Prefrontal dysfunction in drug addiction: Cause or consequence?

Master Thesis

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Abstract

With at least 15,3 million people suffering from illicit drug use disorders and many more alcohol and tobacco abusers, addiction is a worldwide problem that puts a great burden on society. Traditionally, research has focused on the reinforcing effects of drugs of abuse and the underlying neuronal mechanisms. The mesolimbic dopaminergic pathway is now generally accepted as the main target for drugs of abuse and their motivational value. Recently, however, the involvement of other brain areas in developing the addicted state has gained interest, especially the prefrontal cortex. This region is essential in inhibitory control processes which have been demonstrated to be dysfunctional in people suffering from addiction. The present report focuses on the dissimilarities between prefrontal cortex functioning of the addicted brain and healthy controls. Furthermore, this study discusses whether the abnormalities in prefrontal functioning exhibited by substance abusers are preexisting vulnerability traits which lead to addiction or, alternatively, are induced by repeated exposure to drugs of abuse. Accumulating evidence, particularly from animal studies, supports the latter hypothesis by demonstrating drug-induced structural alterations in the prefrontal cortex and drug-induced abnormal behavior associated with prefrontal regions. Nevertheless, some human studies have revealed individual differences which might predict the susceptibility for developing drug addiction. It is postulated that while underdeveloped prefrontal functioning may reflect a predisposition for drug taking and addiction, the drug-induced alterations are likely to facilitate the transitions from drug use to addiction.

Contents

Chapter 1

Introduction

Knowledge of the biological basis of addiction has a great importance for society, since it can lead to the improvement of treatments and development of preventive measures. Drug use is a worldwide problem with 185 million illicit drug users and at least 15.3 million people suffering from drug use disorders. These numbers increase dramatically when alcohol and tobacco use are included (estimate of 2 billion alcohol users and 1,3 billion smokers, World Health Organization (WHO)). Many health problems are related to excessive drug use, including cardiovascular diseases, cancer and HIV [1], and chronic drug use is associated with impaired cognitive functioning [2, 3, 4]. Drug addiction is defined by the WHO as: "a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state" [5]. Since just a small part of all drug users develop into drug addicts, it is important to distinguish between the use of drugs, the abuse of drugs (a pattern of substance use that is causing damage to physical or mental health [5]) and addiction (see table 1.1 for diagnostic guidelines). The question why some people develop an addiction and others do not is still not completely answered. Therefore, the transitions from use to abuse to addiction has been a major focus of recent research and it is now becoming clear that genetic and environmental factors combined with the long lasting changes in the brain after repeated drug exposure contribute to the vulnerability of developing the addicted state [1].

A key element in drug addiction is the concept of reinforcement. Reinforcers can be described as "stimuli that strengthen the association of acts to which they follow i.e. upon which they are contingent" ([7], p.18). Reinforcing effects of drugs of abuse are crucial in the development of addiction and can be divided into primary and secondary effects [8]. Primary reinforcing effects are the unconditioned, rewarding effects of drugs, whereas secondary reinforcers are stimuli that were initially motivationally neutral but became reinforcing through

Table 1.1: The diagnostic guidelines for addiction. A definite diagnosis of addiction is usually made only if three or more of the following guidelines are present. [6]

- a strong desire or sense of compulsion to take the substance
- difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use
- a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
- evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users)
- progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
- persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

conditioned-incentive learning [9]. These stimuli can have reinforcing properties even without the presence of the primary reinforcing drug [10]. It has been hypothesized that drugs of abuse affect associative learning and form abnormally strong stimulus-drug associations, which result in excessive motivational values of the stimuli predicting the drug [7]. In addition, habit learning establishes automatic behavior elicited by drug-associated stimuli [11]. This pattern of behavior, together with the abnormally strong stimulus-drug association, can result in cue-elicited drug seeking behavior even when the primary reinforcing effect is reduced. This compulsive drug-seeking behavior, however, cannot solely be explained by habit learning, stimulus-drug associations and secondary reinforcers. One critical component that needs to be considered regarding the compulsive character of addiction is the loss of cognitive control [10]. Deficits in cognitive control will be discussed in detail in this thesis. First, the reinforcing effects of drugs of abuse and their relation with the development of addiction will be considered.

1.1 The mesocorticolimbic system and addiction

The rewarding effects of drug of abuse are crucial in developing drug addiction. These effects act as primary reinforcers that promote drug intake and in ad-

dition contribute to the learning mechanisms that assign positive motivational value to stimuli associated with drugs [7]. The mesocorticolimbic dopamine system has been the major focus in relation to the reinforcing effects of drugs and natural rewards such as food [12, 13]. The ventral tegmental area, the basal forebrain (e.g. nucleus accumbens, amygdala and frontal cortex) and the connection between these areas are important components of this reward system [8]. Especially the nucleus accumbens, which is part of the ventral striatum, is thought of as a key zone mediating the reinforcing effects of drugs [12]. Evidence for the involvement of the mesocorticolimbic dopamine system in these reinforcing effects has come from pharmacological studies using dopamine receptor antagonists, and selective dopaminergic lesion studies. Both lesions and receptor antagonists reduce the reinforcing properties of psychomotor stimulant drugs, such as cocaine and amphetamines [13]. It is now well known that drugs act on the limbic regions of the mesocorticolimbic system (mesolimbic dopamine system) by increasing the extracellular dopamine levels in e.g. the nucleus accumbens. Depending on the substance, this augmentation is a result of an increased firing rate of dopamine neurons in the ventral tegmental area [14], a blockade of dopamine re-uptake, or a facilitation of dopamine release [12]. These increased dopamine levels are associated with the pleasurable and reinforcing effects of drugs [10]. Interestingly, presentation of conditioned stimuli associated with drugs increase dopamine levels in the nucleus accumbens as well [15]. Although drugs of abuse can differ in initial activity, most drugs act directly or indirectly on dopamine concentrations in the nucleus accumbens [11].

While the increases of dopamine in the nucleus accumbens are closely related to the rewarding effects of drugs of abuse, addiction cannot entirely be explained by this dopamine augmentation. Acute effects of drug intake are characterized by an increase in dopamine levels in the mesolimbic system, however, chronic exposure of drugs of abuse is associated with a decline in dopamine concentrations. Drug abusers seem to have long lasting decreases in dopamine receptor levels compared to controls [16]. These decreased receptor levels could account for the reduced sensitivity for natural rewards seen in addiction, increasing the risk of relapse [10]. Yet, addiction comprises more than abnormal reward sensitivity. Lack of behavioral control and compulsive drug seeking are essential characteristics as well. Therefore, neural circuits besides the reward system, e.g. circuits of motivation/drive, control and memory, are most likely to play a part in addiction too [10]. It is now believed that addiction comprises multiple neuronal changes mediated by different systems. While the increased motivational drive and the decline in sensitivity for natural rewards are largely mediated by mesolimbic dopamine signalling, the lack of cognitive control is associated with prefrontal cortex regions which do not necessarily depend on dopamine transmission. Hence, the mesolimbic dopamine system is still implicated to be crucial for the initiation of addiction, nevertheless other areas particularly in the prefrontal cortex are now believed to be essential in the development of the final addicted state [17].

1.2 Prefrontal cortex and addiction

While the mesolimbic system is relevant for the reinforcing effects of drugs of abuse and therefore the initiation of addictive behavior, the prefrontal cortex is suggested to be involved in the compulsive drug administration and lack of behavioral control [18]. Although the prefrontal cortex receives many glutamatergic inputs, dopaminergic innervation importantly modulates the glutamatergic outputs. This dopaminergic innervation, which is called the mesocortical pathway, comes from the ventral tegmental area and involves the cortical regions of the mesocorticolimbic pathway, including the cingulate gyrus and orbitofrontal cortex. Accumulating evidence ascribes a crucial role for the frontal cortical regions in drug addiction. For example, besides that acute drug exposure increases dopamine levels in the nucleus accumbens, most drugs of abuse elicit augmented dopamine levels in the prefrontal cortex as well [19]. In addition, imaging studies have shown activation of the prefrontal cortex and anterior cingulate gyrus during cocaine intoxication which was correlated to the subjective 'rush' ratings of the participants [20, 21]. Since dopamine may play an important role in several cognitive abilities mediated by the frontal cortex, and drugs alter dopamine levels in these areas, it is suggested that drugs of abuse can affect cognitive functioning [19]. Indeed, chronic exposure of drugs of abuse has been associated with impairments in e.g. decision making, error detection, inhibitory control and cognitive flexibility [3, 22]. Furthermore, associations can be made between these cognitive deficits and functional and structural abnormalities in prefrontal areas [16, 23]. For example, the orbitofrontal cortex is shown to be hypoactive in drug addicts during withdrawal, but hyperactive short after intoxication or during craving [16]. Activity levels of the orbitofrontal cortex are associated with striatal dopamine receptor availability, which is demonstrated to be declined in addicts [24]. Since the orbitofrontal cortex is implicated in motivation, drive and compulsive behavior, it is suggested that the abnormal functioning of this area underlies the obsessive drug seeking behavior seen in addiction [16].

The prefrontal cortex of substance abusers differs unmistakeably from healthy controls regarding both structure and function. The prefrontal abnormalities are accompanied by cognitive deficits displayed by addicts and it is postulated that these deficits, together with the abnormal functioning of the reward system, make up the major part of the compulsive character of addiction. Whether these prefrontal deviations are cause or consequences of chronic drug use is yet an open question. It is possible that the transitions from drug use, to abuse and to eventually addiction are facilitated by changes in the prefrontal regions due to chronic drug exposure. On the contrary, people might develop addictive behavior because of preexisting abnormalities in these regions. For example, when people lack sufficient inhibitory control because of genetic or environmental factors, they might be more susceptible for developing drug addiction. In addition, differences between subjects can exist in the appraisal of the direct reinforcing effects of drugs, suggesting differences in vulnerability. Alternatively,

chronic exposure to drugs of abuse might act directly on the prefrontal cortex regions, thereby modifying its functioning which eventually could lead to impaired cognitive functioning. Human studies of addiction cannot dissociate between these two possibilities since the cognitive capacities before drug exposure of the addicted subjects are unknown. In contrast, animal models provide an opportunity to differentiate between cause and consequence. The effect of chronic drug use on prefrontal cortex structure and functioning can be studied and in doing so these models contribute to our knowledge about the mechanisms underlying addiction.

1.3 Aim of this thesis

The aim of this thesis is to provide an overview of the existing studies that assessed prefrontal cortex dysfunction in addicts and drug-induced changes in animals. Before focussing on these studies and their contribution to the question whether prefrontal dysfunction is a cause or consequence of drug use, chapter 2 first describes the specific prefrontal structures which are believed to be relevant in drug addiction. Chapter 3 elaborates on the cognitive dysfunction and structural abnormalities displayed by addicts, and chapter 4 discusses the effects of chronic drug exposure on the prefrontal cortex. In the last chapter, a summary will be given and the cause or consequence debate will be further discussed referring to the studies described in this report.

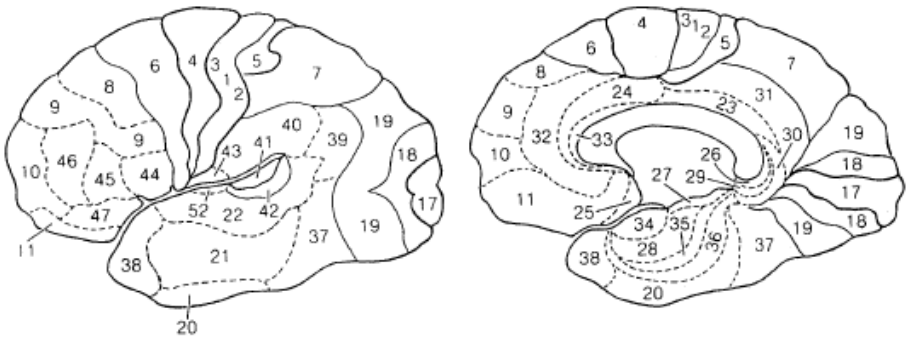
Chapter 2

The prefrontal cortex

As discussed in the introduction, multiple cognitive functions which are demonstrated to be impaired in substance abusers are accompanied by structural changes in the prefrontal cortex. Before elaborating on these cognitive deficits and on the question whether these are preexisting or drug-induced, this chapter will first discuss the different structures and functions of the prefrontal cortex implicated in the development of addictive behavior.

2.1 Structures

The prefrontal cortex (PFC) is a neocortical area which is one of the latest brain areas to develop, phylogenetically as well as in ontogeny. It is most complex in the primate's brain and in humans it comprises almost one-third of the cortex [25]. The prefrontal cortex can be subdivided into orbital, medial and lateral regions, together covering Brodmann's areas 8-13, 24, 32, 46 and 47 (see figure 2.1). An important feature of the prefrontal cortex is that it projects to and receives input from almost all sensory systems, motor areas and subcortical structures. The lateral and mid-dorsal PFC (areas 8, 9, 12, and 46) is strongly associated with sensory cortices and receives visual, auditory and somatosensory input directly from secondary areas. The dorsolateral PFC (DLPFC) is connected in particular to motor structures, implicating this area in behavioral control [26]. In addition, important connections exist between the DLPFC and subcortical areas e.g. the amygdala and hippocampus [27, 28]. The orbital and medial PFC (areas 10, 11, 13, 14, 24 and 32) are associated with limbic structures, such as the amygdala, hippocampus and the thalamus [26]. These limbic connections are especially important for information about the internal states, levels of arousal and motivation and drives [25, 26]. The orbitofrontal cortex (OFC) is connected to several areas implicated in the reward system, e.g. nucleus accumbens, ventral tegmental area, amygdala and hippocampus [29, 30]. These connections makes this area an interesting target for addiction research. The anterior cingulate cortex (ACC, areas 24 and 32) also connects to



(a) Lateral (b) Medial

Figure 2.1: Brodman's areas from lateral and medial view. Source: *Cabeza, R.,& Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. Journal of Cognitive Neuroscience, 12(1).*

the nucleus accumbens, and again this connection makes the ACC an interesting area to investigate regarding drug addiction. In addition to all connections of the PFC to other brain regions, intrinsic connections between the three major subdivisions and within these subdivisions exist [26]. Through all its connections, the prefrontal cortex is well situated to organize a wide variety of neural processes.

2.2 Functions

The prefrontal cortex is particularly important for cognitive control. Cognitive control can be described as the ability to inhibit rapid, conditioned responses in favor of behavior that is in accordance of internal goals [19]. This top-down control over behavior is important especially when a conflict exists between different behavioral outcomes and one outcome is much stronger established in the behavioral repertoire than the other. For example, within the Stroop task subjects have to read words of colors or name the colors in which the word is written. Sometimes the setup is congruent (e.g. BLUE written in blue), however, some trials are incongruent (e.g. BLUE written in red). Reading the words is a behavioral outcome that is better established than naming the colors. When subjects are asked to name the colors in an incongruent setting, a weaker response must be selected over a stronger, more reflexive one. This illustrates a key element of prefrontal functioning and cognitive control [26].

Most of our understanding of the prefrontal cortex implementations has come from neuropsychological studies. In general, damage to the PFC can cause inhibitory deficits which lead to a behavioral output that is dominated by drive, conditioned associations and reflexive responses [19, 31]. Several experimental paradigms have implicated the PFC in inhibitory control. For example, lesions

of the lateral PFC in marmoset monkeys resulted in a loss of inhibitory control in attentional selection [32]. Lesions impaired the monkeys in making attentional shifts from previously learned discriminative stimuli to novel ones. Likewise, PFC lesions elicited other cognitive deficits in marmosets, such as object detour retrieval [33]. During these tasks, subjects need to retrieve a reinforcing object from behind a transparent barrier. Reaching directly for the reward needs to be inhibited and a more cognitive approach is necessary. The behavioral deficits such as attentional shifting and object retrieval seen in these lesion studies, reveal the crucial role of the PFC in inhibitory control.

Although the general role of the prefrontal cortex has been described as top-down control of behavior [26], functional differences are ascribed to different PFC regions. Whereas the orbital and medial regions are associated with emotional behavior, the lateral regions are suggested to be more involved in memory and attention [25]. These dissociations in function are not directly attributed to the topographical distribution of the PFC, instead the functional differences are probably more related to the nature of the information that is processed [25, 26]. Nevertheless, lesion studies of the three major subdivisions of the PFC reveal three different groups of symptoms [25]. First, damage to the OFC is characterized by impulsive, high risk behavior, a tendency of disregarding social and moral principles and attentional problems. These alterations in behavior lead to a major change in personality [34]. Second, lesions of the medial regions of the PFC seem to affect emotion, attention and the general ability to execute spontaneous movements [25]. Third, lesions of the lateral regions commonly result in impairments of organizing and executing behavior, e.g. formulating plans and in carrying them out. These planning impairments are not limited to behavior, but include constructing writings and speech as well [25].

Even though that all regions of the prefrontal cortex are important in behavioral control, this report will focus on specific parts of the PFC since these areas are believed to play a part in developing addictive behavior. Regions that are generally implicated in drug abuse are the DLPFC, the OFC and the ACC. The DLPFC (Brodmann's areas 9 and 46) is essential for working memory and it has been demonstrated that substance abusers perform poorly in working memory paradigms [35]. The OFC, which is a part of the ventromedial prefrontal cortex, has direct connection to brain areas known to be involved in the reinforcing effects of drugs, such as the nucleus accumbens [29]. In addition, patients with OFC damage and addicts seem to have similarities in behavioral deficits [36]. The ACC has been implicated in drug addiction because of its association with error detection [26], a cognitive ability thought to be impaired in drug addiction [4]. The next part of this chapter will elaborate on these three prefrontal cortex structures and their function.

2.2.1 Dorsolateral prefrontal cortex

The dorsolateral prefrontal cortex, and its rodent equivalent the medial PFC (mPFC), comprises Brodmann's areas 9 and 46 and is connected to several cortical and subcortical regions, such as the OFC, amygdala and hippocampus [27, 28]. The involvement of the DLPFC in cognitive control is thought to lie predominantly in the temporal organization of behavior [25]. Cognitive functions underlying this temporal integration are attention, working memory and preparation.

Evidence for the role of the DLPFC in the temporal organization of behavior has come from lesion as well as electrophysiological studies. For example, lesions of the DLPFC in primates and lesions of the mPFC in rats have been demonstrated to impair working memory. In addition, single unit recordings show activity in the DLPFC during delay periods of working memory tasks [37, 38, 39]. Activity in these so called 'memory cells' is present only when the information needs to be retained for a upcoming action. Thus, it seems that these cells "remember for action" ([25], p. 325). Two types of cell unit were distinguished by their activity pattern. The activity of the memory cells decreased during the delay period. In contrast, some cells increased their activity in approach of the motor action [40]. These latter cells were named 'preparatory-set' cells. These findings suggest that two neural substrates coexist in the DLPFC, one for recent events and one for the anticipated future [25].

Beside its role in memory, several studies have emphasized the involvement of the DLPFC in attention mechanisms [32, 41]. As discussed earlier, damage to the DLPFC (area 9) results in a loss of inhibitory control during an attentional selection task [32]. In a study by Dias and colleagues [32], an analogue of the Wisconsin Card Sort Test (see figure 3.1 for the original test) was developed in which marmoset monkeys were trained to discriminate between two visual stimuli. Each stimuli consisted of a black line and a blue figure. The correct response depended for some animals on the shape of the line and for the other animals on the shape of the blue figure. This attentional set (attending to the line or the figure) was maintained over a couple of discrimination series of new stimuli. After surgery, the DLPFC lesion monkeys were still able to remember the discriminations they had previously learned. In addition, they were still able to learn new discriminations when the attended dimension was the same (intra-dimensional shift; either line or figure). However, changing the attentional dimension (extra-dimensional shift; from line to figure or vice versa) was significantly impaired.

Another study examined attention by measuring the activity of the DLPFC during the Stroop test [41]. In this experiment, functional magnetic imaging was performed while the subjects participated in the Stroop task. It was demonstrated that during the color naming, the DLPFC was more active than during the reading task. As mentioned in the first part of this chapter, naming the colors is thought to be attentionally more demanding, since it requires selection of a weaker response over stronger one, i.e. reading. Since the DLPFC was more

active during naming of the colors, it has suggested that this brain area is involved in representing and maintaining the attentional demands of the task [41].

In sum, the dorsolateral prefrontal cortex is a crucial neural substrate for the temporal organization of behavior. Attention, working memory and preparation seem to be necessary cognitive functions underlying this behavioral control. Given that these cognitive functions are sometimes impaired in substance abusers, it is likely that drugs of abuse affect this brain area, or that abnormalities in this area constitute the vulnerability for addiction.

2.2.2 The orbitofrontal cortex

The orbitofrontal cortex is of special interest for exploring the effects of drugs of abuse and addiction because of its connection to the reward system, especially the nucleus accumbens [29]. It receives dopaminergic input from the ventral tegmental area, and it is connected to other regions involved in the reinforcing effects of drugs, e.g. amygdala and hippocampus (for a summary of the OFC connections see [30]). Because of these connection to the reward system and additional connections to cortical regions, the OFC may not only be involved in the direct effects of drugs of abuse, but in addition might integrate information and modulate responses regarding drug administration [16].

An important function of the OFC concerns stimulus-reward associations. The connection between the OFC and the basolateral nucleus of the amygdala is especially important in the early stage of learning stimulus-reinforcement association, as shown by the brain activity patterns during instrumental learning in an olfactory discrimination task in rats [42]. Neurons fired differently depending on the outcome, whether it was positive or negative, suggesting a relation of the neuronal activity and the incentive value of the reward. Furthermore, lesions of the OFC in rats have been shown to affect the pattern of discrimination acquisition in a Go versus No-Go tasks [43]. Lesions did not affect the ability to learn discrimination problems, however they altered the response latencies during learning. The OFC-lesioned rats failed to inhibit responding in negative trials and failed to facilitate responding in positive trials. Since response latencies are thought to be a measure for the incentive value of the expected outcome, these results ascribe an important role for the OFC in the use of the incentive, motivational values in discrimination tasks.

Another experimental paradigm concerning the incentive value in associative learning is that of devaluating rewards. When devaluating the unconditioned stimulus in a stimulus-reward association, respondence to the conditioned stimulus is normally altered. However, in monkeys as well as rats, lesions of the OFC resulted in unchanged responses to the conditioned stimulus after devaluation of the unconditioned stimulus [44, 45]. The animals were impaired in the ability to adjust their behavior in accordance to changes in the predicted outcomes. In humans, a similar behavioral pattern has been observed by Bechara *et al.* [46]. Damage to the OFC resulted in poor performance in gambling tasks [46].

Patients were unable to adjust their behavior to the contingencies of rewards and negative consequences, whereas control subjects learned to optimize their choices.

In reversal learning paradigms, the stimulus previously associated with the reward becomes unrewarded, and the former unrewarded stimulus now predicts the reward. Several studies have demonstrated the importance of the OFC in this ability to reverse stimulus-reinforcement associations [32, 43, 45, 47]. Damage to the OFC seems to impair the ability to alter behavior according to the reinforcing properties of the reward. The previously acquired association cannot be suppressed in favor of the new one, suggesting a loss of inhibitory control [32].

In addition to lesion studies, imaging research has provided evidence for the involvement of the OFC in inhibitory control as well. Within a Go/No-Go task, the volume of activation of the orbitofrontal cortex, measured by functional MRI, was demonstrated to be correlated with the amount of false alarms; the more activation, the less false alarms [48]. Given that the amount of false alarms indicate inhibitory control performances, these findings support the idea that the OFC is critical in inhibitory control.

To summarize, several lines of evidence indicated that the OFC is an important prefrontal cortical area for inhibitory control. Stimulus-reward learning, adjusting behavior in correspondence to devaluating rewards, and reversal discrimination are shown to be mediated by the OFC. Addiction is characterized by the lack of inhibitory control and the adaptation of established behavior seems to be impaired. Therefore, it is plausible to assume that the OFC is important in developing the addicted state.

2.2.3 Anterior cingulate cortex

The anterior cingulate cortex has been implicated in drug addiction because of its direct connections to the nucleus accumbens [49], its involvement in stimulus-reinforcement learning and its associations in response monitoring and response selection [50, 51]. Error detection, a cognitive ability impaired in drug addiction [4], is associated with ACC activity [26] and in addition, human imaging studies have revealed craving-associated ACC activity [52].

The functions of the ACC are multiple and include e.g. motor response selection, anticipation, working memory, novelty detection, competition monitoring, reward assessment and performance monitoring [53]. In general, the ACC functions all concern the mediation of evaluative processes [41]. The involvement of the ACC in performance monitoring has been demonstrated by an experiment that measured brain activity during the Stroop task. More activity was found in incongruent stimuli compared to congruent ones [41]. In addition, more conflict was associated with more ACC activity, given that the largest ACC activation was observed when the time to react was the longest. Conflict situations need more control, and it is therefore suggested that the control execution mediated

by other regions of the prefrontal cortex, e.g the DLPFC, depends on signals from the ACC [26]. Further evidence for the involvement of the ACC in conflict detections has come from a study that explored error detection. Carter *et al.* [51] demonstrated using fMRI that ACC activity was related to the detection of conditions under which errors are likely to occur, rather than to the detection of the actual errors. The ACC was active both during erroneous responses and correct responses, but only when these correct responses occurred under increased response competition conditions.

Besides its role in conflict detection, the ACC has been implicated in stimulus-reinforcement learning [49]. In rats, lesions of the ACC showed that this region is not crucial for the actual stimulus-reinforcement acquisition, however, the ACC is involved in the discrimination of multiple stimuli and their associations with reward [50]. In addition, an event-related functional MRI study showed that the ACC plays a role in reward-based decision-making. In this study, it was demonstrated that during a decision making task a subpopulation of the ACC cells was specifically activated when the rewards were reduced [53], suggesting ACC heterogeneity and involvement in decision making.

Taken together, the ACC has multiple functions which all concern evaluative processes. Lesions of the ACC are demonstrated to impair stimulus-reinforcement learning and performance monitoring and imaging studies have implicated the ACC in error detection and decision making. These anterior cingulate cortex functions are of special interest, since they seem to be impaired in addiction.

2.3 Summary

This chapter described the structures and functions of the prefrontal cortex areas implicated in drug addiction. Whereas the DLPFC is thought to be crucial for attention, working memory and preparation, the OFC and ACC are more related to emotional behavior. The OFC is especially important in adjusting behavior in accordance of motivational significance of stimuli, and the ACC is shown to be involved in evaluative processes such as performance monitoring and error detection. In addition, the OFC and ACC are both involved in stimulus-reward learning. Damage to these three regions has in common that the resulting impairments all concern behavioral and cognitive control and especially behavioral and cognitive inhibition. Interestingly, the cognitive deficits seen in addicted subjects involve disinhibition and it is therefore likely that these discussed prefrontal areas play a key role in developing addiction.

The next chapter will provide an overview of the human studies concerning addiction. These studies investigate the behavioral deficits and the structural en metabolic abnormalities associated with substance abuse.

Chapter 3

PFC and addiction: Human studies

Numerous studies that examined the cognitive abilities of drug abusers, have highlighted the association between chronic drug use and impaired cognitive functioning (reviewed by [2]). Cognitive deficits observed in drug addicts include impaired cognitive flexibility, inhibitory control, attention, planning, decision making and memory [22]. Although most deficits are exhibited by all substance abusers independent of the drug type, some impairments are more pronounced in e.g. psychostimulant addicts compared to opiate addicts [2, 22]. Because of the large amount of research suggesting an association between substance abuse and cognitive functioning, the role of cognition functioning, and thereby the role of the prefrontal cortex, in developing addiction has become more and more prominent. Especially the lack of inhibitory control is believed to be crucial in the process of developing the compulsive character of drug addiction [21].

This chapter will describe some of the behavioral deficits typical for substance abuse and it will discuss the imaging studies that relate these deficits to malfunctioning of specific prefrontal cortical areas. Furthermore, brain areas involved in cue reactivity will be discussed together with the structural and metabolic abnormalities associated with drug addiction.

3.1 Behavioral deficits

3.1.1 Decision-making

Multiple studies have demonstrated impaired decision-making in substance abusers (reviewed in [3, 4]). Decision-making is commonly tested using the Iowa Gambling Tasks. During this task, subjects are asked to select cards from different desks. Some decks have large immediate monetary gains while others have small gains. However, the decks containing the large immediate gains have cards with

higher monetary penalties as well. Selecting cards from the decks with large immediate gains will eventually lead to a net loss. So, with this gambling test, the ability to evaluate immediate gains over long-term losses can be assessed [54]. Despite feedback about winning and losing, drug abusers persist in making disadvantageous choices [55].

Decision-making in these gambling tasks is thought to rely on cognitive and motivational factors, such as learning, memory and attention [4]. Consistent with this assumption, imaging studies have revealed brain regions associated with working memory (DLPFC), performance monitoring (ACC) and motivational significance of stimuli (OFC) to be active during gambling tasks [56]. Hence, impaired decision-making as displayed by addicts, might be elicited by malfunctioning of these prefrontal regions. The involvement of the OFC in decision-making has been emphasized by cognitive modeling studies, which assign impaired decision-making to an extreme focus on wins or hyposensitivity for losses [57]. The hypersensitivity to rewards has been assessed by imaging studies investigating the brain activity during the Iowa Gambling Task [58]. Although no significant difference was found in the performance between abstinent cocaine abusers and controls, brain activity of the abusers was higher in the right OFC and lower in the right DLPFC relative to controls. In controls as well as in cocaine abusers, better performance was associated with greater activation in the right OFC. Thus, substance abusers might be hypersensitive to rewards and more OFC activity may reflect this abnormal intense reward focus. However, the larger OFC activity could also be explained by mechanisms that compensate for a potential low efficiency of the OFC. In other words, the OFC might be more active in substance abusers as a result of a general inefficiency of the OFC or other involved areas. These hypotheses, however, are not mutual exclusive, thereby providing a more elaborated hypothesis about the OFC functioning and decision-making.

Although cognitive models and imaging studies point to the involvement of the OFC and incentive motivational properties of the reward [57, 58], impaired decision-making has also been associated with working memory deficits. Bechara and Martin [35] showed that substance abusers who were nonimpaired in the gambling task, performed significantly worse compared to controls in a delayed nonmatching to sample (DNMS) task. Comparison of the controls and substance abusers who were impaired in the gambling task, revealed that substance abusers again performed significantly worse in the DNMS test. Thus, it seems that poor decision making does not affect working memory, however, malfunctioning of the working memory system can affect decision making [35]. Therefore, working memory and the associated brain areas, e.g. the DLPFC, are suggested to be important for proper decision-making.

Besides the involvement of the orbitofrontal and dorsolateral prefrontal cortices, the anterior cingulate cortex has been associated with decision-making. Poor decision-making in substance abusers is thought to reflect a failure to benefit from feedback [4]. Dysfunction of the OFC and DLPFC could contribute to this failure. However, one particularly important cognitive function that might underlie the deficits seen in the gambling tasks is suggested to be the monitor-

ing of performances. Performance monitoring is a cognitive function associated with the ACC (see section 2.2.3). The hyposensitivity to losses in substance abusers is hypothesized to be a reflection of hypoactivity in the ACC [4]. Multiple studies have demonstrated different ACC functioning of substance abusers compared to controls in several inhibitory control paradigms [59, 60, 61] and it has been suggested that this difference reflects poorer awareness of the errors made by the abusers [4].

Besides the abnormalities in decision-making, which is associated with OFC, DLPFC and ACC functioning, substance abusers are impaired in multiple other cognitive tasks. The majority of these tasks involve inhibitory control. The next section will elaborate on deficits in behavioral and cognitive inhibition and its relation to the abuse of drugs.

3.1.2 Inhibitory control

Inhibitory control can be subdivided into behavioral inhibition and cognitive inhibition. Behavioral inhibition is generally described as the ability to stop an already planned movement, whereas cognitive inhibition is explained as the suppression of a salient stimulus property in favor of a less prominent one (e.g. in the Stroop task) [22]. Go/No-Go and Stop-Signal Reaction Time paradigms are often used to assess behavioral inhibition. Kaufman *et al.* [59] conducted an fMRI study in which brain activity of active cocaine users was assessed during a Go/No-Go task. The subjects were instructed to press a button when a 'Go' stimulus was presented on the screen. A 'No-Go' stimulus required inhibition of the response and consisted of two consecutive presented 'Go' stimuli. Relative to controls, cocaine users showed more false alarms (errors in inhibition) as well as more misses (errors in responding). The activity patterns observed during the Go/No-Go task did not differ between controls and cocaine users, however, some areas were less active in the latter group. During successful inhibitions, the fMRI revealed significantly less activity in the ACC in cocaine users compared to controls. In addition, mean activity levels in the ACC were lower during false alarms as well [59]. Interestingly, no difference in activity was found in areas thought to be important in inhibitory control, such as the OFC [48].

Inhibitory control is often assessed by attentional set shifting paradigms. Attentional set shifting requires cognitive inhibitory control and is suggested to be mediated by the DLPFC (see section 2.2.1). The Wisconsin Card Sort Test evaluates the ability to shift from established attentional response sets to new ones (see figure 3.1). Although the ability to switch between attentional sets is sometimes described as cognitive flexibility [22], it requires inhibitory control because previously attended dimensions need to be ignored in favor of the dimension that is now carrying the necessary information. Chronic amphetamine users exhibit difficulties in extra-dimensional shifts, whereas heroin abusers showed impairments in learning the intra-dimensional shift [62]. Although the involvement of the DLPFC in these attentional set shifts has been demonstrated in monkeys [33], differences in DLPFC activity in cocaine users compared to controls seem

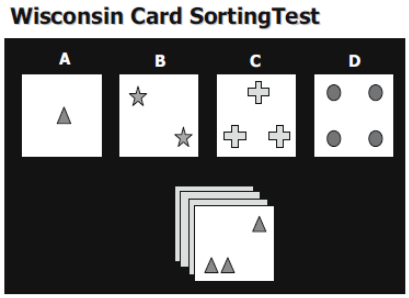


Figure 3.1: In the Wisconsin Card Sorting Test subjects are asked to sort cards from a deck. The cards show stimuli that differ in the dimensions color, shape and number. All dimensions have four possibilities, so four different shapes, four different colors and four numbers. The subjects need to decide how to sort the cards and receive feedback of the correctness of their choice. This feedback changes during the test and the participants need to adapt their sorting strategy by changing the sorting dimension. Source: Ersche and Sahakian 2007.

to be absent, despite the behavioral dissimilarities [60]. In contrast, hypoactivity of the ACC was observed in cocaine abusers relative to healthy controls. Since the ACC is associated with performance monitoring, it is hypothesized that the observed hypoactivity of the ACC in substance abusers reflects impaired performance monitoring and thereby an inability to signal the necessary amount of inhibitory control to the more executive areas, such as the DLPFC [60].

The same reasoning can be applied to the results obtained in a study comparing brain activity of abstinent substance abusers and controls during a modified version of the Stroop task [61]. In this study, the activity of the ACC in substance abusers was also altered, indicating impaired performance monitoring. However, both groups performed equally well in the Stroop task. Moreover, different parts of the ACC revealed dissimilar activity patterns. Substance users showed hypoactivity of the left ACC during incongruent trials, while the right ACC was hyperactive. Therefore, it has been postulated that a compensatory mechanism might be at work, resulting in unimpaired Stroop performances [61]. The hypoactivity of the left ACC could reflect impaired performance monitoring, however, by the hyperactivity of the right ACC this impairment is compensated. Interestingly, the amount of cocaine used before abstinence was negatively correlated with the activity of the rostral ACC which supports the idea that chronic drug exposure can lead to prefrontal dysfunction.

Behavioral inhibition, cognitive inhibition and decision-making have been demonstrated to be dysfunctional in some, but not all substance abusers. Despite sometimes unimpaired behavior, multiple studies have revealed abnormal brain activity in substance abusers. A possible explanation for this unimpaired behavior could be that substance abusers utilize other neural pathways than controls. As shown by Bolla and colleagues [61], cocaine abusers showed hyperactivity of the right ACC and hypoactivity in the left ACC during the Stroop task, suggesting that the right ACC compensates for the left ACC. Abnormalities in this area are often associated with inhibitory control. This implicates impaired performance monitoring as the key problem underlying multiple inhibitory deficits. Hypoactivity in the ACC has been observed repeatedly in sub-

stance abusers and it is hypothesized that this hypoactivity reflects the inability to signal the need for cognitive control to other brain regions. In addition to the alterations in ACC activity, abnormalities in the OFC have been observed. Impaired decision-making is often associated with these OFC abnormalities, however, memory related brain areas, such as the dorsolateral prefrontal cortex, are believed be involved as well.

3.2 Cue-reactivity

Besides the wide range of cognitive deficits associated with chronic drug use, other features of human drug addiction are worth considering. For example, drug-associated cues play an essential role in compulsive drug seeking and taking, relapse and craving. As discussed in the introduction, abnormally strong stimulus-drugs associations can be formed and these initially motivationally neutral stimuli can obtain reinforcing effects even when the primary effects of the drugs of abuse are reduced. Understanding the cue processing in drug addiction and is underlying neural substrates is therefore of great importance.

Multiple studies have examined cue-reactivity in drug addiction (reviewed in [3]). Although the results of these studies show some inconsistencies, the OFC, DLPFC as well as the ACC have all been implicated in processing drug cues [3, 63, 64]. Multiple studies have revealed a hyperactivity of the OFC, DLPFC and ACC after cue presentation and a hypoactivity of the OFC after detoxification [3]. For example, watching a video of a men smoking crack resulted in an increase in activity of several brain areas, as shown by an fMRI study by Garavan *et al.* [63]. The OFC, but also the DLPFC and ACC were associated with cue-induced activity and cue-induced subjective craving. Increased activity was observed in both cocaine users and controls, however, the augmentation was more pronounced in the cocaine group. In addition, in the cocaine group, the same areas were more active watching a drug cue compared to watching a neutral video. These results suggest that the brain areas mentioned above are important in mediating cue reactivity and cue-induced drug craving.

A Positron Emission Tomography (PET) study has revealed metabolic increases in the medial OFC and DLPFC in response to cocaine cues as well [64]. These metabolic increases in the OFC and DLPFC were observed solely in the cocaine abusers, however, only the DLPFC activity was correlated to self-reported drug craving [63]. Craving for cocaine was, besides the DLPFC, also correlated to metabolic increases in subcortical regions associated with memory. Thus, by the involvement of the DLPFC and subcortical areas, these results indicate that cue-elicited craving is likely to entail memory processes as well [64].

In sum, cue-induced craving is likely to involve many prefrontal areas. Cue-induced hyperactivity of the OFC has been observed regularly, however, other areas such as the DLPFC and ACC are often implicated in cue-induced craving. The inconsistencies across the studies can be explained by study design,

treatment status (time of abstinence) and even gender [3]. Craving is a complex process which probably involves several brain areas. Recall of previous experiences and anticipation of future drug rewards may underlie craving, and indeed brain areas involved in memory and anticipation are demonstrated to be active during craving [21]. However, the precise relation between craving and the different brain areas remains unclear.

Less inconsistent are the structural and metabolic neuroimaging studies investigating the brain at rest. These studies will be discussed in the next section.

3.3 Structural and metabolic abnormalities

Several studies have investigated differences in 'brains at rest' between substance abusers and healthy controls (reviewed in [3]). Differences in gray matter concentrations between cocaine patients and controls have been reported in several brain areas e.g. the orbitofrontal and anterior cingulate cortices [65]. The concentrations differed within a range of 5% to 11% between patients and controls, while white matter concentrations were similar.

Moreover, a recent fMRI study found dysfunctional connectivity patterns in heroin users [66]. Brain networks of heroin users were compared with controls and differences in connectivity were found among several brain regions. Interestingly, the dysfunctional connectivity patterns found in heroin users all involved brain areas associated with decision-making, inhibitory control and working memory. Since these cognitive abilities have been demonstrated to be impaired in substance abusers, the observed abnormal connectivity within neural networks in heroin users could well be contributing to these deficits [66].

Furthermore, methamphetamine abusers have significantly lower levels of striatal D_2 receptor levels compared to controls [24]. In abusers as well as controls, the D_2 receptor availability was associated with the metabolic rate in OFC. Thus, abnormal OFC functioning could be mediated by D_2 receptor availability and might underlie several drug associated cognitive impairments. Evidence supporting this hypothesis has come from several other studies which have revealed metabolic abnormalities in substance abusers. These studies are consistent in their finding of OFC hypoactivity after detoxification [3].

Taken together, structural and metabolic abnormalities and dysfunctional connectivity patterns have been demonstrated in addiction. Remarkably, these abnormalities concern brain areas which are all commonly associated with cognitive abilities impaired in drug addiction, such as decision-making, inhibitory control and working memory.

3.4 Summary

In this chapter behavioral deficits, cue-reactivity and structural and metabolic abnormalities have been discussed. Substance abusers show deficits in multiple

cognitive functions, such as decision making and inhibitory control [22]. Addiction is characterized by compulsive drug seeking and relapse, features that are believed to be initiated to a large extent by poor decision-making, lack of inhibitory control and abnormal cue-reactivity. Several brain areas have been associated with the impairments observed in substance abusers, however, the precise role of specific brain regions in these different behavioral deficits remains unclear. Impaired decision-making, for example, is regularly associated with OFC dysfunction, and the deficits seen in amphetamine users resemble deficits seen in OFC damaged patients [36]. Yet other regions, such as the DLPFC, are likely to be involved as well [3]. In addition, the ACC is a key mediator of inhibitory control, and via this function, also affects decision-making [4]. Hypoactivity of the anterior cingulate cortex has been repeatedly observed in substance abusers even without the presence of behavioral inhibitory control impairments. In contrast, drug cues often increase brain activity in the ACC as well as orbitofrontal and dorsolateral cortices. The observation that multiple brain areas underlie cue-induced craving seems reasonable, since craving is a complex process involving recall of experiences as well as anticipation to future drug exposure [21].

In addition to the abnormalities observed in substance misuse during behavioral task paradigms, evidence for the involvement of the OFC, DLPFC and ACC in addiction has come from imaging studies of the brain at rest as well. Structural and metabolic abnormalities together with dysfunctional connectivity patterns has been demonstrated in substance abusers using brain imaging. Abnormalities were found in the OFC, ACC and DLPFC, suggesting the association between these areas and behavioral deficits typical for addition.

Taken together, the behavioral repertoire of substance abusers shows several impairments compared to healthy controls. One important deficit regarding addiction is the lack of inhibitory control, which promotes drug intake and relapse. The PFC plays an essential role in mediating these behaviors and abnormalities are indeed found in the prefrontal areas, particularly the OFC, DLPFC and ACC. From these human studies, however, it can not be concluded whether these abnormalities are drug-induced or preexisting. The next chapter will discuss studies that can explore specifically the drug induced alterations of brain structures and behavior. These studies concern animal models.

Chapter 4

PFC and addiction: Animal models

As mentioned previously, addiction has been associated with prefrontal cortex malfunctioning. Cognitive deficits seen in substance abusers however can be preexisting or caused by repeated drug exposure. To dissociate between these two possibilities, animal models are of great significance. These models provide insight in the changes actually induced by drug exposure and may have important implications in human drug addiction development.

Much work has been done concerning drug-induced changes in subcortical areas. Several studies have demonstrated an association of midbrain and striatal plasticity processes (e.g. in the reward system) and sensitization [67, 68]. Sensitization is a phenomenon that is widely used in animal research addressing addiction. It is characterized by the progressive enhancement of the motor effects of the drugs of abuse [67]. So, after repeated drug exposure the locomotor effects of the drug increase. Molecular and cellular changes of subcortical areas elicited by repeated drug exposure and the corresponding sensitization has been proposed to serve as a model for the plasticity associated with addiction [69].

This chapter, however, will focus on the changes in prefrontal cortical regions induced by repeated drug exposure, instead of subcortical alterations. It has been hypothesized that subcortical changes in synaptic connectivity contribute to the motivational effects of the drugs of abuse and that prefrontal alterations in connectivity induce loss of cognitive control [23]. Thus, both the subcortical and PFC drug-induced alterations may play an important part in developing drug addiction. The next sections will discuss several levels of analysis of prefrontal changes, including long-term cellular, structural, and behavioral alterations.

4.1 Structural and cellular changes

Repeated exposure to many drugs of abuse results in a progressive increase of their psychomotor activating and rewarding effects [67]. Besides the asso-

ciations of sensitization and subcortical modifications, several animal studies have reported drug-induced alterations in prefrontal cortex regions [23, 70, 71, 72]. These alterations are similar to those seen in other forms of experienced-dependent plasticity e.g. learning.

It has been demonstrated that repeated amphetamine treatment, which produces sensitization, induces long-lasting structural changes in the nucleus accumbens and PFC neurons [70]. These changes include increased length of dendrites and increased density of dendritic spines. Similar results have been obtained in an experimental paradigm in which the rats self-administered cocaine [23]. The observed dendritic changes were not due to general learning processes, given that the control rats, who worked for food instead of cocaine, did not show these dendritic modification. In addition to these alterations in dendrites, some prefrontal neurons appeared to be misshaped. These malformed neurons were speculated to represent deficits associated with addiction [23].

Interestingly, drug-induced alterations in dendritic morphology vary between prefrontal cortex regions. Long-term effects of self-administered amphetamine include increased spine density in the nucleus accumbens and medial prefrontal cortex. In contrast, in the OFC amphetamine reduces the spine density [71]. Likewise, different plasticity patterns in the OFC and mPFC have been demonstrated regarding amphetamine-induced neuronal activity. This activity pattern was opposed to the morphological alterations. Amphetamine primarily inhibited mPFC neurons while it excited the OFC neurons [73]. This pattern of inhibition and excitation was amplified over time, indicating neuronal sensitization for amphetamine. It has been suggested that these dendritic changes in the OFC and mPFC are counteracting changes in neuronal activity [73]. In other words, because of the reduced or increased neuronal activity, compensatory mechanisms alter dendritic densities to maintain homeostasis.

The observed morphological alterations in the PFC and subcortical areas induced by repeated drug exposure are suggested to bring about the psychomotor, cognitive and motivational changes seen in addiction [71]. Despite the still hypothetical nature of this idea, these morphological alterations in dendritic spines provide a possible structural mechanism for the observed long lasting changes in neurotransmission after repeated drug use [70]. Dopamine as well as glutamate transmission has been shown to be affected by chronic drug exposure.

As revealed by Sorg and colleagues [72], repeated exposure to cocaine reduces the effect of cocaine on extracellular dopamine levels in the medial PFC in rats. In their experiment, cocaine- and saline- pretreated rats were challenged with cocaine. In both groups, this challenge induced an increase in dopamine levels, however, in the cocaine pretreated group, this augmentation was significantly reduced relative to the controls. This decline in effect of cocaine has been postulated as mechanism underlying tolerance. Interestingly, this apparent tolerance effect was absent when cocaine was replaced by amphetamine [72].

Furthermore, repeated cocaine exposure induces alterations in PFC activity patterns [74]. Chronic cocaine self-administration in rats decreases basal pre-

frontal cortex neuronal activity, whereas it increases the firing rate in response to cocaine. In contrast to rats with cocaine experiences, cocaine exposure in control rats resulted in a decreased firing rate of the PFC. The increased firing rate in cocaine rats supports the idea that drug-related information processing is enhanced and that this enhancement might contribute to the compulsive drug-seeking behavior in addiction [74].

In addition to changes in PFC dopamine levels and firing rates, glutamatergic transmission is affected by chronic drug exposure as well. Medial prefrontal cortex neurons in rats show an increase in responsiveness to glutamate after withdrawal from amphetamine [75]. This increase could promote glutamatergic projections to e.g. the ventral tegmental area [75]. Indeed, amplified glutamatergic signalling from the PFC to the nucleus accumbens has been demonstrated [76]. The cellular mechanism underlying this increased glutamatergic projection is thought to involve the G-protein binding protein AGS3. After withdrawal from repeated cocaine exposure, the levels of AGS3 increases, enhancing the glutamatergic signaling to the nucleus accumbens [76]. This enhanced signalling has been suggested to be a possible mechanism subserving the compulsive drug seeking in addicts [17]. Besides that the increase of AGS3 promotes the glutamatergic projection from the prefrontal cortex to the nucleus accumbens, augmented AGS3 levels are also associated with dopamine signalling. Due to the AGS3 increase, D_2 receptor signalling is reduced, resulting in a relatively enlarged D_1 receptor signalling [76]. It has been proposed that augmented D_1 receptor signalling induces a prefrontal output that is focused on drug-related stimuli, while non-drug-related stimuli are relatively inhibited [77]. Thus, alteration of G-protein signalling in dopamine neurotransmission is believed to promote behavior that is focused on drug associated stimuli, whereas adaptations in glutamatergic projections to the nucleus accumbens is thought to underlie the urge to seek drugs [77].

Although the majority of research has focused on subcortical regions, several studies have explored cellular and molecular mechanisms underlying the long-lasting changes in the prefrontal cortex concerning addiction. One important mechanism implicated in long-term plasticity is that of gene expression regulation. Transcription factors, especially CREB and Δ FosB, have been put forward as candidates responsible for lasting drug-induced changes (reviewed by [14]). In a cocaine self-administration paradigm, increased expression of Δ FosB was observed in the rat OFC [78]. This drug-induced elevation of Δ FosB levels could be mimicked via viral-mediated gene transfer. This transfer induced similar behavioral changes as observed in cocaine self-administration, i.e. tolerance to acute cocaine effects and sensitization to effects of withdrawal. It is suggested that through adaptation, repeated cocaine exposure may result in proper OFC functioning during drug intoxication, however, may also lead to OFC dysfunction after withdrawal. This might contribute to the observed cognitive impairments. Levels of Δ FosB have been hypothesized to mediate these effects of cocaine [78], by the involvement in regulating cAMP pathways. Chronic drug exposure can up-regulate this pathway, which might underlie some effects of drugs of abuse, such as tolerance [79].

Taken together, chronic drug exposure induces modifications in both cortical and subcortical regions. These adaptations include morphological alterations of the dendrites and changes in neurotransmission. The molecular mechanisms underlying these alterations involve modification in G-protein signalling pathways. The observed prefrontal alteration might subserve the behavioral changes, such as locomotor sensitization and cognitive deficits, associated with addiction.

4.2 Behavioral changes

In animals, several behavioral changes have been described regarding chronic exposure to drugs of abuse. These impairments are mostly associated with orbitofrontal malfunctioning and alterations within OFC and basolateral amygdala (ABL) connections [80]. Difficulties in reversal learning and outcome-guided behavior as well as drug-induced deficits in attention and cue-reactivity have been observed. Abnormalities in cue-reactivity and the loss of the ability to guide behavior according to expected outcomes are of special interest, since these deficits might in humans result in relapse and compulsive drug-seeking.

Relative to control rats, cocaine treated rats have been shown to be less able to adjust their behavior to a conditioned stimulus after the reward has been devaluated. In a study by Schoenbaum and Setlow [81], rats were trained to associate a light cue with a food reward. After successful acquisition of the association, the food was devaluated by pairing it with illness. Then the rat's response to the light cue was observed during several sessions. Cocaine-treated rats were unable to modify their behavior according to the devaluation of the reward and did not decrease their conditioned response (the effect was evident a month after the cocaine treatment). This deficit represented the inability to use outcome values rather than the inability to learn stimulus-responses or the changes in general behavioral inhibition. These observed deficits have been demonstrated to reflect altered OFC functioning [82]. OFC neurons in rats previously exposed to cocaine were recorded during a go/no-go discrimination task. Rats had to respond to odor cues to obtain a reward (sucrose) or to avoid an aversive outcome (quinine). Neurons of cocaine-treated rats fired normally to the positive or negative outcome, however, the rats failed to develop cue-selective firing especially when the outcome was aversive. In other words, these OFC neurons became active during cue presentation, but they were equally likely to fire for either odor cue. This resulted in abnormal changes in response latencies during trials with quinine. So the cocaine treated animals could not adapt their response latencies according to the predicted outcome. Similar to the rats in the food devaluation task [81], these rats failed to utilize predicted outcomes for adjusting their behavior.

As a consequence of the inability to modify behavior in accordance with expected outcomes, reversal learning is affected by chronic exposure to drugs of abuse as well. Impaired reversal learning has been demonstrated in non-

contingent cocaine treatments in both rats [82] and monkeys [83], as well as in self-administration paradigms [84]. Again, these effects have been demonstrated to be, at least in rats, associated with OFC functioning. Stalnaker *et al.* [82] showed that, compared to controls, cocaine treated rats display less flexible neuronal activity in the OFC. This inflexibility was reflected by the lower amounts of neurons reversing their cue-selectivity during reversal learning. Interestingly, some cocaine treated rats showed normal reversal performance and these rats exhibited, similar to controls, increased plasticity of cue-selective activity after reversal [82]. In other words, when a cocaine rat displayed normal reversal performance, this was accompanied by normal amounts of neurons reversing their cue-selectivity. So, these results suggest that cocaine can cause behavioral changes and that these changes are associated with OFC functioning.

Besides the difficulties in adjusting behavior in accordance wit expected outcomes, several studies have shown impaired attentional abilities in drug treated animals. Visual attention is demonstrated to be significantly impaired after both cocaine and heroin self-administration in rats. Rats with amphetamine or heroin experience showed a reduced accuracy during a 5-choice serial reaction time test and in addition, failed to respond frequently [85]. These drug-induced behavioral deficits could be reversed by the injection of D_1 receptor agonists in the medial PFC, suggesting the involvement of this dopamine receptor in attentional abilities [86].

Furthermore, rats pre-treated with amphetamine have been demonstrated to be impaired in attentional set shifting, similar to the monkeys with DLPFC lesions (see section 2.2.1). In an experiment by Fletcher and colleagues [87], rats were trained to search for food by choosing between two bowls. Each bowl had two dimensions (texture and odor), but only one dimension predicted the baited bowl. Rats were then tested in several discrimination tasks requiring intra and extra-dimensional shifts, and reversal learning. Amphetamine treatment resulted in impaired reversal learning and extra-dimensional shifts, while the intra-dimensional shift abilities remained unaltered [87]. Again, the behavioral deficits could be reversed by injections of a D_1 agonist in the mPFC, implicating a role for dopamine signalling and the medial PFC in cognitive functioning [87].

The mPFC, the ACC and the OFC have all been implicated in self- administration of drugs of abuse [88]. It has been shown that lesions of the mPFC in rats result in enhanced acquisition of cocaine self-administration [88]. This facilitation was not observed with sucrose as reinforcer, indicating a specific effect of cocaine. Lesions of the mPFC after self-administration establishment did not have an effect on responding. Since the rats with lesions tended to be more active than controls, it has been hypothesized that the enhanced facilitation of cocaine self-administration is related to behavioral disinhibition rather than to an increase in the reinforcing effects of cocaine due to the lesion. However, since lesions of the mPFC did not alter self-administration of sucrose, general behavioral disinhibition cannot be the only explanation. Rats with lesions in

the ACC did not show enhanced acquisition of self-administration of cocaine. Instead, these rats were more likely to self-administer extreme amounts of cocaine. In addition, these rats showed an overall increased spontaneous and cocaine-induced locomotor activity under second-order schedules and they displayed increased anticipatory responding. Because of the associations of the ACC with stimulus-reinforcement learning, it has been hypothesized that the observed increased anticipatory responses and impaired extinction are a result of alterations in cue-cocaine associative learning abilities [88].

It has been suggested that the OFC promotes drug seeking by its involvement in drug cue processing [89]. A study by Fuchs and colleagues [90] examined the effect of the OFC on reinstatement of cocaine self-administration in rats. In this experiment, rats were trained to self-administer cocaine while the injections were paired with a light-tone stimulus. After cocaine self-administration was extinguished, the reinstatement of this behavior was assessed by triggering the rats with the light-tone stimulus or with cocaine injections. Post-training inactivation of the lateral OFC inhibited reinstatement of cocaine seeking induced by the light-tone cue. In contrast, pre-training inactivation failed to affect the reinstatement. When reinstatement was triggered by cocaine priming injections, the pre-, or post-training OFC inactivation had no effect. These data suggest that the OFC is relevant for the assessment of the motivational value of conditioned stimuli and possibly mediates cocaine seeking behavior [90].

In a similar reinstatement paradigm, the involvement of prefrontal cortex D_1 and D_2 dopamine receptors in cocaine primed reinstatement has been determined [91]. Before the reinstatement phase, the rats received infusions of D_1 and D_2 receptor antagonists. Blockade of both receptors decreased cocaine-induced reinstatement of drug-seeking behavior. In addition, the D_2 receptor antagonist increased the self-administration of cocaine whereas the D_1 receptor antagonist did not. These results assign an essential role for dopamine receptors in drug-seeking behavior, however, because of the differential effects, it is likely that both receptor mediate different aspects of this behavior [91]

In sum, many drug-induced behavioral changes seem to involve impaired behavioral inhibition. These observed deficits are associated with prefrontal cortex malfunctioning. Interestingly, drug-induced behavioral adaptations sometimes resemble lesion-induced behavioral alterations as discussed in the previous chapter. Abnormalities in OFC activity reflect difficulties in adjusting behavioral output in accordance with expected outcomes and reversed discrimination stimuli. Additionally, OFC damage alters cue-induced reinstatement of drug-taking. Lesions of the mPFC and the ACC alter attentional functioning, acquisition of cocaine self-administration and overall behavioral inhibition. These changes in behavior observed in animal models are of special interest because of the resemblance with the behavioral deficits present in humans suffering from addiction.

4.3 Summary

In this chapter, drug-induced changes in the prefrontal cortex have been discussed. Chronic drug exposure has been demonstrated to modify both cortical and subcortical regions. These modifications include morphological changes in dendritic spine densities, changes in neurotransmission and behavioral deficits. Molecular mechanisms underlying these drug-induced alterations are likely to involve changes in G-protein signalling pathways, however, these mechanisms within the prefrontal cortex are not yet well understood. Drug-induced changes in neuronal activity have been observed and could account for the long-lasting morphological adaptations. These adaptations may provide a structural mechanism for the changes in neurotransmission and eventually the deficits in the behavioral repertoire. For example, amphetamine exposure has been shown to increase activity in the OFC [73]. Dendritic spine density is however reduced after long-term amphetamine self-administration [71]. Thus, the increased OFC activity, could be compensated by the reduction of spine density. As a consequence of this decline, the OFC functioning is possibly changed which could lead to the behavioral deficits seen in addiction.

The behavioral deficits in these animal models all concern behavioral control. One great advantage of animal models is that all these observed modifications are drug-induced and not preexisting. Whereas in humans this dissociation cannot be made, the animal models suggest that the behavioral deficits in human addiction can be at least in part caused by chronic exposure of the drug of abuse.

Chapter 5

Discussion

With at least 15,3 million people suffering from illicit drug use disorders and many more alcohol and tobacco abusers, addiction is a worldwide problem that puts a great burden on society. Traditionally, research has focused on the reinforcing effects of drugs of abuse and the underlying neuronal mechanisms. The mesolimbic dopaminergic pathway, especially the nucleus accumbens, is considered to be a particularly important target for drugs and their motivational value [12]. Most drugs of abuse act directly or indirectly on this mesolimbic system by increasing the extracellular dopamine concentrations [11].

Recently, however, the involvement of other brain areas in developing addiction has gained interests, especially the prefrontal cortex. This region is crucial in inhibitory control processes [26], which has been demonstrated to be dysfunctional in people suffering from addiction [3, 22]. Addicts display deficits in decision-making, cognitive and behavioral control and abnormalities in cue-reactivity (see section 3.1). These impairments have all been implicated in compulsive drug seeking and relapse. Moreover, addicts assign high motivational values to drugs, however, they seem to be less sensitive to natural rewards, e.g food. While the abnormalities in motivational values of the drugs of abuse are suggested to be mediated by the mesolimbic system, the prefrontal cortex is now believed to be essential in the compulsive character of addiction. Hence, addiction comprises several aspects mediated by different systems [10].

The present report has focused on the involvement of the prefrontal cortex in addiction. Numerous studies have emphasized that prefrontal cortex function and structure differs between addicted people and healthy controls. However, whether these differences are a consequence of drug use or preexisting vulnerability traits is still subject to debate. Therefore, the aim of this report was to provide an overview of the abnormalities seen in the prefrontal areas of the addicted brain and the related behavioral deficits, and in addition to review the actual drug-induced deviations examined by animal models. The animal studies can differentiate between cause and consequence and are therefore essential in understanding the process of addiction and the underlying mechanisms.

As described in the second chapter, several regions of the PFC have been implicated in addiction. The DLPFC is thought to be crucial for attention, working memory and preparation of actions. The OFC is especially important in adjusting behavior in accordance of motivational significance of stimuli, and the ACC is involved in evaluating processes such as performance monitoring and conflict detection. In addition, the OFC and ACC are both involved in stimulus-reward learning. Damage to these areas result in cognitive and behavioral impairments that resemble the deficits seen in addiction. Furthermore, cognitive and behavioral deficits displayed by substance abusers are often associated with abnormalities in these prefrontal cortex areas (see chapter 3). For example, impaired decision making is regularly associated with orbitofrontal dysfunction, and the deficits seen in amphetamine users resemble decision making after orbitofrontal lesions [36]. Imaging studies have revealed structural and metabolic abnormalities in the prefrontal cortex of substance abusers. In animal models it has been demonstrated that chronic drug exposure can lead to structural and metabolic abnormalities in the same areas (see chapter 4). Chronic drug exposure in these animals did not only result in these structural changes, behavioral deficits similar to those observed in addicts were demonstrated in the drug exposed animals as well. The behavioral deficits have in common that they all concern impaired inhibitory control. In both humans and animals, this lack or loss of inhibitory control is associated with prefrontal cortex malfunctioning.

5.1 Role of the DLPFC, OFC and ACC in addiction

When elaborating in more detail on the specific role of the different prefrontal regions in addiction, not all studies are consistent in their results. For example, although damage to the DLPFC is associated with impaired attentional shifting processes in animals [32], substance abusers do not show abnormal DLPFC functioning despite similar attentional deficits [60]. In contrast, differences in performance between substance abusers and controls were related to ACC functioning. The ACC is associated with performance monitoring and it is postulated that the observed hypoactivity of the ACC reflects an inability to signal the necessary amount of cognitive control to the more executive DLPFC. Furthermore, not all substance abusers with abnormal neuronal functioning, exhibit attentional deficits [61]. It is therefore suggested that more neural pathways can be utilized to solve attentional problems and that compensatory mechanisms might be at work. Regardless of the inconsistencies, chronic drug exposure has been demonstrated to alter the DLPFC structure and function in animals. In drug pre-treated rats, the increase in the mPFC dopamine levels after drug exposure has been observed to be attenuated compared to controls [72, 75], and morphological changes in dendritic spines have been described as well [71]. Attentional deficits seen in drug exposed animals are often similar to those seen in lesion

studies and involve, as expected, the DLPFC. Moreover, in humans, working memory related decision making deficits in substance abusers [35] and memory related cue-reactivity [64] are associated with the DLPFC.

Similar to the DLPFC, studies assessing the role of the OFC in addiction show inconsistencies in their findings. Although the OFC is generally implicated in inhibitory control in animal models (see section 2.2.2), several human studies have highlighted the importance of the other areas in inhibition. In animals, the commonly used paradigms for inhibitory control are reversal learning and reward devaluation tasks. In these tasks, behavior must be adjusted to new expected outcomes. In other words, previously acquired associations must be suppressed in favor of new ones. Damage to the OFC results in impaired performance in these tasks, suggesting a role for the OFC in inhibitory control. However, the used inhibitory control paradigms in human research, such as the Go/No-Go and Stroop tasks, sometimes ascribe an essential role to the OFC in inhibitory control while sometimes the involvement of the ACC is emphasized (see section 3.1.2). For example, OFC activity in a Go/No-Go task has been found to be correlated with the amount of false alarms; the more activation, the less false alarms [48]. This result suggests that more inhibitory control is accompanied by more OFC activity. Since substance abusers make significantly more false alarms [59], it can be expected that this impairment is reflected in decreased OFC functioning. Yet, when comparing substance abusers with healthy controls in the same paradigm, instead of changes in the OFC, decreased activity in the ACC was found [59]. This seems especially surprising since an overall hypoactivity of the OFC after detoxification has been observed repeatedly [3] and altered metabolic functioning [16] as well as decreased grey matter in the OFC in humans [65] is associated with drug exposure. In addition to behavioral inhibition, several cognitive inhibitory control studies in substance abusers, e.g. the Stroop task, have been ascribing an essential role to the ACC as well [60, 58]. Thus, whereas animal models predominantly relate inhibitory control to OFC functioning, the ACC is often associated with impaired inhibition in substance abuser.

In a Go/No-Go test in rats, for example, it has been demonstrated that cocaine treatment affects the functioning of the OFC neurons and that this alteration results in abnormal behavioral outcomes [82]. In this study, Stalnaker and colleagues [82] showed that OFC neurons of cocaine pre-treated rats fail to develop cue-prediction specific firing, which resulted in abnormal changes in response latencies in aversive trials. These results are in line with lesion studies [43], in which the rats with OFC lesions failed to inhibit responding in negative trials. In addition, relative to controls, cocaine-treated rats had less neurons that reversed their cue-selectivity after reversal of the outcomes [82]. Thus, the previously acquired associations could not be inhibited in favor of new ones, and this was reflected in the inability of the OFC neurons to signal the expected outcome.

The inability to signal expected outcomes is also thought to underlie deficits in decision making seen in substance abusers [3, 4] and patients with OFC

damage [92]. Both addicts and OFC patients fail to choose advantageously by persisting in choosing immediate gains over long-term losses [3, 4]. In substance abusers, the OFC is shown to be over-active during gambling tasks [58], suggesting a role in decision making. In healthy subjects however, several other prefrontal areas, such as the DLPFC and the ACC, are implicated in decision making as well [56]. Higher OFC activity was correlated with better performance in both abusers and controls. These findings suggest that the over-activity may reflect an attempt to meet the demands of the task due to OFC inefficiency. Alternatively, this over-activation is suggested to reflect enhanced anticipation for the reward [58].

In addition to its role in inhibitory control and decision making, the OFC has a well-described function in processing drug-associated stimuli (reviewed by [93]). In humans [63] as well as in animals, drug-related stimuli trigger OFC activity. Although this OFC activity is often related to subjective feelings of craving in humans, data are not completely consistent and other prefrontal areas are believed to be involved as well [3]. Nevertheless, as shown by multiple animal models, the OFC is crucial in processing drug-cues and the reinstatement of drug-seeking behavior [90]. In a study by Fuchs *et al.* [90], reinstatement of drug seeking behavior in rats was examined. Inactivation of the OFC after training resulted in an inhibition of cocaine seeking induced by the conditioned stimulus. These findings provide evidence for the involvement of the OFC in e.g. relapse. Since the OFC in substance abusers is believed to be dysfunctional, as shown by metabolic and structural alterations, it might be expected that similar to these rats, the reinstatement of drug seeking behavior by drug-cues is inhibited. The opposite pattern however is present, as drug-cues are known to initiate relapse. In addition, cue presentation is, as mentioned before, associated with increased OFC activity. Therefore, it has been hypothesized that the OFC may compensate for its malfunctioning which results in an abnormally strong cue-reactivity [90].

Especially in humans, the anterior cingulate cortex has been regularly implicated in addiction. The functions of the ACC are multiple, including performance monitoring, conflict and error detection [26, 41] and stimulus-reinforcement learning [53]. In addition, the ACC has also been associated with decision making [56] via the ability to monitor the performance and benefit from feedback [4]. In substance abusers, multiple behavioral impairments have been associated with ACC functioning [59, 60, 61]. For example, the ACC is demonstrated to be hypoactive in substance abusers relative to controls during attentional set shifting [60] and hyperactive during incongruent trials of the Stroop test [61]. Differences in grey matter concentration are reported between cocaine users and controls [65] and the addicted brain exhibits dysfunctional connectivity patterns involving the ACC [66]. In animals, however, the majority of studies have implicated other areas, e.g. the orbitofrontal cortex, as responsible for these observed behavioral impairments (see section 4.2). Cue-induced activity is observed in the anterior cingulate cortex and regularly associated with subjective feelings of craving [52, 63]. These findings are in line with the role of the ACC in

stimulus-reinforcement learning in rats [49, 50] and the involvement of the ACC in self-administration of drugs of abuse [88].

The findings that the anterior cingulate cortex is associated with numerous behavioral impairments in substance abusers, suggest a crucial role for this area in behavior, especially inhibitory control. Since the ACC in believed to monitor performance, it has been hypothesized that this function is necessary for normal inhibitory control functioning [26]. During inhibitory control tasks, such as the Stroop task, detection of the conflict situation is crucial and precedes control mediation. It has been suggested that this mediation, executed by other prefrontal regions, depends on signals from the ACC [26]. It is therefore plausible that the altered ACC functioning in substance abusers is a reflection of the inability to signal the necessary amount of cognitive control to prefrontal areas such as the DLPFC and the OFC [60]. A proposed mechanism through which the ACC functioning is affected in drug abuse concerns dopamine transmission [4]. Because of the ACC's connections to the nucleus accumbens and the high levels of dopamine receptors in the ACC, repeated exposure to drugs of abuse can result in a homeostatic down-regulation of dopamine receptors. Thereby the ACC might become hypoactive [4] resulting in multiple behavioral deficits.

5.2 Human studies versus animal models

As discussed, the specific mechanisms underlying the behavioral deficits in substance abusers are still not precisely understood and different areas are implicated in human research compared to animal models. Animal models have provided evidence for the idea that at least some behavioral deficits can be drug-induced, however these models do not explain why some individuals become addicted and others do not. Experimental groups of animals receive a relative modest amount of drugs and do not comply with the excessive and often poly-drug abuse seen in addiction. Furthermore, the compulsive character of drug seeking despite aversive outcomes in humans has not been included in each animal model. These differences between human and animal research could bring about the dissimilarities observed in the involvement of specific prefrontal areas. For example, in rats, post-training OFC damage inhibited cue-induced cocaine seeking [90]. Since it has been demonstrated that the OFC of substance abusers is malfunctioning, it might be expected that cue-induced drug seeking is inhibited as well. However, the opposite pattern has been observed, as substance abusers often display cue-induced relapse. It has been proposed that increased OFC activity after cue presentation in humans is due to compensation for the inefficiency of the damaged OFC. However, the rats might not have developed such a mechanism since they were drug-exposed during a relatively short period. In addition, the rats were trained to self-administer cocaine, however, it was not demonstrated that these rats would continue to do so when the outcome would become aversive as in human addiction. The importance of an extended history of drug-exposure in compulsive drug-seeking

was demonstrated in a paradigm in which rats underwent fear conditioning [94]. In this experiment only the rats with a long history of drug self-administration continued to seek cocaine after presentation of the fear conditioned stimulus. Rats with limited cocaine exposure periods, as well as rats with long history of sucrose self-administration, suppressed their seeking responses. Interestingly, in a slightly different paradigm it was demonstrated that only a small subpopulation continued to seek cocaine after pairing seeking behavior unpredictably with cocaine or foot shock [95]. Remarkably, the percentage of the vulnerable subpopulation in these rats (17-20%) resembles the percentage of human drug users developing and addicted state (15-16% [96]). That not all cocaine exposed rats behave similarly is also reflected in neuronal activity as demonstrated by Stalnaker *et al.* [82]. In this reversal paradigm, some cocaine treated rats exhibited impaired reversal learning which was accompanied by less flexible cue-selective neurons. However, some cocaine rats did reverse their neuronal cue-selectivity and displayed normal behavior.

In essence, although drug exposure can induce behavioral changes, individual vulnerability traits cause differences in responding to drugs of abuse. Not all animals models reveal these differences due to experimental limitations. Since the majority of human research has been focused on only a small part of the drug using population, namely the individuals which were obviously vulnerable to addiction, caution must be taken when comparing human and animal research. The next section will elaborate on the individual differences that may contribute to the transition from drug use to addiction.

5.3 Cause or consequence?

Although the precise role of the specific prefrontal regions in addiction remains unclear, it has been generally accepted that prefrontal dysfunction is associated with inhibitory control impairments in humans and animals, and that chronic drug exposure can cause this dysfunction, at least in animal models. Since multiple studies have demonstrated drug-induced structural and behavioral changes in animals, it is likely that the deficits seen in humans can be at least in part a result of chronic exposure to drugs of abuse. Moreover, some human studies provide evidence for this idea as well, for example, by the observed correlation between the amount of drug used per week and the activity in specific prefrontal areas [61]. However, drug-induced alterations in the prefrontal cortex only provide a mechanism that might facilitate the development of the addicted state and do not explain why some individuals become addicted and why others do not. Recently, several studies have related preexisting individual differences to the vulnerability for developing drug addiction [97, 98].

An interesting study by Volkow and colleagues [97] examined the correlation between striatal D_2 receptor levels and subjective methylphenidate experiences. Significantly lower levels of D_2 receptors were found in subjects who liked the effects of methylphenidate in comparison to subject who disliked the effects. Furthermore, the higher the striatal receptor levels before drug intoxication,

the less pleasant the drug was experienced. This observed correlation between D_2 receptor levels and the reinforcing responses to methylphenidate provides a possible predicting value for the predisposition towards developing addiction [97]. In addition, decreased D_2 receptor level availability has been demonstrated to be associated with decreased orbitofrontal metabolism [99]. Because of the reduced D_2 receptor levels found in addicts, these findings suggest a direct correlation between drug use and impaired cognitive capacities. In monkeys, D_2 receptor availability has been demonstrated to be correlated with the reinforcing effects of cocaine as well [100]. Moreover, dopamine receptor levels were associated with social status, since social housing increased receptor levels solely in dominant monkeys. Cocaine only functioned as a reinforcer in subordinate individuals. These data provide evidence that dopamine receptor levels can predict individual vulnerability to addiction, and in addition propose a direct link between chronic drug use and prefrontal functioning.

Moreover, cognitive and behavioral capacities might act as predicting vulnerability measures for developing the addicted state. It has been hypothesized that rather than a result of drug exposure, poor decision making is what leads to addiction [101]. Poor decision making has been observed in adolescents with behavior disorders who are believed to be at greater risk for developing substance abuse [98]. These adolescents performed equally well as adult substance abusers indicating that this impairment might represent a vulnerability trait. In addition, adolescents with behavioral disorders performed poorly on the Wisconsin Card Sorting test relative to age controls. This difference has been postulated to reflect a high degree of impulsivity in the adolescents with behavioral disorders [98]. Impulsivity, which is related to impaired inhibitory control, is commonly associated with repeated drug exposure [19]. Chronic exposure to drugs of abuse can lead to changes in impulsivity and hypoactivity of specific prefrontal areas, such as the orbitofrontal cortex, has been associated with impulsivity [102]. Thus, it seems that impulsive behavior can be induced by drug use, and although the evidence is still limited, additionally may lead to drug use.

Taken together, inhibitory control deficits observed in substance abusers are likely to be a product of both preexisting vulnerability and drug-induced prefrontal alterations. Individuals with underdeveloped prefrontal cortex function, due to e.g genetics or age, are possibly more susceptible for the process of developing drug addiction. At the same time, the effect of drug use on the prefrontal cortex might facilitate this process. Because of the accumulating evidence that implicates prefrontal cortex dysfunction in addiction, inhibitory control deficits are becoming increasingly more prominent in theories describing addiction. Some theories describe addiction as a two system process; 1) the augmentation of the incentive motivational value of drugs, which is associated more with subcortical areas, and 2) impaired inhibitory control which results from prefrontal dysfunction [19]. Bechara [101] describes these two systems as impulsive (bottom-up) and reflective (top-down) and hypothesizes that addiction is the product of an imbalance between these two separated neural mechanisms.

Although most theories about addiction now include prefrontal dysfunction and the associated inhibitory control impairments [10, 21], the focus on the cause or consequence debate differs regularly. While some theories emphasize that drug-induced prefrontal changes cause addiction [19], others consider the preexisting prefrontal malfunctioning the main reason for developing the addicted state [101]. Future research might elucidate the precise contribution of the preexisting and drug-induced prefrontal dysfunction to the development of drug addiction.

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