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A joint approach: brain structure & function in heavy cannabis users & their relationship with future use

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CHAPTER 1

GENERAL INTRODUCTION

CANNABIS DEPENDENCE, A BRIEF HISTORY

The existence of cannabis dependence has been questioned for a long time (Murray et al., 2007). The debate surrounding cannabis dependence partly stemmed from an outdated view on Substance use Disorders (SUDs; Leshner, 1997), which measured the relative harm of a certain substance of abuse through the severity of physical dependence (tolerance and withdrawal). In early nosologies, a clear distinction was made between physical and psychological dependence (i.e., craving), the latter being relatively harmless. In 1964 the World Health Organization recognized psychological dependence as the driving force behind substance dependence, not physical dependence (Eddy et al., 1965). However, the minimal withdrawal symptoms associated with chronic cannabis use still supported the general consensus that cannabis was not addictive (Murray et al., 2007).

An important turning point came in the late 90s when SUD was defined as a chronic relapsing brain disease characterized by compulsive substance use, despite awareness of its harmful consequences (Leshner, 1997). The core symptomatology derived from this definition was shared between cannabis and other substances of abuse like alcohol, tobacco, cocaine, and heroin. Thus, by considering continued substance use despite awareness of the negative consequences as the core of SUDs, this change in definition impacted views on cannabis dependence. Also, the shared symptomatology, but also the established existence of a physical cannabis withdrawal syndrome (Budney and Hughes, 2006; Chung et al., 2008), and commonalities in mechanisms of drug action on the brain reward system, heritability, and effective treatments for cannabis use disorders and other SUDs contributed to the increased awareness of the addictive potential of cannabis (Murray et al., 2007). Paralleling this increased awareness, treatment demands for cannabis use disorders strongly increased the past decades. Worldwide treatment demands for cannabis related disorders nowadays directly follow demands for alcohol and opiates (UNODC World Drug Report, 2009). Moreover, Δ9-tetrahydrocannabinol (THC) concentration in cannabis has increased, potentially leading to additional health risks (Mehmedic et al., 2010; Pijlman et al., 2005).

There have been multiple attempts to quantify and compare the addictive potential of various substances of abuse. Survey based research among (both research and clinical) specialists indicated that the perceived addictive potential of cannabis is generally lower than heroin, cocaine, amphetamine, alcohol, and nicotine, (Gore and Earleywine, 2007; Nutt et al., 2010; Van Amsterdam et al., 2010; Wagner and Anthony, 2002). Comparing individuals in treatment for a specific SUD with the total number of last year users yielded similar results. For example, 22 per 100 past year opiate users underwent treatment, whereas for cannabis only 1 per 100 in the USA and 1 per 230 in Europe underwent treatment (UNODC World Drug Report, 2009). These findings indicate that there is an established addictive potential of cannabis, but it may be relatively low in comparison to other substances of abuse.

Cannabis is the most frequently used illegal drug in most countries thereby leading to large numbers of individuals with a cannabis use disorder (UNODC World Drug Report, 2009). Moreover, the addictive potential on a population level does not necessarily say anything about problem severity in cannabis users who do develop cannabis dependence. Unfortunately, in comparison to other substances of abuse, relatively little is known about the mechanisms underlying cannabis dependence. Perhaps surprisingly, given its established addictive potential, even studies conducted during the past decade often report on chronic or long-term cannabis use rather than cannabis dependence (Budney, 2006).

UNBALANCED MOTIVATION & CONTROL IN SUDS: A THEORETICAL VIEW

A central paradox in SUDs is the difficulty to control the urges to use drugs, despite awareness of the negative consequences associated with it. Someone with a SUD compulsively continues to use, while failing to cut down or quit. There have been multiple attempts from different research fields to explain how these addictive behaviors develop (e.g., Dawe and Loxton, 2004; Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Robinson and Berridge, 2003; Verdejo-Garcia and Bechara, 2009; Wiers et al., 2007). These different SUD models agree in terms of stressing the importance of an imbalance between strong motivations to use and compromised cognitive control (disinhibition). Repeated pairing of substance use with certain cues like paraphernalia, contexts, and emotional states is thought to cause the substance users' brain to become extremely sensitive towards these cues. Subsequent cue encounters may then trigger sensitized and conditioned responses to use again, thereby favoring continued substance use and relapse. The potency of substances of abuse to induce sensitized and conditioned responses probably lies within the initial reinforcing effects. During the course from recreational to compulsive substance use, this reinforcing value is thought to change from liking (very much) to wanting and needing (Robinson and Berridge, 2008). The addictive potency of a specific substance of abuse may then in part be reflected by the strength of its initial reinforcing effects. Combining sensitized and conditioned responses with compromised cognitive control (either as a pre-existing vulnerability or potentially caused by substance use itself) may then result in an escalation towards compulsive substance use.

The neural substrates underlying SUDs have been studied extensively (Everitt and Robbins, 2005; Koob and Volkow, 2010; Wilson et al., 2004). The multifaceted, complex, and heterogeneous nature of SUDs is reflected in the neural substrates that have been linked to it. Integrative models of the neurobiology underlying SUDs identified at its core circuits involved in reward processing, learning and memory, and behavioral control (Everitt and Robbins, 2005; Koob and Volkow, 2010; Robinson and Berridge, 2008). The brain-reward circuit consists of the dopaminergic projections from ventral tegmental area (VTA) to nucleus accumbens (NAc) and to prefrontal areas like the

orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC). In early stages of SUD, the reward threshold of dopamine neurons in the VTA is thought to change, resulting in increased firing of these neurons in response to substance related cues (Koob and Volkow, 2010). The NAc is thought to connect motivational aspects of salient stimuli with motor actions (Everitt and Robbins, 2005), whereas the ACC has been found to be involved in attention, conflict monitoring, and assessing salience of motivational information (Ridderinkhof et al., 2004). The OFC has been found to play an important role in reward evaluation and, together with the ACC, in the integration of motivational information into cognitive processes (Koob and Volkow, 2010; Li et al., 2010; Mansouri et al., 2009). Regarding learning and memory, particularly the hippocampus and amygdala have been thought to be important substrates of establishing conditioned responses towards substance related cues. In addition, the amygdala has been known to be involved in attributing emotional salience to cues and initiating approach and avoidance actions (Schneider et al., 2001).

During the course from recreational to compulsive substance use, substance use becomes more habitual. The dorsal striatum is predominantly thought to be involved in forming habits as compulsive substance use progresses (Belin and Everitt, 2008; Everitt and Robbins, 2005). This may in part also explain the change of the substance's reinforcing value from liking to wanting and needing (Robinson and Berridge, 2008). One of the main neural substrate thought to be involved in cognitive control is the prefrontal cortex (PFC), of which the dorsolateral prefrontal cortex (DLPFC) and the ACC have been considered key structures (Mansouri et al., 2009). However, most cognitive functions have generally been found to involve widespread neural networks, of which the PFC is consistently a part (Mansouri et al., 2009).

EVIDENCE FOR BIASED MOTIVATION IN SUDS

In the context of this dissertation, the term motivational process refers to the appetitive or aversive emotional processes that guide behavior. Motivational processes would normally bias behavior to maximize reward while minimizing punishment (Naqvi et al., 2006; Paulus, 2005). In case of individuals with a SUD, motivational processes are thought to be biased towards maximizing reward through substance use. Although motivational processes are thought to be triggered relatively automatically, they may also reach consciousness.

Motivational processes in relation to SUDs have predominantly been investigated by measuring cue-reactivity. Cue-reactivity refers to a wide range of behavioral, physiological, and neural responses triggered by substance-related cues (Carter and Tiffany, 1999). The extensive literature on cue-reactivity indicates that substance-related cues indeed bias motivational processes towards substance use as they increase subjective craving, automatically capture attention, activate approach tendencies, and are both implicitly and explicitly evaluated as more

arousing and positive in comparison to neutral cues (for review see Carter and Tiffany, 1999; Wiers et al., 2007). These processes appear to be common for various substances of abuse including heroin, cocaine, alcohol, tobacco and cannabis. Moreover, higher levels of substance use and severity of dependence tend to be associated with stronger cue-reactivity, although not consistently over studies (e.g., Field et al., 2008a; Goldstein et al., 2009a; Janes et al., 2010). The link between biased motivational processes and continued substance use is further supported by studies indicating that cue-reactivity could predict treatment outcome and relapse (e.g., Janes et al., 2010; Marissen et al., 2006; Payne et al., 2006; Waters et al., 2003). Finally, it has been shown that heavy drinkers (Wiers et al., 2010) and alcohol-dependent patients (Wiers et al., 2011) can be retrained to avoid alcohol, which leads to improved treatment outcome in alcohol-dependent patients.

Among the extensive literature on cue-reactivity, subjective craving is one of the most commonly reported measures (Carter and Tiffany, 1999). Subjective craving is thought to be an important contributor to continued substance use and relapse (Franken, 2003; Oslin et al., 2009), and can be seen as intrusive cognitive elaborations of the desire to use, automatically triggered by substance-related cues (Kavanagh et al., 2005). A disadvantage of self-reported measures like craving is that they are relatively easy to fake. Besides, among individuals with a SUD, self-awareness may be compromised as part of the disorder (Goldstein et al., 2009b). In the past decades, more and more studies have used implicit (i.e., indirect) cue-reactivity measures to investigate motivational processes underlying continued substance use and relapse. A variety of tasks have been developed to measure implicit motivations, typically requiring participants to respond as fast as possible in the context of substance-related cues and control cues. These tasks can roughly be divided into measures of attentional bias, approach bias, and implicit memory associations (Wiers et al., 2007). There is evidence suggesting that implicit measures are more sensitive and harder to fake than explicit self-reports (De Houwer et al., 2009). Importantly, there are also indications that different implicit measures uniquely contribute to substance use-related behaviors (Rooke et al., 2008; Stacy and Wiers, 2010). Thus, although the generally belief is that different cue-reactivity measures are all manifestations of sensitized and conditioned responses towards substance related cues, they are not necessarily measures of a single underlying process. This idea is further supported by a recent meta-analysis of the association between subjective craving and attentional bias, indicating that motivational measures like craving and attentional bias do share some variance, but that the correlation was rather low (Field et al., 2009). These findings thereby stress the importance of investigating and differentiating between the various motivational processes.

The neural mechanisms underlying cue-reactivity, specifically in relation to cue-induced craving have repeatedly been investigated by exposing individuals with a SUD and healthy controls to substance-related cues (i.e. pictures, words, tactile cues, olfactory cues, movies, personalized

scripts) while simultaneously measuring brain activity with functional Magnetic Resonance Imaging (fMRI). These studies show that the multi-faceted nature of cue-reactivity is reflected in the underlying neural substrates: exposure to substance-related cues (compared to neutral cues) is related to widespread activations in reward, motivation, cognitive control, and memory circuits (e.g., Garavan et al., 2000; Goldstein et al., 2009a; Janes et al., 2010; McClernon et al., 2005; Myrick et al., 2004; Smolka et al., 2006; Zijlstra et al., 2009). In agreement with theoretical SUD models, the brain regions commonly associated with cue-reactivity are the brain reward circuit and amygdala (Everitt and Robbins, 2005; Wilson et al., 2004). The subjective/conscious experience of craving has been primary linked to OFC, ACC, and insula (Naqvi and Bechara, 2009; Volkow et al., 2004). Moreover, increased dorsal striatum activation in response to alcohol cues has been observed in heavy-social, but not light-social drinkers (Vollstadt-Klein et al., 2010), supporting a role of the dorsal striatum in habit formation as compulsive substance use progresses (Everitt and Robbins, 2005; Porrino et al., 2007; Wilson et al., 2004).

Most studies investigating cue-reactivity in the brain use paradigms during which participants only observe, feel, or smell substance-related and neutral cues. An irrelevant task may be integrated to ensure maintained attention. Although these studies are valuable to our knowledge of the mechanisms underlying cue-reactivity, the employed paradigms are rather coarse to disentangle different motivational processes since the brain areas found to be activated by those tasks play a role in many different processes. Unfortunately only a limited number of studies investigated the neural mechanisms underlying attentional bias. In current tobacco smokers compared to non-smoking controls the attentional bias has been found to relate to activation of brain areas involved in executive control (Luijten et al., 2011; Stippekohl et al., in press). A study comparing current and ex-tobacco smokers indicated that only ex-smokers show higher attentional bias related activity in brain areas involved in executive control (Nestor et al., 2011). These results have been interpreted as engagement in an active strategy to prevent motivational responses to the smoking cues from interfering with task performance. A study in cocaine dependent individuals showed that attentional bias related activity in brain areas associated with cognitive control predicted treatment outcome (Brewer et al., 2008). Interestingly, two studies, one in smokers and one in alcoholics, showed that the attentional bias measured with an offline implicit behavioral task correlated positively with brain activity in areas involved in motivation (Janes et al., 2012; Vollstadt-Klein et al., 2012). To the best of our knowledge there are no published studies investigating the neural mechanisms underlying approach bias and implicit memory association, indicating a clear research gap between the recent progress of behavioral studies and neuroimaging studies regarding implicit measures of motivation. Nevertheless, these studies suggest that biased motivational processes may not just reflect bottom-up sensitized and conditioned responses, but show an important interaction with executive control function.

EVIDENCE FOR COMPROMISED COGNITIVE CONTROL IN SUDS

The evolution of the human prefrontal cortex brought about great behavioral flexibility, but also conflict and uncertainty as the options we can choose from are numerous (Miller and Cohen, 2001). Along with it evolved mechanisms of cognitive control, that is, the processes involved in top-down adaptation of moment to moment behavior depending on current internal goals (Mansouri et al., 2009). Cognitive control involves many different regulatory or executive functions including response inhibition, task shifting, sustained attention, problem solving, working-memory (the capacity to maintain and manipulate the information 'online'), conflict monitoring, decision-making, planning, organizing, and episodic memory. Functions like decision-making itself are also a complex interaction between various functions: coming to an appropriate decision involves evaluation of positive and negative consequences, the capacity to retrieve this information from memory, and working-memory (Paulus, 2005).

There is no general consensus on the sub-processes involved in cognitive control and its complexity is reflected in studies investigating it. Studies have found broad impairments in individuals with a SUD compared to healthy controls, especially in inhibition (Fernandez-Serrano et al., 2011; Van Holst and Schilt, 2011). Given the broadness of the impairments, a recent review tried to differentiate between SUD specific and SUD general deficits in cognitive control functions after various periods of abstinence (Fernandez-Serrano et al., 2011). Especially those functions that remain impaired after prolonged abstinence might be at the core of SUDs (and behavioral addictions like pathological gambling). It appears that both substance specific and general impairments in cognitive control functions decrease with prolonged abstinence. Although only a limited number of studies investigated cognitive control functions after prolonged abstinence, there are indications that working-memory might be a SUD general deficit still impaired after prolonged abstinence. Also, psychostimulant-related deficits in cognitive flexibility, planning, and episodic memory may be persistent even after several years of abstinence. Important to note, the relationship between cognitive deficits and substance use is suggested to be bidirectional, being both cause and a consequence of substance use (Verdejo-Garcia et al., 2006).

Working memory is a central executive function and its integrity is required for a broad range of cognitive functions (Baddeley, 2010; Kane and Engle, 2002). Working-memory capacity sets a limit to attentional control and is especially important when interfering signals trigger behavioral tendencies conflicting with pursued goals (Kane and Engle, 2002). This suggests that when motivational processes to use drugs are strong, people with relatively poor working-memory more easily give in to the urge to use. Indeed, recent studies have shown that individual differences in working-memory capacity moderate the relationship between motivational processes and substance use (Grenard et al., 2008; Thush et al., 2008). Further supporting the link between working-memory and continued substance use, working-memory impairment in tobacco

smokers has been found to predict relapse (Patterson et al., 2010). Moreover, interventions that train working-memory have been found effective in improving cognitive dysfunction in stimulant dependent individuals (Bickel et al., 2011), and in reducing alcohol intake in problem drinkers (Houben et al., 2011). These findings suggest an important role for working-memory function in SUDs.

Decision-making as measured with the Iowa gambling task (IGT) is one of the most replicated executive deficits associated with SUDs (Fernandez-Serrano et al., 2011). The IGT is a monetary decision-making task that measures decision-making under risk, involving choices between small immediate gains with small long-term losses and large immediate gains with even larger losses (Bechara et al., 1994). The concept of the IGT is intuitively closely related with real life decision-making deficits observed in SUD populations: they choose the immediate rewarding effects of substance use, despite knowledge of the negative consequences. Normative IGT data shows that healthy individuals start off choosing relatively disadvantageously (i.e., large immediate gains with larger losses) but eventually develop an advantageous strategy by choosing small immediate gains with small long-term losses (Bechara et al., 1994). However, SUD populations generally keep on making disadvantageous decisions during the IGT (for a review see Buelow and Suhr, 2009).

Neuroimaging studies investigating deficits in cognitive control functions in SUD populations generally agree with theoretical SUD models, assigning a primary role to the PFC and its sub-regions (Koob and Volkow, 2010). Decision-making deficits have mostly been linked to poor functioning of the OFC including the ventromedial prefrontal cortex (VMPFC), an area important in integration of motivational and cognitive information (Paulus, 2005; Verdejo-Garcia et al., 2006). Moreover, neural activation patterns during decision-making have been found to predict relapse (Paulus et al., 2005). Dysfunction of the DLPFC has been linked to working-memory deficits, whereas dysfunction of the ACC has been linked to poor response inhibition in SUD populations (Verdejo-Garcia et al., 2006). Also, neural activation patterns during working-memory appear to be associated with quantitative substance use and withdrawal (Tapert et al., 2004). The above-mentioned findings do not exclusively link compromised control functions to the PFC. Other brain areas have also been implicated but a comprehensive description of those findings is beyond the scope of this thesis.

BRAIN STRUCTURE ABNORMALITIES & SUDS

In addition to altered brain functions, the underlying brain structures also appear to be affected in SUD individuals. Volume reductions have generally been reported for the core neural substrates of SUDs (e.g., Chang et al., 2005; Franklin et al., 2002; Lyoo et al., 2006; Makris et al., 2004; Matochik et al., 2003), and found to relate to history of substance use (Bjork et al., 2003). Moreover,

structural abnormalities have been reported in healthy individuals with a family history of substance dependence (Benegal et al., 2007; Sjoerds et al., in press), indicating that these abnormalities may be pre-existent, predisposing individuals to developing a SUD. Structural abnormalities have also been linked to specific functional impairment in SUD individuals. For example, reduced OFC volume has been linked to poor IGT performance (Tanabe et al., 2009), and reduced hippocampal volume has been linked to poor episodic memory (Thompson et al., 2004). Moreover, structural changes in the OFC, insula, and striatum have been related to individual differences in duration of dependence, inattention and compulsivity of cocaine consumption (Ersche et al., 2011). Studies investigating the white matter connections between brain areas showed white-matter abnormalities in the connections from the insula and striatum to the OFC and VMPFC (Bartzokis et al., 1999; Lim et al., 2002; Lyoo et al., 2004). In sum, there is sufficient evidence of brain structure abnormalities related to SUD. Whether this relationship is causally related or a consequence of SUDs use remains to be tested.

CANNABIS USE, ABUSE, DEPENDENCE & THE BRAIN: WHAT DO WE KNOW?

The terminology used to describe levels of cannabis use, abuse, and dependence greatly varies in the literature. Dependent cannabis users have been called chronic or long-term users and the definitions of frequent, heavy, and chronic use appear to differ between studies. Within the context of this dissertation, cannabis dependence refers to individuals with a DSM diagnosis of cannabis dependence, chronic cannabis use refers to almost daily cannabis use for at least 5 years without a proper DSM diagnosis and heavy cannabis use refers to more than weekly cannabis use for at least two years. Although this definition of chronic and heavy cannabis use is relatively arbitrary, it provides some insight into the extent of cannabis use. Moreover, this distinction between subgroups by no means signifies the absence of cannabis dependent individuals among heavy and chronic users.

Recently, evidence has emerged that biased motivational processes are also evident in heavy, chronic and dependent cannabis users. Cannabis cues have been found to induce craving and arousal as measured with skin conductance in cannabis dependent individuals (Gray et al., 2011; Lundahl and Johanson, 2011) and chronic cannabis users (Wolfling et al., 2008). Unlike controls, heavy cannabis users are biased in detecting subtle cannabis-related changes in complex scenes (Jones et al., 2002; Jones et al., 2003), implying higher attention to cannabis than neutral cues. Further, in heavy cannabis users, an attentional bias for cannabis-related words is associated with craving, frequency of use, and severity of dependence (Field, 2005; Field et al., 2004). Compared to non-users, heavy cannabis users maintain their gaze longer upon cannabis cues, are faster in approaching cannabis cues, and rate cannabis cues as more pleasant compared to neutral

cues (Field et al., 2006). However, the acute effects of cannabis use on motivational processes remain to be investigated.

Little is known about the neural mechanisms underlying cue-reactivity in cannabis users. One study in heavy cannabis users showed that tactile cannabis cues activated various brain areas previously implicated in cue-reactivity, including OFC, ACC, striatum, VTA, and amygdala (Filbey et al., 2009). Moreover, problems related to cannabis use correlated positively with activation in the OFC and NAc. These findings suggest similar cue-reactivity mechanisms for cannabis compared to other substances of abuse. However, an important limitation of this study was lack of a control group.

The acute effects of cannabis use on cognitive control have been well characterized. THC intoxication has been linked to impairments in planning, organizing, problem solving, decision-making, memory, and emotional control (Crean et al. 2011). These deficits are also evident in chronic cannabis users and show great overlap with cognitive control deficits related to other SUDs (Fernandez-Serrano et al., 2011). However, two recent reviews conclude that there is little evidence for long-lasting effects of chronic cannabis use after abstinence (Fernandez-Serrano et al., 2011; Van Holst and Schilt, 2011). The same holds true for the acute and chronic effects of cannabis on the neural circuitry involved in SUDs. Both acute and chronic cannabis use is associated with functional alterations of the brain reward system and PFC, overlapping functional alterations related to other SUDs (Quickfall and Crockford, 2006). Moreover, these functional abnormalities appear to improve and sometimes even fully recover with abstinence.

THC is stored in fat cells and only slowly released, causing the sub-acute effects of cannabis to last up to four weeks in adults and up to six weeks in adolescents (Pope et al., 2002; Schweinsburg et al., 2008a). The deficits observed in (short-term abstinent) chronic cannabis users may then solemnly reflect sub-acute cannabis effects that will eventually wane with abstinence. However, some recent evidence suggests that recovery of cognitive control is hindered by an adolescent onset age, longer duration of cannabis use, and higher quantity cannabis use (Grant et al., 2003; Medina et al., 2007a). Moreover, some of these deficits may be pre-existent, increasing the initial risk to start with cannabis. Finally, there are some indications that there is a (high) threshold at which cannabis use affects cognitive control functions like decision-making (Bolla et al., 2005).

The recovery of cognitive control functions in chronic cannabis users also suggests that the toxicity of cannabis in the human brain may be relatively low. Nevertheless, irrespective of potential drug-specific neurotoxic effects, the development of addictive behaviors is thought to involve neuroplasticity in the ventral striatum and OFC, and eventually other parts of the PFC, ACC, amygdala and dorsal striatum as the addiction progresses (Koob and Volkow, 2010). This is supported by similar brain function deficits observed in SUD individuals compared to pathological gamblers (Van Holst et al., 2010). Unfortunately, to the best of our knowledge there are no studies

investigating cognitive control functions in dependent cannabis users (as characterized by the DSM-IV) who are abstinent for more than a month. Also, there is great variability in studies regarding quantitative cannabis use, definition of problem severity, and dependence (Quickfall and Crockford, 2006). Given the long-lasting sub-acute effects of cannabis and the current literature, it is difficult to differentiate sub-acute from chronic cannabis effects, let alone draw strong conclusions about effects of cannabis dependence on brain function.

The extent to which cannabis use affects brain structure also remains unclear (Lorenzetti et al., 2010). Even though the cognitive recovery observed in chronic cannabis users suggests relatively low toxicity, animal studies have shown neurotoxicity and structural changes in the neurocircuitry underlying SUD after (chronic) exposure to relatively high THC concentrations (Downer et al., 2001; Heath et al., 1980; Lawston et al., 2000; Scallet et al., 1987). Human studies have reported conflicting results regarding the effect of cannabis use on brain morphology. Structural abnormalities in the hippocampus have been observed most consistently in chronic cannabis users (Demirakca et al., 2011; Matochik et al., 2005; Yucel et al., 2008; Yucel et al., 2010). Also, increased cerebellar volume has been linked to diminished cognitive control in one month abstinent chronic cannabis users (Medina et al., 2010). Yet, discrepancies between studies, possibly associated with individual characteristics of cannabis use and related problems, preclude strong conclusions about the relation between brain structure and cannabis use, abuse, and dependence.

NEUROCOGNITIVE PREDICTORS OF SUDS

A fundamentally important question is why some individuals develop a SUD while others do not, even after prolonged heavy substance use. There is great variability in the individual vulnerability to develop SUDs and most substance users will not develop dependence (Swendsen and Le Moal, 2011). Moreover, substance use and related disorders tend to peak during adolescence and young adulthood (Bachman et al., 2002; Schulenberg et al., 2005), indicating that a substantial part of the young users who meet diagnostic criteria of a substance use disorder is able to cut-down or quit when reaching adulthood. This may in part be explained by normative trajectories of brain development: motivational processes reach adulthood early in comparison to prefrontal regulatory functions, of which maturation is suggested to last up to the third decade of life (Somerville and Casey, 2010). In order to prevent individuals from lapsing into chronic abuse, a better understanding of processes underlying the progression from recreational substance use towards dependence is needed. The difficulty to treat SUDs further emphasizes the importance of identifying predictors, with the ultimate goal to develop effective prevention strategies (Oslin, 2011).

Many different factors contribute to an individuals' risk to develop a SUD, ranging from specific genetic to social factors (Swendsen and Le Moal, 2011). Studying brain function with neurocognitive tasks and neuroimaging techniques may provide information about vulnerable intermediate phenotypes to which these factors give rise. As mentioned before, an additional advantage of neurocognitive tasks and neuroimaging techniques is that they do not rely on self-reports, especially since self-insight may be compromised in individuals with a SUD (Goldstein et al., 2009b). From a theoretical perspective, both strong substance-use oriented motivational processes and compromised cognitive control functions may increase SUD risk (e.g., Dawe and Loxton, 2004; Koob and Volkow, 2010; Verdejo-Garcia and Bechara, 2009; Wiers et al., 2007). Motivational and cognitive control functions are heterogeneous within the general population, some of the deficits observed in SUD individuals may thereby precede substance use, predisposing certain individuals to escalate into chronic substance use.

Prospective studies investigating the association between motivation and cognitive control on the one hand and escalation of substance-use and eventually development of a SUD on the other hand are scarce. However, the importance of these processes in the development and maintenance of addictive behaviors has been supported by various studies. First, cross-sectional studies within substance using groups have shown higher levels of use and dependence to correlate with stronger motivational biases (Field et al., 2008a; Ostafin and Palfai, 2006; Palfai and Ostafin, 2003) and worse cognitive control functions (Bolla et al., 2005). Second, both strong motivational biases and poor cognitive control functions have been found to predict the course of substance use and relapse (e.g., Goudriaan et al., 2011; Janes et al., 2010; Marissen et al., 2006; Patterson et al., 2010; Paulus et al., 2005; Payne et al., 2006; Waters et al., 2003). Third, approach bias retraining has been shown to improve treatment outcome in alcoholics (Wiers et al., 2011) and working-memory training has been shown to improve cognitive functions in stimulant dependent individuals (Bickel et al., 2011). In addition, the interaction between motivation and control is stressed by studies showing that working-memory may moderate the relationship between motivational processes and (future) substance use (Grenard et al., 2008; Thush et al., 2008). One longitudinal study investigated the causal relationship between cognitive control functions and substance dependence, indicating poor impulse control as a predictive factor and good working-memory as a protective for alcohol dependence (Penick et al., 2010). Moreover, poor behavioral control at age three has been found to predict adults gambling disorder (Slutske et al., 2012). Furthermore, children with Attention Deficit Hyperactivity Disorder (ADHD) and/or Conduct Disorder (CD), disorders associated with disrupted motivational and control processes, are more likely to develop a SUD later in life (Charach et al., 2011; Lee et al., 2011). As indicated by all these findings, there may be a lot to gain from studying specific motivational processes and cognitive control functions in relationship to future substance use and dependence, as it may identify important new targets for prevention and treatment.

AIM AND OUTLINE OF THIS THESIS

The lack of knowledge regarding the mechanisms responsible for the initiation of cannabis use and the development of cannabis abuse, and dependence, and the high world-wide prevalence of cannabis dependence calls for research to investigate the relationship between brain function and cannabis use, abuse and dependence. The general aim of this thesis was two-fold. First, to profile brain structure and function in heavy cannabis users, brain function assessed at the level of behavior and brain activity, looking at various motivational processes and cognitive control functions. Second, to determine the extent to which these motivational processes and cognitive control functions predict cannabis use and problems prospectively.

The studies compare a large community sample of non-treatment seeking heavy cannabis users at risk for escalation of cannabis use and cannabis-related problems with healthy matched controls. At-risk cannabis use was based on the level of cannabis consumption (at least 10 days per months during the last two years, on average of 5 days per week) and age (18-25), as the PFC is still developing (Casey et al., 2008). Since comorbid substance use is a problem in many cannabis studies, an important selection criteria for the heavy cannabis users was the lack of intensive use of other illicit drugs (Quickfall and Crockford, 2006). The control group consisted of individuals who never used cannabis and individuals who sporadically used cannabis.

The studies described in this dissertation gradually move from brain structure to brain function, from the study of motivational processes, to the study of cognitive control, and finally to the integration of motivational processes and cognitive control. Within those, cross-sectional studies are first discussed, followed by studies investigating the predictive association between motivational and control processes and future cannabis use and cannabis use-related problems. Brain function was studied with behavior tasks and while recording brain activity with fMRI.

Chapter 2 describes the study of brain morphology in relationship to current and lifetime severity of cannabis use and cannabis use-related problems. Voxel-based morphometry (VBM) was used to assess differences in regional grey and white matter volume between heavy cannabis users and controls. Within the group of heavy cannabis users, grey and white matter volume was correlated with measures of cannabis use and cannabis use/related problems.

Chapter 3 describes the neural mechanisms underlying cue-reactivity and their relationship with cannabis use and cannabis use-related problems. Using fMRI, neural responses to neutral and cannabis related cues were compared between heavy cannabis users, sporadic cannabis users, and cannabis-naive controls. In addition, fMRI findings were correlated with the level of cannabis use, problem severity, and craving.

Chapter 4 describes the relationship between implicit affective memory activations and cannabis use. Implicit positive-arousal, sedation, and negative associations towards cannabis were measured with three Single Category Implicit Association Tests (SC-IAT's) and compared between

heavy cannabis users and controls. Moreover, the association between these implicit measures and measures of cannabis use and craving was assessed.

Chapter 5 studies the behavioral cannabis approach bias. Approach and avoidance action-tendencies in response to cannabis and neutral images were measured with a joystick approach-avoidance task (AAT) and compared between heavy cannabis users and controls. Moreover, within the group of heavy cannabis users, the predictive relationship was investigated between an approach bias for cannabis-related materials and levels of cannabis use, craving, and the course of cannabis use over six months.

Chapter 6 investigates the neural mechanisms underlying the cannabis approach bias and its predictive association with future cannabis use and cannabis use-related problems. Using fMRI, neural approach bias activations were measured with a Stimulus Response Compatibility task (SRC) and compared between heavy cannabis users and controls. In addition, associations were examined between approach bias activations and cannabis use and cannabis use-related problems at baseline and at after six months.

Chapter 7 investigates the predictive association between neural mechanisms underlying risky decision-making and future cannabis use and cannabis use-related problems. Brain activity during a monetary decision-making task (IGT) was compared between heavy cannabis users and controls using fMRI. Within the group of heavy cannabis users, associations were examined between task-related brain activations, cannabis use and cannabis use-related problems at baseline and at six-month follow-up.

Chapter 8 describes a study investigating the predictive power of working-memory network function for future cannabis use and cannabis use-related problems in heavy cannabis users. Tensor Independent Component Analysis (Tensor-ICA) was used to investigate differences in working-memory network function between heavy cannabis users and controls during an N-back working-memory task. In addition, associations were examined between working-memory network function and cannabis use and problem severity at baseline and at six-month follow-up. A secondary aim of this study was to evaluate the unique variance explained by this method after controlling for more simple behavioral indices (e.g., questionnaires, behavioral tasks) predicting cannabis use and problem severity

Chapter 9 provides an overview and a general discussion of the main findings. A focus is put on the integration of the findings into a model of cannabis abuse. Moreover, clinical implications, limitations and future directions are discussed.