NoGo task, participants have to respond as quickly as possible to frequently occurring 'Go' stimuli, and to inhibit responses to infrequent 'NoGo' stimuli. Results of studies on response inhibition in smokers have been inconsistent. That is, some studies have found response inhibition during a Go/NoGo task to be impaired in smokers relative to controls (Spinella 2002) whereas other studies did not find this group difference in performance on the Go/NoGo task (Dinn, et al. 2004), nor on other behavioral tasks measuring response inhibition (Monterosso, et al. 2005; Reynolds, et al. 2007). The recording of electroencephalographic (EEG) activity during response inhibition has been suggested to yield more sensitive indices (i.e., event-related potentials, ERPs) of response inhibition and may therefore clarify the inconsistent results. Two major ERP components have been reported to be enhanced for NoGo trials as compared to Go trials suggesting that these reflect changes in brain activity related to response inhibition in a Go/NoGo task. The first of these ERP-components is the NoGo N2 which is a negative wave that emerges approximately 200-300 ms after stimulus presentation and has maximum peaks on frontal scalp sites. Mounting evidence suggests that the NoGo N2 amplitude is a valuable measure for response inhibition. The NoGo N2 amplitude has been consistently found to be related to behavioral outcomes of inhibitory control on Go/NoGo tasks (Falkenstein, et al. 1999) irrespective of the stimulus modality used in these tasks (Kaiser, et al. 2006; Nakata, et al. 2004). Although, Go and NoGo trials differ with respect to the overt motor response, which could

influence the difference between Go and NoGo N2 amplitudes, it has been found that the NoGo N2 is not restricted to tasks requiring these overt motor responses (Burle, et al. 2004), furthermore a modulation of the N2 ERP by response inhibition requirements has been observed in other inhibition-related paradigms besides the Go/NoGo task (Dimoska, et al. 2006; Heil, et al. 2000; Kopp, et al. 1996).

The second ERP component that has been associated with response inhibition research, is the NoGo P3 which is a positive wave that emerges circa 300-500 ms after stimulus onset and has a more central distribution. There are some concerns about the exact role or meaning of P3 amplitudes in response inhibition processes (Falkenstein, et al. 1999; Smith, et al. 2008). In contrast to the NoGo N2, the NoGo P3 does not seem to be consistently related to response inhibition on a behavioral level. However, some studies show a clear relationship between NoGo P3 amplitude and behavioral outcomes of response inhibition tasks (Bruin, et al. 2002; Burle, et al. 2004). Moreover, because the P3 is a rather late ERP-component (> 300 ms) it has been suggested that it does not reflect the initial reflexive stage of the inhibition process but rather a later stage of the inhibition process that is closely related to the actual inhibition of the motor system in the premotor cortex (Dimoska, et al. 2006; Kok, et al. 2004). In any event, both decreased NoGo P3 and N2 amplitudes have been reported in various populations with reduced inhibitory control such as children with ADHD (Johnstone, et al. 2009; Smith, et al. 2004) and impulsive violent offenders (Chen, et al. 2005) suggesting that both ERP components are adequate indices of inhibitory processes in impulsive populations.

Few studies have used ERPs to investigate response inhibition with ERPs in substance-dependent patients (Evans, et al. 2009; Gamma, et al. 2005; Kamarajan, et al. 2005; Pfefferbaum, et al. 1987; Yang, et al. 2009) and, to our knowledge, only one of these studies has focused on smokers (Evans, et al. 2009). Remarkably, with the exception of the study by Yang et al. (2009), analyses of all these studies were confined to the P3 amplitude whereas studies in other psychiatric populations have usually investigated both the N2 and P3 amplitudes (Chen, et al. 2005; Johnstone, et al. 2009; Kaiser, et al. 2003; Kiehl, et al. 2000; Kim, et al. 2007; Ruchsow, et al. 2007; Ruchsow, et al. 2008a; Ruchsow, et al. 2008b; Smith, et al. 2004). ERP studies investigating response inhibition in substance-dependent patients have generally found NoGo P3 amplitudes to be reduced (Evans, et al. 2009; Gamma, et al. 2005; Kamarajan, et al. 2005) as compared to healthy controls. However, in heroin patients only the NoGo N2 amplitude appeared to be reduced; no differences were found on the NoGo P3 (Yang, et al. 2009).

All the above-mentioned studies investigated general response inhibition in addicted individuals by using affectively neutral task paradigms. It has been proposed, however, that the reactivity to conditioned drug-related stimuli and processes of executive functioning may impact each other in a synergistic way (Dawe, et al. 2004a; Jentsch, et al. 1999). This means that persons with a stronger reactivity towards drug-related cues may experience more problems with inhibiting their behavior. Over the course of addiction drug-related stimuli become extremely attractive to the addicted person and tend to grab the attention (i.e., attentional bias: Field, et al. 2008; Franken 2003). A recent study demonstrated that participants' attentional bias for alcohol-related words was positively correlated with reduced inhibitory control in decision-making, particularly when the decisions were related to obtaining alcohol (Field, et al. 2007). Altogether, a reciprocal relation between the attention grabbing properties of drug cues and inhibitory control has been proposed suggesting that decreased inhibitory control may be more enhanced during direct exposure to drug-related stimuli (Field, et al. 2008).

To test the idea that inhibitory control in substance-dependent individuals is particularly impaired in the presence of substance-related cues, the current study investigated response inhibition to both neutral and smoking-related cues in smokers and non-smoking controls. For this purpose a novel Go/NoGo paradigm was developed including smoking and neutral pictures. It is expected that smokers will generally show reduced response inhibition as compared to non-smoking controls. More specifically, on a behavioral level, it is expected that smokers will make more mistakes when they have to inhibit their response to infrequent NoGo stimuli. On an electrophysiological level we expect that N2 and P3 amplitudes during NoGo trials will be decreased in smokers as compared to non-smokers. Finally, we expect these effects to be more pronounced on trials which include smoking-related stimuli.

Materials and Methods

Participants

Nineteen smokers (mean age = 21.36 years, *SD* = 1.98, 14 male) and 20 non-smoking controls (mean age = 21.55 years, *SD* = 2.18, 14 male) participated in this study. Exclusion criteria were (a) the current abuse of a substance (other than nicotine for the smoking group), and (b) the current presence of a physical

or psychiatric illness. There were no significant differences between the groups in mean age, $t(37) = .27$; ns, or gender ratio, χ^2 (1, n = 39) = .07; ns. Smokers smoked at least 10 cigarettes per day (*M* = 17.95, *SD* = 5.88; range 10-30) for a duration of at least two years (*M* = 5.74, *SD* = 3.53, range = 2-17). Fagerström scores (FTND) were suggestive of medium levels of nicotine dependence, *M* = 5.05, *SD* = 2.27, range = 0-8 (Heatherton, et al. 1991; Vink, et al. 2005). Non-smokers had smoked ten or less cigarettes in their lifetime (*M* = 1.22, *SD* = 2.34, range = 0-10). Participants were undergraduate students, who received course credits or a financial compensation for their participation. The study was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written informed consent of the subjects. The study protocol was approved by the Ethics Committee of the Institute of Psychology of the Erasmus University Rotterdam.

Instruments

Breath carbon monoxide concentration was measured using a Micro+ Smokerlyzer (Bedfort Scientific Ltd., Rochester, UK) in order to objectively identify smokers and non-smokers. Next to the FTND, smokers also completed the brief version of the Questionnaire of Smoking Urges (QSU, Cox, et al. 2001) to assess their subjective craving for a cigarette.

Task paradigm

A smoking-related Go/NoGo task was developed for the aim of the current study. In this task participants were presented with a series of pictorial stimuli with a smoking or non-smoking-related content. Each picture was displayed for 200 ms and had a blue or yellow frame (see figure 1 for an example of a smoking and non-smoking trial). The frame color indicated whether a stimulus was a Go or a NoGo trial. The attribution of the frame color to Go versus NoGo trials was counterbalanced across participants. Each stimulus was followed by a black screen for a randomly varying duration between 1020 ms and 1220 ms. Participants were instructed to respond to the pictures in Go trials by pressing a button with the right index finger as fast as possible, and to withhold their response in the NoGo trials. They were explicitly instructed to maintain accuracy during the whole task. The task consisted of 112 different smoking-related pictures and 112 non-smoking-related pictures. Smoking-related pictures displayed smoking related objects (e.g., lighter, ashtray etc.) or scenes of people engaged in smoking behavior, whereas non-smoking-related pictures displayed neutral items or scenes of people engaged in non-smoking behavior. Each

picture was presented for four times during the whole task, once as a NoGo stimulus and three times as a Go stimulus. This means that 25% of all trials were NoGo trials and that the proportion of smoking and non-smoking pictures in the task was equal (i.e., 112 NoGo trials per picture category and 336 Go trials per picture category). The order of picture content (smoking versus neutral) was completely randomized and the order of trial type (Go versus NoGo) was quasi randomized such that at most four Go and two NoGo trials were presented consecutively. Before the start of the actual task, participants were given to opportunity to practice in 23 practice trials, involving additional non-smoking pictures. At four time moments during the task, participants were given the opportunity to take a short break. Total task duration was about 22 minutes, depending on the length of the breaks.

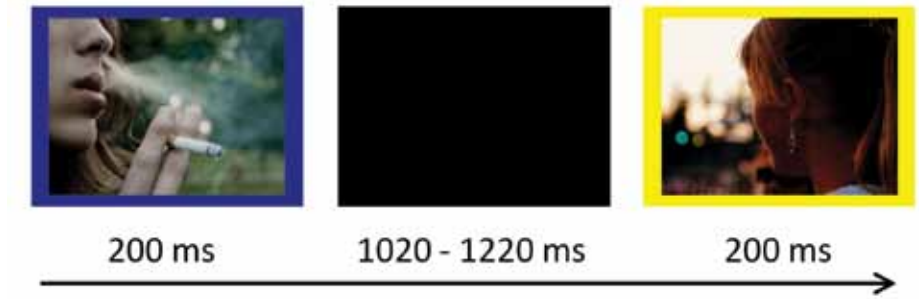

Figure 1

Example of a Go and NoGo trial combined with a smoking and a neutral pictures in the smoking cue Go/NoGo task

Procedure

Smokers were instructed to abstain from smoking for at least one hour before the start of the experiment. This short period of smoking deprivation was introduced in order to reduce the acute effects of nicotine on ERP amplitudes (Houlihan, et al. 1996; Houlihan, et al. 2001) without introducing withdrawal effects. Participants approved participation by signing informed consent. The CO breath sample was taken and questionnaires were completed. Subsequently, participants were seated in a comfortable EEG chair in a light and sound-attenuated room. Electrodes were attached and task instructions were explained. Participants performed the smoking Go/NoGo tasks during EEG recording. Smokers completed the QSU-brief a second time at the end of the experiment.

EEG recording and data reduction

The EEG was recorded using the Biosemi Active-Two amplifier system (Biosemi, Amsterdam, the Netherlands) from 34 scalp sites (positioned following the 10-20 International System with two additional electrodes at FCz and CPz) with active Ag/AgCl electrodes mounted in an elastic cap. Six additional electrodes were attached to the left and right mastoids, to the two outer canthi of both eyes (HEOG), and to an infraorbital and a supraorbital region of the right eye (VEOG). All signals were digitalized with a sample rate of 512 Hz and 24-bit A/D conversion with a bandpass of 0-134 Hz. Data were off-line re-referenced to computed mastoids. Off-line, EEG and EOG activity was filtered with a bandpass of 0.10-30 Hz (phase shift-free Butterworth filters; 24dB/octave slope). Data were segmented in epochs of 1 second (200ms before and 800ms after response or stimulus presentations). After ocular correction (Gratton, et al. 1983) epochs including an EEG signal exceeding ± 75 μV were excluded from the average. The mean 200 ms pre-response or pre-stimulus period served as baseline. After baseline correction, average ERP waves were calculated for artifact-free trials at each scalp site for correct and incorrect responses separately. Segments with incorrect responses (miss for GO trials or false alarm for NoGo trials) were excluded from EEG analyses. The N2 was defined as the most negative value within the 200-300 ms time interval after stimulus onset and was studied at a cluster of frontocentral electrodes, including Fz, FC1, FC2, FCz and Cz (Kiefer, et al. 1998). The P3 was defined as the most positive value within the 300-500 ms time interval after stimulus onset. The P3 was studied at a cluster of central electrodes, including FCz, Cz, C3, C4 and CPz (Kiefer, et al. 1998). The mean number of analyzable Go and NoGo epochs for smoking pictures was 248.50 and 56.00 respectively and 250.57 and 55.26 for non-smoking pictures. One non-smoker was excluded from ERP analyses because of less than 10 artifact free ERP epochs in at least one of the task conditions. This participant was included in all remaining data analyses.

Statistical analysis

The difference in self-reported craving before and after task performance was analyzed by means of a paired samples *t*-test. Repeated Measures Analyses of Variance (RM-ANOVA; with Greenhouse-Geisser adjusted *p*-values) were applied to analyze behavioral outcomes of performance on the Go/NoGo task, as well as ERP indices of response inhibition. The between-subjects factor in all RM-ANOVA's was Group (smokers versus non-smokers). Two-level within-subject factors were of interest, namely (a) Inhibition (Go versus NoGo), and (b) Picture (smoking versus non-smoking pictures). A Group x Inhibition x Picture

RM-ANOVA was employed to analyze the behavioral accuracy during the Go/NoGo task, and a Group x Picture RM-ANOVA was chosen to analyze reaction times in Go trials. Electrode (Fz, FC1, FC2, FCz, Cz for N2 and FCz, Cz, C3, C4, and CPz for P3) was included as a five-level within subject factor in the ERP analyses. That is, a Group x Inhibition x Picture x Electrode RM-ANOVA was performed for the ERP analyses. Post-hoc tests for interactions were performed only for interactions including the between subject factor Group. A Bonferroni correction for multiple comparisons was applied in all post-hoc analyses. Finally, Spearman correlation coefficients were calculated for the number of cigarettes per day on the one hand and NoGo accuracy rates and average cluster peaks across all electrodes for the NoGo N2 and P3 on the other hand.

Results

Breath CO levels and questionnaires

In line with expectancies, smokers had a higher breath concentration of carbon monoxide (CO; in parts per million, $M = 12.89$, $SD = 7.15$) as compared to non-smoking controls ($M = 1.15$, $SD = 1.04$), $t(37) = 7.27$, $p < 0.001$. Subjective craving in smokers increased significantly from the start ($M = 37.53$, $SD = 10.02$) to the end ($M = 46.05$, $SD = 9.79$) of the experiment, $t(18) = 4.35$, $p < .001$.

Behavioral data

The accuracy rates for both the smoking and non-smoking group on the smoking-related Go/NoGo task are displayed in figure 2. A robust main effect of Inhibition was found, $F(1,37) = 184.55$, $p < 0.001$ showing that participants were less accurate on NoGo trials (69.63% versus 96.86% respectively). There was also a main effect for Group, $F(1,37) = 4.12$, $p = .05$, which indicated that overall task performance was less accurate in smokers than in non-smoking controls (80.47% 86.03%, respectively). A trend to significance was found for the Group x Inhibition interaction, $F(1,37) = 3.27$, $p = 0.08$. Post-hoc t-tests revealed that, particularly on NoGo trials, smokers performed less accurate than non-smoking controls ($p = 0.05$; 65.05% versus. 74.23 %), whereas there was no difference on accuracy between the groups for Go trials. No main or interaction effects of Picture were found for accuracy of responding. We additionally performed two separate RM-ANOVA's for Go and NoGo accuracy scores because of differences

in the distribution for Go and NoGo accuracy which may lead to subsequent differences in the magnitude of effects for Go and NoGo accuracy. Results showed the same pattern as the combined analysis. A main effect for Group was found for NoGo accuracy. $F(1,37) = 4.02$, $p = 0.05$ confirming that smokers were less accurate than controls on NoGo trials. No difference on accuracy between groups was found for Go trials. No main or interaction effects of Picture were found for accuracy of responding in either NoGo or Go trials.

With regard to the reaction time data, a main effect of Picture was found, $F(1,37) = 6.28$, $p < .05$ indicating that participants generally responded faster to smoking-related Go trials than to neutral Go trials ($M = 259.69$ ms versus $M = 261.89$ ms). No other significant effects were found for reaction times. No significant correlations were found between the number of cigarettes smoked per day and accuracy rates for NoGo trials.

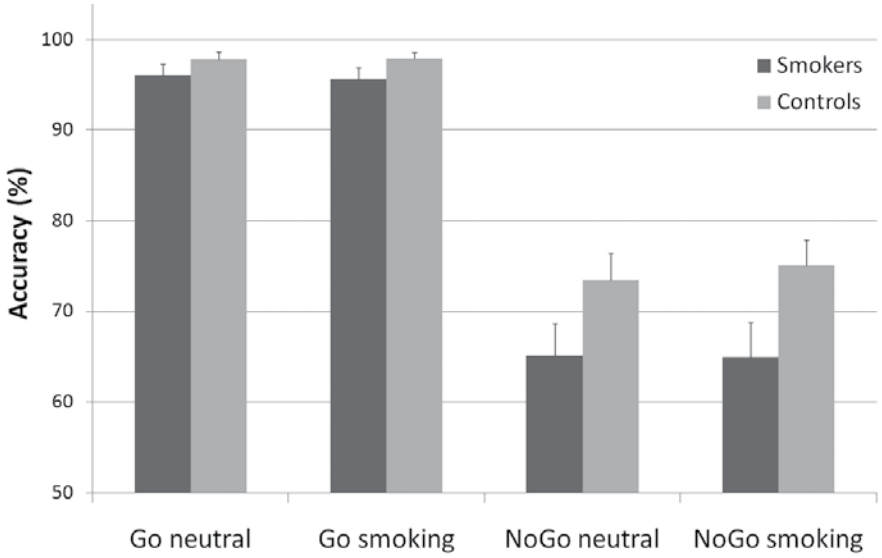

Figure 2

Accuracy rates in smokers and non-smoking controls on the smoking cue Go/NoGo task

N2 amplitudes

The N2 amplitude for smoking-related and neutral pictures in both groups is displayed in figure 3. In line with the hypotheses, a robust main effect was found for Inhibition, $F(1,36) = 36.83$, $p < .001$ on the N2 component at the frontocentral electrode cluster. This result demonstrates that N2 amplitudes were generally

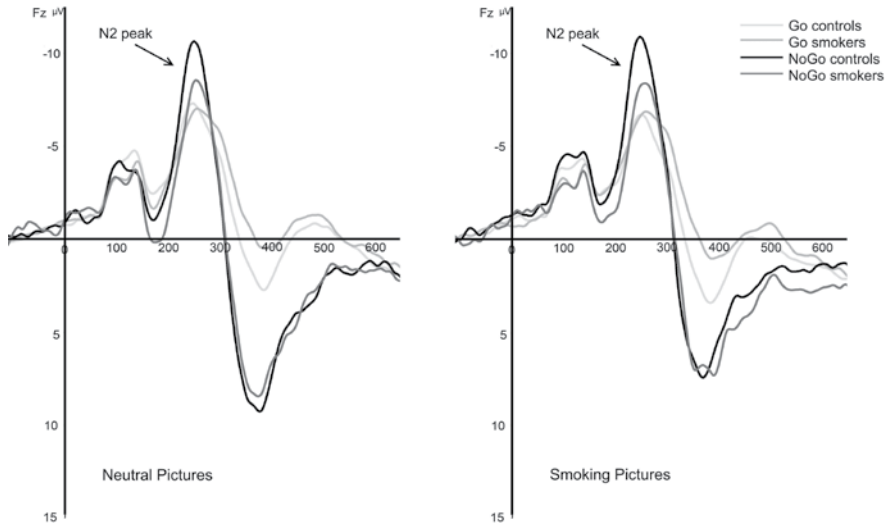

Figure 3

Grand-average stimulus-locked waveforms for neutral and smoking pictures at Fz for correct Go and NoGo trials in smokers and non-smoking controls

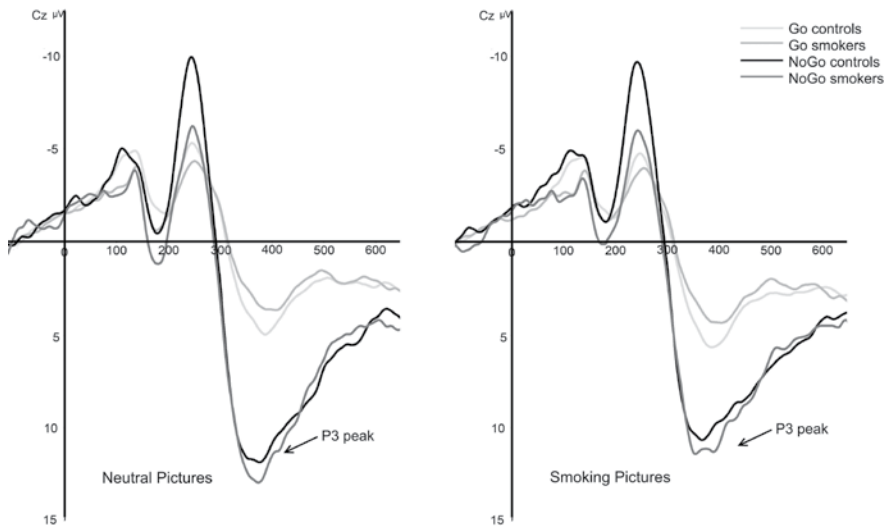

Figure 4

Grand-average stimulus-locked waveforms for neutral and smoking pictures at Cz for correct Go and NoGo trials in smokers and non-smoking controls

larger for NoGo trials than for Go trials. Importantly, a Group x Inhibition interaction effect was found, $F(1,36) = 6.31$, $p = .017$. Post-hoc t-tests indicated that only on NoGo trials the N2 was significantly reduced in smokers as compared to non-smoking controls ($p = .046$), whereas there were no between-group differences on N2 amplitude in response to Go trials. Furthermore, a main effect for electrode was found, $F(4,144) = 25.67$, $p < .001$. No Picture-related main or interaction effects were found for the N2 component. No significant correlations were found between the number of cigarettes smoked per day and the cluster combined N2 peak amplitudes for NoGo trials.

P3 amplitudes

Figure 4 shows the P3 amplitudes for smoking and neutral pictures in both groups. As expected for the P3 at the central electrode cluster, a robust main effect was found for Inhibition, $F(1,36) = 138.85$, $p < .001$. This result indicates that the P3 peaks were generally larger for NoGo trials than for Go trials. Furthermore, a main effect for electrode was found, $F(4,144) = 18.73$, $p < .001$. No other significant main or interaction effects including Group were found for P3 amplitude. No significant correlations were found between the number of cigarettes smoked per day and the cluster combined P3 peak amplitudes for NoGo trials.

Discussion

The main purpose of the present study was to investigate differences in response inhibition on a behavioral as well as on an electrophysiological level using a smoking-modified Go/NoGo paradigm in combination with the recording of event-related potentials. Consistent with the notion that the N2 reflects an inhibitory process, the N2 was significantly enhanced on NoGo trials as compared to Go trials. More importantly and in line with our primary hypothesis differences between smokers and non-smokers were found on both behavioral and electrophysiological indices of response inhibition. That is, performance on the Go/NoGo task was generally less accurate in smokers than non-smokers in such that smokers displayed significantly more difficulties to inhibit their responses in NoGo trials. This deficit in general response inhibition was also reflected in reduced N2 amplitudes in NoGo trials in smokers as compared to non-smokers.

Previous studies on inhibitory control in smokers, which used behavioral paradigms, such as the Go/NoGo task generally yielded inconsistent results (Dinn, et al. 2004; Monterosso, et al. 2005; Reynolds, et al. 2007; Spinella 2002). The difficulty level of the task of the current study, however, was different than previous studies. The Go/NoGo task that was used in the present study placed high demands on inhibition capacities because stimulus presentation was fast and NoGo trials were infrequent. This is supported by the fact that 31.4% of the NoGo trials resulted in commission errors in the current study while this is usually much lower (e.g., 5% percent in Dinn et al. 2004). In addition, the present study was the very first to include the N2 component as an additional index of inhibitory control in smokers. The NoGo N2 amplitude is an index of response inhibition which is believed to be more sensitive than behavioral outcomes in the Go/NoGo paradigm (Falkenstein 2006; Nakata, et al. 2006). The fact that reduced inhibitory control was found in behavioral accuracy as well on the N2 component of the ERP provides support for the hypothesis that there is a general shortcoming in response inhibition in smokers relative to non-smokers. It must be noted, however, that the current study design does not allow drawing conclusions on causality. It may be that reduced inhibitory control is the result of prolonged nicotine dependence, for example via abnormalities in the dopamine system, or that reduced inhibitory control is a predisposition to start smoking. The latter interpretation may be more convincing according to the results of the current study because of the lack of association between measures of inhibitory control and nicotine exposure (i.e., the number of cigarettes smoked per day). This association could be expected if reduced inhibitory control is the result of a modulation of brain systems by nicotine intake.

With regard to P3, enlarged amplitudes in NoGo trials than Go trials were observed confirming that, like the N2 amplitude, P3 amplitude is related to response inhibition processes. However, contrary to N2 and behavioral accuracy, no differences between groups were found in NoGo P3 amplitude. It has been suggested that, whereas the NoGo N2 might be related to an early stage of the response inhibition process, the NoGo P3 might reflect a later stage of the inhibition process that is closely related to the actual inhibition of the motor system (Kok, et al. 2004). Accordingly, the present study results suggest that the reduced inhibitory control in smokers reflect a dysfunctional activation of inhibitory processes at an early stage of cortical processing while later stages of the inhibition process may be intact. This is in line with findings in heroin dependent patients (Yang, et al. 2009) but in contrast to previous findings in alcohol dependent patients (Kamarajan, et al. 2005), ecstasy

polydrug users (Gamma, et al. 2005) and smokers (Evans, et al. 2009). Unfortunately, the latter studies did not investigate N2 amplitudes making complete comparisons with the present study impossible. Furthermore, the diverse characteristics of the Go/NoGo paradigms used in these studies might have contributed to differential findings (Kamarajan, et al. 2005). For example, the probability of NoGo trials, and thereby the demand on response inhibition capacities, varies largely among these ERP studies just as in the studies investigating behavioral accuracy. Furthermore, it is not clear whether previous studies separated successful and unsuccessful trials in examining P3 amplitudes which is important because P3 amplitudes are influenced by inhibition success or failure (Kok, et al. 2004).

The present study was the first that investigated not only general response inhibition in smokers, but specific response inhibition towards smoking-related stimuli as well. Several authors suggest that inhibitory control in substance-dependent individuals is especially reduced when exposed to drug-related cues and that this eventually may contribute to compulsive cue-elicited drug intake (Dawe, et al. 2004b; Field, et al. 2008; Jentsch, et al. 1999). The findings in the current study could not confirm that reduced inhibitory control in smokers is more pronounced in the presence of smoking cues. In fact, the current findings show that inhibitory control is reduced in smokers during smoking cue exposure and during neutral affective conditions suggesting that these deficits found in smokers are of a more general category, which may be in favor of the diagnostic value and theoretical importance of the Go/NoGo task paradigm. Furthermore, these results imply that decreased inhibitory control may not only influence smoking-related behavior but also other impulsive and possibly maladaptive behaviors. This idea is supported by the high proportion of smokers in, for example, conduct disorder (Bagot, et al. 2007) and problem gambling (Verdejo-Garcia, et al. 2008). However, the influence of drug cue-exposure on levels of inhibitory control should be further investigated in future studies. Possibly, the overall reduced inhibitory capacity of smokers, which was observed in the present study, reflects a general effect of nicotine craving. That is, controlling the craving elicited by the smoking-related pictures during the task might have required cognitive resources (Tiffany 1999) which might have resulted in an overall reduced inhibitory capacity. In the present study, smokers reported significantly increased craving after task performance as compared to before showing that smokers had to deal with increasing levels of craving evoked by the smoking-related pictures used in the Go/NoGo task. One way to examine if craving has a general effect on performance of the smoking-modified Go/NoGo paradigm, could be to

present the stimuli to participants in a blocked design, with one block of neutral pictures being presented first, followed by a block of smoking-related pictures to measure response inhibition under low and high conditions of craving separately.

In conclusion, results of the current study showed reduced inhibitory control in smokers both at behavioral and physiological measures. Decreased N2 amplitudes for NoGo trials were accompanied by reduced accuracy for NoGo trials. However, the hypothesis that reduced response inhibition would be more pronounced for smoking-related cues could not be confirmed. These results suggest that smokers have difficulties with inhibitory control, which might be an important factor in the initiation and continuation of smoking behaviors as well as relapse in smoking behaviors. These findings can eventually be implemented in smoking cessation programs.

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Chapter Five

Effects of reward and punishment on brain activations associated with inhibitory control in cigarette smokers

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Submitted for publication

Abstract

Difficulties inhibiting substance related behaviors may be the result of the preference for an immediate small reward relative to a larger delayed reward or may be the result of insensitivity to punishment. The current fMRI study examined the neural basis of inhibiting an immediately rewarding stimulus in order to obtain a larger delayed reward in smokers and non-smoking controls. We also investigated whether punishment insensitivity contributed to deficient inhibitory control. The Monetary Incentive Go/NoGo task was administered that provided three types of reward outcomes contingent on inhibitory control performance over rewarding stimuli: inhibition failure was either followed by no monetary reward (neutral condition), a small monetary reward with immediate feedback (reward condition) or immediate monetary punishment (punishment condition). In the reward and punishment conditions, successful inhibitory control resulted in larger delayed rewards. Nineteen smokers were compared with seventeen demographically matched non-smoking controls. Results showed that smokers had hyperactivation in the pre-SMA, right anterior insula, right IFG/MFG and right DLPFC both during inhibition of an immediately rewarding stimulus in order to obtain a larger delayed reward, and during inhibition of neutral stimuli. Group differences in brain activity were no longer significant in the punishment condition, most likely as a result of increased activation in non-smoking controls. The current results suggest that smokers need additional neural resources to inhibit rewarding stimuli and provide tentative evidence that smokers are less sensitive to punishment as a strategy to guide control over rewarding stimuli.

Introduction

Reduced cognitive control has been identified as one of the key mechanisms contributing to addictive behaviors (Dawe, et al. 2004a; Goldstein, et al. 2011; Jentsch, et al. 1999; Verdejo-Garcia, et al. 2008). Previous studies have shown that smokers, as well as other addicted groups, show poor inhibitory control (e.g., Kaufman, et al. 2003; Luijten, et al. 2011a; Nestor, et al. 2011). Poor inhibitory control refers to the decreased ability to suppress automatic and habitual behaviors. Research examining the neural mechanisms underlying decreased inhibitory control in smokers has shown dysfunctional cortical activity in regions critically involved in inhibitory control, such as the inferior frontal gyrus (IFG), the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex / pre-supplementary motor area (ACC / pre-SMA) and the anterior insula (De Ruiter, et al. 2012; Nestor, et al. 2011). Reduced inhibitory control as a consequence of impaired prefrontal brain function may be especially problematic when habitual and rigid behavioral patterns require alteration, such as during an attempt to give up smoking. Difficulties inhibiting substance-related behaviors may be the result of the preference for an immediate small reward relative to a larger delayed reward (Reynolds 2006) or may be the result of insensitivity to punishment (Vanderschuren, et al. 2004). However, the neural mechanisms that contribute to reduced inhibitory control in substance dependent humans have not been investigated as yet. Therefore, the current study examined whether enhanced reward sensitivity and/or reduced punishment sensitivity is associated with reduced inhibitory control in smokers.

The preference for smaller immediate rewards over larger delayed rewards has consistently been found in addicted individuals and is referred to as increased delayed discounting (Bickel, et al. 2001; Hoffman, et al. 2008; Petry 2002; Reynolds 2006; Sheffer, et al. 2012). Increased discounting of delayed rewards implicates that the extent to which outcomes influence the effectiveness to control behavior decreases to a larger extent in addicted individuals as a function of the delay to their occurrence (Reynolds 2006). Decreased delay discounting in smokers has been associated with higher smoking rates (Heyman, et al. 2006) and unsuccessful quit attempts (Sheffer, et al. 2012). In line with addiction theories, it is likely that persons with heightened reward sensitivity for the substance of abuse will experience stronger prepotent approach tendencies and these would require greater levels of cognitive inhibition (Dawe, et al. 2004a; Goldstein, et al. 2002; Volkow, et al. 2004). Thus far, research examining inhibitory control in substance use typically employed Go/NoGo and Stop Signal tasks involving neutral, rather than rewarding stimuli. A few studies in

smokers, however, have investigated control over craving evoked by smoking-related pictures or videos. Although this may represent a slightly different process compared to inhibitory control measured using Go/NoGo and Stop Signal tasks, these studies may provide clues about the neural mechanism underlying the inhibition of rewarding stimuli. For example, Kober and colleagues (2010) showed that inhibition of craving is associated with increased activation in regions implicated in inhibitory control, such as the right inferior frontal gyrus, while reductions in activity were reported in reward-related areas such as the striatum. Similarly, increased dorsal ACC and decreased activation bilaterally in the cuneus and occipital gyrus was found in another study in which smokers were instructed to resist craving during exposure to smoking-cues (Brody, et al. 2007). These studies suggest that applying control over reward-related stimuli may be associated with changes in the balance between prefrontal control regions and subcortical regions, as well as brain regions involved in visual processing. The current study examined whether inhibition of an immediately rewarding stimulus over a larger delayed reward also requires additional recruitment of control regions, consistent with the patterns of activation reported for the suppression of craving evoked by drug-related stimuli.

Punishment insensitivity in addicted individuals may be another factor contributing to deficient inhibitory control (Vanderschuren, et al. 2004). Although this is a relatively unexplored area, reduced sensitivity to punishment in behavioral performance has been shown in addicted individuals (Bechara et al., 2002; Ersche et al., 2005; Fridberg et al., 2010; Goudriaan et al., 2008; Grant et al., 2000). Neuroimaging studies of drug dependent patients have also shown a diminished neural response to monetary loss (Beck et al., 2009; Bjork et al., 2008a; Bjork et al., 2008b; Wrase et al., 2007), in both sub-cortical 'limbic' regions including the striatum as well as cortical regions such as the anterior cingulate cortices. In addition, a recent fMRI study in smokers showed reduced activity in the ventrolateral prefrontal cortex when compared to healthy controls during punishment trials of a reversal learning task (De Ruiter, et al. 2009). These studies have typically not examined the consequences of such a reduced loss-response to the ability to control behavior (Hommer et al., 2011). Importantly, preclinical research in rats showed that with extended cocaine self-administration the rats develop resistance to the inhibitory effect of punishment on drug self-administration, while punishment stimulated the inhibition of drug self-administration in rats without a history of extended self-administration of cocaine (Pelloux, et al. 2007; Vanderschuren, et al. 2004; Xue, et al. 2012). Thus, reduced punishment sensitivity may be a critical factor contributing to unsuccessful control over drug use.

To examine the effect of reward and punishment on brain activation associated with inhibitory control, a modified version of the Go/NoGo response-inhibition paradigm (i.e., the Monetary Incentive Go/NoGo task) was administered to smokers and non-smoking controls. This task was designed to examine neural activity during attempts to inhibit a prepotent response to a rewarding NoGo stimulus. To mimic the reward scenario present during an abstinence intervention, the following contingencies were introduced to participants: First, NoGo stimuli were assigned that had been employed in the previous block as a monetary reward Go stimulus. Second, in the reward condition of the task, failed inhibitory control over NoGo trials resulted in small immediate monetary rewards, while in the punishment condition failure to inhibit resulted in immediate money loss. Successful inhibitory control over NoGo trials in both reward and punishment conditions resulted in a larger reward (calculated using the sum of the longest consecutive run of correct inhibitions). Finally, the task also involved NoGo trials without any rewarding or punishing contingencies, to be able to compare inhibitory control over rewarding NoGo trials under immediate reward and punishment conditions to an effectively neutral condition. In line with the above-mentioned addiction theories, we hypothesized that smokers would have significantly greater difficulty inhibiting their response to a rewarding stimulus when compared to matched control participants, neutral conditions or both. With regard to punishment sensitivity, we expected that non-smoking controls would adopt a more cautious responding style when failed inhibition resulted in an immediate punishment, while this was not expected to influence behavior to the same extent in smokers.

Materials and Methods

Participants

Nineteen smokers (mean age = 26.89 years, *SD* = 8.11, 6 male) and seventeen non-smoking controls (mean age = 27.47 years, *SD* = 7.79, 7 male) participated in this study. There were no significant differences between the groups in mean age, $t(34) = 0.22$; ns, estimated IQ (National Adult Reading Test: Nelson 1982), $t(26) = 0.97$, ns, $M_{smokers} = 114.72$, $SD_{smokers} = 5.00$, $M_{controls} = 114.80$, $SD_{controls} = 7.67$, and gender ratio, χ^2 (1, $n = 36$) = 0.55; ns. Exclusion criteria for both groups were (a) current substance abuse or dependence (other than nicotine for the smoking group), (b) the current presence of any physical or psychological illness, (c) any use of psychotropic medication or medication that

may affect blood circulation and/or respiration, (d) fMRI contraindications, and (e) left-handedness (as determined by the Edinburgh Handedness Inventory, (Oldfield 1971). Smokers smoked at least 15 cigarettes per day (*M* = 18.95, *SD* = 4.40; range 15-30) for a duration of at least two years (*M* = 9.19, *SD* = 4.61, range = 2.5-25). The average score on the Fagerström Test for Nicotine Dependence (FTND: Heatherton, et al. 1991) for smokers was 3.79, *SD* = 2.10, range = 1-8. Non-smokers had smoked ten cigarettes or less during their lifetime. Smokers were instructed to abstain from smoking for one hour before the experiment. This short period of smoking deprivation was introduced in order to reduce the acute effects of nicotine on cognitive performance without introducing significant withdrawal effects on cognitive performance. The study was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written informed consent of the subjects. The ethics committee of the Melbourne School of Psychology – The University of Melbourne approved this study.

Task paradigm

Participants completed the Monetary Incentive Go/NoGo (MI-Go/NoGo) task (see figure 1) that consisted of 8 separate blocks. A similar version of the MI-Go/NoGo task has previously been described elsewhere (O'Connor, et al. in press; Rossiter, et al. 2012). The MI-Go/NoGo task consisted of two types of Go trials and three types of NoGo trials. Regular Go trials consisted of the presentation of white double-digit numbers (different, e.g., 21, 23 but not 22), centrally on a black background for 750ms, followed immediately by a 1250ms inter stimulus interval (ISI) presenting only the black background. Participants were asked to respond to Go trials by making a single button press response as quickly as possible upon Go trial presentation. The second type of Go trials, referred to as Go-Money trials, consisted of same-digit double-digit numbers (e.g., 11, 22 or 33) and required participants to make a single button press response as quickly as possible. Go-Money trials were presented for 750ms, followed by a feedback screen for 750ms and blank-screen ISI (500ms) and paid monetary rewards in proportion to how quickly participants responded to the Go-Money trial presentation. Successful button presses for a Go-Money trial stimulus provided an immediate monetary reward with a maximum value of 20c (AUD). The monetary reward for Go-Money trials was calculated by subtracting the reaction time from the 1000ms response window duration. For example, if a participant's reaction time was 300ms in a Go-Money trial, the monetary gain would be 14 cents [(1000 – 300)/50) = 14]. Two different same-digit double-digit numbers (e.g., 22 and 44) were presented as Go-Money trial stimuli for each block.

NoGo trials were pseudo-randomly interspersed throughout the Go and Go-Money trials. The NoGo stimulus was presented for 750ms, followed by a 1250ms ISI, a 1000ms feedback screen and 1000ms ISI. Participants were informed prior to the beginning of each block which double-digit number was designated as the forthcoming NoGo stimulus. Participants were asked to withhold their button response upon presentation of this NoGo stimulus. The MI-Go/NoGo task involved three different types of NoGo trials (NoGo neutral, NoGo reward, NoGo punishment) that varied according to the task condition. During the Neutral condition, no monetary reinforcement was applied to inhibition success or failure of NoGo trials, only Go-Money trials were rewarded. NoGo trials in the neutral condition consisted of new same-digit double-digits. In the reward and punishment condition, NoGo stimuli were selected that had been employed in the previous block as a Go-Money trial that was monetarily rewarded for rapid responses with immediate feedback. Consequently, the double-digits used as NoGo trials in the Reward and Punishment conditions were learned to be associated with immediate monetary reward in the previous block. NoGo reward and NoGo punishment trials were differentiated by their contingencies relating to inhibitory control success and failure during these trials. During the Reward condition, rather than receiving an immediate reward for successful inhibitory control during the NoGo trial, participants were provided with monetary reward feedback at the end of each block based upon the highest number of consecutive successfully inhibited NoGo trials during the block, multiplied by 40c. For example, if, within one block, the highest number of successful consecutive response inhibitions were seven, then the participant was awarded $2.80 (7 x 40c). Consequently, immediate feedback for successful inhibitory control of individual NoGo trials in the reward condition informed participants that no money had yet been accrued. In contrast, failure to inhibit during a NoGo trial in the reward condition led to an immediate reward. Feedback during the ISI period signaled performance failure and a monetary reward commensurate with RT, thereby remaining consistent with the response-reward relationship experienced during Go-Money trials. Such a paradigm was devised to model real-world behavior in which abstinence is required over an immediate and tangible reward (i.e., reward amount is based on reaction time with immediate feedback) in order to obtain a larger yet less tangible reward (i.e., reward amount is based on an accumulation of consecutive inhibitions with no immediate feedback).

In summary, the reward-response associations of Reward NoGo trials were cultivated in two ways. First, Reward NoGo stimuli were selected from the Go-Money trial stimuli that had been employed in the previous block, wherein

these stimuli had received monetary rewards for rapid responses. Second, failure to exert control over Reward NoGo trials resulted in small monetary rewards for which immediate feedback was provided, whereas successful inhibitory control resulted in no immediate reward, but a larger delayed reward comprising the sum of the longest run of consecutive successful inhibitions. Feedback during the Punishment condition for correct NoGo trials was similar to that of the Reward condition (i.e., no immediate feedback, however, feedback at the end of each block based upon the highest number of consecutive successfully inhibited NoGo trials during the block). Incorrect NoGo performance in the punishment condition resulted in immediate negative feedback (40c punishment), such that failed inhibition of the previously rewarding stimulus (from the preceding block) resulted in immediate punishment.

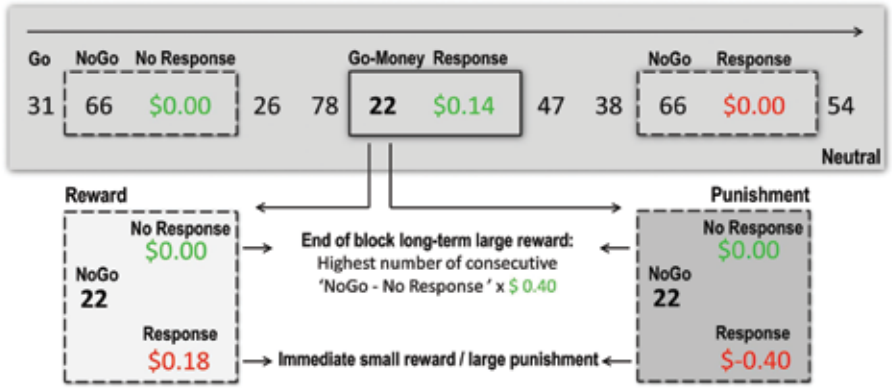

Figure 1

Schematic illustration of the Monetary Incentive Go/NoGo task

Note figure 1 *The upper row of numbers represents the stimuli presented one by one to the participants. Different-digits double-digits are Go-stimuli. Number 22 in this figure is an example of a Go-Money trial for which responses are rewarded corresponding to response speed. Subsequently, this number is transferred to the next block (either a block in the reward or punishment condition) in which it is now presented as a NoGo stimulus. Feedback and reward/punishment contingencies for NoGo trials in the Neutral, Reward and Punishment are displayed in the dashed squares. Correct inhibition of NoGo trials in the reward and punishment condition is rewarded by a large delayed monetary reward at the end of a block based on the highest number of consecutive correct inhibited NoGo trials. Failed inhibition of NoGo trials in the reward and punishment condition is followed by a small immediate reward or a large immediate punishment respectively.*

The current MI-Go/NoGo task consisted of eight blocks divided over the three conditions. Three consecutive blocks of Reward and Punishment conditions were presented to participants, with a Neutral condition block preceding each of these. Block order for reward and punishment was counterbalanced across participants. Each block consisted of 120 Go trials, 20 Go-Money trials and 20 NoGo trials. Trial types were pseudo-randomly presented such that NoGo and Go-Money trials were always separated by at least two Go trials.

Image acquisition

Functional MR images were acquired at a 3T scanner (Siemens Magnetrom TrioTim, Erlangen, Germany). 183 echo-planar imaging (EPI) sequences providing T2*-weighted blood oxygenation level-dependent (BOLD) were acquired for each functional run with the following parameters: repetition time (TR), 2000ms; echo time, 35ms; flip angle, 90°; 32 contiguous slices of 4mm thickness. Eight functional runs were collected for each participant. A rapid-acquisition gradient echo T1-weighted image was acquired in 208 contiguous axial slices with TR of 1900 ms, TE of 2.3 ms, FOV of 250 mm, and isotropic voxel size of 0.8 mm3 for anatomical reference.

Data analyses

Imaging data were analyzed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Pre-processing of the functional data included realignment of all functional images. Next, the anatomical scan was coregistered to the mean T2*-weighted image and subsequently segmented into grey and white matter and cerebrospinal fluid. Segmentation parameters were used for normalization using the SPM T1-weighted MNI template. Functional scans were spatially smoothed using a 3D full-width at half-maximum Gaussian kernel of 8 mm. Correct trials for the NoGo conditions (NoGo neutral, NoGo reward and NoGo punishment) as well as Go-Money trials were modeled in the context of the general linear model using delta functions convolved with a canonical hemodynamic response function. Additional regressors for events not of interest to this study included errors and feedback epochs. The baseline estimate was the mean activation recorded during the ongoing trial period (Go trials), such that the activation observed during successful NoGo trial responses represents activation over and above that required for the ongoing Go trials. Group activation clusters in whole-brain analyses for the three NoGo conditions (Neutral, Reward, and

Punishment) for smokers and controls separately were used to create functionally-derived regions of interest (ROIs), thereby preventing biases in ROI selection for either group or condition. The group activation maps were determined with one-sample *t*-tests and thresholded at $p < 0.05$, Family Wise Error (FWE) corrected and required cluster size of at least 50 voxels (400 mm3). Activation clusters from these whole-brain analyses were used to create a combined activation map including significant voxels in any of the constituent maps (NoGo Neutral, Reward or Punishment in either smokers or non-smokers). Beta-values (activation estimates) for both groups in the three NoGo conditions were extracted in activated clusters in the combined map using Marsbar (Brett, et al. 2002). Due to a priori interest in the activity of the ventral striatum an anatomically defined ROI (8 mm sphere, x = ±10, y = 12, z = -2: Knutson, et al. 2008) was created in the right and left nucleus accumbens (NAcc). Activation estimates in the regions of interest were analyzed using a Group x Condition Repeated Measures Analyses of Variance (RM-ANOVA) in SPSS. Group was included as a two-level between-subject factor (smokers versus controls) and Condition as a two level within subject factor (NoGo Neutral versus NoGo Reward for the first research question and NoGo Neutral versus NoGo Punishment for the second research question). Accuracy rates and reaction times for Go, NoGo and Go-Money trials were analyzed using the same Group x Condition RM-ANOVA's. In addition, the amount of money smokers and non-smoking controls earned during the punishment and reward conditions was compared using two-sample t-tests. In order to investigate NAcc activation associated with immediate reward without the need for inhibition, activation estimates for Money trials in the NAcc were analyzed using a Group x Condition RM-ANOVA. Condition was included as a 3-level within subject factor in this analysis as no specific hypotheses were specified for Go-Money activation during the Reward or Punishment condition versus the Neutral condition.

Results

The accuracy rates and reaction times for both the smoking and non-smoking group on the Go/NoGo task are displayed in table 1. A Group (smokers versus controls) x Trial (NoGo, Go, Go-Money) RM-ANOVA was performed to show overall accuracy and reaction times patterns irrespective of task condition (i.e., irrespective of whether the trial was presented in the neutral, reward or punishment condition). A main effect of Trial was found for both accuracy rates

and reaction times, $F(2,33) = 106.17$, $p < 0.001$ and $F(2,21) = 45.48$, $p < 0.001$ respectively. Post-hoc tests revealed that accuracy rates for NoGo trials were lower than Go and Go-Money trials. Accuracy for Go trials was higher than for Go-Money trials (all *p*'s < 0.001). Reaction times showed that reaction times for failed NoGo trials were faster compared to Go and Go-Money trials (*p*'s < 0.001). Reaction times did not differ between Go and Go-Money trials ($p = 0.11$). No group effects were observed.

Behavioral results reward

Group (smokers versus controls) x Condition (Neutral versus Reward) RM-ANOVA's did not show significant main or interaction effects of Group and Condition for either NoGo, Go and Go-Money accuracy rates (all *p*'s > 0.08). NoGo reaction times did not show a main effect of Group or Condition. However, a Group x Condition interaction was found, $F(1,23) = 4.19$, $p = 0.05$. Post-hoc t-tests revealed that NoGo reaction times in smokers were faster in the reward condition relative to the neutral condition ($p < 0.05$), whereas there was no effect of Condition on NoGo reaction times for non-smoking controls. Go reaction times showed a main effect of Condition, $F(1,34) = 18.17$, $p < 0.001$, indicating Go reaction times were faster for both groups in the reward versus neutral condition. No main or interaction effects of Group were found for Go reaction times (*p*'s > 0.95). Go-Money reaction times showed a similar pattern. A main effect of Condition, $F(1,34) = 30.06$, $p < 0.001$, showed that Go-Money reaction times were faster in both groups in the reward versus neutral condition. No main or interaction effects of Group were found for Go-Money reaction times (*p*'s > 0.65). The amount of money that smokers and non-smoking controls earned ($M_{smokers}$ = $AUD 22.01, $SD_{smokers} = 5.44$; $M_{controls}$ = $AUD 19.55, $SD_{controls} = 4.39$) during the reward condition did not differ significantly $t(34) = 1.48$, $p = 0.15$).

Behavioral results punishment

Group (smokers versus controls) x Condition (Neutral versus Punishment) RM-ANOVA's did not show significant main or interaction effects of Group and Condition for either NoGo, Go and Go-Money accuracy rates (all *p*'s > 0.06). NoGo reaction times did not show a main effect of Group or Condition. However, a Group x Condition interaction was found, $F(1,23) = 4.19$, $p = 0.05$. Post-hoc t-tests revealed that NoGo reaction times in controls were slower in the punishment condition relative to the neutral condition ($p < 0.05$), whereas there was no effect of Condition on NoGo reaction times for smokers. No significant

main or interaction effects of Group and Condition were found for either Go or Go-Money reaction times (all p's > 0.18). The amount of money that smokers and non-smoking controls earned ($M_{smokers}$ = 12.29, $SD_{smokers}$ = 7.19; $M_{controls}$ = 14.59, $SD_{controls}$ = 5.84) during the punishment condition did not differ significantly $t(34) = 1.06$, p=0.30).

Table 1

Accuracy rates and reaction times for both the smoking and non-smoking group on the Go/NoGo task

	Accuracy				Reaction Times			
	Smokers		Controls		Smokers		Controls	
Category	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
NoGo								
Neutral	79.16	14.83	81.12	13.15	376.70[a]	65.56	359.72[b]	51.15
Reward	82.65	10.29	82.29	10.29	349.30[a]	47.59	370.80	49.26
Punishment	78.00	11.67	82.65	7.47	362.13	38.11	389.46[b]	46.77
Go								
Neutral	99.11	2.28	96.59	12.38	407.13[c]	52.54	406.26[c]	47.97
Reward	99.42	0.96	97.41	8.13	392.25[c]	44.92	391.16[c]	43.80
Punishment	95.53	1.02	99.29	1.96	408.90	40.47	414.83	53.07
Go-Money								
Neutral	96.63	4.03	93.76	12.16	398.92[d]	38.42	404.07[d]	42.07
Reward	98.05	3.36	96.76	8.34	379.49[d]	38.20	381.11[d]	44.49
Punishment	97.47	2.59	97.41	4.64	407.23	32.67	406.47	51.30

Note table 1 *[a] RM-ANOVA revealed that NoGo reaction times in smokers were faster in the reward condition relative to the neutral condition ($p< 0.05$). [b] RM-ANOVA revealed that NoGo reaction times in controls were slower in the punishment condition relative to the neutral condition ($p< 0.05$). [c] RM-ANOVA revealed that Go-Money reaction times were faster in both groups in the reward versus neutral condition ($p< 0.001$). [d] RM-ANOVA revealed that Go-Money reaction times were faster in both groups in the reward versus neutral condition ($p< 0.001$).*

Imaging results

Activation associated with inhibitory control in the combined activation map was primarily right lateralized and included the right inferior/middle frontal gyrus (IFG/MFG), the dorsolateral prefrontal cortex (DLPFC), the right pre-supplementary motor area (pre-SMA), the right anterior insula, the right inferior parietal lobe (IPL), the right superior temporal gyrus (STG) and bilateral occipital regions. MNI coordinates and cluster volumes are shown in table 2. These regions were subsequently used for functionally defined ROI analyses to investigate the effects or reward and punishment on inhibitory control related brain activation.

NoGo imaging results in the reward condition

Activation for inhibitory control during neutral and reward conditions showed increased activation in smokers relative to non-smoking controls in the right IFG/MFG, the right DLPFC, the right anterior insula, the pre-SMA and the right IPL. No main effect of Condition, nor Group x Condition interaction effects were found indicating that activation in smokers relative to controls is increased both during neutral and reward conditions. No main effect of Group, Condition or Group x Condition interactions was found in the bilateral NAcc, the right STG and occipital regions. See figure 2 and table 2 for details of results in all regions of interest, including F- and p-values.

NoGo imaging results in the punishment condition

Activation for inhibitory control during neutral and punishment conditions showed Group x Condition interactions in the right anterior insula, right IFG/MFG, right DLPFC and the right occipital region. Post-hoc tests in the right insula, right IFG/MFG and right DLPFC revealed similar activation patterns. During the neutral condition, smokers showed increased activation relative to controls in these regions, whereas no group differences were found during the punishment condition. Post-hoc tests in the right occipital region revealed that inhibitory control related brain activation in controls was increased in the punishment condition relative to the neutral condition, whereas there was no effect of Condition on activity for smokers. Brain activation associated with inhibitory control in the pre-SMA and right IPL was increased in smokers relative to control regardless of task condition. No main effect of Group, Condition or Group x Condition interactions were found in the bilateral NAcc, the right STG and left occipital region. See figure 2 and table 2 for details of results in all regions of interest such as F- and p-values.

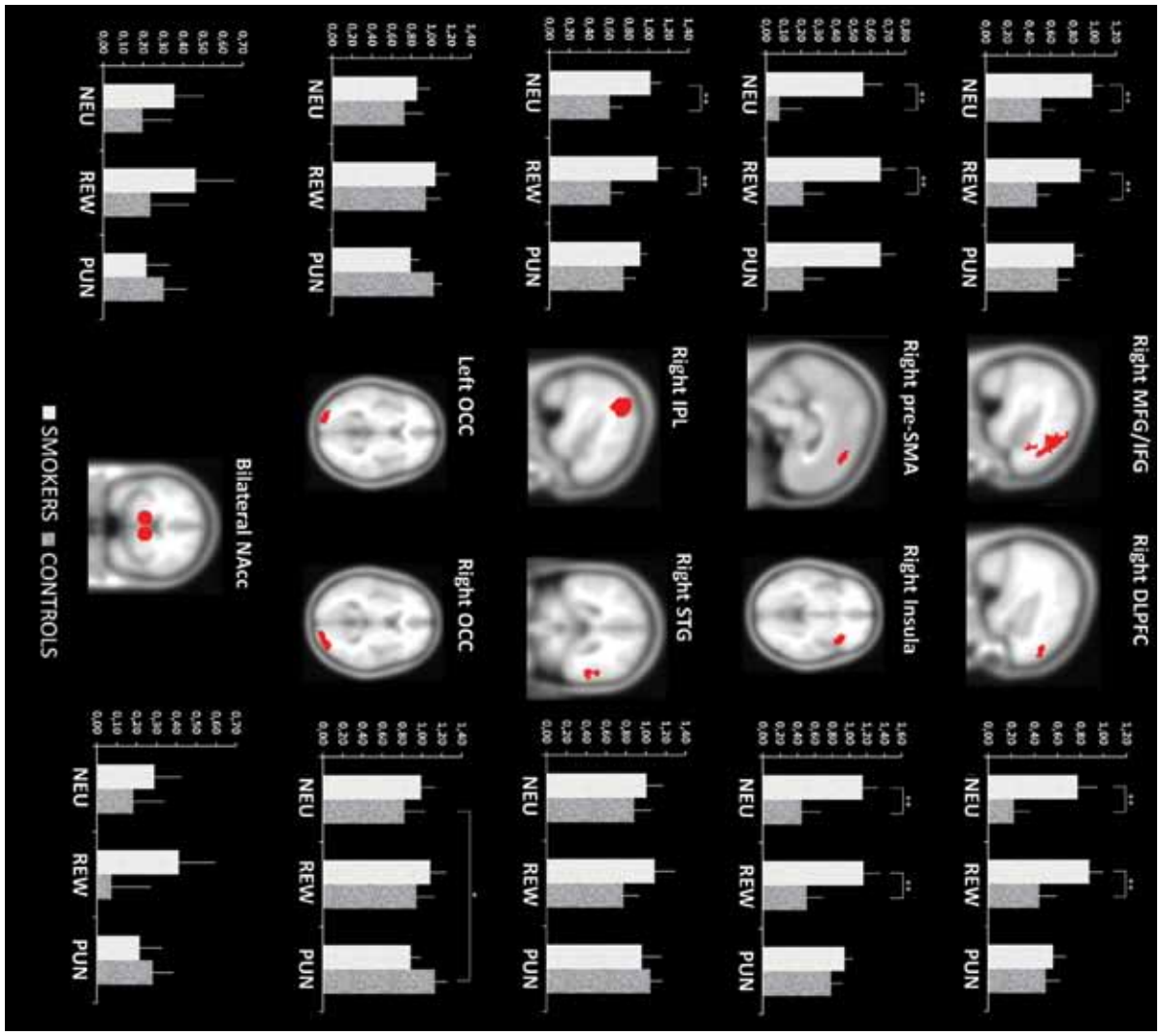

Figure 2
Activation patterns during successful NoGo trials in Neutral, Reward and Punishment conditions

Note figure 2 ** p <0.05; ** p ≤ 0.001; NEU: neutral; REW: reward; PUN: punishment; MFG/IFG: middle frontal gyrus / inferior frontal gyrus; DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobe; STG: superior temporal gyrus; OCC: occipital; NAcc: Nucleus accumbens.*

Table 2
Regions of event-related activation during successful NoGo trials

Region	MNI coordinates			mm^3	Reward	Punishment		
	X	Y	Z		Group	Group	Condition	Interaction
Pre-SMA	5	25	48	744	Main effect S > C $F(1,34) = 15.86$ $p< 0.001$	Main effect S > C $F(1,34) = 5.56$ $p< 0.05$	- -	- -
Right Insula	38	21	4	2056	Main effect S > C $F(1,34) = 10.46$ $p< 0.01$	Neutral S >C $F(1,34) = 7.05$ $p< 0.05$ Punishment - -	- -	$F(1,34) = 4.89$, $p< 0.05$
Right IFG/MFG	43	16	32	9824	Main effect S > C $F(1,34) = 12.78$ $p= 0.001$	Neutral S > C $F(1,34) = 9.84$ $p< 0.01$ Punishment - -	- -	$F(1,34) = 4.00$, $p= 0.05$
Right DLPFC	37	45	20	720	Main effect S > C $F(1,34) = 12.75$ $p= 0.001$	Neutral S > C $F(1,34) = 6.95$ $p= 0.01$ Punishment - -	- -	$F(1,34) = 4.00$, $p= 0.05$
Right IPL	40	-50	44	15368	Main effect S > C $F(1,34) = 13.03$ $p= 0.001$	Main effect S > C $F(1,34) = 5.33$ $p< 0.05$	- -	- -
Right STG	57	-43	6	1032	- -	- -	- -	- -
Left OCC	-25	-81	-1	6688	- -	- -	- -	- -
Right OCC	28	-74	-5	9704	- -	- -	Controls: Punishment > Neutral $F(1,34) = 4.66$, $p< 0.05$ Smokers:	$F(1,34) = 4.37$, $p< 0.05$
Left NAcc	-10	12	-2	4120	- -	- -	- -	- -
Right NAcc	10	12	-2	4120	- -	- -	- -	- -

Note table 2 *Pre-SMA: pre-supplementary motor area; IFG: Inferior frontal gyrus; MFG: middle frontal gyrus; DLPFC: dorsolateral prefrontal gyrus; IPL: inferior parietal lobe; STG: superior temporal gyrus; OCC: occipital; NAcc: Nucleus Accumbens; S: smokers, C: controls.*

Nucleus accumbens activation for Go-Money trials

A main effect of Group in the left NAcc showed that brain activation in smokers was enhanced for Go-Money trials across Neutral, Reward and Punishment conditions $F(1,34)=4.41$, $p< 0.05$. No main or interaction effect of Condition was found. No main effect of Group, Condition or Group x Condition interactions were found for activation in the right NAcc during Go-Money trials (all p's > 0.06).

Discussion

The current study examined the neural basis of inhibiting an immediately rewarding response in order to obtain a larger delayed reward in smokers and non-smoking controls. We also investigated whether punishment insensitivity could contribute to inefficient inhibitory control. Results showed enhanced activation in the left NAcc in smokers relative to controls when they could earn money without the need for inhibition (i.e., in Go-Money trials), which confirms increased sensitivity in addicted individuals for immediate reward (Bjork, et al. 2008; Van Hell, et al. 2010). With regard to the inhibition of rewarding stimuli, the hypothesis that smokers would have difficulty inhibiting an immediate reward in order to obtain a larger delayed reward was not confirmed by behavioral measures such as accuracy rates. However, greater BOLD activity in the pre-SMA, right IFG/MFG, right DLPFC and right IPL was found in smokers compared to non-smoking controls during successful inhibition of rewarding NoGo trials. This heightened brain activation in smokers was also found during inhibition of neutral stimuli, suggesting that differences in brain activation associated with inhibitory controls in smokers may also occur in neutral situations without a reward-related context. Increased brain activation in regions that are crucial for inhibitory control has previously been found during affectively neutral conditions in cannabis users (Hester, et al. 2009b; Tapert, et al. 2007) and has been interpreted as a compensatory mechanism (Goh, et al. 2009; Wilkinson, et al. 2004), where maintaining equivalent performance compared to non-addicted individuals requires recruitment of additional cortical activation. As an alternative explanation, additional recruitment of cortical activation for NoGo trials might be consistent with tonic versus phasic changes in Go/NoGo task related activation (Simoes-Franklin, et al. 2010). Research on individual differences in response inhibition task performance indicates that better performance on tasks such as the Go/NoGo is associated with a more cautious response style,

or high tonic levels of proactive cognitive control (Braver 2012). Smokers appear to implement less tonic control during our task, reflected in faster failed NoGo reaction times, hence when a NoGo trial appears, an increased phasic control response and associated neural activation must be implemented to successfully withhold the prepotent Go response. Also, the relative short time-frame of smoking abstinence in the current study (one hour) may have contributed to the observed pattern of equal behavioral performance for smokers and non-smoking controls in combination with increased brain activation in smokers, as previous studies have shown that smoking abstinence and withdrawal modulate cognitive performance and prefrontal brain function (Azizian, et al. 2010; Froeliger, et al. 2012).

The current study further examined whether punishment insensitivity might contribute to inefficient inhibitory control. It was hypothesized that punishment, via an immediate monetary fine for failed response inhibition, would not significantly improve inhibitory control performance in smokers when compared to non-smoking controls. The behavioral data show such a trend, with control participants showing improved accuracy during the punishment condition (relative to neutral) and smokers showing a decline, but the small effect size renders this difference undetectable with our samples. Despite this, brain activation in the right anterior insula, right IFG/MFG and right DLPFC was increased in smokers relative to non-smoking controls during neutral and reward conditions, but not during the punishment conditions. Activation patterns (see figure 2) suggest that the lack of group differences under conditions of punishment reflects additional activation in non-smoking controls during the punishment compared to the neutral condition, an effect that was significant in right visual areas and was not observed in smokers. Involvement of visual areas in controlling behavior was previously observed by Brody and colleagues (Brody, et al. 2007) when smokers decreased visual processing of smoking cues in order to inhibit feelings of craving. Increased visual processing of NoGo stimuli during the punishment condition by non-smoking controls would be consistent with the heightened salience of punishment for non-smoking controls and may be associated with avoiding future punishment. Therefore, these findings provide tentative evidence that smokers, in contrast to non-smoking controls, may be by less sensitive to punishment as a strategy to improve inhibitory control. Reduced punishment sensitivity has previously been found in harmful drinkers using the same MI-Go/NoGo task (Rossiter, et al. 2012).

It should be noted that accuracy rates in the current study were not significantly influenced by reward and punishment conditions. Consequently,

brain activation data should be interpreted in terms of compensation/more efficient recruitment of cortical regions leading to similar performance levels across conditions (Wilkinson, et al. 2004). Reaction times, however, showed expected effects according to task conditions. For example, Go and Go-Money reaction times were faster in the reward versus neutral condition, suggesting that the availability of immediate reward elicited a higher degree of impulsive responding.

In conclusion, the current study demonstrated that smokers had hyperactivation in the pre-SMA, right anterior insula, right IFG/MFG and right DLPFC compared to non-smoking controls during inhibition of an immediately rewarding stimulus in order to obtain a larger delayed reward. In addition, tentative evidence is provided that smokers are insensitive to the inhibitory effect of punishment to guide control over rewarding stimuli. Future studies should examine the role of punishment insensitivity as a core component of compulsive substance use. More knowledge regarding punishment insensitivity could guide treatment strategies to stimulate smoking abstinence.

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Chapter Six

The role of dopamine in inhibitory control in smokers and non-smokers: a pharmacological fMRI study

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Abstract

Contemporary theoretical models of substance dependence posit that deficits in inhibitory control play an important role in substance dependence. The neural network underlying inhibitory control and its association with substance dependence have been widely investigated. However, the pharmacology of inhibitory control is still insufficiently clear. The aims of the current study were twofold. First, we investigated the role of dopamine in inhibitory control and associated brain activation. Second, the proposed link between dopamine and impaired inhibitory control in nicotine dependence was investigated by comparing smokers and non-smoking controls. Haloperidol (2mg), a dopamine D2/D3 receptor antagonist, and placebo were administered to 25 smokers and 25 non-smoking controls in a double-blind randomized cross-over design while performing a Go/NoGo task during fMRI scanning. Haloperidol reduced NoGo accuracy and associated brain activation in the ACC, IFG and MFG, showing that optimal dopamine levels are crucial to effectively implement inhibitory control. In addition, smokers showed behavioral deficits on the Go/NoGo task as well as hypoactivity in the left IFG, right MFG and ACC after placebo, supporting the hypothesis of a hypoactive prefrontal system in smokers. Haloperidol had a stronger impact on prefrontal brain activation in non-smoking controls compared to smokers, which is in line with the inverted 'U' curve theory of dopamine and cognitive control. The current findings suggest that altered baseline dopamine levels in addicted individuals may contribute to the often observed reduction in inhibitory control in these populations.

Introduction

Contemporary theoretical models of substance dependence posit that deficits in inhibitory control are of key importance in the development and continuation of substance dependence (Goldstein, et al. 2011; Jentsch, et al. 1999; Lubman, et al. 2004). Deficits in inhibitory control may contribute to the inability to stop taking drugs despite negative consequences. Inhibitory control is accomplished through a mainly right lateralized brain network including the inferior frontal gyrus (IFG), the anterior cingulate gyrus (ACC)/ pre-supplementary motor area (pre-SMA) and dorsolateral prefrontal cortex (DLPFC), as well as parietal and subcortical areas (Aron, et al. 2006; Chambers, et al. 2009; Swick, et al. 2011). Hypoactivation in prefrontal brain regions has been reported in substance dependent individuals including smokers (De Ruiter, et al. 2012; Hester, et al. 2004b; Kaufman, et al. 2003; Li, et al. 2009; Nestor, et al. 2011). Additionally, hypoactivation in these regions seems to be related to difficulties in controlling substance use in daily life as it was found to be associated with a strong coupling between subjective craving and smoking (Berkman, et al. 2011).

Although the neural network underlying inhibitory control and its association with substance dependence have been widely investigated, the pharmacology of inhibitory control is an ongoing scientific endeavor. Animal studies suggest that dopamine plays an important role in overall executive functioning. For example, a hallmark study by Brozoski and colleagues (1979) indicated that dopamine depletion of the monkey prefrontal cortex impaired spatial working memory. In addition, reduced dopamine D2/D3 receptor availability in rats appeared to be associated with elevated impulsivity levels (Dalley, et al. 2007). Based on human studies, theorists assume that the relation between dopamine and cognitive control follows an inverted U-shaped curve such that either too low or too high levels of prefrontal dopamine are disadvantageous for cognitive functioning (Cools, et al. 2011). This hypothesis is mainly based on working memory performance, but it is likely that other cognitive functions depending on prefrontal brain activation are similarly characterized by an inverted U-shaped curve. Recent studies in humans have shown that optimal dopamine levels (i.e., extracellular dopamine and receptor densities) exist for attentional capacity (Finke, et al. 2010) and also inhibitory control (Nandam, et al. 2011), although these studies are still scarce. It is important to gain more knowledge on how dopamine affects neural networks underlying inhibitory control, especially to better understand disorders such as substance dependence that are characterized by dysfunctional dopamine systems (Balfour 2009; Berkman, et al. 2011; Diekhof, et al. 2008; Franken, et al.

2005; Koob, et al. 1997; Volkow, et al. 2009). For example, reduced dopamine D2 receptor densities in the striatum have been consistently found in substance dependent individuals (Martinez, et al. 2004; Volkow, et al. 2001; Volkow, et al. 2002; Wang, et al. 1997) including smokers (Fehr, et al. 2008). These reduced dopamine D2 densities have also been linked to reduced metabolism in prefrontal areas (Volkow, et al. 1993; Volkow, et al. 2001; Volkow, et al. 2007). Altogether, it is suggested that alterations in dopaminergic functioning in substance dependent individuals may underlie the observed deficits in inhibitory control as well as hypoactivation in associated prefrontal regions. To the best of our knowledge, only one study employed a dopamine manipulation in substance dependent individuals while measuring inhibitory control (Li, et al. 2010). It was shown that the dopamine agonist methylphenidate enhanced inhibitory control compared to placebo in cocaine dependent individuals. The behavioral improvement in inhibitory control was positively associated with activation in the middle frontal gyrus and negatively with activation in the ventromedial prefrontal cortex (Li, et al. 2010). Although this study provided valuable insights, a control group consisting of healthy participants was lacking.

The aims of the current study were twofold. First, a dopamine manipulation was employed to investigate the role of dopamine in inhibitory control and associated brain activation. Second, the potential link of dopamine with impaired inhibitory control in nicotine dependence was investigated by comparing the effects of dopaminergic manipulation between smokers and non-smoking controls. As part of a larger study, participants received placebo and haloperidol, a dopamine D2/D3 receptor antagonist, in a double-blind randomized cross-over design while performing a Go/NoGo task during fMRI scanning. In line with previous studies showing beneficial effects of a dopamine agonist (Li, et al. 2010; Nandam, et al. 2011), we hypothesized that haloperidol will reduce inhibitory control and associated brain activation. Second, based on the inverted 'U' curve theory of dopamine and cognitive control, and reported baseline differences between smokers and controls in dopamine D2 receptor density, we expected that haloperidol will have differential effects on brain activation associated with inhibitory control in smokers and non-smokers.

Materials and Methods

Participants

Twenty-five smokers and twenty-five non-smoking controls participated in this study. Data from two non-smokers were discarded due to technical problems during data acquisition and analysis. The final sample consisted of 25 smokers (mean age = 22.56 years, *SD* = 2.84, 18 male) and 23 non-smoking controls (mean age = 21.74 years, *SD* = 1.82, 14 male). Smokers smoked at least 15 cigarettes per day (*M* = 19.12, *SD* = 3.37; range 15-25) for a duration of at least three years (*M* = 7.20, *SD* = 3.01, range = 3-14). The average score on the Fagerström Test for Nicotine Dependence (FTND: Heatherton, et al. 1991; Vink, et al. 2005) for smokers was 3.80, *SD* = 3.37, range = 1-8. Non-smokers had smoked ten cigarettes or less during their lifetime (*M* = 1.73, *SD* = 2.62, range = 0-10). All participants underwent a medical examination by a psychiatrist to assure eligibility for a single dose of 2 mg oral haloperidol. Exclusion criteria for both groups were (a) current substance abuse or dependence (other than nicotine for the smoking group), (b) the current presence of any physical or psychological illness, (c) any use of psychotropic medication or medication that may affect blood circulation and/or respiration, (d) fMRI contraindications, and (e) left-handedness (see supplementary materials for details on medical screening). There were no significant differences between the groups in mean age, $t(46) = 1.20$; ns, gender ratio, χ^2 (1, $n = 48$) = 0.67; ns and education level χ^2 (2, $n = 47$) = 3.19; ns. The study was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written informed consent of the subjects. The ethics committee of Erasmus MC – University Medical Centre Rotterdam approved this study.

Dopaminergic manipulation

A single oral dose of 2 mg haloperidol and a placebo was administered to participants in a double-blind randomized cross-over design. Haloperidol is a selective dopamine D2/D3 receptor antagonist for postsynaptic receptors. Using positron emission tomography (PET), Nordstrom, Farde and Halldin (1992) demonstrated that striatal D2 receptor occupancy three hours after oral administration of a single dose of 2mg haloperidol was 18% and 52% after six hours. In the present study, the fMRI session took place four hours after administration which, according to the Nordstrom (1992) study results in about 30% D2 receptor occupancy. Haloperidol has also been found to block

dopamine bursts in the prefrontal cortex (Wang, et al. 2004) and previous studies showed that 2 mg haloperidol successfully reduced processing biases in substance dependent individuals (Franken, et al. 2004; Mahler, et al. 2005). None of the participants reported any side effects of medication. After the second fMRI session, participants answered a single additional question in which they had to guess on the type of medication they received for each scanning session. Participants' guesses were not above chance (46.7% of the participants correctly indicated in which test occasion they received haloperidol, p=0.7.

Procedures

After confirmation of study eligibility by the medical screening performed by a psychiatrist, two scanning sessions were scheduled that were separated by one week. Similar to previous studies using haloperidol (Franken, et al. 2008; Franken, et al. 2004), participants took the medication four hours before both scanning sessions. Smokers were not allowed to smoke after taking the medication until scanning was finished to ensure that indirect nicotine effects on dopamine levels did not interfere with the binding of haloperidol to D2/D3 receptors in the brain. Breath carbon monoxide (CO) concentration was measured in all subjects using a calibrated Micro+Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) to verify smoking abstinence and to objectively define smokers and nonsmokers. In addition, smokers completed the FTND (Heatherton, et al. 1991; Vink, et al. 2005) to measure nicotine dependence on the first scanning session only and the Questionnaire of Smoking Urges (QSU: Cox et al., 2001) to indicate their current subjective craving for a cigarette during both scanning sessions.

Task paradigm

Participants completed a Go/NoGo task in which letters were presented at 1 Hz (similar to previous studies such as Nestor, et al. 2011). Each letter was presented for 700 ms followed by a blank screen (the inter stimulus interval) for 300 ms. Participants were required to make a button press response as fast as possible to each letter (Go trials) and to withhold this response whenever the letter was the same as the previous one (NoGo trials). NoGo trials were presented unpredictably by introducing jitter in the number of intervening Go trials (M =7.25, range = 3-16). The task consisted of 817 Go and 110 NoGo trials such that twelve percent of all trials were NoGo trials. Four fifteen seconds rest periods were included in the task. Behavioral outcome measures for this task

are Go and NoGo accuracy (percentage correct trials) and reaction times for correct Go and incorrect NoGo trials

Image acquisition

Data were acquired on a 3T GE Healthcare (The Discovery® MRI 750 3.0T, Milwaukee, US) scanner. Blood oxygen level-dependent (BOLD) sensitive functional T2*-weighted images were acquired in 44 axial slices covering the entire supratentorial brain with a repetition time (TR) of 2500 ms, echo time (TE) of 30 ms, field of view (FOV) of 240 mm, and isotropic voxel size of 2.5 mm3. A structural 3-dimensional (3D) inversion recovery fast spoiled gradient echo T1-weighted image was acquired in 164 contiguous axial slices with TR of 7.9 ms, TE of 3.1 ms, FOV of 240 mm, and isotropic voxel size of 1 mm3 for anatomical reference.

Image processing

Imaging data were analyzed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing of the functional data included realignment of all functional images. Next, the anatomical scan was coregistered to the mean T2*-weighted image and subsequently segmented into grey and white matter and cerebrospinal fluid. Segmentation parameters were used for normalization using the SPM T1-weighted MNI template. Functional scans were spatially smoothed using a 3D full-width at half-maximum Gaussian kernel of 4 mm. The four conditions (NoGo correct, NoGo incorrect, Go correct and Go incorrect) were modeled in the context of the general linear model for both types of medication (placebo, haloperidol) using delta functions convolved with a canonical hemodynamic response function. Subsequently, the NoGo correct minus Go correct contrast representing brain activation associated with inhibitory control was calculated for placebo and haloperidol separately.

In order to show that the current Go/NoGo task activated the inhibitory control network the main effect for brain activation associated with inhibitory control was calculated using a single random effects one-sample t-test that included both medication types and both groups.

To investigate the overall effect of haloperidol in all participants on brain activation associated with inhibitory control a main effect of medication (placebo minus haloperidol and vice versa) was calculated by means of a

random effects paired-sample *t*-test of both groups combined. The same analysis was performed for Go trials to investigate whether haloperidol altered baseline activation (see supplementary materials for details).

To assess Group x Medication interactions for brain activation associated with inhibitory control, first an OR map was created according to the methods used in Hester et al. (2009b). The OR map shows voxels in which group differences were significant in either of the constituent maps (i.e., brain activation for placebo and haloperidol). Using the OR map, group differences are identified while biases towards either of the medication types are avoided. Second, contrast values (parameter estimates) for both groups and medication types were extracted for significant clusters in the OR map. Subsequently, extracted contrast values were entered in Medication x Group Repeated Measures Analyses of Variance (RM-ANOVA) using SPSS (version 17, Armonk). In addition, the extracted contrast values from the OR map were correlated with NoGo accuracy for both groups and medication types separately to assess associations between brain activation and behavioral outcome measures. The association between the effects of haloperidol on behavioral measures and brain activation was investigated by calculating Pearson correlation coefficients for placebo minus haloperidol NoGo accuracy scores and placebo minus haloperidol brain activation.

The correction for multiple comparisons in the between medication and the between group analyses (OR map) was performed using a Monte Carlo simulation. One thousand permutations determined that a cluster of 536mm3 was needed to correct an individual voxel type 1 error of $p<.01$ to a cluster corrected threshold of $p<.01$. The main effect for task related brain activation was corrected to $p<0.01$ using an individual threshold of 0.0000001 and cluster size restriction of 16 mm3.

Data analyses questionnaires and behavioral performance

RM-ANOVA's were performed in SPSS for CO levels, QSU scores and behavioral outcomes of the Go/NoGo task. Medication was used as two-level within-subject factor (haloperidol versus placebo) and Group was used as two-level between-subject factor (smokers versus controls) for CO levels and behavioral outcomes. In addition, Task Condition was added as a within-subject factor for behavioral performance (Go versus NoGo correct for accuracy rates and Go versus NoGo incorrect for reaction times).

Results

CO levels and questionnaire data

Smokers had a higher CO breath concentration (in parts per million, $M_{haloperidol}$= 6.20, SD = 3.39, $M_{placebo}$= 6.72, SD = 3.50) as compared to non-smoking controls ($M_{haloperidol}$= 1.43, SD = 0.79, $M_{placebo}$= 1.65, SD = 0.51), $F(1,46)$ = 52.77, $p< 0.001$. CO levels did not differ between medication types for either group, $F(1,46)$ = 1.68, ns. Subjective craving in smokers was equal for placebo (M = 39.71, SD = 11.48) and haloperidol (M = 38.08, SD = 11.80) conditions $F(1,23)$ = 0.44, ns.

Behavioral performance

Accuracy rates revealed a robust main effect of Task Condition (Go versus NoGo), $F(1,46)$ = 458.45, $p<.001$, showing that participants were generally less accurate for NoGo than for Go trials (57.66 versus 97.97%). Furthermore, a main effect of Medication type was found, indicating that accuracy rates were lower during the haloperidol than the placebo condition, $F(1,46)$ = 10.62, $p<0.01$. A Medication x Task Condition interaction, $F(1,46)$ = 504.23, $p< .01$, showed that the decrease in performance was driven by the NoGo condition as the effect of medication was significant for the NoGo condition ($M_{NoGo/haloperidol}$= 54.02, SD = 17.22, $M_{NoGo/placebo}$= 61.19, SD = 14.49, $F(1,46)$= 10.91, $p< 0.01$), and not for the Go condition ($M_{Go/haloperidol}$= 97.58, SD = 3.59, $M_{Go/placebo}$= 98.17, SD = 3.44). No main, $F(1,46)$= 0.28, ns, or interaction effect, $F(1,46)$= 0.78, ns, was found for Group. We performed an additional explorative Group x Condition RM-ANOVA for accuracy rates on the first test occasion in order to exclude possible learning effects on task performance. A Group x Task Condition interaction was found, $F(1,46)$= 4.72, $p< 0.05$. Post-hoc *t*-tests revealed that, for NoGo trials, smokers performed less accurately than non-smoking controls ($p< 0.05$; $M_{smokers}$=53.31, SD = 14.22, $M_{controls}$=61.90, SD = 15.10), whereas there was no difference for Go accuracy between the groups, $F(1,46)$= 0.33, ns.

With regard to the reaction time data, a main effect of Task Condition was found, $F(1,46)$ = 42.03, $p< .001$, indicating that participants generally responded faster for incorrect NoGo trials ($M_{NoGo\ incorrect/smokers}$ = 350.77, SD = 49.31, $M_{NoGo\ incorrect/controls}$ = 313.85, SD = 41.71) than for Go trials ($M_{Go/smokers}$ = 367.51, SD = 45.81, $M_{Go/controls}$ = 337.83, SD = 40.50). Furthermore, a main effect was found for Group showing that smokers had generally slower response times, $F(1,45)$ = 7.10, $p<0.05$. No main or interaction effects of Medication were found for reaction times (all F's smaller than 0.82).

fMRI data

In line with meta-analyses (Garavan, et al. 2006; Swick, et al. 2011), inhibitory control was associated with brain activation in bilateral IFG, ACC/pre-SMA, DLPFC, anterior insula, temporoparietal junction (TPJ), caudate and putamen, and bilateral superior parietal regions (for an overview of activated brain areas for NoGo minus Go see supplementary figure 1).

Haloperidol was found to decrease, as compared to placebo, brain activation associated with inhibitory control across groups in the ACC, right superior frontal gyrus (SFG), left IFG, posterior cingulate cortex (PCC), and left middle temporal gyrus (MTG; see figure 1 and table 1 for details). There was no increase in brain activation with haloperidol compared with placebo. An additional analysis on the effect of haloperidol on Go-trials confirmed that the reduction in brain activation for inhibitory control was not due to baseline alterations associated with haloperidol (see supplementary materials).

The OR map showed differences between smokers and non-smoking controls in the ACC, PCC, right middle frontal gyrus (MFG), left IFG, and right temporoparietal junction (TPJ). Overall, smokers had reduced activation in the ACC relative to controls. Group x Medication interactions were significant in the right MFG, left IFG, PCC and right TPJ. Post-hoc analyses revealed that activation differences between smokers and non-smoking controls were mainly found after placebo. Activation was reduced in smokers relative to controls after placebo in the right MFG and left IFG and increased in the TPJ. Haloperidol was found to reduce brain activation associated with inhibitory control in the left IFG and right MFG only in controls, whereas it reduced brain activation in the PCC in smokers. See figure 2 and table 2 for details concerning group differences and Group x Medication interactions.

Correlation analyses of average contrast values extracted from brain activation showing between group differences (ACC, left IFG, right MFG, PCC and right TPJ) with NoGo accuracy (figure 3) revealed that activation in the ACC during haloperidol was positively associated with NoGo accuracy $r = 0.43$, $p < 0.05$ in non-smoking controls. The difference in NoGo accuracy between placebo and haloperidol administration in controls was further associated with the difference in brain activation in this area, $r = 0.41$, $p = 0.05$, indicating that a decrease in brain activation after haloperidol administration correlated with a decrease in accuracy. This association between haloperidol-induced differences in brain activation and NoGo accuracy was also found in controls in the right MFG, $r = 49$, $p < 0.05$. No significant correlations between brain activation and behavioral measures were found in smokers.

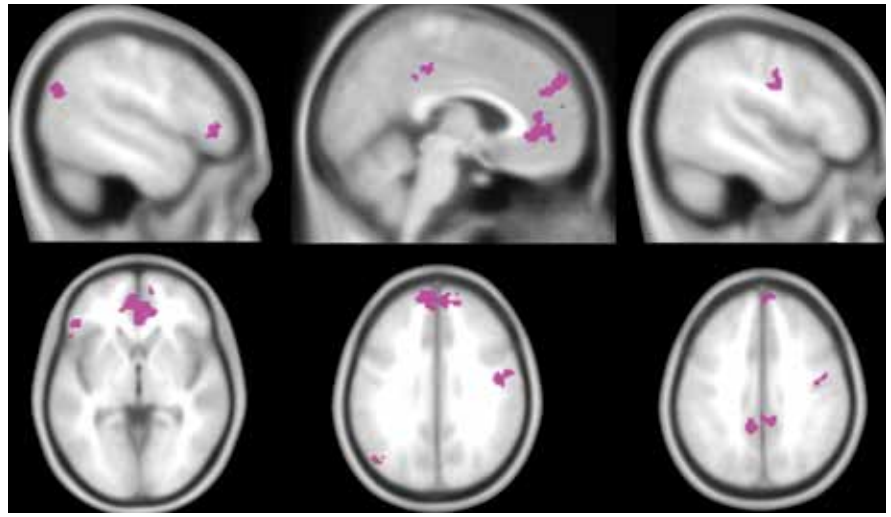


Figure 1

Haloperidol reduced brain activation associated with inhibitory control

Note figure 1 *Reduced brain activation associated with inhibitory control after haloperidol of both smokers and non-smoking controls. $p < 0.01$ (corrected for multiple comparisons using a Monte Carlo simulation). See table 1 for anatomical localization of active regions.*

Table 1

Medication effects for brain activation associated with inhibitory control

Region	MNI coordinates (X Y Z)	mm^3	Z-value[a]
ACC	-8 52 2	7816	4.12
r-SFG	20 -12 30	744	3.48
l- IFG	-52 34 2	544	3.54
PCC	-8 -46 38	1304	3.44
l-MTG	-50 -70 26	768	3.95

Note table 1 *[a] $p < 0.01$, corrected for multiple comparisons using a Monte Carlo simulation AAC: anterior cingulate cortex; r-SFG: right superior frontal gyrus; l-IFG: left inferior frontal gyrus; PCC: posterior cingulate cortex; l-MTG: left middle temporal gyrus.*

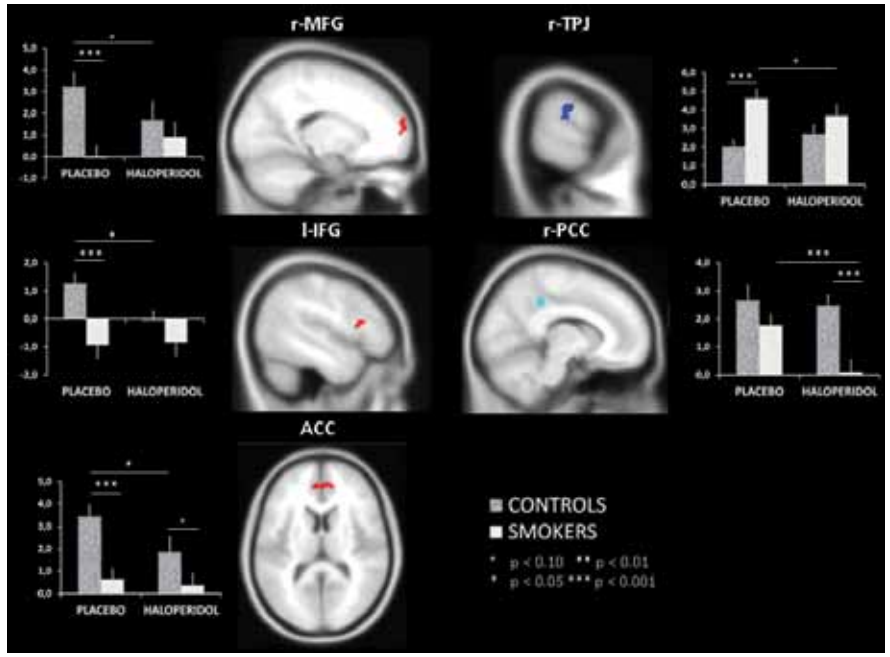


Figure 2
Group differences of brain activation associated with inhibitory control

Note figure 2 *This figure shows brain regions in which group differences were significant either after placebo or after haloperidol, p< 0.01 (corrected for multiple comparisons using a Monte Carlo simulation). Group x Medication effects were significant in the right middle frontal gyrus (r-MFG), left inferior frontal gyrus (l-IFG), right temporoparietal junction (r-TPJ) and posterior cingulate cortex (PCC). See table 2 for details regarding interaction and medication effect.*

Table 2
Group differences in brain activation associated with inhibitory control

Region	MNI coordinates (X Y Z)	mm^3	ZValue[a]	Group x Medication[b]	Group effects[b]	Medication effects[b]
r-MFG	20 64 12	640	3.59	$F = 4.55, p < 0.05$	PL: smokers < controls $F = 16.30, p<0.001$ HA: ns	HA < PL in controls $F = 3.29, p=0.08$
l-IFG	-52 18 16	592	3.27	$F = 4.20, p < 0.05$	PL: smokers < controls $F = 13.71, p=0.001$ HA: ns	HA < PL in controls $F = 6.92, p<0.05$
ACC	14 40 8	888	3.66	ns	Main effect: smokers < control $F = 14.60, p<0.001$	Main effect: HA < PL $F = 3.37, p= 0.07$
r-TPJ	64 -20 30	864	3.57	$F = 4.18, p<0.05$	PL: smokers > controls $F = 19.67, p<0.001$ HA: ns	HA < PL in smokers $F = 2.87, p=0.10$
r-PCC	8 -38 42	672	4.23	$F = 5.63, p < 0.05$	PL: ns HA: smokers < controls $F = 17.33, p<0.001$	HA < PL in smokers $F = 14.54$, $p <0.001$

Note table 2 *[a] Z-value for group differences in OR map with p< 0.01, corrected for multiple comparisons using a monte-carlo simulation; [b] degrees of freedom F-test: 1,46; r-MFG: right middle frontal gyrus; l-IFG: left inferior frontal gyrus; AAC: anterior cingulate gyrus; r-TPJ: right temporoparietal junction; r-PCC: right posterior cingulate cortex; ns: non significant; PL.: placebo; HA: haloperidol.*

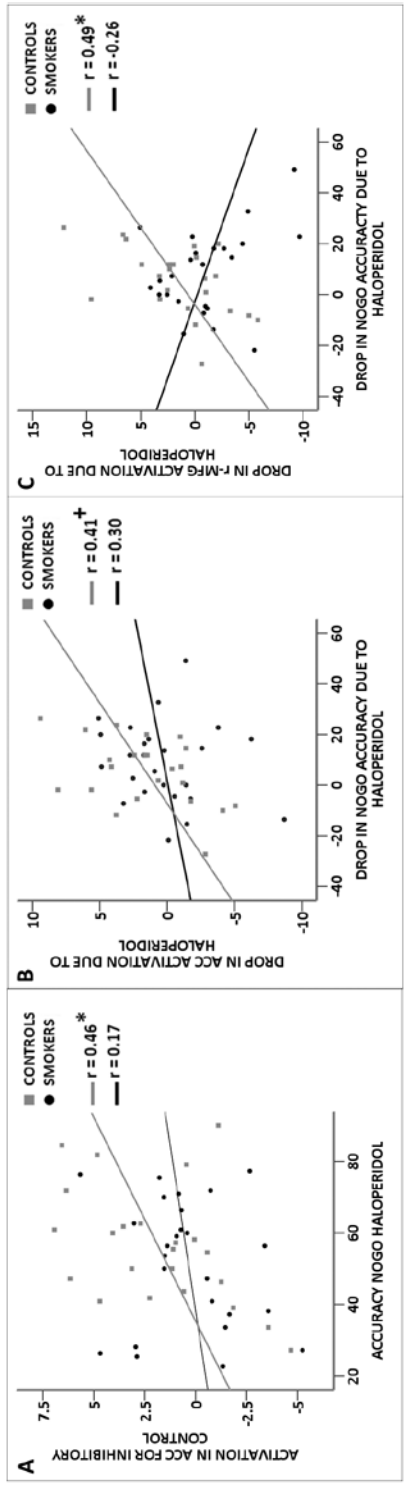


Figure 3
Correlations for NoGo task performance and brain activation associated with inhibitory control

Note figure 3 *$^{+}$ $p = 0.053$, $^{*}p < 0.05$; Part A displays the association between NoGo accuracy and brain activation associated with inhibitory control in the anterior cingulate cortex (ACC) during haloperidol. Part B and C displays the association between the drop in NoGo accuracy due to haloperidol (calculated by NoGo accuracy placebo minus NoGo accuracy haloperidol) and the drop in brain activation for inhibitory control in the ACC and the right middle frontal gyrus (r-MFG) due to haloperidol respectively (calculated by brain activation during placebo minus brain activation during haloperidol). The ACC and r-MFG correspond to the brain regions displayed in figure 2.*

Discussion

The aim of the current study was to elucidate the role of dopamine in inhibitory control and associated brain activation. In addition, by comparing smokers and non-smokers the potential link between dopamine and reduced inhibitory control in addiction was investigated. The current results confirmed the hypothesis that reduced dopamine levels after haloperidol intake are associated with impairments in inhibitory control. Haloperidol reduced NoGo accuracy rates in both groups, while Go accuracy and reaction times were unaffected, indicating a specific effect of dopamine on inhibitory control. Impaired inhibitory control after haloperidol was accompanied by reduced activation in prefrontal regions associated with inhibitory control including the ACC, IFG and MFG. The relationship between reduced regional brain activation and impaired behavioral performance was corroborated by correlations in non-smoking controls showing an association between a decrease in brain activation in the ACC and right MFG after haloperidol and a decrease in behavioral performance. These findings are in line with the notion that low dopamine levels are disadvantageous for cognitive control (Cools, et al. 2011; Nandam, et al. 2011). Previous studies that investigated the role of dopamine in cognitive control employed working memory and mental flexibility paradigms, which do not specifically address inhibitory control (Bertolino, et al. 2010; Braskie, et al. 2011; Stelzel, et al. 2010). As far as we know, the current study is the first to demonstrate the link between dopamine levels and brain activation associated with inhibitory control in healthy controls and in smokers.

Results of the current study also replicated previous findings of impaired performance on a Go/NoGo task in smokers (Luijten, et al. 2011a; Nestor, et al. 2011). Smokers had generally longer reaction times and reduced NoGo accuracy rates for the first test occasion. Longer reaction times on Go trials suggest less efficient task performance or the use of different strategies. Besides behavioral performance deficits, group differences between smokers and non-smoking controls in brain activation associated with inhibitory control were mainly found after placebo. Activation in prefrontal brain regions including the ACC, left IFG and right MFG was found to be reduced in smokers relative to non-smoking controls. These results therefore replicate previous studies showing hypoactivity during inhibitory control in smokers in prefrontal areas (De Ruiter, et al. 2012; Nestor, et al. 2011). In addition to reduced prefrontal activation, activation of the right TPJ was enhanced in smokers, suggesting compensational activation of this brain region known to be involved in attention processing (Corbetta, et al. 2002). In contrast to these findings during the placebo condition, no differences between

smokers and controls were found in the r-MFG, l-IFG and r-TPJ after haloperidol administration. Haloperidol intake, however, was associated with reduced activity relative to placebo in prefrontal regions in non-smoking controls, but not in smokers. This implies that dopamine D2/D3 receptor blockade by haloperidol renders non-smoking controls more similar to smokers regarding reduced inhibitory control and hence presumably regarding dopamine levels. The lack of an effect of haloperidol administration on prefrontal brain activation in smokers further implies a relative insensitivity in prefrontal brain regions to dopamine antagonist administration in this group. Differences in baseline dopamine levels between smokers and non-smoking controls may underlie the differential effects of haloperidol in both groups. The findings of this study are in line with the inverted 'U' shape theory stating that there is an optimum for dopamine levels in the brain to efficiently execute cognitive control (Cools, et al. 2011). The reduction in inhibitory control after haloperidol in both groups and the larger impact of haloperidol on prefrontal brain activation in non-smoking controls provides indirect evidence that impairments in inhibitory control in smokers and other addicted population may be due to suboptimal dopamine levels. Therefore it can be concluded that the effects of reduced dopamine receptor densities in smokers (Fehr, et al. 2008), or in substance dependence in general, may not be limited to motivational processes linked to dopamine such as reward sensitivity, but could also be the underlying neurobiological mechanism for reduced inhibitory control. It would be interesting for future studies to administer both a dopamine agonist and antagonist in order to examine the full range of the inverted U-curve theory on dopamine levels and cognitive control and their consequences for nicotine dependence. In addition, future studies may seek to combine fMRI with simultaneous PET imaging to directly assess dopaminergic transmission together with brain activation associated with specific cognitive processes such as inhibitory control (Judenhofer, et al. 2008).

In conclusion, an experimental reduction in dopamine levels was associated with impaired inhibitory control and reduced brain activation in smokers and non-smokers. In line with contemporary theories on addiction, smokers showed behavioral deficits on the Go/NoGo task as well as hypoactivity in the left IFG, right MFG and ACC during placebo, thereby confirming previous findings of prefrontal hypoactivation in smokers. Prefrontal brain activation associated with inhibitory control in smokers and non-smokers appears to be differentially affected by the experimental manipulation of dopamine levels, which is in line with the inverted 'U' curve theory of dopamine and cognitive control. The current findings suggest that optimal dopamine levels are crucial to effectively implement inhibitory control. Altered baseline dopamine levels in

addicted individuals may contribute to the often observed reduction in inhibitory control in these populations. Based on these findings pharmacotherapy should be targeted at restoring the dopamine balance in smokers, specifically in prefrontal brain regions.

Acknowledgements

We would like to thank Esther Spittel for her assistance with data collection and participant recruitment.

Supplementary Materials

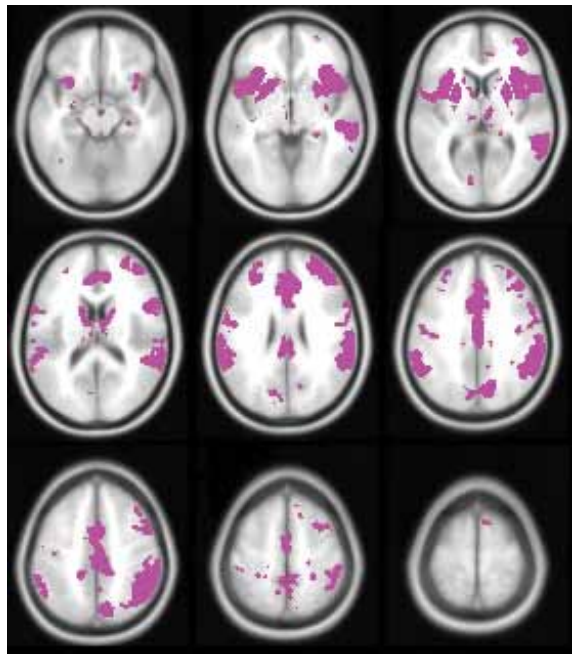
Medical screening

All participants were screened by a Psychiatrist. The screening included a check for contraindications for haloperidol (lifetime prevalence of epileptic seizure, heart disease and first degree relatives with diseases affecting dopaminergic transmission such as Parkinson disease, Huntington disease or psychosis. Participants were also provided with information on potential side effects such as drowsiness and muscle stiffness and were explained that these side effects are not expected to occur with a single low dose of 2 mg haloperidol. In addition, participants were screened for neurological and psychiatric diseases to make sure that participants had no lifetime neurological or psychiatric diagnoses and that they did not use any medication that crosses the blood brain barrier.

Effect of haloperidol on baseline Go activation

To check whether the observed effects of haloperidol on brain activation associated with inhibitory control are not due to baseline alterations of non-cognitive brain activation we performed an additional paired samples t-test to compare brain activation after placebo and haloperidol for the Go correct condition including both groups. Given the high percentage of Go-stimuli (78%), the low cognitive demands for these stimuli and presentation of Go stimuli in a continuous stream one could consider brain activation associated with GO stimuli as baseline activation in this Go/NoGo paradigm. Note that the current task included four fifteen second rest periods such that Go-activation is relative to activation in rest periods. Results of this analysis showed that haloperidol increased baseline activation in the left occipital gyrus (MNI coordinates, -16

-92 22, z = 3.31, 832 mm3) and the right insula (MNI coordinates, 42 -14 -8, z = 3.81, 1144 mm3). No regions showed a reduction in activation after haloperidol. These findings, as well as the absence of effects of haloperidol on reaction times and Go accuracy support the idea that the observed reduction in inhibitory control after haloperidol is due to a reduction in prefrontal brain activation associated with inhibitory control and not due to a reduction in baseline activity, a general slowdown in reaction times or a general performance deficit.



Supplementary Figure 1

Brain activation associated with Inhibitory control (NoGo minus Go) for both groups and medication types combined

Note supplementary figure 1 *p < 0.01 corrected, corrected for multiple comparisons using a Monte Carlo simulation.*

Chapter Seven

Neurobiological substrate of smoking related attentional bias

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Abstract

Substance dependent patients automatically and involuntarily allocate their attention to drug cues in the environment, a process referred to as attentional bias. Attentional bias is increased during periods of subjective craving and predictive of treatment outcome and relapse in substance dependence. Despite recent theoretical and clinical advances with regard to attentional bias, the underlying neurobiological mechanisms are largely unknown. The objective of the current study was to investigate the neural substrate of attentional bias and associated subjective craving in smokers. A group of smokers (n = 20) and a group of age and gender matched non-smoking controls (n = 22) were recruited from the general population and participated in a single session of fMRI scanning while attentional processes were manipulated. Main Outcome Measures were Blood oxygen level dependent (BOLD) fMRI activation during an attentional bias paradigm and self-reported cigarette craving. Results of the current study show that the dorsal anterior cingulate cortex, the superior parietal gyrus and the superior temporal gyrus were more strongly activated in smokers, as compared to controls, when they had to pay attention to task-relevant information (line counting) while smoking cues were present as distracters (attentional bias). Subjective craving measures during attentional bias correlated with brain activation in the insula and putamen. To our knowledge, this is the first controlled study that shows the brain regions involved in attentional bias in smokers. The current study demonstrates that brain regions contributing to top-down attentional processing are implicated in attentional bias in smokers, suggesting that smokers have to employ more attentional resources to focus on a standard cognitive task when smoking cues are present.

Introduction

Substance abuse and addiction are commonly associated with enhanced reactivity to substance-related cues. Attentional bias is one of the key cognitive processes involved in cue reactivity and involves the tendency of substance dependent patients to automatically and involuntarily allocate and maintain their attention to conditioned drug cues (Field, et al. 2008). Attentional bias for drug cues is thought to result from acquired motivational and attention grabbing properties of these cues due to sensitization of dopamine systems in the brain (Robinson, et al. 2008). For substance-dependent patients, drug cues become extremely salient, become the focus of attention and elicit behaviors like drug seeking and consumption. Attentional bias has consistently been found in various types of addiction (for reviews see Field, et al. 2008; Franken 2003; Robbins, et al. 2004) utilizing a wide range of experimental paradigms including attentional tasks such as the emotional Stroop and visual probe task. Smokers, for example, are slower to name the color of smoking-related words when compared to neutral words during the smoking Stroop task (Munafo, et al. 2003), and they are faster to respond to probes replacing smoking pictures than to probes replacing non-smoking pictures (Bradley, et al. 2004; Ehrman, et al. 2002; Mogg, et al. 2005) during the visual probe task. Eye-tracking and Event-Related Potential studies (Field, et al. 2004; Littel, et al. 2007; Mogg, et al. 2003) have also indicated enhanced attentional processing of drug cues in smokers. As predicted by theoretical models, attentional bias is associated with current craving, the strong subjective urge to consume a substance of abuse (Field, et al. 2009; Franken 2003). Recently, attentional bias has been proven to be a clinically relevant construct that is associated with relapse rates or treatment outcome in smokers (Waters, et al. 2003), alcohol (Cox, et al. 2002), cocaine (Carpenter, et al. 2006) and heroin dependent patients (Marissen, et al. 2006). Further, preliminary evidence has been provided that attentional bias extinction training reduces conditioned cigarette craving in smoking males (Attwood, et al. 2008) and drinking behavior in alcohol dependent patients (Attwood, et al. 2008; Field, et al. 2005; Field, et al. 2007; Schoenmakers, et al. 2007). Despite these theoretical and clinical advances, the neurobiological mechanisms of attentional bias are largely unknown.

Previous studies have shown that conditioned drug cues elicit a response in substance dependent patients in a general network of brain regions mainly consisting of the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and ventral striatum, as well as superior parietal and temporal brain areas (for review see Wilson, et al. 2004).

Although these studies have provided important information regarding the neurophysiology of addiction, they do not clarify the contribution of brain structures within this network to specific processes that occur during exposure to drug related stimuli, such as attentional bias and craving. Several brain regions activated during cue-exposure are known to be involved in attentional processing and may be involved in attentional bias for alcohol, drug, and smoking cues as well. Although empirical studies are largely lacking, an important role for the ACC in attentional bias has been hypothesized (Franken 2003). The ACC is a heterogeneous brain region consisting of several functionally distinct areas, and regulates attention that serves both cognitive and emotional processing (Bush, et al. 2000; Bush, et al. 2001; Vogt, et al. 2005; Weissman, et al. 2005). A widely supported view of ACC functioning is that cognitive and emotional information is processed separately in two major subdivisions (Bush, et al. 2000). The rostral-ventral zone of the ACC (rvACC) is involved in emotional processing, more specifically in emotional conflict, salience attribution and emotional response (Bishop, et al. 2004; Compton, et al. 2003; Etkin, et al. 2006; Fujiwara, et al. 2009). Other brain structures supposed to be involved in the bottom-up process of salience attribution are the OFC, ventral striatum and amygdala; areas that are anatomically connected to the rvACC (Goldstein, et al. 2002; Volkow, et al. 2004). Together, they may constitute a ventral attentional system involved in attentional bias that operates in a stimulus driven fashion by directing attention to salient stimuli. In contrast, the dorsal ACC (dACC) has been implicated in top-down attention (Silton, et al. 2010). Activity in the dACC contributes to focused attention on relevant stimuli, especially when the achievement of behavioral goals is threatened by distracting events (i.e., salient stimuli, Weissman, et al. 2005). In addition to the dACC, superior parietal and dorsolateral prefrontal brain regions are involved in attention and executive control (Cavanna, et al. 2006; Kompus, et al. 2009; Liu, et al. 2004; Silton, et al. 2010). The dACC, superior parietal and dorsolateral prefrontal regions may thus be involved in attentional bias and constitute a more dorsal top-down attentional system. Currently, there is some evidence that these regions are hypoactive in substance dependent patients during performance of non-affective cognitive paradigms (Forman, et al. 2004; Kaufman, et al. 2003; Volkow, et al. 2004). On the other hand, it has been suggested that these regions may become overactive during cue exposure as a result of increased effort to maintain cognitive control (Lubman, et al. 2004).

To the best of our knowledge, there are no controlled studies in the literature that are explicitly designed to examine brain regions involved in substance-related attentional bias. Although several fMRI studies have been

published in which substance abusers perform an attention demanding task while being exposed to drug cues (Goldstein, et al. 2007; Goldstein, et al. 2009b; Goldstein, et al. 2009a; Hester, et al. 2009a; Tapert, et al. 2004) the results of these studies are difficult to interpret with regard to brain processes involved in attentional bias for several reasons. First, two studies employing the drug Stroop task did not report drug cue specific activations, therefore it is unclear if differential processing of drug cues relative to neutral cues occurred (Goldstein, et al. 2007; Goldstein, et al. 2009b). Second, modifications of the Stroop task paradigm (Goldstein, et al. 2009b; Goldstein, et al. 2009a; Tapert, et al. 2004), such as the addition of a reward component (participants could earn money as a function of task performance in Goldstein, et al. 2009b; Goldstein, et al. 2009a) tend to confound interpretation in terms of attentional bias. Besides these conceptual issues, some of these studies suffer from methodological problems, such as low power (Goldstein, et al. 2007; Tapert, et al. 2004) or the lack of a control group (Goldstein, et al. 2007; Hester, et al. 2009a), the latter precluding conclusions regarding involvement of specific brain regions in substance abuse patients. Although the results of these studies most likely do not reflect the neural substrates of attentional bias per se, they suggest that substance dependent patients show deviant brain activation in both subregions of the ACC (Goldstein, et al. 2007; Goldstein, et al. 2009a; Tapert, et al. 2004), the dorsolateral prefrontal (Tapert, et al. 2004) and inferior frontal gyrus (Hester, et al. 2009a), the superior parietal lobe (Goldstein, et al. 2009a; Tapert, et al. 2004) and the brain stem (Goldstein, et al. 2009b). In addition to the above-reviewed methodological issues, there is also an important conceptual issue that is likely to be present in standard (non-adapted) attentional bias paradigms like the drug word Stroop task. Notably, it cannot be ruled out that differential brain activation in these task paradigms is the result of differences in simple cue-reactivity to drug cues between substance dependent patients and controls. Therefore, in the present study we developed a new pictorial task paradigm to elicit brain activations specifically associated with attentional bias in smokers while controlling for non-specific activations resulting from other processes involved in cue-reactivity (i.e., picture viewing), including arousal and familiarity.

Based on the previous studies and theoretical accounts, we hypothesized that both subregions of the ACC are involved in attentional bias. Specifically, we expected that the dACC will be overactive in smokers during the attentional bias paradigm. This dACC activity will contribute to focused attention on the primary task, as smokers will be highly distracted by the conditioned smoking cues. In keeping with the other brain regions involved in salience attribution and top-down attention, we expected the OFC, ventral striatum,

amygdala, superior parietal and dorsolateral frontal cortex to be similarly hyperactive due to their involvement in attentional bias for smoking-related stimuli as well.

Materials and Methods

Subjects

A total of 20 smokers and 22 non-smoking controls participated in the study. Subjects were recruited via advertisements on the internet and were screened by telephone for study eligibility. Exclusion criteria for both groups were (a) drug abuse other than nicotine, (b) current physical or psychological illness (c) any use of medication and (d) fMRI contraindications. Data from two smokers and three non-smoking controls was discarded due to scanner failure. The final sample consisted of 18 smokers (mean age = 23.6 years, *SD* = 4.1, 13 men) and 19 non-smokers (mean age = 22.8 years, *SD* = 2.1, 12 men). Smokers smoked at least 10 cigarettes per day (mean = 16.7 cigarettes per day, range = 10-25) for a duration of at least two years (mean = 7.1 years, range = 2-14). The Fagerström test for nicotine dependence (FTND: Heatherton, et al. 1991) served as a measure of nicotine dependence in smokers (mean score = 3.72, range = 0-7). Non-smokers had smoked less than five cigarettes during lifetime, except for one non-smoker who had smoked 20 cigarettes more than 10 years ago (mean = 2.1 cigarettes lifetime, range = 0-20). Although a study from Jacobsen (Jacobsen, et al. 2002) and colleagues suggests that nicotine does not alter the coupling between BOLD signal and neural activity, smokers abstained from smoking for three hours before scanning in order to avoid direct pharmacological confounds without introducing marked withdrawal effects. Both smokers and non-smoking controls abstained from alcohol for at least 24 hours before scanning. All subjects provided written informed consent. The study was approved by the Ethics Committee of Erasmus Medical Center Rotterdam.

Paradigm

An experimental paradigm, the attentional bias line counting task, was developed to detect brain regions specifically involved in attentional bias. During each trial in this task, a picture with either smoking-related stimuli (people engaged in smoking behavior or smoking-related objects) or neutral stimuli (people

engaged in non-smoking behavior or neutral objects) was presented for 900ms (figure 1). A fixation cross was shown for an average of 2100ms (jittered from 1100 to 3100ms, steps of 250ms), prior to the presentation of the next picture stimulus. Two to five lines were displayed within each picture, with semi-randomly distributed spaces between these lines. Instructions for participants varied over blocks. In one block (counting lines) participants were asked to count the number of lines presented in the picture and to press the corresponding button as fast as possible. Note that for this task the content of the picture is irrelevant to task performance. In the other block (naming pictures) participants had to indicate whether the content of the picture included smoking stimuli or neutral stimuli by pressing the corresponding button. This is an easy and straightforward task, with low cognitive demands. Before each block, task-instructions were presented for 4 seconds. Within each block, smoking and neutral pictures were semi-randomly presented. In total, 72 trials were presented in each of the following conditions: line-counting smoke picture (LCSP), line-counting neutral picture (LCNP), picture-naming smoke picture (PNSP), and picture-naming neutral picture (PNNP). Based on these conditions three contrasts were defined for analyses. First, the LCSP and LCNP relative to baseline contrast (overall cognitive effort) was computed to assess the overall effects of line counting irrespective of picture content. Brain activation related to this contrast reflects overall cognitive effort during line counting in smoking and neutral pictures. Second, the LCSP minus LCNP contrast (attentional bias) represents brain activation associated with attentional bias for smoking stimuli, as all brain activation related to line counting is cancelled out. What remains is the brain activation reflecting the task irrelevant (automatic) attentional bias for the smoking pictures. Third, the LCSP minus PNSP contrast (cue-exposure corrected attention) was computed. This contrast reflects attention to the smoking pictures during line counting while correcting for cue reactivity to these smoking cues, and therefore serves as a check to ensure that group

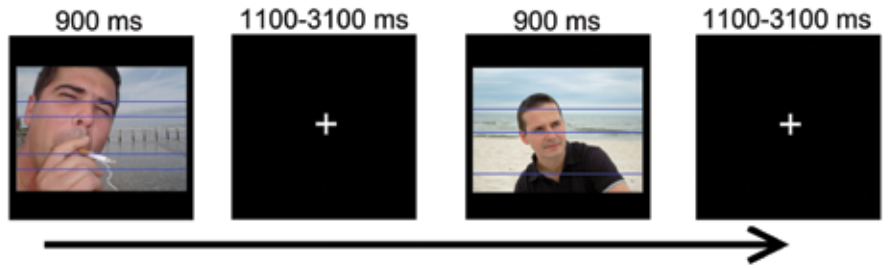

Figure 1

The attentional bias line counting task

differences in brain activation in the attentional bias contrast (LCSP minus LCNP) does not solely reflect cue-reactivity induced by the content of the pictures.

Procedures

After arrival, participants approved participation by signing informed consent. Breath carbon monoxide concentration was measured in all subjects using a calibrated Micro+ Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) to objectively define smokers and non-smokers. In addition, smokers completed the FTND (Heatherton, et al. 1991) to measure nicotine dependence and the Questionnaire of Smoking Urges (QSU: Cox, et al. 2001) to indicate their current subjective craving for a cigarette. All subjects completed several questionnaires, including the positive affect negative affect scale (PANAS: Watson, et al. 1988) and the Snaith-Hamilton Pleasure Scale (SHAPS: Snaith, et al. 1995) to measure mood state and anhedonia. These questionnaires were administered in order to ensure that differences between smokers and non-smoking controls were not the result of differences in mood states. Participants performed two tasks during fMRI scanning. The attentional bias line counting task was administered after a cognitive paradigm (not addressed in this paper). Smokers completed the QSU again immediately after the scanning session.

Imaging acquisition and data analysis

Blood oxygen level-dependent (BOLD) fMRI data were acquired on a 3T General Electric Healthcare (HDx platform, Milwaukee, WI) scanner. Functional T2*-weighted images were acquired in 26 axial slices (thickness = 3.5 mm, interslice gap = 0.5 mm) covering the entire supratentorial brain with a repetition time (TR) of 2000 ms, echo time (TE) of 30 ms, field of view (FOV) of 220 mm, and matrix size 96 x 64. A structural 3 dimensional inversion recovery (IR) fast spoiled gradient recalled echo (FSPGR) T1-weighted image was acquired in 192 axial slices (thickness = 1.6 and 0.8 mm overlap) with TR: 10.6 ms, TE: 2.2 ms, FOV: 250 mm, and matrix size 416 x 256 mm.

Imaging data were analyzed using SPM5 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, United Kingdom). Preprocessing of the functional data included realignment and slice time correction. Next, the anatomical scan was co-registered to the first T2*-weighted image. The data was normalized using a SPM T1 template and the data was spatially smoothed using a Full Width Half Maximum Gaussian kernel

of 8 mm. The four conditions; LCSP, LCNP, PNSP, PNNP were modeled in the context of the general linear model, using delta functions convolved with a canonical hemodynamic response function. The three contrasts for overall cognitive effort, attentional bias and cue exposure corrected attention were first calculated at single-subject level, and subsequently fed into second-level (random effects) analyses for main effects (one-sample *t*-test) and between-group comparisons (independent samples *t*-test). Differences between groups for all contrasts are reported at $p < 0.001$ (uncorrected) masked inclusively with the appropriate main effect to reduce the number of comparisons. Finally, the increase in craving during task performance was calculated for each smoker and whole brain correlations were performed on the attentional bias (LCSP minus LCNP) contrast. Craving related brain activation in attentional bias is reported at $p < 0.001$ (uncorrected).

Demographics and task performance data were analyzed in SPSS (Version 16.0 for Windows; SPSSInc., Chicago, IL). We used repeated measures ANOVA to analyze task performance (separately for accuracy and reaction times during line counting) with group as the between subject factor and picture type (smoking picture or neutral picture) as the within subject factor.

Results

Questionnaires and Breath analysis

As expected, smokers showed higher CO breath levels (mean = 8.3, range 3-21) than non-smoking controls (mean = 1.5, range 0-5), $t(36) = 6.55$, $p < 0.001$. Groups did not differ on anhedonia, positive and negative affect scores (all p's$> .05$). Smokers differed in their changes in craving after the attentional bias line counting task. Twelve out of eighteen smokers showed an increase in craving after the attentional bias line counting task. However, this increase was not significant for those smokers with all fMRI data available $t(17) = 1.72$, $p = 0.1$. This non-significant result is probably due to low statistical power, because when all available smokers were included (n=20) the *p*-value was found to be 0.04.

Behavioral performance

Both groups performed the line counting task accurately: overall accuracy was 92%. Repeated measures analysis of accuracy performance did not show a

main effect for group. A main effect of picture content on accuracy was found, $F(1,35) = 4.82, p< 0.05$, with both groups performing less accurately at counting lines in smoking pictures than in neutral pictures (91% versus 92%). The picture x group interaction was not significant. With regard to reaction times, no main effect for group or picture was found. However, a trend for the main effect of picture, $F(1,35) = 3.98, p< .1$, could be observed indicating that reaction times to smoking pictures were slightly faster (791ms versus 796). No picture x group interaction was found, $F(1,35) = 0.82, p< .05$,. Although the interaction was non-significant, we observed that the difference in reaction times between smoking and neutral pictures was significant in controls, $t(17) = 2.43, p< 0.05$ but not in smokers. Non-smoking controls were significantly faster on indicating the number of lines in smoking pictures than in neutral pictures.

fMRI results

Overall cognitive effort (LCSP and LCNP) was associated with robust brain activation in bilateral occipital, parietal, and prefrontal brain regions, as well as in motor areas, the ACC and several subcortical regions (table 1). Smokers showed less brain activation associated with overall cognitive effort than controls in the rvACC, the left caudate nucleus, left intraparietal lobe, left lingual gyrus and the left parahippocampal gyrus (table 1). Both groups showed attentional bias (LCSP minus LCNP) related brain activation in visual brain regions (table 2). Most importantly, smokers showed significantly more attentional bias related brain activation as compared to controls in the rostral zone of the dACC, extending into supplementary motor area (as functionally defined by Ridderinkhof et al., (2004a), the right superior parietal lobe (SPL) and the left superior temporal gyrus (STG) (table 2, figure 2). Both groups showed more activation in visual, parietal and motor areas (table 2) during cue-exposure corrected attention (LCSP minus PNSP). Importantly, smokers, as compared to controls, showed more brain activation related to cue-exposure corrected attention for smoking cues in the rostral zone of the dACC (x=15 y=30 z= 33, Z=3.13; table 2) confirming that attentional bias related brain activation in this region does not arise from mere cue-exposure effects.

Self-reported craving in smokers during the attentional bias paradigm was significantly associated with activation in the right putamen (x=24 y =-6 z =24 Z =3.63) and the left insula (x=-36 y=-39 z=18 Z=3.52; figure 3).

Table 1

Main and group effects for overall cognitive effort (LCSP and LCNP)

	MNI Coordinates					MNI Coordinates			
	x	y	z	*Z*-value		x	y	z	*Z*-value
Overall cognitive effort (LCSP and LCNP)									
Main effects smokers and controls					*Main effects smokers and controls continued*				
l- occipital	-42	-75	-6	> 8	l- PCG	-27	-12	54	5.07
l- precuneus					l- PCG	-30	-15	66	4.95
l- SPL					r- culmen	9	-54	-9	4.96
r- MOG	27	-93	6	> 8	l- IFG	-51	3	33	4.93
r- SOG	30	-84	24	7.79	r- PHG	24	-30	-6	4.89
r- precuneus					r- thalamus	18	-36	0	4.71
r- SPL									
l- medial frontal gyrus	-3	0	57	6.32	*Smokers > Controls*				
l- ACC					- - -				
r- middle frontal gyrus	27	-12	63	5.95					
r- PCG	36	-18	63	5.43	*Smokers < Controls*				
l- PHG	-21	-36	-3	5.91					
l- caudate	-24	-42	6	5.43	r-rvACC	15	36	3	3.81
r- IFG	45	3	30	5.31	l-lingual gyrus	-12	-48	-3	3.64
r- IPL	45	-39	51	5.30	l-IPL	-63	-27	27	3.60
r- postcentral gyrus	48	-24	54	4.56	l-PHG	-18	-54	-9	3.39

Note table 1 *Main effects are reported at p<0.05 FWE corrected. Group effects are masked for main effects and reported at p<0.001 uncorrected. Abbreviations: PCG,* precentral gyrus; *SPL, superior parietal lobe; MOG, middle occipital gyrus; SOG, superior occipital gyrus; ACC, anterior cingulate cortex; PHG, parahippocampal gyrus; IFG, inferior frontal gyrus; rvACC, rostro-ventral anterior cingulate cortex; IPL, inferior parietal lobe.*

Table 2

Main and group effects on attentional bias (LCSP minus LCNP) and cue exposure corrected attention (LCSP minus PNSP)

	MNI coordinates					MNI coordinates			
	x	y	z	*Z*-value		x	y	z	*Z*-value
Attentional bias (LCSP minus LCNP)									
Main effects smokers and controls					*Smokers >Controls*				
l-OCC/ITG	45	-66	-3	5.16	l-STG	-60	-12	-3	3.71
l-MOG	-45	-81	3	4.54	r-dACC	9	21	48	3.63
l-MOG	-48	-75	-9	3.72	r-SPL	27	-75	39	3.18
r-MTG	51	-75	6	4.21					
r-MOG	45	-81	6	4.18	*Smokers< Controls*				
					- - -				
Cue exposure corrected attentions (LCSP minus PNSP)									
Main effects smokers and controls					*Smokers >Controls*				
r-MFG	27	-9	57	4.89	r-dACC	15	30	33	3.13
r- precuneus	27	-75	39	4.76					
r-IPL	42	-39	51	4.66	*Smokers <Controls*				
l-MOG	-30	-87	15	4.20	- - -				
r-IFG	51	3	24	4.16					
r-STG	54	-21	9	3.86					
l-lingual gyrus	-9	-87	2	3.81					
l-precuneus	-18	-72	51	3.42					
l-culmen	-6	-63	-12	3.41					

Note table 2 *Main effects are reported at p<0.05 FDR corrected. Group effects are masked for main effects and reported at p< 0.001 uncorrected. Abbreviations: OCC, occipital; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; MFG: middle frontal gyrus; STP, superior temporal gyrus; dACC, dorsal anterior cingulate cortex.*

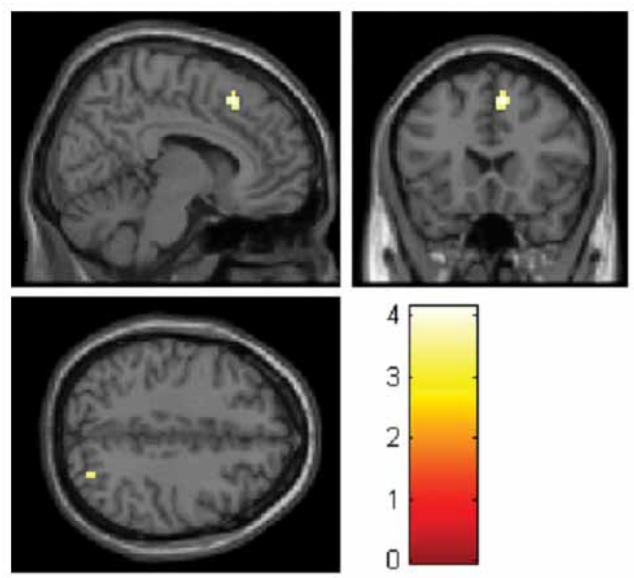

Figure 2

Group effect in the dACC and the right SPL for the LCSP versus LCNP contrast

Note figure 2 *all effects and details are listed in table 2.*

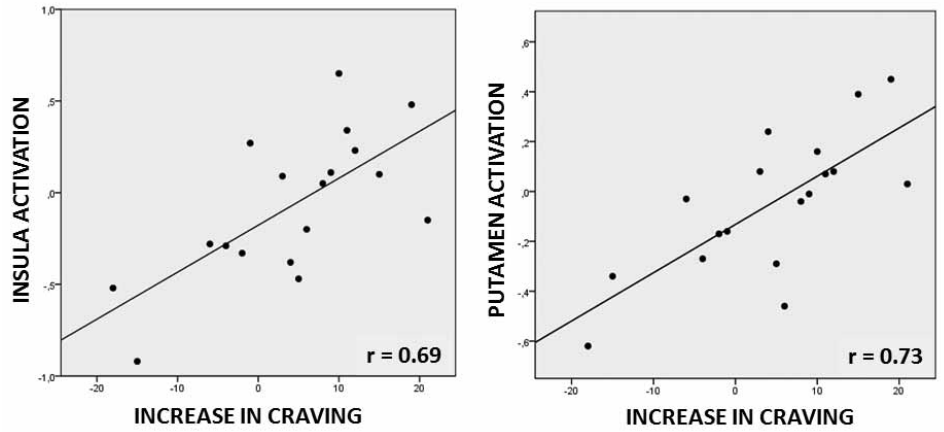

Figure 3

Correlation between craving and attentional bias related brain activation in the left insula and right putamen

Discussion

To our knowledge, this is the first controlled study showing the neural correlates of attentional bias in smokers. In line with our hypothesis, we observed greater brain activation in smokers relative to healthy controls in the dACC and right SPL during an attentional bias task paradigm. Unexpectedly, a similar effect was also observed in the left STG. Importantly, we showed that dACC hyperactivation in smokers could not be attributed to processes arising from mere cue-exposure or cue-exposure related phenomena, including enhanced familiarity to smoking cues and arousal. Additionally, activations in the left insula and the right putamen were found to be associated with attentional bias related craving. Further, in line with the cocaine study of Goldstein et al. (2009a) we found that smokers showed hypoactivation in the rvACC during overall cognitive effort.

Current theories of ACC function suggest that the dorsal region of the ACC is involved in conflict monitoring (Botvinick, et al. 2004; Egner, et al. 2008; Etkin, et al. 2006; Fan, et al. 2008; Haas, et al. 2006) and reducing possible interference effects from distracting stimuli, by boosting attention toward task relevant stimuli (Fan, et al. 2008; Weissman, et al. 2004; Weissman, et al. 2005). Therefore, the current finding that attentional bias in smokers is associated with dACC hyperactivation suggests that smokers experience more cognitive conflict and need more focused (top-down) attention when performing a simple cognitive task (line counting) while smoking stimuli are present in the background. This enhanced activation in the dACC is probably needed to compensate the effects of the automatic (bottom-up) distraction by the conditioned smoking cues.

Attentional bias associated brain activation was also observed in the right SPL and the left STG. The SPL has been implicated in top-down attention processing (Szczepanski, et al. 2010), more precisely, it has been suggested that the SPL is involved in directing attention in space (Cavanna, et al. 2006). Therefore, the activation in the SPL is in accordance with our interpretation that smokers have to employ more attentional top-down resources to stay involved in the primary task. Hyperactivation in the STG is in line with previously observed temporal activation in several cue reactivity studies (David, et al. 2007; Due, et al. 2002; Garavan, et al. 2000; Lee, et al. 2005; McBride, et al. 2006; Park, et al. 2007; Schneider, et al. 2001). Although speculative, we suggest that this effect is related to greater in-depth visual processing, in accordance with a theory of STG function proposed by Kartnath (2001). The hypothesis of more elaborate visual processing receives some support from the fact that STG hyperactivation in smokers was not observed during cue exposure corrected attention.

The current finding of hyperactivation in the dACC in smokers is in contrast with the observed hypoactivation of this region in Goldstein et al. (2009a) during performance of the cocaine word Stroop task. There may be several reasons for this discrepancy. First, the observed hypoactivation in the Goldstein et al. (2009a) study was not specific to drug cues and may therefore reflect a more general cognitive deficit in drug abusers and not a specific attentional bias process. Second, the cocaine Stroop task as employed in their study also included a monetary reward component, which may have biased dACC activation since this region is also involved in reward based decision making (Bush, et al. 2002; Fujiwara, et al. 2009). Third, the substance users in Goldstein et al. (2009a) consisted of cocaine users, who may not be comparable to our smoking group. It is known that cocaine users have more pronounced cognitive dysfunctions (Verdejo-Garcia, et al. 2007a; Verdejo-Garcia, et al. 2007b) as compared to smokers. Finally, we cannot unequivocally state that our smoking group is nicotine dependent as FTND scores indicate medium dependence levels only. However, smokers in the current study smoked at least ten cigarettes per day, and half of our sample smoked at least 20 cigarettes per day. Still, it would be important to replicate the current finding of dACC hyperactivation in another population diagnosed with substance dependence.

In the present study, we did not observe attentional bias related brain activation in brain regions involved in salience attribution or stimulus driven attention including the OFC, ventral striatum and amygdala. Activation in these brain regions was expected since environmental drug cues tend to capture the attention of drug users, due to the established salience of these cues (Robinson, et al. 2008). The absence of activation in these regions is probably due to our fast event-related paradigm that was specifically designed to measure attentional bias and to keep other constructs such as prolonged cue-exposure and emotional involvement to a minimum. In line with Goldstein et al. (2009a) we did find more pronounced hypoactivation in smokers in the rvACC during overall cognitive effort. This finding supports the notion that hypoactivation in this region is not related to specific drug cue processing or attentional bias in substance dependent patients. The rvACC facilitates emotional processing, and is involved in emotional conflict, most likely by salience attribution and emotional responsiveness. It has been suggested that hypoactivation in the rvACC during focused attention contributes to the dynamic interplay between continuous cognitive and emotional processes (Gusnard, et al. 2001; Raichle, et al. 2001). The hypoactivation in smokers during overall cognitive effort in this region may therefore reflect a conflict between cognitive performance and emotional involvement as experienced by smokers.

We also found that subjective craving induced by the attentional bias paradigm was related to activation in the insula and putamen. This suggests that these regions are involved in the reciprocal relation between attentional bias and craving (Field, et al. 2009). The insula has currently attracted attention as an important brain region in addiction by representing conscious urges to the drug of abuse via connections with the ventromedial prefrontal cortex and the amygdala (Naqvi, et al. 2007; Naqvi, et al. 2009). Furthermore, Paulus et al. (2005) demonstrated that activation in the insula, amongst other brain regions, predicted relapse in abstinent methamphetamine dependent subjects. In addition, the putamen is supposed to play a role in addictive behavior through modulation of the mesolimbic dopaminergic system via D1 and D2 receptors (Ito, et al. 2002; Naha, et al. 2009).

A limitation of the current study is that behavioral measures are not fully supportive for attentional bias to conditioned smoking cues in smokers. However, reaction time data did show that non-smoking controls were faster in counting the number of lines in smoking pictures than in neutral pictures, whereas this difference was not evident for smokers. These results suggest that non-smoking controls are faster in counting lines in smoking pictures by ignoring the content of the picture, whereas smokers are less able to ignore the content of the smoking related pictures. However, such an interpretation must be viewed with caution due to the lack of a significant omnibus interaction effect.

To conclude, we demonstrated, for the first time, hyperactivation in smokers compared to non-smokers in the dACC, the right SPL and the left STG associated with attentional bias. Furthermore, we demonstrated that brain activation related to attentional bias in the dACC cannot be attributed to other processes as a result of cue-exposure. As converging evidence suggests that ACC dysfunction may be a biomarker for addiction (Goldstein, et al. 2009a; Hong, et al. 2009; Ma, et al. 2010; Romero, et al. 2010), it would be interesting to further investigate the differential contribution of the dorsal and ventral parts of the ACC in various specific task paradigms. It has also been hypothesized that dopamine plays an important role in attentional bias and craving (Franken, et al. 2005; Franken, et al. 2004). The most important regions found to be implicated in attentional bias and craving in the current study, the dACC, the putamen and the insula, all have efferent and afferent dopaminergic projections. It would therefore be a future research agenda to examine the role of dopamine in attentional bias and craving related brain activation.

Chapter Eight

Brain activation associated with attentional bias in smokers is modulated by a dopamine antagonist

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Neuropsychopharmacology, in press

Abstract

Attentional bias in substance dependent individuals is the tendency to automatically direct the attention to substance-related cues in the environment. Attentional bias is known to be associated with clinical measures such as relapse or successful quitting in smokers. It has been suggested that attentional bias emerges as a consequence of dopaminergic activity evoked by substance-related cues. The current fMRI study employed a dopaminergic challenge in order to test whether brain activation associated with attentional bias in smokers could be modulated by a dopamine antagonist. 25 smokers were compared with 24 controls. Participants were scanned twice while performing a pictorial attentional bias task. Haloperidol (2mg), a selective D2/D3 dopamine antagonist, or placebo was orally administered four hours before each scanning session in a double-blind randomized cross-over design. Imaging analyses were performed in a-priori selected regions of interest. Results showed that smokers had enhanced brain activation compared to controls in the dorsal anterior cingulate cortex (dACC), right dorsolateral prefrontal cortex (r-DLPFC) and left superior parietal lobe (l-SPL) after placebo. Group x Medication interactions were found in the dACC and r-DLPFC, with no differences between groups in these regions after haloperidol. The current findings suggest that a pharmacologically induced reduction in dopamine normalizes brain activation associated with attentional bias in the dACC and DLPFC in smokers, probably because salience of these cues is no longer detected when dopamine activity is reduced.

Introduction

Substance abuse and addiction are associated with enhanced processing of substance-related cues (e.g., Franken, et al. 2003; Kuhn, et al. 2011). Attentional bias is one of the mechanisms underlying enhanced processing of these cues and is defined as the tendency of substance dependent people to automatically and involuntarily allocate and maintain their attention to conditioned drug cues (for reviews see: Field, et al. 2008; Franken 2003; Robbins, et al. 2004). Attentional bias has been linked to craving (Field, et al. 2009) as well as to the temptation to use substances (Waters, et al. 2012), treatment outcome (Carpenter, et al. 2006; Cox, et al. 2002) and relapse rates (Marissen, et al. 2006; Waters, et al. 2003). Preliminary evidence has further suggested that attentional bias extinction training reduces conditioned cigarette craving in smoking males (Attwood, et al. 2008) and drinking behavior in alcohol dependent patients (Fadardi, et al. 2009; Schoenmakers, et al. 2010). However, it seems that a single training session is not successful to reduce smoking behavior (Attwood, et al. 2008; Field, et al. 2009; McHugh, et al. 2010b).

Theoretical models propose that attentional bias is a consequence of a dopamine signal that triggers attention to substance-related cues (Franken 2003; Robinson, et al. 2003). After repeated drug intake, substance-related cues become conditioned cues and elicit dopaminergic activity (Volkow, et al. 2006; Wong, et al. 2006; Zijlstra, et al. 2008) thereby signaling the expectation of a future reward (i.e., the intake of the substance of abuse). Gradually, the dopaminergic system becomes sensitized for substance-related cues so that they become extremely salient, become the focus of attention and elicit behaviors like drug seeking and consumption (Phillips, et al. 2003; Robinson, et al. 2008). Consequently, it can be predicted that attentional bias will be attenuated when dopamine is no longer able to signal the salience of conditioned substance-related cues. A few studies tested this hypothesis. Two studies used acute tyrosine/phenylalanine depletion to reduce dopamine levels in smokers (Hitsman, et al. 2008; Munafo, et al. 2007). Both studies found that attentional bias in smokers was reduced when dopamine levels were decreased. Similar results were found in heroin users, in which attentional bias was attenuated after a single dose of the dopamine antagonist haloperidol (Franken, et al. 2004). As these studies did not measure brain activation, it is not yet known whether a pharmacologically induced reduction in dopamine also reduces brain activation in those regions involved in salience detection and attentional bias. Only recently progress has been made to elucidate the neurobiological substrate of attentional bias. Functional magnetic resonance imaging (fMRI) has shown that attentional bias is associated with

increased activation in brain regions innervated by dopaminergic projection such as the ACC and the ventral striatum (Janes, et al. 2010a; Luijten, et al. 2011c; Nestor, et al. 2011; Vollstadt-Klein, et al. in press). In addition, dorsolateral and inferior frontal regions, as well as the insula, amygdala, superior parietal and superior and middle temporal gyri were implicated in attentional bias for substance-related cues (Ersche, et al. 2010; Hester, et al. 2009a; Janes, et al. 2010a; Luijten, et al. 2011c; Vollstadt-Klein, et al. in press). Ersche et al. (2010) showed that a dopamine agonist enhanced attentional bias and associated brain activation in the left ventral prefrontal cortex and the cerebellum in high-compulsive stimulant dependent individuals, whereas it reduced activation in these regions in low-compulsive stimulant users. The Ersche et al. study could not demonstrate a reduction in attentional bias and associated brain activation following administration of the dopamine antagonist amilsulpride. Consequently, it is still unknown whether a pharmacologically induced reduction in dopamine levels could normalize brain activation associated with attentional bias. In the current study attentional bias related brain activation was measured twice in smokers and non-smokers using an attentional bias task involving pictorial stimuli (Luijten, et al. 2011c). The D2/D3 dopamine antagonist haloperidol was used to reduce dopamine levels and was compared to placebo in a double-blind randomized cross-over design. Based on theoretical accounts and our previous study in smokers (Luijten, et al. 2011c), we hypothesized that brain activation associated with attentional bias in dopaminergic innervated regions such as the ACC and other prefrontal regions will normalize in smokers after haloperidol administration. That is, no differences between smokers and non-smokers in attentional bias related brain activation were expected after haloperidol.

Materials and methods

Participants

Twenty-five smokers and twenty-five non-smokers participated in this study. Data from one non-smoker was discarded due to technical problems during data analyses. The final sample consisted of 25 smokers (mean age = 22.56 years, *SD* = 2.84, 18 male) and 24 non-smokers (mean age = 21.75 years, *SD* = 1.78, 14 male). Smokers smoked at least 15 cigarettes per day (*M* = 19.12, *SD* = 3.37; range 15-25) for a duration of at least three years (*M* = 7.20, *SD* = 3.01, range= 3-14). The average score on the Fagerström Test for Nicotine Dependence (Vink, et al. 2005) for smokers was 3.80, *SD* = 3.37, range= 1-8. Non-smokers had

smoked ten cigarettes or less during their lifetime (*M* = 1.73, *SD* = 2.62, range= 0-10). Participants underwent a medical examination by a psychiatrist to assure eligibility for a single dose of 2 mg oral haloperidol (see supplementary materials for details). Exclusion criteria for both groups were (a) current substance abuse or dependence (other than nicotine for smokers), (b) any physical or psychological illness, (c) any use of psychotropic medication or medication that may affect blood circulation and/or respiration, (d) fMRI contraindications and (e) left handedness. There were no significant differences between the groups in age, $t(47) = 2.40$; ns, or gender, χ^2 (1, n= 49) = 0.32; ns. The study was conducted in accordance with the Declaration of Helsinki and all procedures were carried out after participants signed informed consent. The ethics committee of Erasmus MC-University Medical Centre Rotterdam approved this study.

Dopaminergic manipulation

Participants were administered a single oral dose of 2 mg haloperidol and a placebo employing a double-blind randomized cross-over design. Haloperidol is a selective post-synaptic dopamine D2/D3 receptor antagonist. Using positron emission tomography (PET), it has been shown that striatal D2 receptor occupancy three hours after administration of 2mg haloperidol is 18% and 52% after six hours (Nordstrom, et al. 1992). The present fMRI session took place four hours after administration which, according to the Nordstrom study, results in about 30% D2 receptor occupancy. The dose and time interval was further based on previous studies using haloperidol (Franken, et al. 2008; Franken, et al. 2004; Mahler, et al. 2005) that showed attenuated cue-reactivity in smokers (Mahler, et al. 2005) and attentional bias in heroin users (Franken, et al. 2004) after haloperidol. No side effects were reported by the participants. Participants' guesses on the type of medication they received for each scanning session were not above chance (48.97% of the participants correctly indicated in which test occasion they received haloperidol, $p = 0.56$).

Procedures

Two scanning sessions were scheduled that were separated by one week. Smokers were not allowed to smoke after taking the medication until scanning was finished to ensure that indirect nicotine effects on dopamine levels did not interfere with the binding of haloperidol to D2/D3 receptors in the brain. Breath carbon monoxide (CO) concentration was measured in all subjects using a calibrated Micro+Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK). Smokers completed the FTND (Heatherton, et al. 1991; Vink, et al. 2005) to measure

nicotine dependence on the first scanning session only and the Questionnaire of Smoking Urges (QSU: Cox, et al. 2001) to indicate their current subjective craving for a cigarette during both scanning sessions. Participants performed the attentional bias line counting task during fMRI scanning. Smokers indicated their craving levels on a 100-point visual analogue scale (VAS) immediately before and after task performance.

Task paradigm

The attentional bias line counting (ABLC) task was used to measure brain activation related to attentional bias, and has previously been described by Luijten et al. (2011c). In each trial, a picture with either smoking-related stimuli (people engaged in smoking behavior or smoking-related objects) or neutral stimuli (people engaged in non-smoking behavior or neutral objects) was presented for 900ms (figure 1). Two to five lines were displayed within each picture, with semi-randomly distributed spaces between these lines. Instructions for participants varied over blocks. In one block (counting lines) participants were asked to count the number of lines presented in the picture and to press the corresponding button as fast as possible. In the other block (naming pictures) participants had to indicate whether the content of the picture included smoking-related stimuli or neutral stimuli by pressing the corresponding button. Within each block, smoking-related and neutral pictures were semi-randomly presented. Seventy-two trials were presented for each condition: line-counting smoke picture (LCSP), line-counting neutral picture (LCNP), picture-naming smoke picture (PNSP), and picture-naming neutral picture (PNNP). Based on these conditions four contrasts can be defined for analyses. The main contrast reflecting brain activation associated with attentional bias is the LCSP minus LCNP contrast. For the line counting condition smoking cues are unrelated to task performance, so that brain activation for LCSP relative to LCNP shows the disruption of ongoing behavior (line counting) because of the enhanced attentional and motivational properties of the smoking pictures. The other three contrasts do not reflect attentional bias and accordingly are not associated with the main focus of this paper. See supplementary materials for the definition and results of these contrasts.

Data analyses questionnaires and behavioral performance

A Group (Smokers versus Non-smokers) x Medication (Placebo versus Haloperidol) Repeated Measures Analyses of Variance (RM-ANOVA) was applied to analyze CO levels. A Group x Medication x Picture (Smoking-related pictures

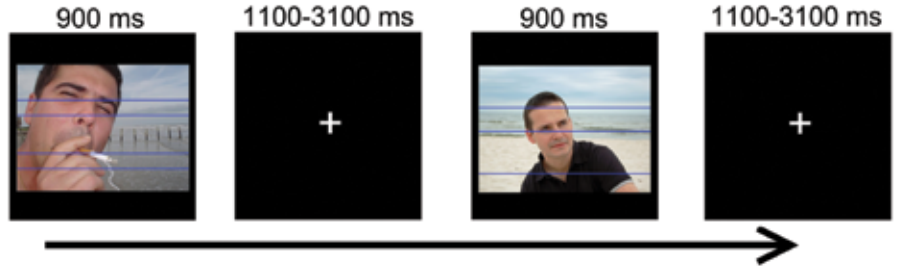

Figure 1 The attentional bias line counting task

versus Neutral pictures) RM-ANOVA was performed to investigate reaction times and accuracy during line counting. QSU craving scores in smokers were analyzed with Medication as a single within subject factor. To investigate the effect of task performance on craving levels a Medication x Time (before versus after task performance) RM-ANOVA was performed for craving VAS scores.

Image acquisition

Imaging data were acquired on a 3T GE Healthcare (The Discovery® MRI 750 3.0T, Milwaukee, US) scanner. Blood oxygen level-dependent (BOLD) sensitive functional T2*-weighted images were acquired in 44 axial slices covering the entire supratentorial brain with a repetition time (TR) of 2500 ms, echo time (TE) of 30 ms, field of view (FOV) of 240 mm, and isotropic voxel size of 2.5 mm3. A structural 3-dimensional (3D) inversion recovery fast spoiled gradient echo T1-weighted image was acquired in 164 contiguous axial slices with TR of 7.9 ms, TE of 3.1 ms, FOV of 240 mm, and isotropic voxel size of 1 mm3 for anatomical reference.

Image processing

Imaging data were analyzed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing of the functional data included realignment and unwarping of functional images. The anatomical scan was coregistered to the mean T2*-weighted image and subsequently segmented into grey and white matter. Segmentation parameters were used for normalization using the SPM T1 MNI template. Functional scans were spatially smoothed using a full-width at half-maximum Gaussian kernel of 8 mm. Correct trials for the four conditions (LCSP, LCNP, PNSP, PNNP) were modeled in the context of the general linear model for both medication conditions, using delta functions convolved with a canonical hemodynamic response function.

Incorrect trials were modeled separately as regressors of non-interest. The contrast reflecting brain activation associated with attentional bias (LCSP minus LCNP) was calculated for each individual for both medication conditions. Subsequently, a random effects RM-ANOVA with Group as between subject factor and Medication as within subject factor was performed to investigate Group x Medication interactions. Between Group and between Medication t-tests were performed (i.e., differences between groups for placebo and haloperidol separately and medication effects in smokers and non-smokers separately), masked inclusively by voxels showing a Group x Medication interaction in the RM-ANOVA (p< 0.01 uncorrected), thus ensuring that group differences and medication effects met the requirement of a Group x Medication interaction. Furthermore, we report results for the between group two sample t-test for placebo without masking for the interaction effect, with the aim to replicate findings from our previous study (Luijten, et al. 2011c). Finally, cue induced craving during task performance was calculated for each smoker for placebo and haloperidol separately (craving VAS score after task performance minus craving VAS score before task performance) and was correlated with brain activation associated with attentional bias in each medication condition separately. Given findings of previous studies the ACC, superior parietal lobe (SPL), superior temporal gyrus (STG), dorsolateral prefrontal gyrus (DLPFC), inferior frontal gyrus (IFG), amygdala, insula and nucleus accumbens (NACC) were selected as a-priori regions of interest. ROIs were defined using the automatic anatomical labeling (AAL) atlas (Tzourio-Mazoyer, et al. 2002). As the NACC is not included in the AAL atlas, a 10 mm sphere with MNI coordinates ±10 12 -2 was created as a ROI for the NACC (Knutson, et al. 2008). Results were thresholded at p< 0.05, Family Wise Error (FWE) corrected for multiple comparisons across the search volume (Small volume correction: Friston, et al. 1996; Worsley, et al. 1996). In order to do so, analyses were first thresholded at p< 0.001 uncorrected with 20 contingently activated voxels (160mm3), and then corrected using a small volume correction (p< 0.05 FWE corrected) in which the search volume was defined by the AAL template corresponding to the a-priori defined ROI.

Results

Breath CO levels and questionnaire data

Smokers had a higher breath CO concentration ($M_{haloperidol}$= 6.20, SD = 3.39, $M_{placebo}$= 6.72, SD = 3.50) than non-smokers ($M_{haloperidol}$= 1.42, SD = 0.78, $M_{placebo}$= 1.67, SD = 0.64), F(1,47) = 55.15, p< 0.001. CO levels did not differ between medication conditions, F(1,47) = 1,91, ns. Haloperidol did not influence QSU ($M_{haloperidol}$= 38.03, SD = 11.80, $M_{placebo}$= 39.71, SD = 11.48) and VAS craving scores. However, VAS craving scores increased after task performance confirming the presence of cue-evoked craving, F(1,24) = 21.36, p<.001, ($M_{haloperidol/before}$= 58.96, SD = 21.49, $M_{haloperidol/after}$= 67.00, SD = 17.84, $M_{placebo/before}$= 62.60, SD = 23.21, $M_{placebo/after}$= 68.64, SD = 23.38).

Behavioral performance

Accuracy scores and reaction times are displayed in figure 2. Repeated measures analysis for performance accuracy did not show a main effect of group F(1,47) = 2.96, ns. A main effect of medication showed that haloperidol decreased task performance relative to placebo, F(1,47) = 10.36, p< 0.01. Furthermore, a main effect of picture was found for accuracy, F(1,47) = 11.10, p< 0.01, with both groups performing less accurately for line counting in smoking-related pictures than in neutral pictures. Regarding reaction times, no main effect of group or medication was found, both F's< 3.71, ns. A main effect of picture was found, F(1,37) = 4.14, p< .05, indicating that reaction times to smoking-related pictures were faster. No interaction effects were found, all F's< 2.87, ns. The combination of reduced accuracy and faster reaction times to smoking-related pictures suggests that there may be an impulsive response style to smoking-related pictures in both groups.

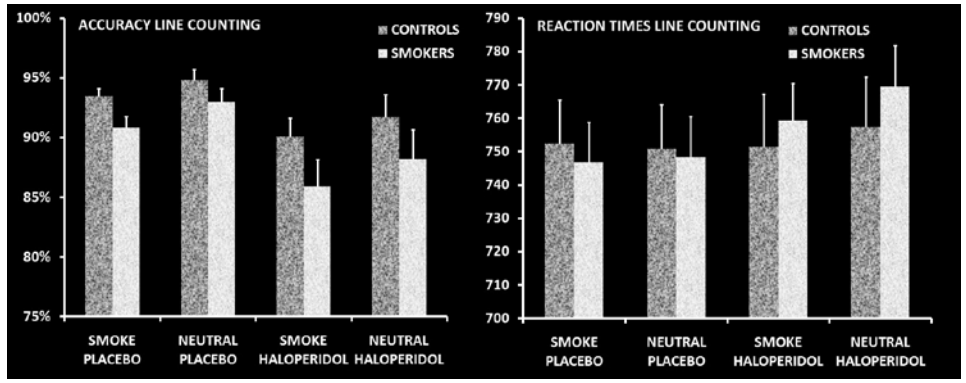

Figure 2

Behavioral measures for the attentional bias line counting task

Note figure 2 *RM-ANOVA for accuracy rates and reaction times during line counting showed that both smokers and non-smoking controls were less accurate for smoking related pictures and showed shorter reaction times for smoking related pictures. Both groups were less accurate after haloperidol.*

Imaging results

After placebo, smokers showed attentional bias related brain activation (i.e., more activation than controls on the LCSP minus LCNP contrast) in the dorsal zone of the ACC (dACC), the left superior parietal lobe (SPL) and the right DLPFC. After masking for the Group x Medication interaction, group differences remained present in the dACC and the right DLPFC. No differences between groups were found in attentional bias related brain activation after haloperidol administration. See figure 3 and table 1 for details. These findings suggest that the dACC, right DLPFC left SPL are involved in attentional bias in smokers. Group x Medication interactions and the lack of group differences

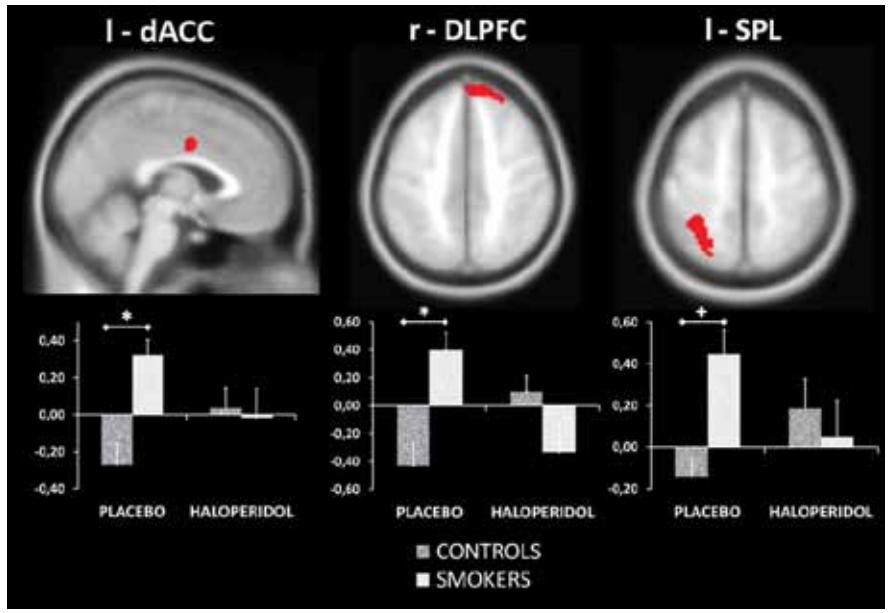

Figure 3

Group differences for brain activation associated with attentional bias

Note figure 3 ** p< 0.05 FWE small volume corrected both with and without masking for the Group x Medication interaction, + p < 0.05 FWE small volume corrected only without masking for the Group x Medication interaction. The values on the Y-axis represent contrast values for LCSP minus LCNP, consequently positive values on the Y-axis indicate more brain activation for line counting when smoking related pictures are presented on the background relative to when neutral pictures are presented on the background. l: left; r: right; dACC: dorsal anterior cingulate gyrus; DLPFC: dorsolateral prefrontal cortex; SPL: superior parietal lobe; LCSP: line counting smoking picture; LCNP: line counting neutral picture.*

after haloperidol suggest that brain activation associated with attentional bias in smokers is normalized when dopamine levels are reduced by haloperidol. Paired *t*-tests, however, did not reveal significant medication effects in either smokers or non-smokers at the FWE corrected level. We therefore extracted parameter estimates in those regions showing a whole brain group x medication interaction and significant group differences (dACC and right DLPFC). Subsequently, paired sample *t*-tests in SPSS were performed for both groups separately. Results showed a significant reduction in brain activation in smokers for the right DLPFC, $t(24) = 3.07$, $p< 0.01$, and a trend for the dACC, $t(24) = 1.99$, $p< 0.058$. Brain activation in the right DLPFC was significantly increased by haloperidol for non-smokers, $t(23) = 2.67$, $p<0.05$.

Brain activation associated with attentional bias in smokers was neither positively nor negatively correlated with cue evoked craving during task performance in any of our a-priori defined regions of interest. See supplementary table 7 and 8 for (non-significant) correlation coefficients between craving and brain and behavioral indices of attentional bias.

Table 1

Group differences for brain activation associated with attentional bias

	MNI coordinates				
	X	Y	Z	*Z*-value[a]	mm^3
Placebo					
Smokers > Controls					
left dACC	-2	-2	36	4.00	360[b]
right DLPFC	24	44	46	4.03	456
left SPL[c]	-34	-46	56	3.85	616
Smokers < Controls	- - -				
Haloperidol					
Smokers > Controls	- - -				
Smokers < Controls	- - -				

Note table 1 *[a] p < 0.05 FWE small volume corrected, [b] After masking with the Group x Medication interaction the size of this cluster reduced to 176 mm^3, [c] After masking with the Group x Medication interaction this cluster no longer met the requirements to correct for multiple comparisons. dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal gyrus; SPL: superior parietal lobe.*

Discussion

The main purpose of the current study was to investigate whether brain activation associated with attentional bias in smokers could be modulated by a dopamine antagonist. The current results provide support for the proposed role of dopamine in attentional bias. In line with our hypotheses, smokers showed increased activation associated with attentional bias in the dACC, right DLPFC, and left SPL after placebo, whereas this activation was normalized when dopamine levels were reduced following administration of a dopamine antagonist. That is, no differences in brain activation between smokers and non-smokers were found after haloperidol intake. These results are in line with a previous study showing that the dopamine antagonist amisulpride normalized cue induced brain activation in alcohol dependent patients (Hermann, et al. 2006).

The current findings replicate and extend findings of our previous study using the same pictorial attentional bias task (Luijten, et al. 2011c). Again, our results implicate a role for the dACC in attentional bias in smokers. The dACC is known to be involved in multiple cognitive processes (Shackman, et al. 2011) such as salience detection (Seeley, et al. 2007), behavioral monitoring and top-down control of attention (Bush, et al. 2000; Weissman, et al. 2005). The dopaminergic signal in the striatum evoked by conditioned substance cues (Volkow, et al. 2006; Wong, et al. 2006; Zijlstra, et al. 2008) may modulate dACC activation via connections between the dACC and the ventral striatum (Kunishio, et al. 1994) such that the salience of these cues is detected. Meanwhile, the dACC may signal conflict of attentional resources, since attention is automatically allocated to the substance cues and withdrawn from ongoing behavior. Given the multi-functionality of the dACC (Shackman, et al. 2011), we suggest that the dACC is involved in salience detection of conditioned substance cues and subsequent allocation of additional cognitive resources. To increase cognitive control for the continuation of ongoing behavior during smoking-cue exposure, the ACC may cooperate with the DLPFC, a region that was also found to be associated with attentional bias in smokers. For example, it has been shown that co-activation of the dACC and DLPFC contributes to the implementation of adjustments in activation of future behavior (Kerns, et al. 2004). In the present study we showed that when dopamine transmission in response to conditioned smoking cues is reduced by a dopamine antagonist the activation in the dACC and DLPFC associated with attentional bias in smokers is reduced accordingly. For future studies it would be interesting to examine whether individual differences in dopaminergic activation in smokers are associated with differences in attentional bias related brain activation. Although

the dopaminergic theory for attentional bias does not involve an inverted U-shape aspect as yet, it may be that the association between dopamine and the attentional control aspects of attentional bias, follows a similar inverted U-shape curve as previously described in the domain of cognitive control (Cools, et al. 2011). In studies addressing this hypothesis, a group of smokers with a broad range of attentional bias scores should be included to sample all parts of the U-shaped curve. Also, dopamine levels would preferably be measured with positron emission tomography in order to obtain a more direct estimation of dopamine levels.

The findings in the current study provide a proof of principles for the role of dopamine in attentional bias related brain activation and may guide the development of new pharmacotherapies for smoking addiction. However, some findings in the current study suggest that the association between dopamine and controlling substance-related behavioral may be rather complex. First, it was found that haloperidol reduced overall performance accuracy and activation in the medial prefrontal and bilateral DLPFC during line counting (see supplementary table 5) suggesting that dopamine antagonists may reduce overall cognitive control. Given that reduced cognitive control is also associated with problems controlling substance use (Feil, et al. 2010a; Goldstein, et al. 2011) a reduction in cognitive control may constitute an unfavorable effect. Second, the single dose of haloperidol was not able to reduce subjective craving in smokers, which is in line with previous studies failing to show reduced craving after a short term reduction in dopamine levels (Ersche, et al. 2010; Franken, et al. 2004; Hitsman, et al. 2008; Munafo, et al. 2007). Various explanations exist for the discrepancy in findings between attentional bias related brain activation and subjective craving. First, we could not replicate the association between attentional bias related brain activation and subjective craving as shown in our previous study (Luijten, et al. 2011c). This inconsistency remains currently unresolved, as previous imaging studies investigating attentional bias in addicted individuals have not examined this association (Ersche, et al. 2010; Hester, et al. 2009a; Janes, et al. 2010a; Janes, et al. 2010b; Nestor, et al. 2011). The discrepancy in effects of the dopaminergic manipulation as well as the lack of an consistent association between attentional bias related brain activation and craving may arise as a consequence of differences between phasic and tonic dopamine neurotransmission. Phasic dopamine transmission has been suggested to be involved in attentional bias while tonic dopamine levels may mediate symptoms associated with withdrawal such as subjective craving (Hitsman, et al. 2008). Furthermore, it has been proposed that brain activation is a rather sensitive measure to detect abnormalities in addicted individuals

regarding cue reactivity compared to other subjective measures such as craving (Goldstein, et al. 2011). The latter is also in line with behavioral data in the current study that could not differentiate between smokers and non-smokers. In fact, behavioral data indicated that smoking-related pictures disrupt ongoing behavior in both groups indicating that brain activation differences between groups after placebo should be interpreted as increased neural effort in smokers to reach similar performance. Enhanced activation in non-smokers for picture naming of smoking-related versus neutral pictures (see supplementary table 4) further support that non-smokers may react stronger to smoking cues. While interference for smoking cues in non-smokers is not typically found, a previous study that also showed this interference effect in non-smokers suggested that it may be due to non-addiction reasons such as negative valence (Stippekohl, et al. 2012). Another unexpected finding in non-smokers is that brain activation associated with attentional bias after haloperidol was significantly increased. Activation patterns (see figure 3) suggest that non-smokers are characterized by reduced activation for line counting in smoking-related pictures relative to neutral pictures after placebo, an effect that disappeared after haloperidol administration. Although highly speculative, we suggest that the increase in brain activation in the DLPFC for smoking-related pictures reflects an attempt to prevent a further decrement in performance levels as performance is lowest after haloperidol and for smoking-related pictures in general.

A final important consideration regarding the current study is that smokers did not smoke for four hours before testing as this could have interfered with medication effects. Given the current study design we cannot completely rule out withdrawal effects on our results. We could demonstrate, however, that withdrawal was not influenced by medication type and was not associated with individual differences in task performance (see supplementary materials). In our previous study showing similar attentional bias related brain activation (Luijten, et al. 2011c), smokers were abstinent for three hours, while smokers smoked did not abstain in other studies investigating attentional bias related brain activation in smokers (Janes, et al. 2010a; Janes, et al. 2010b; Nestor, et al. 2011; Stippekohl, et al. 2012). Generally, it is assumed that attentional bias is augmented after longer periods of abstinence (Waters, et al. 2000), therefore the four hours abstinence period is important to consider when interpreting the current results.

To conclude, it was shown that administration of a dopamine antagonist normalized activation associated with attentional bias in the dACC and DLPFC in smokers. This finding supports theoretical accounts of the role of dopamine

in attentional bias, and may have implications for the development of new pharmacotherapies for smoking addiction. However, our finding that haloperidol reduced overall task performance and associated brain activation indicates that it should be a future research agenda to investigate whether an optimal balance of dopamine in different brain regions in smokers can be achieved.

Acknowledgements

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Supplementary Materials

Medical screening

All participants were screened by a Psychiatrist. The screening included a check for contraindications for haloperidol (lifetime prevalence of epileptic seizure, heart disease and first degree relatives with diseases affecting dopaminergic transmission such as Parkinson disease, Huntington disease or psychosis. Participants were also provided with information on potential side effects such as drowsiness and muscle stiffness and were explained that these side effects are not expected to occur with a single low dose of 2 mg haloperidol. In addition, participants were screened for neurological and psychiatric diseases to make sure that participants had no lifetime neurological or psychiatric diagnoses and that they did not use any medication that crosses the blood brain barrier.

Additional imaging analyses

The four task conditions of the attentional bias line counting task (line-counting smoke picture: LCSP; line-counting neutral picture: LCNP; picture-naming smoke picture: PNSP; picture-naming neutral picture: PNNP) are associated with four contrasts to be defined for second level analyses (Luijten et al., 2011). Results for the main contrast reflecting brain activation associated with attentional bias are reported in the main text. The second contrast in the ABLC task reflects cue-exposure corrected attention (LCSP minus PNSP). This contrast reflects attention to the smoking-related pictures during line counting while correcting for differences between smokers and controls in smoking cue-reactivity such as arousal and familiarity for smoking cues. The

third contrast (PNSP minus PNNP) reflects overall cue-reactivity effects for smoking pictures. Finally, the fourth contrast (overall cognitive effort) reflects brain activation associated with overall cognitive effort during line counting irrespective of picture content (LCSP and LCNP relative to baseline contrast). This contrast is defined in order to show whether the task robustly elicits brain activation and to investigate main effects of group and medication for overall task performance regardless of picture type.

Attentional bias (LCSP minus LCNP)

In addition to the analyses described in the main manuscript, we here report main effects (i.e., one-sample *t*-tests) per group per medication condition for the attentional bias contrast. Main effects were not limited to regions showing a Group x Medication interaction. The same ROIs were used for these analyses as in the main text and included the bilateral ACC, SPL, superior temporal gyrus, DLPFC, IFG, amygdala, insula and nucleus accumbens. ROIs were defined using the automatic anatomical labeling (AAL) atlas (Tzourio-Mazoyer, et al. 2002). As the nucleus accumbens is not included in the AAL atlas, a 10 mm sphere with MNI coordinates ± 10 12 -2 was created as a ROI for the nucleus accumbens (Knutson, et al. 2008). Results were thresholded at $p< 0.05$, Family Wise Error (FWE) corrected for multiple comparisons across the search volume (Small volume correction: Friston, et al. 1996; Worsley, et al. 1996). In order to do so, analyses were first thresholded at $p< 0.001$ uncorrected with 20 contingently activated voxels (160mm3), and then corrected using a small volume correction ($p<0.05$ FWE corrected) in which the search volume was defined by the AAL template corresponding to the a-priori defined ROI.

Cue-exposure corrected attention (LCSP minus PNSP) and cue-reactivity (PNSP minus PNNP)

The same analyses were applied to these contrasts as to the attentional bias contrast described in the main text and supplementary materials. Shortly, for both contrasts a random effects Group x Medication RM-ANOVA was performed to investigate Group x Medication interactions. Planned between group and between medication t-tests were performed (i.e., differences between groups for placebo and haloperidol separately and medication effects in smokers and non-smoking controls separately), masked by voxels showing a Group x Medication interaction in the RM-ANOVA ($p< 0.01$ uncorrected). In order to replicate the main findings from our previous study results for the between group two sample *t*-test for placebo will also be reported without masking for

the interaction effect. Furthermore, main effects (one-sample *t*-tests) per group per medication condition for both contrasts were calculated. Main effects were not limited to regions showing a Group x Medication interaction. The same ROIs and methods to correct for multiple analyses were used as for the attentional bias contrast.

Overall cognitive effort (LCSP and LCNP relative to baseline)

The first aim of the overall cognitive effort contrast was to show that the ABLT task robustly elicited brain activation during the line counting condition. For this aim a one sample *t*-test across groups was performed for the overall cognitive effort contrast after placebo ($p< 0.05$ whole brain FWE corrected). A second aim was to investigate whether smokers and non-smoking controls differed regarding brain activation associated with overall cognitive effort (i.e., line counting regardless of picture type). Therefore, a two-sample *t*-test (smokers versus non-smoking controls) for the overall cognitive effort contrast was performed collapsed across medication conditions. Finally, the overall effects of haloperidol on brain activation associated with overall cognitive effort was investigated using a paired *t*-test (placebo versus haloperidol) collapsed across smokers and non-smoking controls. Between group and between medication analyses were performed in the above mentioned a-priori defined ROIs using small volume corrections.

Additional imaging results

Attentional bias

Main effects per group per medication condition show attentional bias related brain activation in smokers after placebo in the left SPL and right IFG. No attentional bias related brain activation was found in smokers after haloperidol. Non-smoking controls activated the left DLPFC after haloperidol. See supplementary table 1 for details.

Supplementary Table 1

Brain activation associated with attentional bias for smokers and non-smoking controls during placebo and haloperidol

Placebo	MNI coordinates					Haloperidol	MNI coordinates				
	X	Y	Z	*Z*-value[a]	mm^3		X	Y	Z	*Z*-value[a]	mm^3
Smokers						Smokers					
left SPL	-28	-58	54	3.94	1208	---					
right IFG	42	42	-2	3.74	328						
Controls						*Controls*					
---						left DLPFC	-16	56	10	4.10	264

Note supplementary table 1 *Active regions in this table reflects brain activation associated with attentional bias (contrast line counting smoking pictures minus line counting neutral pictures). [a] p< 0.05 FWE small volume corrected SPL: superior parietal lobe; IFG: inferior frontal gyrus; DLPFC: dorsolateral prefrontal cortex.*

Cue-exposure corrected attention

After placebo smokers showed reduced activation for cue-exposure corrected attention relative to non-smoking controls in the bilateral ventral zone of the ACC and the bilateral nucleus accumbens (see supplementary table 2 for details). These group differences after placebo were not found after masking with the Group x Medication effect. No group differences were observed after haloperidol. Main affects show extended activation in prefrontal, insular, parietal and temporal regions in both smokers and non-smoking controls after placebo. After haloperidol, activation in smokers was largely reduced whereas non-smoking controls still showed extended activation patterns. See supplementary table 3 for a complete overview and details of the main effects for the cue-exposure corrected attention contrast. No significant effects of medication type were found in either smokers or non-smoking controls.

Supplementary Table 2

Group effects for brain activation associated with cue-exposure corrected attention

	MNI coordinates				
	X	Y	Z	*Z*-value[a]	mm^3
Smokers > Controls	---				
Smokers < Controls					
left vACC	-10	44	4	3.95	1256
right ACC	14	32	16	3.66	264
left NACC	-10	12	8	3.68	496
right NACC	6	14	-2	4.52	520

Note supplementary table 2 *Group differences in this table reflect differences in brain activation associated with cue-corrected attention (contrast line counting smoking pictures minus picture naming smoking picture). [a] p< 0.05 FWE small volume corrected; (v)ACC: (ventral) anterior cingulate cortex; NACC: nucleus accumbens.*

Supplementary Table 3

Brain activation associated with cue-exposure corrected attention in smokers and non-smoking controls for placebo and haloperidol

Placebo	MNI coordinates					Haloperidol	MNI coordinates				
	X	Y	Z	*Z*-value[a]	mm^3		X	Y	Z	*Z*-value[a]	mm^3
Smokers						*Smokers*					
left SPL	-20	-58	54	4.48	1768	right SPL	16	-66	54	4.48	1320
left SPL	-36	-42	56	4.35	192	left DLPFC	-22	-8	58	4.12	664
right SPL	20	-62	56	5.06	3624						
left STG	-48	0	-6	4.72	3544						
left DLPFC	-24	-8	50	6.75	1984						
right DPLFC	28	-2	52	5.96	3784						
left insula	-38	-16	2	4.51	4608						
right insula	34	-14	8	4.07	1016						
Controls						*Controls*					
left ACC	-8	-24	34	3.98	344	left ACC	-10	-30	34	3.89	248
right ACC	12	-32	40	3.78	712	left ACC	-10	-10	36	3.59	232
left SPL	-20	-54	52	5.81	4496	left SPL	-24	-52	58	5.99	4736
right SPL	18	-64	58	6.32	5440	right SPL	26	-52	60	6.86	5568
left STG	-52	-36	14	3.93	1136	left STG	-46	-22	4	4.18	5712
left STG	-48	-18	6	3.63	424	right STG	52	0	-6	4.14	1504
left DLPFC	-24	-6	52	5.57	3152	left DLPFC	-22	-10	60	5.59	4256
right DLPFC	28	-2	52	5.40	4912	right DLPFC	32	-6	66	5.62	5112
right IFG	44	4	22	4.48	712	left IFG	-40	0	24	3.79	400
right insula	42	2	10	3.54	208	right IFG	42	4	24	3.71	424
right insula	34	-4	8	3.50	256	left insula	-34	-6	12	3.96	952
left NACC	-12	10	6	3.53	176	right insula	50	4	-6	4.20	640
						right insula	38	-16	14	3.76	736
						right insula	38	-2	8	3.56	168

Note supplementary table 3 *Active regions in this table reflects brain activation associated with cue-exposure corrected attention (contrast line counting smoking pictures minus picture naming smoking pictures).[a] p< 0.05 FWE small volume corrected. SPL: superior parietal lobe; STG: superior temporal gyrus; DLPFC: dorsolateral prefrontal gyrus; ACC: anterior cingulate cortex; IFG: inferior frontal gyrus; NACC: nucleus accumbens.*

Supplementary Table 4

Brain activation associated with cue-reactivity for smokers and non-smoking controls during placebo and haloperidol

Placebo	MNI coordinates					Haloperidol	MNI coordinates				
	X	Y	Z	*Z*-value[a]	mm^3		X	Y	Z	*Z*-value[a]	mm^3
Smokers						*Smokers*					
left vACC	0	38	-2	3.66	264	left insula	-38	-20	14	4.22	392
right vACC	6	40	-2	3.71	456						
left insula	-36	-18	14	4.84	760						
left STG	-52	-20	12	4.59	536						
Controls						*Controls*					
left insula	-34	-18	8	5.79	1720	left insula	-36	-20	18	4.17	616
left STG	-62	-26	16	4.37	1128						

Note supplementary table 4 *Active regions in this table reflects brain activation associated with cue reactivity (contrast picture naming smoking pictures minus picture naming neutral pictures).[a] p< 0.05 FWE small volume corrected. vACC: ventral anterior cingulate cortex; STG: superior temporal gyrus.*

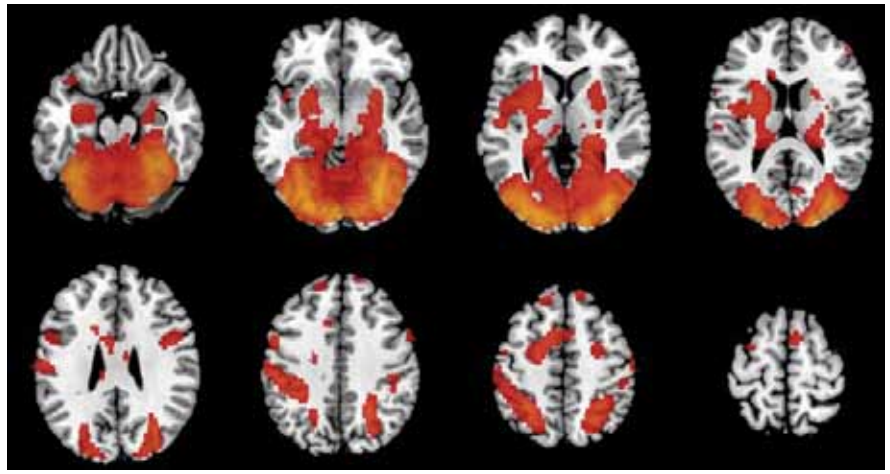
Cue-reactivity

No significant group differences were found regarding cue reactivity related brain activation after placebo or haloperidol. Main effects per group per medication condition showed that smokers and non-smokers had similar cue-reactivity responses after placebo in the insula and STG. Only the ventral ACC was uniquely activated in smokers after placebo. Cue-reactivity related brain activation in the ventral ACC in smokers was not found after haloperidol. See supplementary table 4 for main effects of cue-reactivity related brain activation. No significant medication effects were found in either smokers or non-smoking controls.

Overall cognitive effort

During placebo overall cognitive effort across groups was associated with robust brain activation in bilateral occipital, inferior and superior parietal, and dorsolateral prefrontal brain regions, as well as in motor areas, the insula, the ACC and subcortical regions including the thalamus and caudate (p < 0.05 FWE corrected; see supplementary figure 1). In addition, haloperidol reduced brain activation in the right medial prefrontal cortex and bilateral DLPFC (see

supplementary table 5 for details). None of the brain regions showed increased activation after haloperidol. Brain activation associated with overall cognitive effort did not differ between smokers and non-smoking controls.



Supplementary Figure 1

Brain activation associated with overall cognitive effort after placebo across smokers and non-smoking controls

Note supplementary figure 1 *p<0.05 FWE corrected (whole brain).*

Withdrawal

Smokers were not allowed to smoke after taking the medication, which was four hours before scanning and could have introduced withdrawal. Withdrawal was assessed using the withdrawal subscale of the Questionnaire of Smoking Urges (Cox, et al. 2001). Withdrawal scores in smokers were analyzed with Medication as a single within subject factor. Results showed that medication type did not influence withdrawal scores $F(1,23) = 0.65$, $p= 0.8$. As individual differences in withdrawal may influence cognitive performance we correlated withdrawal scores with line counting accuracy and reaction times per medication condition. No significant correlations were found, all p's> 0.14 suggesting that individual differences in withdrawal in smokers were not associated with cognitive performance. However, given the current study design it cannot be completely ruled out that withdrawal may have influenced cognitive performance.

Lifetime substance use

Supplementary table 6 shows lifetime substance use for smokers and non-smoking controls. Although groups do not differ significantly on any of the substances of abuse, it seems that smokers have used cannabis more often than non-smoking controls. More specifically, two smokers were identified as outliers as they have used cannabis more than 150 times lifetime. Although it is theoretically unlikely that cannabis use would have an impact on nicotine-related attentional bias (i.e., attentional biases are known to be substance-specific), we conducted an additional analyses excluding the two smokers who have used cannabis more than 150 times lifetime for brain and behavioral indices of attentional bias. These analyses were exactly similar to the analyses described in the paper. Removing these two subjects did not change results substantially. Two minor differences were noticed. First, the p-value for the main effect of Picture for reaction times increased from $p= 0.048$ to $p= 0.06$. Second, although activation levels were still significant at the $p< 0.05$ FWE corrected level, the volume of increased brain activation in smokers after placebo in the dACC decreased from 176 mm^3 to 40 mm^3 when masked for the Group x Medication interaction. These minor differences are most likely the result of reduced statistical power.

Supplementary Table 5

Medication effects for brain activation associated with overall cognitive effort

	MNI coordinates				
	X	Y	Z	*Z*-value[a]	mm^3
Haloperidol < Placebo					
right medial PFC	8	38	34	3.74	160
left DLPFC	-20	34	30	4.25	3632
right DLPFC	20	52	34	3.81	848
Haloperidol > Placebo	- - -				

Note supplementary table 5 *Medication effects in this table reflect differences in brain activation associated with overall cognitive effort (contrast line counting smoking pictures and line counting neutral pictures versus baseline). [a] p< 0.05 FWE small volume corrected. PFC: prefrontal cortex; DLPFC: dorsolateral prefrontal cortex.*

Supplementary Table 6

Lifetime occasions of drug use for smokers and non-smoking controls

Substance	Smokers		Controls	
	Mean	*SD*	**Mean**	*SD*
Cannabis	205.67	717.74	1.54	1.69
Cocaine	1.32	5.99	0.04	0.20
Amphetamines	1.12	3.53	0.04	0.20
Ecstasy	3.28	8.36	0.21	1.02
Opiates	-	-	-	-
Alcohol [ab]	17.63	3.47	12.84	3.34

Note supplementary table 6 *[a]Sum scores representing quantity and frequency of alcohol consumption measured utilizing the Quantity-Frequency-Variability Index (QFV-index: Lemmens, et al. 1992). In this questionnaire three items are employed in order to determine the drinking quantity (number of glasses), frequency (drinking days), and variability (binge drinking) during the last six months. [b] Significant group difference p< 0.001, SD: Standard deviation.*

Supplementary Table 7

Correlations between cue induced craving in smokers and behavioral and brain indices of attentional bias

Cue induced craving	Placebo (ρ)	Haloperidol (ρ)
Reaction times	-.03	.01
Accuracy	-.16	.07
dACC	-.11	.16
Right DLPFC	-.01	.20
Left SPL	-.26	.05

Note supplementary table 7 *ρ = spearman rank correlation coefficients for cue induced craving during performance of the attentional bias line counting task and behavioral and brain indices. None of the correlations are significant. Behavioral and brain indices are based on the contrast line counting smoking pictures minus line counting neutral pictures. Brain indices reflect those regions in which group differences were found. dACC: dorsal anterior cingulate gyrus; DLPFC: dorsolateral prefrontal cortex; SPL: superior parietal lobe.*

Supplementary Table 8

Correlations between behavioral measures and brain activation

	Placebo (ρ)		Haloperidol (ρ)	
	Reaction times	Accuracy	Reaction times	Accuracy
dACC	-.12	.04	.24	.06
Right DLPFC	-.28	-.27	.21	.19
Left SPL	-.22	-.10	.07	.03

Note supplementary table 8 *ρ = spearman rank correlation coefficients for behavioral measures and brain activation. None of the correlations are significant. Behavioral and brain indices are based on the contrast line counting smoking pictures minus line counting neutral pictures. Brain indices reflect those regions in which group differences were found. dACC: dorsal anterior cingulate gyrus; DLPFC: dorsolateral prefrontal cortex; SPL: superior parietal lobe.*

Chapter Nine

Summary, discussion and concluding remarks

The main objective of this thesis was to gain more knowledge concerning neurocognitive processes involved in smoking behavior. For this purpose, brain functions associated with cognitive control and attentional bias were investigated in smokers and healthy controls. First, we focused on inhibitory control and error-processing as two core processes of cognitive control. We investigated whether these functions are dysfunctional in smokers due to alterations in the cognitive control brain circuit. The second major objective of this thesis was to identify the neural substrate of attentional bias in smokers. We aimed to provide empirical evidence for the idea that attentional bias is associated with enhanced brain activation in the mesocorticolimbic system when smokers are confronted with smoking-related cues. In addition, the dopaminergic basis of attentional bias was investigated by measuring brain activation associated with attentional bias while manipulating dopamine levels in the brain.

Greater insight into the malfunction of neural networks associated with cognitive control and attentional bias in smokers could provide valuable information to understand the maintenance of smoking behavior. Eventually, neurocognitive insights in smoking behavior may contribute to the development of new treatments supporting attempts to quit smoking. The current chapter provides a summary and discussion of the main results described in this thesis.

Cognitive control in addicted individuals

The role of cognitive control in substance dependence is emphasized in several contemporary theoretical models of substance dependence (Dawe, et al. 2004a; Goldstein, et al. 2011; Jentsch, et al. 1999; Lubman, et al. 2004; Verdejo-Garcia, et al. 2008). Substance dependent individuals are characterized by the inability to adequately control behavior related to substance use such as abstaining from substances of abuse. In addition, the reduced ability to perform goal directed behavior in substance dependent individuals is often accompanied by an apparent failure to adaptively learn from previous harmful behavior (Franken, et al. 2007). The ability to guide our behavior in accordance with our long-term goals requires the inhibition of automatic behavior and the monitoring of ongoing behavior, with both these functions being implemented by cognitive control circuits in our brain. More specifically, inhibitory control and error-processing are two core components of cognitive control that are associated with specific neural networks; the former to implement the inhibition of inappropriate behavior and the latter to monitor performance errors in order to prevent future mistakes (Ridderinkhof, et al. 2004a). Given the important role of cognitive control in substance dependence, greater insight into the malfunction

of neural networks in substance dependent individuals could provide valuable information for understanding the problems associated with controlling substance use. A rapidly increasing number of studies have examined inhibitory control and error-processing in substance dependent individuals by using neuroimaging techniques such as event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI). Therefore, the main goal of **chapter 2** was to evaluate fMRI and ERP studies in the domains of inhibitory control and error-processing in order to evaluate the consistency of the findings across neuroimaging studies in the most common substance dependent populations. In light of the new update of the DSM-V that will include a section 'Addictive behaviors', studies in pathological gamblers and excessive internet users are also included in the review described in chapter 2. Thirty-two ERP and fMRI studies were evaluated. Reduced N2 amplitudes were found in addicted individuals in the domain of inhibitory control. Reduced N2 amplitudes suggest that deficits in inhibitory control in addiction may be due to problems with early cognitive processes such as conflict detection that are necessary to execute inhibitory control. Complementary to reduced N2 amplitudes, fMRI studies showed deviant activation in addicted individuals mainly in the anterior cingulate cortex (ACC), inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex (DLPFC) but also in inferior and superior parietal gyri. From these findings, it can be concluded that substantial parts of the network that forms the basis of inhibitory control are dysfunctional in addicted individuals including smokers and cannabis-, alcohol-, opiate-, and stimulant-dependent individuals.

With regard to error-processing, several studies showed that addicted individuals are characterized by reduced activation in the ACC; the most critical area for error-processing. Additionally, reduced activity in other regions such as superior and inferior frontal gyri and the insula was reported. ERP findings both confirm and complement fMRI findings. Reduced error-related negativity (ERN) amplitudes were found in substance dependent individuals confirming reduced initial error detection in addicted individuals. Given that the ACC is the neural generator of the ERN (Herrmann, et al. 2004; Ridderinkhof, et al. 2004a; Van Veen, et al. 2002), both ERN and fMRI findings suggest that ACC dysfunction (i.e., hypoactivation) associated with error-processing could be a marker for addiction. Pe findings complement fMRI findings by providing information on the timeframe of error-processing deficits. Reduced Pe amplitudes in substance dependent individuals suggest that, besides the initial error detection, more conscious processing of errors is reduced in addicted individuals. ERP and fMRI findings regarding error-processing in alcohol dependence constitutes an exception on the generally observed hypoactivation in addicted individuals. In

contrast to other addicted individuals, alcohol dependent individuals show enhanced processing of errors as reflected by enlarged ERN amplitudes and increased error related activation in the ACC. Findings in the study by Schellekens et al. (2010) provide a plausible explanation for these findings as ERN amplitudes in high anxious alcohol dependent individuals were larger than in low anxious alcohol dependent individuals. These findings of increased ERN amplitudes in high anxious alcohol dependent individuals suggest that the often observed comorbid internalizing psychopathology (i.e., anxiety-related disorders) in alcohol dependent individuals (Bacon, et al. 2010; Baillie, et al. 2010) may be responsible for the increase in error-processing. An overview of ERN findings in both internalizing and externalizing psychopathology confirms that internalizing psychopathology is associated with enhanced ERN amplitudes while externalizing psychopathology is associated with reduced ERN amplitudes (Olvet, et al. 2008). The effects of anxiety in alcohol dependent individuals on error related brain activation suggest that comorbidity with internalizing psychopathology may be a confounding factor in studies in substance dependent individuals. It would be interesting if future studies report comorbidity and investigate individual differences within substance dependent individuals.

Finally, the evaluation of studies in individuals showing excessive addiction-like behaviors, as described in chapter 2, provided preliminary evidence for similar neural deficits associated with inhibitory control and error-processing in behavioral addictions and substance dependence.

Error-processing in smokers

The main goal of the study described in **chapter 3** was to evaluate the ability to monitor ongoing behavior during exposure to salient smoking cues in smokers. For this aim, an Eriksen-Flanker task (Eriksen, et al. 1974) including smoking cues was developed and behavioral and brain responses to performance errors were recorded in smokers and non-smoking controls. It was expected that during smoking cue exposure limited capacity may be available to monitor ongoing performance. As a consequence, smokers will show reduced error-processing compared to non-smoking controls. Additionally, the nature of error-processing deficits was examined in more detail by investigating their associations with trait impulsivity, severity of nicotine dependence and cigarette craving. Results indeed showed behavioral and physiological evidence of reduced error-processing in smokers during a task in which participants were exposed to smoking cues. On the behavioral level, smokers showed less post-error slowing than non-smoking controls suggesting that behavioral adaptation

after an error (e.g., slowing down in order to prevent another error) is reduced in smokers. Furthermore, smokers showed reduced ERN and Pe amplitudes following incorrect responses as compared to non-smoking controls. Reduced ERN and Pe amplitudes suggest that both initial error detection as well as the more conscious evaluation of errors is reduced in smokers. In addition, self-reported levels of impulsivity, which were higher in smokers, were associated with a reduced ERN across smokers and non-smokers. Moreover, higher nicotine dependence levels among smokers were also associated with smaller ERN responses. Together, these results suggest that both personality traits and specific nicotine dependent characteristics are associated with diminished error-processing. Since adequate error-processing is required to adapt behavior properly, reduced error-processing may contribute to the development and maintenance of addictive behaviors.

Inhibitory Control in Smokers

In **chapter 4**, inhibitory control in smokers is investigated using ERPs. The aim of this study was twofold. First, it was investigated whether inhibitory control is reduced in smokers, as behavioral findings this far have been inconsistent and neuroimaging studies in smokers were largely lacking. Second, it was investigated whether deficits in inhibitory control in smokers are more evident when smokers are confronted with highly salient smoking-related cues. Both behavioral accuracy as well as N2 and P3 event-related potentials were evaluated in smokers and non-smoking controls in the context of an adapted Go/NoGo task that included both neutral and smoking-related stimuli. Differences between smokers and non-smokers were found on both behavioral and electrophysiological indices of inhibitory control. That is, performance on the Go/NoGo task was generally less accurate in smokers than in non-smokers, i.e., smokers showed significantly more difficulties inhibiting their responses for NoGo trials. This deficit in inhibitory control was reflected in reduced N2 amplitudes for NoGo trials in smokers as compared to non-smokers. The findings in the current study did not show more distinct deficits in inhibitory control in smokers in the presence of smoking cues. In fact, the findings described in chapter 4 suggest that deficits in inhibitory control in smokers are of a more general nature and are present both during neutral and smoking cue exposure conditions.

The study described in **chapter 5** investigated the neural basis to inhibit an immediately rewarding stimulus in order to obtain a larger delayed reward in smokers. It was also investigated whether punishment insensitivity

could be another factor contributing to inefficient inhibitory control over rewarding stimuli. For this purpose a modified version of the Go/NoGo paradigm was designed that included specific reward and punishment contingencies. In line with contemporary theories on addiction, it was hypothesized that smokers would have significantly greater difficulty inhibiting their response to a rewarding stimulus when compared to matched control participants. With regard to punishment sensitivity, it was expected that smokers are less sensitive to the effects of punishment to guide control over rewarding stimuli. More specifically, we expected that non-smoking controls would adopt a more cautious responding style when failed inhibition resulted in an immediate punishment, while this was not expected to influence behavior to the same extent in smokers. Results showed that task performance was equal for smokers and non-smoking controls. At the neural level, however, it was found that smokers needed additional activation in the pre-supplementary motor area, right anterior insula, right inferior/middle frontal gyrus and right DLPFC both during inhibition of an immediate rewarding stimulus in order to obtain a larger delayed reward as well as during inhibition of neutral non-rewarding stimuli. Tentative evidence was found for the idea that smokers are insensitive to the inhibitory effect of punishment to guide control over rewarding stimuli.

When combining results of chapter 4 and chapter 5, it is interesting to note that group differences between smokers and non-smoking controls were neither influenced by smoking cue exposure nor by the availability of immediate monetary reward. These results could imply that inefficient inhibitory control in smokers may not be specific for smoking-related or rewarding cues but may reflect a general problem with inhibitory control across a broad range of situations. Therefore, inefficient inhibitory control in smokers may not only be associated with addictive behaviors but could also be associated with other impulsive and possibly maladaptive behaviors. This idea is supported by the high proportion of smokers in, for example, conduct disorder (Bagot, et al. 2007) and problem gambling (Verdejo-Garcia, et al. 2008). However, the implications of inefficient inhibitory control on tasks such as the Go/NoGo task for daily behaviors should be further investigated in future studies.

The pharmacology of inhibitory control

The pharmacology of inhibitory control is an ongoing scientific endeavor. Theorists assume that the relation between dopamine and cognitive control follows an inverted U-shaped curve such that either too low or too high levels of prefrontal dopamine are disadvantageous for cognitive functioning (Cools, et al.

2011). It is important to gain more knowledge on how dopamine affects neural networks that form the basis of inhibitory control, especially to better understand disorders such as substance dependence that are characterized by dysfunctional dopamine systems (Balfour 2009; Berkman, et al. 2011; Diekhof, et al. 2008; Franken, et al. 2005; Koob, et al. 1997; Volkow, et al. 2009). Given the dysfunctional dopamine system in smokers and the inverted U-shaped curve theory, it is likely that deficiencies in dopaminergic functioning may contribute to problems in inhibitory control. Therefore, the study described in **chapter 6** employed a dopaminergic challenge in order to test the hypothesis that brain activation associated with inhibitory control is modulated by dopamine. To manipulate dopamine levels, Haloperidol (2mg), a selective D2/D3 dopamine antagonist, or placebo was orally administered in a double-blind randomized cross-over design in smokers and non-smoking controls. A Go/NoGo task was used to measure inhibitory control. It was hypothesized that a reduction in dopamine levels after haloperidol reduced inhibitory control and associated brain activation in both smokers and non-smoking controls. In addition, based on baseline differences in dopaminergic functioning between smokers and non-smoking controls it was expected that haloperidol would have differential effects on brain activation associated with inhibitory control in smokers and non smokers. At the behavioral level, results showed that smokers generally had longer reaction times and reduced NoGo accuracy rates for the first test occasion. Longer reaction times on Go trials suggest less efficient task performance or the use of different strategies. Besides behavioral performance deficits, group differences between smokers and non-smoking controls in brain activation associated with inhibitory control were found after the administration of placebo. Activation in prefrontal brain regions including the ACC, left IFG and right middle frontal gyrus (MFG) was found to be reduced in smokers compared to non-smoking controls. This study further confirmed the hypothesis that reduced dopamine levels after haloperidol intake are associated with impairments in inhibitory control. Haloperidol reduced NoGo accuracy rates in both groups, while Go accuracy and reaction times were unaffected, indicating a specific effect of dopamine on inhibitory control. Impaired inhibitory control after haloperidol was accompanied by reduced activation in prefrontal regions associated with inhibitory control including the ACC, IFG and MFG. Haloperidol intake, however, was associated with reduced activity relative to placebo in prefrontal regions in non-smoking controls, but not in smokers. This implies that dopamine D2/D3 receptor blockade by haloperidol renders non-smoking controls more similar to smokers regarding reduced inhibitory control and hence presumably regarding dopamine levels. The differential effects of haloperidol in both groups may be due to the previously observed differences in

baseline dopamine levels between smokers and non-smoking controls (Fehr, et al. 2008). Findings in this study suggest that the effects of reduced dopamine receptor densities in smokers (Fehr, et al. 2008), or in substance dependence in general, may not be limited to motivational processes linked to dopamine such as reward sensitivity, but could also be the underlying neurobiological mechanism for reduced inhibitory control. It would be interesting for future studies to administer both a dopamine agonist and antagonist in order to examine the full range of the inverted U-curve theory on dopamine levels and cognitive control and their consequences for nicotine dependence.

When comparing findings of the three studies investigating inhibitory control in smokers, it is striking that smokers have reduced N2 amplitudes and reduced prefrontal activation relative to non-smoking controls in the studies described in chapters 4 and 6, whereas chapter 5 describes increased prefrontal activation in smokers. Differences between studies in terms of hypo- versus hyperactivation in addicted individuals were also noticed in the review of neuroimaging studies in chapter 2. Generally, the interpretation of hypo- versus hyperactivation in ERP and fMRI studies in clinical populations compared to healthy controls remains difficult. Behavioral findings as well as task difficulty may be key factors to guide the interpretation of hypo- or hyperactivation, at least in our findings in smokers. Hypoactivation in combination with reduced accuracy (chapters 4 and 6) is relatively straightforward and most likely signals reduced neural capacities leading to behavioral deficits. Hyperactivation coupled with intact behavioral performance (chapter 5) is often interpreted as an increased neural effort or the use of alternative cognitive strategies to reach normal levels of behavioral performance. Task difficulty may have determined whether the smokers in the current studies were able to compensate in order to reach similar accuracy as non-smoking controls, or whether smokers could no longer compensate and reduced behavioral performance was found in combination with hypoactivation in the cognitive control circuit. This idea is supported by the fact that NoGo accuracy rates were lower in the two studies reporting hypoactivation in smokers combined with behavioral deficits (69.63% and 57.66%) than in the study in which smokers showed hyperactivation without behavioral deficits (80.12%). In line with this notion, literature in the field of aging shows that initial cognitive decline is characterized by a combination of increased frontal engagement and intact behavioral performance (for review see: Goh, et al. 2009).

Neurobiological correlates of attentional bias

Smokers are characterized by enhanced attentional processing of smoking-related cues, a process referred to as attentional bias. Theoretical models suggest that attentional bias is a consequence of a dopamine signal that triggers attention to substance-related cues whenever they are encountered by substance dependent individuals (Franken 2003; Robinson, et al. 2003). After repeated drug intake, substance-related cues become conditioned cues and elicit dopaminergic activity (Volkow, et al. 2006; Wong, et al. 2006; Zijlstra, et al. 2008) thereby signaling the expectation of a future reward (i.e., the intake of the substance of abuse). Gradually, the dopaminergic system becomes sensitized to substance-related cues so that they become extremely salient, become the focus of attention and elicit behaviors like drug seeking and consumption (Phillips, et al. 2003; Robinson, et al. 2008). Despite these theoretical advances, the neurobiological mechanisms of attentional bias are largely unknown. Brain activation associated with attentional bias provides a direct measure of the enhanced processing of smoking-related cues and contributes to an increased understanding of the underlying mechanisms of attentional bias. Therefore, the neuroanatomical substrate of attentional bias and associated subjective craving in smokers was investigated in **chapter 7.** For this aim a new pictorial attentional bias task was developed (the attentional bias line counting task, i.e., ABLCT). Smokers and non smoking controls performed this task while brain activation was measured using fMRI. The ABLCT was developed for two major reasons. First, we expected that pictures capture the attention more easily than smoking-related words (Hester, et al. 2006) that are often used to measure attentional bias in the smoking-word Stroop task. In addition, the ABLCT addressed another important conceptual issue that may confound results in non-adapted attentional bias paradigms. That is, if non-adapted attentional bias paradigms were used for an fMRI study it cannot be ruled out that differential brain activation in these task paradigms is the result of differences in simple cue-reactivity to smoking cues between smokers and non-smoking controls. Therefore, the ABLCT involved extra task conditions to be able to measure brain activation associated with attentional bias while controlling for non-specific activations resulting from other processes involved in cue-reactivity (i.e., picture viewing), including arousal and familiarity. Results of the study described in chapter 7 indicated more brain activation in smokers versus healthy controls in the dorsal ACC (dACC) and right superior parietal lobe (SPL) during the ABLCT. Unexpectedly, a similar effect was also observed in the left superior temporal gyrus (STG). Because of the design of the ABLCT we could demonstrate that dACC hyperactivation in smokers cannot be attributed to processes arising from mere cue-exposure or cue-exposure related phenomena, including enhanced

familiarity to smoking cues and arousal. Additionally, activations in the left insula and the right putamen were found to be associated with attentional bias related craving. In the study described in **chapter 8** we investigated whether brain activation associated with attentional bias could be modulated by dopamine. Based on the theory that explains attentional bias as a consequence of dopaminergic firing elicited by conditioned substance cues, it can be expected that attentional bias related brain activation would be attenuated when dopamine is no longer able to signal the salience of conditioned substance-related cues. The pharmacological fMRI study described in chapter 8 employed a dopaminergic challenge in order to test this hypothesis. To manipulate dopamine levels, Haloperidol (2mg), a selective D2/D3 dopamine antagonist, or placebo was orally administered in a double-blind randomized cross-over design in smokers and non-smoking controls. The same pictorial attentional bias task (the ABLCT) was used in this study to be able to compare findings of this study with the findings in chapter 7. In line with findings in chapter 7, smokers showed enhanced brain activation associated with attentional bias after administration of placebo in the dACC and the SPL. Additionally, smokers showed increased activation in the DLPFC. Studies performed in other labs also suggest that the ACC may be associated with attentional bias in smokers (Janes, et al. 2010a) and alcohol dependent individuals (Vollstadt-Klein, et al. in press). The dACC is known to be involved in multiple cognitive processes (Shackman, et al. 2011) such as salience detection (Seeley, et al. 2007), behavioral monitoring and cognitive control including guidance of attention (Bush, et al. 2000; Weissman, et al. 2005). The dopaminergic signal in the striatum evoked by conditioned substance cues (Volkow, et al. 2006; Wong, et al. 2006; Zijlstra, et al. 2008) may trigger dACC activation via connections between these regions (Kunishio, et al. 1994). As a consequence, salience of these cues is detected. Meanwhile, the dACC may signal a conflict of attentional resources, since attention is automatically allocated to the substance cues and withdrawn from ongoing behavior. Therefore we suggest that the consistent finding of enhanced activation in smokers during the ABLCT in the dACC is both associated with salience detection of smoking cues and is used to increase cognitive control in order to continue ongoing behavior when smoking cues are presented. In order to increase cognitive control the dACC may cooperate with the SPL and DLPFC. Most importantly, results in chapter 8 show that the enhanced activation in smokers in the dACC and DLPFC on the ABLCT was normalized when dopamine levels were reduced following administration of a dopamine antagonist. That is, no differences in brain activation between smokers and non-smokers were found after a single dose of haloperidol. Attentional bias has recently been shown to be associated with clinical measures of substance use such as

successful quitting and relapse (Marissen, et al. 2006; Waters, et al. 2003). This association between attentional bias and treatment outcome suggests that normalizing attentional bias related brain activation following administration of a dopamine antagonist may eventually contribute to the development of new therapies. However, some other findings in the study described in chapter 8, as well as findings described in chapter 6, suggest that the association between dopamine and controlling substance-related behavioral may be rather complex. Both in the ATBLC task and in the Go/NoGo task described in chapter 6, haloperidol was found to reduce performance accuracy and brain activation associated with inhibitory control and overall cognitive effort (i.e., line counting across neutral and smoking picture conditions in the ABLCT). These findings suggest that dopamine antagonists, besides normalizing brain activation associated with attentional bias, may also reduce general cognitive functioning which may constitute an unfavorable effect. This may be one of the causes why dopamine antagonists do not seem to be successful in treatment of cocaine dependence (Amato, et al. 2007). The current results of normalization of brain activation associated with attentional bias should therefore rather be interpreted as a proof of principle for the role of dopamine in attentional bias instead of a direct clinical relevant finding.

Several other findings in chapter 7 and 8 deserve more discussion. First, both studies using the ABLCT did not show group differences in brain regions involved in emotion processing or stimulus driven attention such as the orbitofrontal cortex (OFC), ventral striatum and amygdala. Activation in these brain regions was expected since environmental drug cues tend to capture the attention of drug users, due to the established salience of these cues (Robinson, et al. 2008). The absence of activation in these regions in smokers is probably due to our fast event-related paradigm that was specifically designed to measure attentional bias and to keep other processes such as prolonged cue-exposure and emotional involvement to a minimum. The requirement to count lines as the main instruction for the participants may have caused a shift in brain activation to the cognitive control brain regions.

Second, while both studies consistently found attentional bias related brain activation in smokers in the dACC, we could not consistently show that the activation in the dACC is still present when controlling for differences between smokers and non-smoking controls in familiarity and arousal evoked by the smoking cues. Also, the association between craving and attentional bias related brain activation in the insula and the putamen could not be replicated in the study described in chapter 8. This discrepancy between the two studies may

be due to order-effects, as participants performed the ABLCT twice in the study described in chapter 8 and participants received placebo either on the first or second scan session. Differences between the two studies in methodology to control for multiple comparisons may also contribute to discrepancies between the two studies.

Finally, we were not able to demonstrate group differences between smokers and non-smoking controls for accuracy rates and reaction times on the ABLCT in neither study employing this paradigm. In fact, behavioral findings suggest that both smokers and non-smoking controls have decreased accuracy rates in combination with faster reaction times for line counting in smoking-related pictures. The combination of reduced accuracy and faster reaction times for smoking-related pictures may indicate that ongoing behavior is interrupted due to an impulsive response style evoked by the smoking-related content of the pictures. This may probably happen in non-smoking controls for non-addiction reasons such as negative valence (Stippekohl, et al. 2010). Although the behavioral measures could not discriminate between smokers and non-smoking control, fMRI findings detected differences between smokers and non-smoking controls in both studies. Several explanations exist for this discrepancy. It may be that brain activation is a more direct or sensitive measure to detect group differences compared to reaction times and accuracy rates. Goldstein and Volkow (2011), for example, argued that neuroimaging measures are more sensitive in detecting group differences in conditioned responses to drug-related cues compared to subjective valence or arousal measures, or even autonomic reactions such as skin conductance responses. In addition, in a meta-analysis it was shown that the association between craving and brain activation measured with ERPs was stronger than the association between craving and behavioral measures such as reaction times (r = .37 and .15 respectively: Field, et al. 2009). The probably limited sensitivity of behavioral findings on the ABLCT may be due to the recent finding that the internal reliability of event-related behavioral measures in attentional bias paradigms is disappointing (Ataya, et al. 2012; Field, et al. 2012). However, the reliability of attentional bias related brain activation measured with neuroimaging techniques remains to be investigated.

Limitations of the described studies

In the current thesis, cross-sectional study designs we used to investigate neurocognitive functions in smokers. Although differences between smokers and non-smoking controls were found in neurocognitive functioning, no causal

inferences can be drawn from these studies. That is, based on the current thesis it is unknown whether differences in neurocognitive functioning between smokers and non-smoking controls predispose individuals to start smoking or whether these differences are a consequence of the effects of smoking on the brain. Two types of research should be performed in order to find out whether neurocognitive deficits in smokers, or in substance dependent individuals in general, are causes for or consequences of addictive behaviors. First, neurocognitive performance should be investigated in high-risk groups, such as children of substance dependent parents. Second, and most importantly, longitudinal population based neuroimaging studies should be performed to examine whether neurocognitive functioning could be used to differentiate individuals who will develop addiction later in life from those who will not. Currently, these kinds of studies are mainly lacking, with the exception of one large population study in adolescents in the domain of inhibitory control (N = 1896, Whelan, et al. 2012). Findings of this study suggest that hypoactivity associated with inhibitory control in the OFC may be a risk factor for the initiation of substance use, including smoking and alcohol use, whereas hyperactivity in right prefrontal cortex may result as a consequence of illicit substance use.

A second limitation of the studies in the current thesis is that they were all performed in young, healthy and highly educated smokers, thereby reducing the generalizability of results to the complete population of smokers. Differentiating types of smokers based on education levels, age, gender and smoking motives may be useful to see whether subgroups exist within the smoking population that show different neurocognitive profiles. Stress relief and perception of enjoyment of smoking have been reported as the most common motives for smoking (Fidler, et al. 2009). It is plausible that cognitive control and attentional bias differs between those who mainly smoke for stress relief and those who smoke for enjoyment of smoking. For example, a study in current and former opiate users showed an association between stress and attentional bias. Former opiate users, in contrast to current users, showed a bias away from substance-related stimuli after a stress induction and this correlated positively with their length of abstinence (Constantinou, et al. 2010). With regard to gender effects, it has recently been proposed that nicotine interacts with estrogen and the dopamine reward system (Van Voorhees, et al. 2012) suggesting that differences between female and male smokers may exist in terms of attentional bias or cognitive control. Larger participant numbers are needed to increase statistical power when one aims to investigate individual differences in neurocognitive functioning, especially when exploring multiple sources of variance in a single study.

Finally, although measuring brain activation in smokers using ERPs and fMRI provides valuable information regarding the functionality of the brain during cognitive performance, it does not provide a complete picture of brain functioning. Various other imaging techniques and methods to analyze imaging data could provide complementary insights in addictive behaviors. For example, recent structural magnetic resonance imaging and diffusion tensor imaging studies start to demonstrate that smokers could also be characterized by alterations in respectively gray and white matter integrity (Almeida, et al. 2008; Almeida, et al. 2011; Froeliger, et al. 2010; Zhang, et al. 2011a; Zhang, et al. 2011b). In addition, functional connectivity patterns in addicted individuals, both during task performance and during rest, could provide new insights regarding the cooperation of brain regions within in a neural network supporting neurocognitive functioning (Janes, et al. 2012; Yu, et al. 2011).

Treatment implications and future research suggestions

Contemporary effective treatments for smoking involve nicotine replacement therapy, pharmacotherapy, face-to-face counseling and internet guided interventions (Eisenberg, et al. 2008; Hays, et al. 2009; Shahab, et al. 2009). Nevertheless, relapse rates in smokers as well as in other addictions are still high so there is ample room for improvement. Several treatment targets for addiction can be suggested based on the findings described in the current thesis and merit further investigations. First, cognitive control capacities and underlying neural networks could be trained to increase cognitive control. A recent study indicates that explicit training of inhibition of drinking cues via pairing with NoGo trials results in a reduction in drinking behavior in social drinking (Houben, et al. 2011). It is still an unanswered question whether training of inhibitory control can also impact substance use in clinical populations. Another more implicit possibility to increase inhibitory control could be the direct training of brain regions such as the ACC, IFG and DLPFC via neurofeedback techniques (deCharms 2008). Previous research has shown that participants can regulate their ACC activation by providing them with real-time feedback on ACC activation (deCharms, et al. 2005). Another potential treatment method for addiction with the brain as a direct target is transcranial magnetic stimulation (TMS, Barr, et al. 2008; Feil, et al. 2010b). Repetitive stimulation of the DLPFC in depressive individuals reduced Hamilton Depression Rating Scale scores (Wassermann, et al. 2012). It would be interesting to see whether repetitive TMS can also be effective in addictive individuals by improving cognitive control via TMS stimulation of the prefrontal cortex. The dACC may be a good target region for both neurofeedback techniques and transcranial magnetic stimulation as

dysfunctions in this region are among the most consistent findings in this thesis and in the addiction literature in general (for reviews see Goldstein, et al. 2011; Kuhn, et al. 2011).

As shown in this thesis, investigations into the role of neurotransmitters such as dopamine in inhibitory control could provide valuable insights concerning the biochemistry underlying deficits in inhibitory control. Besides dopamine, other neurotransmitters such as norepinephrine and acetylcholine could be related to cognitive control (Nieuwenhuis, et al. 2011; Sarter, et al. 2009). Currently, it is investigated whether the use of cognitive enhancer medication such as modafinil may enhance cognitive control via its effects on both norepinephrine and dopamine (Brady, et al. 2011). For example, it has been shown that modafinil in methamphetamine dependent individuals was able to improve task performance on a Go/NoGo task (Dean, et al. 2011).

Individual differences in cognitive control capacities can also be used in clinical practice to guide and personalize treatment plans. It has been shown for example that deficits in cognitive control are associated with reduced capacities to recognize problems with substance abuse and lower motivation to enter treatment (Severtson, et al. 2010). Furthermore, an increasing number of studies indicated that substance dependent individuals with reduced cognitive control tend to drop out in treatment programs more often (Ersche, et al. 2007). A study by Berkman et al. (2011) showed that individual differences in activation in the inhibitory control network are linked to the ability to inhibit craving in daily life in order to prevent smoking. This study is a good illustration on how neuroimaging research could develop to become more clinically relevant. A related line of future research is the prediction of relapse based on neuroimaging data. Most studies in the domain of cognitive control are cross-sectional and cannot link brain activation with the ability of substance dependent individuals to remain abstinent. Studies investigating the link between relapse and brain activation associated with cognitive control are crucial to understand how deficits in cognitive control contribute to the maintenance of addiction.

Studies in the domain of attentional bias already showed that behavioral measures of attentional bias could be predictive for relapse rates and treatment outcome in addicted individuals including smokers (Carpenter, et al. 2006; Cox, et al. 2002; Marissen, et al. 2006; Waters, et al. 2003; Waters, et al. 2012). It should be noted, however, that the association between attentional bias and successful treatment was not found in smokers in a study by Spiegelhalder and colleagues (2011). In order to become a valuable treatment marker, a causal

relationship between attentional bias and addictive behaviors should be demonstrated in experimental studies. A few studies in alcohol dependent individuals and smokers have tried to manipulate attentional bias by means of an attentional bias modification (ABM) training (Attwood, et al. 2008; Fadardi, et al. 2009; Field, et al. 2009; McHugh, et al. 2010b; Schoenmakers, et al. 2007; Schoenmakers, et al. 2010). Some of these studies showed that attentional bias can be either increased or decreased using a single ABM training (Attwood, et al. 2008; Fadardi, et al. 2009; Field, et al. 2009; Schoenmakers, et al. 2007). Unfortunately, the effect of a single training on attentional bias was not associated with addictive behaviors or treatment success in most of these studies (Attwood, et al. 2008; Field, et al. 2009; Schoenmakers, et al. 2007). Several methodological issues in this research domain are worth discussing as they may clarify the current difficulties to improve treatment outcome using ABM training. First, the optimal dose and generalizability of ABM training may be a crucial aspect of training success. In alcohol dependent individuals, it has been shown that a single ABM training does not influence drinking behaviors (Schoenmakers, et al. 2007), while a training consisting of five ABM sessions did improve treatment success (Schoenmakers, et al. 2010). This study (Schoenmakers, et al. 2010) further showed that after completion of the five sessions of ABM training, attentional bias was also reduced for a new set of alcohol-related stimuli. This generalizability could not be demonstrated in studies using a single session training (Field, et al. 2009; McHugh, et al. 2010b; Schoenmakers, et al. 2007) and may be a requisite for the link between ABM training and a reduction in addictive behaviors. For future studies it would be interesting to investigate whether brain activation related to attentional bias could be a valuable additional marker for relapse rates in addicted individuals.

Another more explicit way to reduce attentional processing of substance-related cues is the use of cognitive reappraisal techniques. The idea of reappraisal techniques is that they can be applied by substance dependent individuals as a strategy to reduce cue-exposure effects such as enhanced attentional processing and craving. Examples of reappraisal strategies are to think about long-term consequences associated with smoking, to view the cue from an uninvolved perspective or to distract yourself by focusing on visual aspects of the scene. Brain activation measures could be particularly useful to investigate the effectiveness of reappraisal techniques as they provide objective indices of cue-reactivity that are less likely to be influenced by subjective expectations and social desirability. Recently, in a study employing event-related potentials as indices for attentional processing of smoking-related cues, it was shown that different reappraisal strategies were successful to reduce processing

of smoking-related cues in smokers to the level of neutral cues (Littel, et al. 2011). Furthermore, Kober et al. (2010) showed that regulation of craving by reappraisal techniques associated with increased activation in cognitive control regions, such as the DLPFC and dorsomedial cortices, is supported by decreased activation in regions previously shown to be associated with craving, such as the ventral striatum and the amygdala. It remains to be investigated whether substance dependent individuals are able to implement cognitive reappraisal strategies in their daily lives and if so, whether this is associated with reduced relapse rates.

Main conclusions

Several conclusions can be formulated based on the studies described in this thesis. First, it can be concluded that smokers are characterized by a dysfunction in substantial parts of the neural circuits underlying cognitive control. More specifically it seems that: 1) dysfunctions in neural circuits associated with cognitive control in smokers partly overlap with patients dependent on illicit substances of abuse as well as with individuals characterized by excessive addiction-like behaviors; 2) smokers are characterized by reduced processing of errors in ongoing behavior; 3) inhibitory control is decreased in smokers both under neutral and smoking cue-exposure conditions; 4) or smokers need more neural effort to reach similar performance levels as non-smoking controls, both when they inhibit immediate rewarding and neutral stimuli and 5) reduced dopamine levels may contribute to problems associated with inhibitory control. With regard to attentional bias, the studies described in this thesis showed that: 1) smokers have increased activation during performance of an attentional bias task in brain regions involved in salience detection and top down attentional control suggesting that these regions have to compensate to continue ongoing behavior when smokers are exposed to smoking-related cues; 2) increased brain activation in smokers on the attentional bias task paradigm can be normalized by administration of a dopamine antagonist.

Overall, the findings of the current thesis provide neurocognitive insights that increase the understanding of the continuation of smoking despite knowledge of long-term negative consequences.

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Nederlandse Samenvatting

Achtergrond

Zevenentwintig procent van de huidige Nederlandse bevolking rookt. Van degenen die ooit gerookt hebben ontwikkelt 32% binnen tien jaar een verslaving. Dit percentage voor nicotine is hoger dan voor andere verslavende middelen (bijvoorbeeld 23 procent voor heroïne: Anthony, et al. 1994). Deze cijfers laten zien dat roken zeer verslavend is. Van alle rokers heeft 80% de intentie in de toekomst te stoppen. Echter, het overgrote deel van de rokers heeft hier grote moeite mee. Dit blijkt uit onderzoek dat aantoont dat 80-95% van de stoppogingen na een jaar mislukt is (International Tobacco Control Policy Evaluation Project 2011). Nicotine afhankelijkheid is momenteel opgenomen in het Diagnostisch en Statistisch Handboek (DSM-IV-TR) als officiële stoornis in middelengebruik. Voorbeelden van diagnostische criteria zijn (a) tolerantie; het steeds meer moeten roken voor hetzelfde subjectieve effect, (b) ontwenningsverschijnselen wanneer men niet kan roken; (c) meer roken dan men van plan is en (d) blijven roken ondanks de kennis van de negatieve lange termijn gevolgen zoals de serieuze gezondheidsrisico's die gepaard gaan met roken (Schmitz, et al. 2003). De hierboven omschreven kenmerken tonen aan dat roken een serieus en chronisch probleem is dat in een groot deel van de samenleving voorkomt.

In de afgelopen decennia heeft dierexperimenteel en humaan onderzoek geleid tot neurobiologische modellen die verslaving verklaren als het gevolg van een verstoorde balans in de hersenen (Everitt, et al. 2005; Field, et al. 2008; Franken 2003; Goldstein, et al. 2011; Volkow, et al. 2004; Wiers, et al. 2007). Aan de ene kant lijkt het systeem in de hersenen dat controle uitoefent over ons gedrag minder goed te werken bij middelen afhankelijke patiënten, terwijl aan de andere kant het systeem dat waarde en motivatie toekent aan prikkels uit de omgeving overactief is voor prikkels die gekoppeld zijn aan de verslaving (ook wel verslavings-gerelateerde cues genoemd).

Het hierboven genoemde controlesysteem is voornamelijk gelokaliseerd in het voorste deel van onze hersenen, ook wel de prefrontale cortex genoemd (Chambers, et al. 2009; Garavan, et al. 2006; Simmonds, et al. 2008). Als men wil stoppen met middelengebruik of roken is een goed functionerend controlesysteem van cruciaal belang. Het is hiervoor belangrijk dat het verslavingsgedrag onderdrukt kan worden en dat eventuele misstappen goed verwerkt worden om fouten in de toekomst te kunnen voorkomen. Het onderdrukken van ons gedrag wordt ook wel impulscontrole genoemd en wordt gedefinieerd als de mogelijkheid automatisch, onveilig of ongepast gedrag te

onderdrukken (Chambers, et al. 2007). Het evalueren van onze alledaagse fouten wordt ook wel foutverwerking genoemd dat meer specifiek de continue evaluatie en verwerking van ons gedrag weerspiegelt met als doel toekomstig gedrag optimaal uit te kunnen voeren (Overbeek, et al. 2005; Ridderinkhof, et al. 2004a). Deze functies worden beide aangestuurd door het controlesysteem in onze hersenen (Ridderinkhof, et al. 2004a).

Tegenover het verminderde controlesysteem staat het overactieve motivationele systeem, dat ook wel het mesocorticolimbisch systeem genoemd wordt. Een van de processen die voortkomt uit het overactieve motivationele systeem is aandachtsbias. Aandachtsbias is de automatische neiging van middelenafhankelijke patiënten en rokers om de aandacht te richten op alles wat met de verslaving te maken heeft (Field, et al. 2008; Franken 2003). Een voorbeeld hiervan is een roker die in zijn ooghoeken ziet dat er een pakje sigaretten op tafel ligt. De betreffende roker zal dit pakje sigaretten snel opmerken (de initiële aandacht wordt automatisch getrokken) en de aandacht van de roker zal langer blijven hangen op het pakje sigaretten (dit wordt ook wel volgehouden aandacht genoemd). De verhoogde initiële en volgehouden aandacht voor verschillende aan roken gerelateerde cues zorgt ervoor dat de roker minder aandacht heeft voor datgene waar hij /zij oorspronkelijk mee bezig was. Ook krijgt de roker door de verhoogde aandacht voor roken-gerelateerde cues gevoelens van craving, ofwel een sterke drang om te gaan roken (Field, et al. 2009). Neurobiologische modellen suggereren dat aandachtsbias ontstaat door herhaalde koppeling van middelen-gerelateerde cues en het vuren van dopamine na het gebruik van het verslavende middel (Robinson, et al. 1993). Dopamine is een neurotransmitter die onder andere de communicatie tussen de neuronen verzorgt in het motivationele systeem. Het wordt verondersteld dat leereffecten optreden na veelvuldige koppeling van de middelen-gerelateerde cues en het middelengebruik. Een gevolg hiervan is dat op den duur het dopamine systeem al gaat vuren bij het zien van de middelen-gerelateerde cues nog voordat het middel tot zich genomen wordt. De middelen-gerelateerde cues krijgen hierdoor een hoge motivationele waarde (ook wel salience genoemd) en zullen daardoor de aandacht trekken en vasthouden (Franken 2003). Het overactieve motivationele systeem met betrekking tot middelen-gerelateerde cues in combinatie met een verminderd functionerend controlesysteem zou kunnen verklaren waarom verslaving gekenmerkt wordt door het onvermogen het middelengebruik te beheersen.

Doel en relevantie van het proefschrift

Het belangrijkste doel van dit proefschrift was meer inzicht te krijgen in de neurocognitieve processen, zoals impulscontrole, foutverwerking en aandachtsbias, die ten grondslag liggen de verslaving van rokers. Aan het begin van dit promotieproject (februari 2008) was nog weinig bekend over het functioneren van het controlesysteem in de hersenen van rokers. Het was dan ook onduidelijk of rokers, net als middelenafhankelijke patiënten voor illegale drugs en alcohol, gekenmerkt worden door een verminderd functionerend controlesysteem in de hersenen. Daarom is in dit proefschrift met behulp van neuroimaging technieken onderzocht of rokers inderdaad gekenmerkt worden door verminderde impulscontrole en foutwerking als gevolg van eventuele afwijkingen in het onderliggende controlesysteem in de hersenen.

Het onderzoeken van de neurobiologische achtergrond van aandachtsbias bij rokers was het tweede belangrijke doel van dit proefschrift. Dit omdat de huidige neurobiologische modellen met betrekking tot aandachtsbias voornamelijk gebaseerd zijn op dierexperimenteel onderzoek en omdat deze modellen niet uitvoerig getoetst zijn met behulp van humaan neuroimaging onderzoek. Bij het onderzoeken van de neurobiologische achtergrond van aandachtsbias bij rokers hebben we met name bekeken welke hersengebieden hierbij betrokken zijn. Ook is de rol van dopamine in hersenactiviteit gerelateerd aan aandachtsbias nader onderzocht.

Meer inzicht in de neurocognitieve achtergrond van de verslaving van rokers kan belangrijke informatie opleveren waardoor een beter begrip ontstaat van het verslavingsgedrag. Uiteindelijk kunnen deze neurocognitieve inzichten bijdragen aan de ontwikkeling van nieuwe interventies zodat stoppogingen in de toekomst beter ondersteund kunnen worden. Hieronder volgt een beschrijving van de gebruikte neuroimaging technieken in dit proefschrift en een samenvatting van de opzet en resultaten van de uitgevoerde studies. Deze samenvatting wordt afgesloten met suggesties voor toekomstig onderzoek en de belangrijkste conclusies die voortkomen uit dit proefschrift.

Neuroimaging technieken

Om de neurale achtergrond van de verschillende cognitieve processen van rokers te kunnen onderzoeken zijn neuroimaging technieken nodig die de hersenactiviteit registreren. Deze neuroimaging technieken worden gebruikt in combinatie met cognitieve taken. De cognitieve taken worden aangeboden via een computer en brengen hersenactiviteit teweeg gerelateerd aan de cognitieve

processen die men wil onderzoeken (zoals impulscontrole, foutverwerking of aandachtsbias). In het huidige proefschrift hebben we gebruik gemaakt van twee verschillende neuroimaging technieken. Voor de studies omschreven in hoofdstuk 3 en hoofdstuk 4 hebben we gebruikt gemaakt van event-related potentials (ERPs; ofwel gebeurtenis gerelateerde golven) die gemeten kunnen worden door middel van elektro-encefalografie (EEG). ERPs representeren activiteit in de hersenen die met grote temporele precisie te relateren zijn aan een specifieke gebeurtenis tijdens de cognitieve taak (Fabiani, et al. 2000). Voor foutverwerking zijn bijvoorbeeld twee ERPs aan te wijzen in het EEG die de hersenactiviteit reflecteren na het maken van een fout (Overbeek, et al. 2005). De error-related negativity (ERN; ofwel fout gerelateerde negativiteit) is de eerste golf die optreed in de hersenactiviteit na het maken van een fout (gemiddeld na 50-100 ms) en staat voor de snelle detectie van de gemaakte fout. De error-positiviteit (Pe) volgt na de ERN en staat voor een meer diepere, bewustere verwerking van de fout (Overbeek, et al. 2005). Op deze manier zijn aan iedere cognitieve functie een aantal ERPs verbonden. Het voordeel van ERPs is dat ze veel informatie verschaffen over de timing van de cognitieve functies in de hersenen. Helaas is het met ERPs lastiger de anatomische locatie van de activiteit vast te stellen.

Functionele magnetic resonance imaging (fMRI) is de andere neuroimaging techniek die toegepast is voor de studies omschreven in de hoofdstukken 5,6,7 en 8 in dit proefschrift. fMRI is in staat de anatomische locatie van hersenactiviteit activiteit vast te stellen met een hoge spatiale resolutie. Het signaal gemeten met fMRI is een indirecte maar betrouwbare schatting van de neuronale activiteit in een bepaald gebied (Logothetis, et al. 2001) en komt tot stand op basis van verschillen in de zuurstof via bloedtoevoer in een actief gebied ten opzichte van datzelfde gebied in rust. De verhouding tussen zuurstofarm en zuurstofrijk bloed gemeten met fMRI wordt ook wel de Blood Oxygenation Level-Dependent (BOLD) response genoemd. Ook voor fMRI wordt gebruik gemaakt van cognitieve taken die de activiteit in de hersenen oproept gerelateerd aan het cognitieve proces dat men wilt meten. Daarnaast kan fMRI in combinatie met een farmacologische manipulatie toegepast worden, dit wordt dan ook wel farmacologische fMRI genoemd. Farmacologische fMRI wordt gebruikt om de rol van bepaalde neurotransmitters, zoals dopamine, te onderzoeken voor het cognitieve proces van interesse en de daaraan gerelateerde hersenactiviteit. In farmacologische fMRI studies wordt veelal een medicijn toegediend dat de niveaus van een bepaalde neurotransmitter in de hersenen beïnvloedt. De hersenactiviteit na inname van dit middel wordt dan vergeleken met de hersenactiviteit na inname van een neppil (ofwel placebo)

zodat de rol van de neurotransmitter in de hersenactiviteit duidelijk wordt. In de studies omschreven in hoofdstuk 6 en hoofdstuk 8 hebben we farmacologische fMRI toegepast om de rol van dopamine in impulscontrole en aandachtsbias te onderzoeken.

De hierboven beschreven kenmerken van ERPs en fMRI maken deze technieken zeer geschikt voor het onderzoeken van neurocognitieve functies van rokers. Door onderzoeksresultaten van zowel ERP als fMRI studies te evalueren kan aanvullende informatie verkregen worden met betrekking tot de timing en de anatomische locatie van de neurocognitieve aspecten van verslaving bij rokers.

Samenvatting onderzoeksbevindingen

In **hoofdstuk 2** worden impulscontrole en foutverwerking in meer detail besproken. Zowel de ERPs die verbonden zijn aan deze processen als de neuro-anatomische basis van impulscontrole en foutverwerking wordt uiteengezet. Ook worden de cognitieve paradigma's die gebruikt worden om impulscontrole en error-processing te meten besproken. Het hoofddoel van hoofdstuk 2 is een overzicht te geven van de gepubliceerde ERP en fMRI studies op het gebied van impulscontrole en foutverwerking in de verschillende groepen van middelenafhankelijke patiënten en rokers. Op deze manier kunnen consistente bevindingen tussen de verschillende studies opgespoord worden en kan er een beter beeld gecreëerd worden van de afwijkende neurocognitieve processen in de hersenen die ten grondslag liggen aan de verminderde controle over het verslavingsgedrag. Op deze manier kan er ook onderzocht worden of er verschillen zijn tussen de verschillende groepen middelenafhankelijke patiënten met betrekking tot mogelijke afwijkingen in de hersenen. Daarnaast zijn in hoofdstuk 2 ook studies besproken die uitgevoerd zijn in de zogenoemde 'gedragsverslavingen' zoals gokken en excessief internetgebruik. Het doel hiervan is te onderzoeken of mogelijke neurale afwijkingen met betrekking tot impulscontrole en foutverwerking in deze excessieve gedragingen overeenkomen met die van middelenafhankelijkheid. Hierdoor kan een bijdrage geleverd worden aan de discussie of deze excessieve gedragingen op dezelfde manier gediagnostiseerd en behandeld zouden kunnen worden als die van

middelenafhankelijkheid. De studies die besproken zijn in hoofdstuk 2 werden geselecteerd op basis van zoektermen in Pubmed en Embase. De bevindingen in hoofdstuk 2 komen overeen met de huidige verslavingsmodellen en ondersteunen het idee dat verslaving gekenmerkt wordt door afwijkingen in het neurale systeem dat ten grondslag ligt aan impulscontrole en foutverwerking. Met betrekking tot de ERPs waren de meest consistente bevindingen verlaagde N2 en ERN amplituden in middelenafhankelijke patiënten en rokers. Omdat zowel de N2 als de ERN golven zijn die vroeg in het cognitieve proces optreden suggereren deze bevindingen dat de neurale processen die ten grondslag liggen aan impulscontrole en foutverwerking al in een vroeg, mogelijk onbewust, stadium afwijkend zijn. Wat betreft de neuro-anatomische achtergrond van verminderde cognitieve controle was de meest voorkomende bevinding verlaagde activiteit in de anterieure cingulate cortex (ACC), inferieure frontale gyrus (IFG) en de dorsolaterale prefrontale cortex (DLPFC). Ondanks de gevonden overeenkomsten tussen de beschreven studies waren er ook grote verschillen tussen de studies. Sommige studies lieten afwijkingen zien in het controlesysteem terwijl de middelenafhankelijke patiënten of rokers even goed als gezonde controles presteerden op het cognitieve paradigma dat gebruikt werd om impulscontrole of foutverwerking te meten. Dit maakt de interpretatie van verschillen in hersenactiviteit tussen middelenafhankelijke patiënten of rokers en gezonde controle deelnemers lastig. Een van de verklaringen voor de verschillen in bevindingen tussen de studies is de grote variatie in methodologie tussen de studies. Daarom is het voor toekomstig onderzoek aan te raden dat er meer overeenstemming wordt bereikt met betrekking tot het gebruik van de cognitieve taken. De resultaten beschreven in hoofdstuk 2 toonden ook verschillen aan tussen de verschillende groepen middelenafhankelijke patiënten. Zo werden alcoholisten bijvoorbeeld gekenmerkt door verhoogde foutverwerking in plaats van de verlaagde foutverwerking die bij rokers en andere groepen middelenafhankelijke patiënten te zien was. Tenslotte werd in hoofdstuk 2 ook voorzichtig bewijs gevonden voor het idee dat ook gokkers en excessieve internetgebruikers gekenmerkt worden door afwijkingen in het neurale systeem dat ten grondslag ligt aan cognitieve controle. Dit is een eerste voorzichtige aanwijzing dat de mechanismen achter dit excessieve niet-middelen gebonden gedrag overeenkomsten vertoond met middelenafhankelijkheid.

Foutverwerking bij rokers

Foutverwerking is een cruciaal onderdeel om ons gedrag op de lange termijn te kunnen sturen en controleren (Ridderinkhof, et al. 2004a). In de studie beschreven in **hoofdstuk 3** hebben we onderzocht of rokers gekenmerkt worden door een

verminderde verwerking van fouten in de hersenen. Om dit te kunnen onderzoeken hebben zowel rokers als niet-rokers een Eriksen-Flanker taak (Eriksen, et al. 1974) uitgevoerd terwijl ERPs gerelateerd aan foutverwerking gemeten werden. De Eriksen-Flanker taak is speciaal ontwikkeld om deelnemers fouten te laten maken zodat onderzocht kan worden hoe deze fouten verwerkt worden in de hersenen. Om het extra uitdagend te maken voor rokers bevatte de gebruikte Eriksen-Flanker taak ook foto's met roken-gerelateerde cues. De verwachting was dat rokers hun fouten minder goed zouden verwerken tijdens de blootstelling aan de roken-gerelateerde cues omdat deze cues ook hersencapaciteit in beslag nemen. De bevindingen beschreven in hoofdstuk 3 laten zien dat rokers inderdaad gekenmerkt worden door verminderde foutverwerking ten opzichte van niet-rokers. De resultaten laten zien dat rokers hun gedrag minder goed aanpassen na het maken van een fout (niet-rokers werden langzamer na het maken van een fout, terwijl rokers op hetzelfde tempo doorgingen). Beide ERPs die gelinkt zijn aan foutverwerking (de ERN en Pe) waren verlaagd in rokers. Dit geeft aan dat de hersenen van rokers de fout zowel minder goed detecteren en de fout vervolgens minder diep verwerken. Op basis van deze resultaten kan men concluderen dat rokers gekenmerkt worden door een verminderde verwerking van fouten in de hersenen tijdens blootstelling aan roken-gerelateerde cues.

Impulscontrole in rokers

In **hoofdstuk 4** wordt een studie beschreven waarin de impulscontrole van rokers is onderzocht door middel van ERPs. Het doel van deze studie was tweeledig. In de eerste plaats werd onderzocht of er inderdaad sprake is van verminderde impulscontrole bij rokers en daarbij behorende mogelijke neurale afwijkingen. In de tweede plaats werd onderzocht of mogelijke problemen met impulscontrole in rokers sterker aanwezig zijn wanneer rokers blootgesteld worden aan roken-gerelateerde cues met een hoge motivationele waarde. Om dit te onderzoeken werd een Go/NoGo taak gebruikt. Tijdens het uitvoeren van een Go/NoGo taak moeten deelnemers plotseling en infrequent het gedrag onderdrukken. Om de onderzoeksvraag te beantwoorden werd zowel de accuratesse van rokers en niet-rokers vergeleken tijdens het uitvoeren van de Go/NoGo taak, als de ERPs die geassocieerd zijn aan impulscontrole (N2 en P3 golven). De resultaten beschreven in hoofdstuk 4 laten zien dat rokers, in vergelijking met niet-rokers, minder goed waren in impulscontrole. Dit wil zeggen dat rokers tijdens het uitvoeren van de Go/NoGo taak vaker niet in staat waren hun gedrag te onderdrukken. Deze verminderde prestatie ging gepaard met verlaagde N2 golven. Deze verlaagde N2 golven tonen aan dat de hersenen van rokers al in een vroeg stadium afwijkingen laten zien waardoor problemen op kunnen treden met het

onderdrukken van gedrag. De beschreven resultaten in hoofdstuk 4 tonen aan dat de problemen met impulscontrole in rokers aanwezig zijn tijdens blootstelling aan roken-gerelateerde cues. Echter, omdat verminderde impulscontrole zowel aanwezig was tijdens neutrale condities als tijdens blootstelling aan roken-gerelateerd cues zijn de beschreven resultaten in overeenstemming met het idee dat rokers in het algemeen gekenmerkt worden door een verminderde impulscontrole en niet alleen wanneer er roken-gerelateerde cues in de omgeving aanwezig zijn.

Het doel van de studie beschreven in **hoofdstuk 5** was te onderzoeken of beloning en straf een rol spelen in de hersenactiviteit die gepaard gaat met impulscontrole in rokers. Verslavingsmodellen veronderstellen dat middelen-afhankelijke patiënten en rokers vooral problemen ervaren met het onderdrukken van stimuli die voorheen gepaard gingen met een beloning zoals een sigaret wanneer men wilt stoppen (Jentsch, et al. 1999; Volkow, et al. 2010). Ook zijn er voorzichtige aanwijzingen in de literatuur dat middelenafhankelijke patiënten en rokers minder gevoelig zijn voor het gebruik van straf om het gedrag te sturen (Vanderschuren, et al. 2004). Om de rol van beloning en straf in de hersenactiviteit gerelateerd aan impulscontrole te kunnen onderzoeken werd gebruik gemaakt van een cognitieve taak die gebaseerd is op de Go/NoGo taak. In deze taak werd gebruik gemaakt van verschillende typen beloning en straf voor het al dan niet succesvol onderdrukken van gedrag door middel van het winnen of verliezen van geld. Hersenactiviteit in deze studie werd gemeten door middel van fMRI. De resultaten van deze studie laten zien dat rokers meer hersenactiviteit nodig hebben in het controlesysteem om tot een gelijke prestatie te komen als niet-rokers. Meer specifiek lieten de resultaten zien dat rokers zowel tijdens het onderdrukken van stimuli, die een belonende waarde hebben, als tijdens het onderdrukken van neutrale stimuli, verhoogde activiteit hebben in de ACC, de insula, IFG en DLPFC. Deze resultaten tonen aan dat rokers meer moeite moeten doen om belonende stimuli te onderdrukken. Echter, net als in hoofdstuk 4, werd dit ook gevonden voor neutrale stimuli. Met betrekking tot gevoeligheid voor straf zijn er in deze studie voorzichtige aanwijzingen gevonden dat niet-rokers meer moeite doen hun gedrag te onderdrukken wanneer er mogelijk een straf volgt dan rokers. Dit blijkt onder andere uit verhoogde visuele verwerking bij niet-rokers van de stimuli die onderdrukt moeten worden wanneer er de mogelijkheid op straf was.

Over de farmacologische basis van impulscontrole is in de wetenschappelijke literatuur nog weinig bekend. Er zijn aanwijzingen dat de neurotransmitter dopamine een sturende rol heeft in het controlesysteem in de hersenen (Cools, et al. 2011). Meer informatie over de rol van dopamine in

impulscontrole kan belangrijke informatie opleveren voor stoornissen die gepaard gaan met afwijkingen in het dopaminerge systeem zoals verslaving (Volkow, et al. 2009). Het kan bijvoorbeeld aanknopingspunten opleveren over de manier waarop impulscontrole verbeterd zou kunnen worden met behulp van farmacologische behandeling. Daarom onderzochten we in de studie beschreven in **hoofdstuk 6** de rol van dopamine in de impulscontrole van rokers en niet-rokers. We hebben hiervoor gebruikt gemaakt van farmacologische fMRI. Alle deelnemers voerden twee keer de Go/NoGo taak uit terwijl de hersenactiviteit gemeten werd met fMRI. De ene keer kregen rokers en niet-rokers een eenmalige dosis-haloperidol die het dopamine niveau in de hersenen verlaagt. De andere keer kregen de deelnemers een placebo. De toediening van de medicatie werd gerandomiseerd en dubbel blind uitgevoerd. Dit betekent dat er geen systeem zat in de volgorde waarin de deelnemers haloperidol of placebo kregen en dat zowel de deelnemers als de onderzoekers niet wisten wanneer welk type medicatie toegediend werd. De resultaten van deze studie tonen aan dat dopamine inderdaad een belangrijke rol heeft in impulscontrole. Het verlagen van het dopamineniveau in de hersenen had tot gevolg dat zowel rokers als niet-rokers minder goed werden in het onderdrukken van gedrag. Dit ging gepaard met verminderde activiteit in het controlesysteem in de hersenen. Rokers waren minder goed dan niet-rokers in het onderdrukken van gedrag tijdens de eerste keer dat ze de Go/NoGo taak uitvoerden. In overeenkomst met verslavingsmodellen hadden rokers ook verminderde activiteit in het controlesysteem (ACC, linker IFG rechter middel frontale gyrus, MFG) na placebo. Nadat dopamine niveaus verlaagd werden door middel van haloperidol waren er geen verschillen meer in de hersenactiviteit tussen rokers en niet-rokers in sommige delen van het controlesysteem zoals de ACC, IFG en MFG. Dit kwam met name omdat haloperidol de activiteit in de niet-rokers verlaagde tot het niveau van de rokers. Het verschillende effect van haloperidol voor rokers en niet-rokers zou verklaard kunnen worden door verschillen in algemene dopamine niveaus tussen rokers en niet-rokers (Fehr, et al. 2008). Op basis van de resultaten beschreven in hoofdstuk 6 kunnen we concluderen dat dopamine inderdaad een belangrijke rol speelt in impulscontrole en het controlesysteem in de hersenen dat hieraan ten grondslag ligt. Deze bevindingen laten zien dat problemen met impulscontrole in verslaving mogelijk het gevolg zijn van verstoringen in het dopaminesysteem en bieden aanknopingspunten voor toekomstig onderzoek met als doel impulscontrole te verbeteren op basis van farmacologische behandelingen.

De neurobiologische achtergrond van aandachtsbias in rokers

In de studies beschreven in hoofdstuk 7 en 8 is de neurobiologische achtergrond van aandachtsbias in rokers onderzocht. In **hoofdstuk 7** beschrijven we een fMRI studie waarin bekeken werd welke hersengebieden betrokken zijn bij de aandachtsbias van rokers. We hebben hiervoor een cognitieve taak ontwikkeld (de aandachtsbias lijnen-tellen taak) waarbij deelnemers lijnen tellen die door roken-gerelateerde foto's en neutrale foto's heen stonden. Op deze manier waren we in staat de hersenactiviteit te bekijken die rokers extra nodig hebben voor het tellen van lijnen in roken-gerelateerde foto's ten opzichte van neutrale foto's en ten opzichte van niet-rokers. Deze extra hersenactiviteit reflecteert de automatische aandacht (de aandachtsbias) voor roken-gerelateerde cues omdat deze cues niet relevant zijn voor de opdracht die deelnemers uit moeten voeren, namelijk het tellen van lijnen. De resultaten van deze studie lieten zien dat hersenactiviteit geassocieerd aan aandachtsbias voortkomt uit activiteit in de ACC, de superieure pariëtale gyrus (SPG) en de superieure temporale gyrus (STG). De ACC en SPG zijn beide betrokken bij het sturen en controleren van de aandacht. Deze bevindingen suggereren dan ook dat rokers meer hersenactiviteit nodig hebben in gebieden die de aandacht sturen en controleren om een simpele taak zoals lijnen tellen uit te voeren wanneer roken-gerelateerde cues op de achtergrond aanwezig zijn. In de studie beschreven in **hoofdstuk 8** hebben we dezelfde cognitieve taak gebruikt om aandachtsbias gerelateerde hersenactiviteit te meten als in hoofdstuk 7. In deze studie onderzochten we de rol van dopamine in hersenactiviteit gerelateerd aan aandachtsbias. Dezelfde gerandomiseerde dubbel blinde methode werd gebruikt voor het toedienen van haloperidol en placebo zoals omschreven bij de samenvatting van hoofdstuk 6. De verwachting was dat lagere dopamine niveaus in rokers door toediening van haloperidol er voor zou zorgen dat de overmatige hersenactiviteit gerelateerd aan aandachtsbias in rokers genormaliseerd zou worden. De bevindingen waren in overeenstemming met de verwachtingen. We toonden opnieuw aan dat de ACC en de SPG betrokken zijn bij aandachtsbias in rokers na placebo. In deze studie vonden we daarnaast dat ook de DLPFC betrokken is bij aandachtsbias in rokers. De belangrijkste bevinding van deze studie was dat de overmatige activiteit van rokers in de ACC en de DLPFC verminderde tot hetzelfde niveau als in niet-rokers na inname van haloperidol. Deze resultaten bevestigen hiermee het idee dat aandachtsbias gerelateerde hersenactiviteit afhankelijk is van dopamine niveaus en geeft nieuwe aanknopingspunten voor toekomstig onderzoek met als doel de aandachtsbias te verminderen.

Beperkingen van de besproken studies

Bij het interpreteren van de resultaten van de hierboven genoemde studies is het belangrijk een aantal beperkingen van de studies aan te geven. Op de eerste plaats zijn de studies cross-sectioneel van aard. Dit betekent dat rokers op één specifiek moment in de tijd vergeleken zijn met niet-rokers en dat deelnemers niet voor langere tijd gevolgd en getest werden op meerdere momenten. Vanwege dit cross-sectionele karakter van het onderzoek kunnen we geen uitspraken doen met betrekking tot oorzaak en gevolg. We kunnen hierdoor niet concluderen dat verminderde impulscontrole het gevolg is van de effecten van nicotine in de hersenen of dat de verminderde impulscontrole de oorzaak is voor het ontstaan van verslaving in rokers. Grootschalig onderzoek waarin deelnemers op meerdere momenten getest worden over een langere tijdsperiode is noodzakelijk om uitspraken te kunnen doen over oorzaak en gevolg.

Een tweede beperking van het huidige onderzoek is dat de meeste rokers in de uitgevoerde studies jong, gezond en veelal hoogopgeleid zijn. Dit vermindert de toepasbaarheid van de resultaten voor alle rokers in de algemene bevolking. Ook hebben we niet gekeken naar individuele verschillen tussen rokers. Het kan zijn dat verschillen in leeftijd, geslacht, opleidingsniveau of motieven om te roken kunnen leiden tot verschillen in onderliggende neurocognitieve functies (Constantinou, et al. 2010; Van Voorhees, et al. 2012).

Ondanks dat ERP en fMRI studies belangrijke informatie opleveren met betrekking tot de neurocognitieve processen betrokken bij verslaving in rokers geven zij geen compleet beeld van het functioneren van de hersenen. Er zijn verschillende andere neuroimaging technieken beschikbaar die aanvullende informatie op kunnen leveren. Zo kan diffusie tensor imaging en structurele MRI meer inzicht geven in mogelijke structurele afwijkingen in de hersenen van middelenafhankelijke patiënten en rokers (Almeida, et al. 2008; Almeida, et al. 2011; Froeliger, et al. 2010; Zhang, et al. 2011a; Zhang, et al. 2011b). Analyses gericht op de samenwerking tussen de verschillende gebieden tijdens een cognitieve taak of tijdens rust kunnen ook aanvullende waardevolle inzichten opleveren (Janes, et al. 2012; Yu, et al. 2011).

Klinische toepassing en suggesties voor vervolgonderzoek

Gebaseerd op bevindingen in dit proefschrift kunnen een aantal aanbevelingen gedaan worden voor toekomstig onderzoek. Gezien behandelingen voor middelenafhankelijkheid en roken nog steeds beperkt succesvol zijn zal toekomstig onderzoek zich met name moeten richten op de klinische toepassing van de opgedane neurocognitieve inzichten. Zo zou het bijvoorbeeld interessant zijn te onderzoeken of de verschillende neurocognitieve processen zoals impulscontrole, foutverwerking en aandachtsbias verbeterd kunnen worden bij rokers. Door het verbeteren van deze functies is het mogelijk dat ook de kans op een succesvolle stoppoging toeneemt. Trainen van neurocognitieve functies kan op verschillende manieren bereikt worden. Men kan bijvoorbeeld gebruik maken van cognitieve taken die frequent uitgevoerd moeten worden zodat men de impulscontrole, foutverwerking of aandachtsbias traint. Het verminderen van aandachtsbias door middel van training met behulp van cognitieve taken is in eerdere studies gedaan, echter met wisselende resultaten (Attwood, et al. 2008; Field, et al. 2009; McHugh, et al. 2010b; Schoenmakers, et al. 2010). Meer onderzoek zal nodig zijn om de juiste training te ontwikkelen zodat aandachtsbias kan verminderen. Neurocognitieve functies kunnen ook getraind worden door middel van directe verandering van de activiteit in de onderliggende systemen in de hersenen. Neurofeedback is een methode waarbij de deelnemer directe feedback krijgt over de activiteit in een bepaald hersengebied (deCharms 2008). Op basis van deze directe feedback kan men de eigen hersenactiviteit beïnvloeden. Eerder onderzoek heeft bijvoorbeeld aangetoond dat men de activiteit in de ACC kan aanpassen op basis van onmiddellijke feedback over de activiteit in dat gebied (deCharms, et al. 2005). Een andere manier om hersenactiviteit te kunnen beïnvloeden is door gebruik te maken van Transcraniële Magnetische Stimulatie (TMS: Feil, et al. 2010b). TMS is een techniek waarbij van buitenaf de hersenactiviteit in een bepaald gebied gestimuleerd of onderdrukt kan worden. Toekomstige studies zullen uit moeten wijzen of het manipuleren van hersenactiviteit door middel van neurofeedback of TMS bij kan dragen aan betere behandelingen voor verslaving.

Een andere klinische toepassing is het afstemmen van behandelstrategieën op basis van de individuele verschillen in middelenafhankelijke patiënten met betrekking tot de verschillende neurocognitieve functies. Het is bijvoorbeeld bekend uit eerder onderzoek dat middelenafhankelijke patiënten met verminderde cognitieve controle gekenmerkt worden door verminderde herkenning van problemen gerelateerd aan het middelengebruik, een lagere motivatie om een behandeling te starten en een grote kans de behandeling niet af te maken (Ersche, et al. 2007; Severtson, et al. 2010). Een hieraan gerelateerde onderzoekslijn heeft betrekking op de vraag of neurocognitieve functies gebruikt kunnen worden voor het voorspellen van behandelsucces of stopsucces bij rokers. Onderzoek op het gebied van aandachtsbias heeft al aangetoond dat

aandachtsbias gemeten met gedragsexperimentele taken van voorspellende waarde kan zijn voor terugval (e.g., Waters, et al. 2012). Toekomstig onderzoek zal uit moeten wijzen of de hersenactiviteit geassocieerd aan de verschillende neurocognitieve processen een betrouwbare voorspelling op kan leveren voor terugval in middelengebruik of roken.

Met betrekking tot farmacologisch onderzoek zou het interessant zijn als toekomstige studies zich niet alleen richten op de rol van dopamine in verslaving, maar ook op de rol van andere neurotransmitters zoals noradrenaline en acetylcholine onderzoeken (Nieuwenhuis, et al. 2011; Sarter, et al. 2009). Recent onderzoek suggereert dat cognitieve controle mogelijkerwijs verbeterd kan worden door middel van psychoactieve medicatie (Brady, et al. 2011). Dit type medicatie wordt 'cognitieve versterker' genoemd en dankt het mogelijke positieve effect aan het stimuleren van het noradrenerge en dopaminerge systeem

Conclusies

Dit proefschrift leverde een aantal waardevolle conclusies op. Ten eerste kan geconcludeerd worden dat rokers gekenmerkt worden door een verminderd functioneren van een substantieel deel van het cognitieve controlesysteem in de hersenen. Meer specifiek lijkt het erop dat: 1) de afwijkingen in het controlesysteem in de hersenen van rokers deels overeenkomen met de gevonden afwijkingen in andere middelen gebonden verslavingen en excessief niet-middelen gebonden gedrag; 2) rokers worden gekenmerkt door een verminderde verwerking van fouten in het gedrag; 3) rokers gekenmerkt worden door een verminderde impulscontrole zowel tijdens blootstelling aan roken-gerelateerde als neutrale cues; 4) dat rokers meer neurale activiteit nodig hebben in het controlesysteem om tot hetzelfde niveau van impulscontrole te komen als niet-rokers tijdens het onderdrukken van belonende en neutrale stimuli en 5) verlaagde dopamineniveaus in de hersenen kunnen bijdragen aan een verlaagde impulscontrole.

De studies in dit proefschrift met betrekking tot aandachtsbias laten zien dat: 1) rokers meer activiteit nodig hebben tijdens het uitvoeren van een cognitieve taak die aandachtsbias meet in hersengebieden die de aandacht sturen en controleren. De verhoogde activiteit in deze gebieden suggereert dat

rokers meer moeite moeten doen om een simpele taak uit te voeren als roken-gerelateerde cues aanwezig zijn; 2) deze toegenomen activiteit van rokers genormaliseerd kan worden door toediening van een dopamine remmend middel.

Over het geheel genomen geven de bevindingen in dit proefschrift belangrijke neurocognitieve inzichten met betrekking tot verslaving bij rokers. Deze neurocognitieve inzichten dragen eraan bij dat we beter begrijpen waarom rokers doorgaan met roken ondanks de kennis over de negatieve lange termijn gevolgen.

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Curriculum Vitae

Maartje Luijten was born in Breda, The Netherlands, on June 21st, 1984. After completing secondary education (VWO) at 'Mencia de Mendoza Lyceum' in Breda, she started studying Psychology at Maastricht University. In 2005, she obtained her Bachelor's degree in Biological Psychology and in 2007 she received her Master's degree (cum laude) for completing the research master 'Cognitive Neuroscience, Neuropsychology and Psychopathology'. For her master thesis, she assisted in a study investigating brain functions in adolescent cannabis users at the University Medical Centre in Utrecht, where she also worked as a research-assistant after graduation. In February 2008, she started her PhD research at the Institute of Psychology, Erasmus University Rotterdam of which the results are described in this thesis. The studies in this PhD project focused on neurocognitive processes in smokers and were supervised by Prof. dr. I.H.A. Franken and Prof. dr. D.J. Veltman (Department of Psychiatry, VU University Medical Center). The fMRI studies described in this thesis were conducted in close collaboration with the Department of Radiology, Erasmus MC - University Medical Center Rotterdam. From 2009 onwards, she coordinated the fMRI research conducted at the Institute of Psychology. In 2011, she spent four months as a visiting academic at the Department of Psychological Sciences, University of Melbourne, Australia. As a PhD student she participated in the education program of the Dutch-Flemish post-graduate research school 'Experimental Psychopathology'. She was also engaged in teaching several (clinical) psychology bachelor and master courses, she supervised research projects of bachelor and master students and (guest) lectured on clinical subjects. In addition, she reviewed empirical articles for international journals. In August 2012, she started working as a PostDoc at the Department of Psychology, Erasmus University Rotterdam.

Publications

International peer-reviewed papers

Luijten M, Veltman DJ, Hester R, Smits M, Pepplinkhuizen L, Franken IHA (in press). Brain activation associated with attentional bias in smokers is modulated by a dopamine antagonist. *Neuropsychopharmacology*

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Invited presentations

Luijten M (2012). Brain activation associated with attentional bias in smokers is modulated by a dopamine antagonist, 25th meeting of the European college of Neuropsychopharmacology, Vienna, Austria

Luijten M (2012). Neurocognitive insights in addiction, *Thematic Meeting on Addiction*, Texel, The Netherlands

Luijten M (2012). The role of dopamine in reduced inhibitory control in substance dependence, *74th Annual Meeting – College on Problems of Drug Dependence*, Palm Springs, USA

Luijten M (2012). De relatie tussen verstoorde foutendetectie en verslaving, *SPON-Postdoctorale opleidingen*, Utrecht, The Netherlands

Luijten M (2012). The role of dopamine in attentional bias, *Battle of the Brains, Graduate School Experimental Psychopathology*, Utrecht, The Netherlands

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