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

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CHAPTER 9

INTEGRATIVE FINDINGS & DISCUSSION

The general aim of the studies described in this thesis was two-fold. The first aim was to profile brain structure and function in heavy cannabis users. Brain function was assessed at the level of behavior and at the level of brain activity, looking at motivational processes and cognitive control functions. The second aim was to determine the extent to which these motivational processes and cognitive control functions predicted cannabis use and related problems prospectively. In this final chapter the empirical findings will be summarized, integrated, and critically discussed, starting with a detailed profile of brain structure and function in heavy cannabis users compared to healthy controls. Based on the predictive relationship observed between motivational and control processes and cannabis use and problem severity after six months, an integrative model of cannabis abuse is proposed. Moreover, challenges and clinical implications will be discussed, concluding with future research directions.

A PROFILE OF BRAIN STRUCTURE & FUNCTION IN HEAVY CANNABIS USERS

Partly due to the ongoing discussion regarding the addictive potential of cannabis, compared to other substances of abuse, relatively little is known about the brain processes underlying regular cannabis use, abuse and dependence. The rising treatment demand for cannabis use disorders calls for more research investigating the mechanisms underlying continued cannabis use. The heavy cannabis users described in this thesis used cannabis at least 10 days per month for at least 2 years, on average 5 days per week for a period of 2.5 years. This group had no treatment demand or any cannabis treatment history. However, part of the group may already have met criteria of cannabis dependence. It can generally be concluded that this level of cannabis use is associated with mild differences in brain structure and function compared to healthy matched controls. Moreover, differences in brain structure and function appear strongest in heavy cannabis users with higher levels of use and problems. Heavy cannabis use was most consistently associated with altered motivational processes: cannabis cue-induced brain activity, implicit cannabis associations, and approach action tendencies towards cannabis differed between heavy cannabis users and controls. However, the results provide little evidence for behavioral impairments in regulatory functions like decision-making or working-memory in heavy cannabis users. These findings imply that motivational processes may change relatively early in time during the course of cannabis use towards dependence, compared to cognitive control deficits. However, longitudinal studies are needed to confirm this.

Brain structure, cannabis use & problems

To date, the few studies available report conflicting results regarding the effect of cannabis use on brain morphology (for a review see Lorenzetti et al., 2010). Discrepancies between studies, possibly associated with differences in characteristics of cannabis use and related problems

between studies, preclude strong conclusions about the relation between cannabis use and brain morphology. In chapter 2 Voxel-based morphometry (VBM) was used to investigate differences in brain morphology related to current and lifetime severity of cannabis use. If cannabis use affects brain morphology, this is to be expected in areas like the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), striatum, amygdala, hippocampus, and cerebellum, regions implicated in substance dependence and/or with high cannabinoid receptor type 1 (CB1) concentrations (Burns et al., 2007; Koob and Volkow, 2010). It was found that regional grey matter volume in the anterior cerebellum was larger in heavy cannabis users compared to controls. Within the group of heavy cannabis users, hippocampal grey matter volume correlated negatively with cannabis use (grams per week) and amygdala grey matter volume correlated negatively with cannabis problem severity. No associations were found between white matter volume and measures of cannabis use or dependence. These findings indicate that associations between heavy cannabis use and brain structure are complex. Heavy cannabis use may not necessarily be related to structural changes in the forebrain and striatum, whereas changes in grey matter may only be present in those individuals who consume large quantities of cannabis almost daily and have symptoms of dependence. As indicated by the correlation with weekly cannabis use, reductions of hippocampal volume may occur relatively early in time as a more direct effect of consuming high amounts of cannabis. Neuroadaptations in the amygdala probably occur when cannabis use becomes a conditioned response and part of a dependence syndrome (Koob and Volkow, 2010).

Biased motivations in heavy cannabis users

In someone with a SUD, exposure to substance-related cues is known to bias motivation towards substance use (for reviews see Carter and Tiffany, 1999; Wiers et al., 2007). These biased motivations are thought to play an important role in continued substance use and relapse. The current literature on motivational processes related to cannabis use is very limited. However, evidence has recently emerged that these processes may also be present in heavy cannabis users (Ames et al., 2007; Field, 2005; Field et al., 2006; Jones et al., 2002; Jones et al., 2003). Motivational processes related to current and lifetime severity of cannabis use were investigated in chapter 3 – 6. Various cue-reactivity tasks were used to measure behavior and brain activity, moving from general mechanisms of cue-reactivity to more specific processes like implicit memory associations, and finally approach and avoidance tendencies. In chapter 3, neural mechanisms underlying cannabis cue-reactivity were investigated. Cue-reactivity in the brain has extensively been studied in individuals with a SUD (Carter and Tiffany, 1999). These studies, during which participant observe, feel, or smell substance-related and neutral cues showed that the OFC, ACC, striatum, ventral tegmental area (VTA), and amygdala are commonly activated by substance-related cues. To the best of our knowledge there are no studies that investigated cue-induced brain activations in cannabis users compared to controls. Brain responses to cannabis and

neutral cues were compared between heavy cannabis users, sporadic cannabis users and cannabis-naive controls. This distinction between sporadic users and non-users was made because according to the incentive sensitization theory and with support from animal and some human studies, repeated sporadic exposure to addictive substances may suffice to induce sensitization and conditioned responses to substance-related cues (Leyton, 2007; Robinson and Berridge, 2000).

For the first time it was shown that in heavy users compared to sporadic users and controls, cannabis images rendered higher activation in the VTA. Activation of the OFC, ACC, and striatum was only higher in a subgroup of heavy users with high compared to low problem severity. Activity in the right putamen and right dorsolateral prefrontal cortex (DLPFC) correlated negatively with subjective craving. Moreover, activity was not correlated with level of cannabis use. These findings indicate that cannabis cues activate areas associated with addiction pathology in heavy cannabis users compared to sporadic users and controls. Interestingly, cue-reactivity seems to be primarily associated with problem severity, not with amount of cannabis use, implying neural cue-reactivity as a biomarker for cannabis dependence. Prospective studies in (dependent) cannabis users are necessary to confirm this. Importantly, since cue-induced brain activations did not significantly differ between sporadic users and cannabis-naive controls, sensitized and conditioned responses towards cannabis cues in sporadic users are unlikely. Based on these results, sporadic users and cannabis-naive controls were considered as one control group in all further cue-reactivity studies.

These findings are valuable to our understanding of the neural mechanisms underlying cannabis abuse, as they support similar cue-reactivity mechanisms for cannabis compared to other substances of abuse. However, reflected by the widespread activations in reward, motivation, cognitive control, and memory circuits, the paradigm employed in chapter 3 is too coarse to disentangle different motivational processes. Therefore, in chapter 4, Single Category Implicit Association Tests (IATs) were used to investigate the relationship of implicit (e.g., spontaneous, automatic) negative, positive-arousal, and sedation cannabis associations with cannabis use, cannabis-related problems, and craving. Implicit positive-arousal and sedation associations are hypothesized to be automatic appetitive responses towards substance-related cues and have repeatedly been found to explain unique variance in substance use (Ames et al., 2007; Kahler et al., 2007; Wiers et al., 2007). In the present sample of heavy cannabis users weaker negative, but stronger positive-arousal associations with cannabis words were observed compared to controls. However, the more cannabis was used (grams per week) the stronger the implicit negative association, decreasing the difference between cannabis users and controls. Moreover, in contrast to our hypotheses no associations were observed between implicit associations and other measures of quantitative cannabis use, use-related problems, and subjective craving. These findings indicate that, in contrast to other substances of abuse like

alcohol and tobacco (Wiers et al., 2007), the relationship between current and lifetime severity of cannabis use and implicit memory associations appears to be weak in heavy cannabis users.

Substance-related cues are not only thought to spontaneously trigger memory associations, they are also thought to activate approach rather than avoid action tendencies (approach bias). In chapter 5 the behavioral approach bias was investigated with a joystick Approach-Avoidance Task (AAT), a relatively new task that mimics actual approach and avoidance by combining arm flexion and extension with a zooming feature (Rinck and Becker, 2007; Wiers et al., 2009b; Wiers et al., 2010). The participants were asked to respond to the tilt of cannabis and neutral images, not the content of the images. Heavy cannabis users demonstrated an approach bias specifically for cannabis images, as compared to controls: They pulled the joystick faster than they pushed it in response to cannabis images. This approach bias correlated with the amount of cannabis that was used and the severity of cannabis related problems. These findings support the idea that the approach bias for substance-related stimuli is a general addiction-relevant phenomenon which is present in cannabis users as well as in alcohol users and tobacco smokers (Bradley et al., 2004; Field et al., 2008a; Mogg et al., 2005; Ostafin and Palfai, 2006; Palfai and Ostafin, 2003; Wiers et al., 2009b).

With a different task, the Stimulus Response Compatibility (SRC) task, the neural mechanisms underlying cannabis approach and avoidance were investigated. In contrast to the AAT, participants are explicitly instructed to respond to the content of the images. The tasks consists of approach blocks during which participants move a manikin towards cannabis-related images and away from other (control) images, and avoid blocks during which the instructions are reversed (e.g., Field et al., 2006). To the best of our knowledge, no published studies investigating the neural mechanisms of unbalanced approach and avoidance behavior related to substance use. Content relevant tasks like the SRC may be more reliable in measuring behavioral approach and avoidance compared to content-irrelevant tasks (for a task comparison see Krieglmeyer and Deutsch, 2010), and thus it was decided to measure brain activation patterns during the SRC rather than the AAT. In contrast to our hypothesis, no brain areas showed greater approach bias activations in heavy cannabis users compared to controls. Moreover, both heavy cannabis users and controls had a behavioral approach bias towards cannabis. Within the heavy cannabis users group, approach bias activations were more pronounced with increased lifetime use in various fronto-limbic areas including the amygdala, insula, inferior frontal gyrus, medial frontal gyrus, and para-hippocampal gyrus but also visual areas, precuneus, and the cerebellum. This is in line with previous studies on human approach-avoidance learning showing short-term experience-related increases in all these areas during approach and avoidance learning (Schlund et al., 2011). The observed relationship between lifetime use and brain activity probably reflects increased salience and motivation for cannabis over time in more chronic cannabis users, suggesting that a history of cannabis use alone in the present sample may not suffice to alter brain functions in relation to

cannabis approach and avoidance behavior. Moreover, if the observed results indeed reflect increased salience and motivation for cannabis, the findings should be replicable with a content irrelevant task like the AAT, which remains to be tested.

Cognitive control in heavy cannabis users

Cognitive control refers to the processes implicated in top-down adaption of moment to moment behavior depending on current internal goals and includes many different regulatory or executive functions (Mansouri et al., 2009). Just like biased motivations directed towards substance use, compromised cognitive control is thought to play an important role in continued substance use and relapse (e.g., Everitt and Robbins, 2005; Koob and Volkow, 2010; Verdejo-Garcia and Bechara, 2009; Wiers et al., 2007). Indeed, impairments in cognitive control functions have generally been found in individuals with a SUD compared to healthy controls (for review see Fernandez-Serrano et al., 2011; Van Holst and Schilt, 2011). Showing great overlap with cognitive control deficits related to other SUDs, these deficits are also evident in chronic cannabis users (Fernandez-Serrano et al., 2011). In chapter 7 and 8 it was investigated if deficits in cognitive control are already evident in heavy cannabis users, by investigating different regulatory functions that play an important role in cognitive control.

In chapter 7, the neural mechanisms underlying decision-making during the Iowa Gambling Task (IGT) were investigated in heavy cannabis users compared to controls. Moreover, associations were examined between task-related brain activations, IGT behavioral performance, cannabis use and cannabis use related problems. The IGT is a monetary decision-making task that is widely used to measure decision-making under risk, a function predominantly thought to be mediated by prefrontal cortex (Bechara et al., 1994). Impulsive decision-making as measured with the IGT is one of the most replicated executive deficits in SUD populations (Fernandez-Serrano et al., 2011). Despite normal task performance, heavy cannabis users compared to controls showed higher activation during wins in core areas associated with decision-making e.g., the right OFC and insula. Moreover, within the group of heavy cannabis users, weekly cannabis use was positively associated with activity in the insula, VLPFC, and caudate. Interestingly, the group differences and association with weekly cannabis use were specific for reward evaluation relative to punishment, suggesting that (chronic/heavy) cannabis use may impair decision-making in a dose-related way through enhanced motivational processes rather than executive process deficits. More research is needed to confirm this. These findings are generally in line with previous studies (Bolla et al., 2005; Vaidya et al., 2012; Wesley et al., 2011) and indicate that although behavioral IGT performance in heavy cannabis users did not (yet) deviate from normal controls, they do show abnormal functioning of the underlying neurocircuitry.

In chapter 8, the relationship between cannabis use and the working-memory brain network during an N-Back task was investigated. Working memory is a central executive function

(Kane and Engle, 2002) and working-memory impairments have been suggested to be general to SUDs and to remain impaired after prolonged abstinence (Fernandez-Serrano et al., 2011). Given that cognitive deficits in neuropsychiatric disorders are generally not restricted to a single brain region, model-free multivariate approaches may prove to be more sensitive than standard univariate analyses based on the general linear model (Kim et al., 2009). Therefore, Tensor Independent Component Analysis (Tensor-ICA; Beckmann and Smith, 2005) was used to investigate differences in working-memory network function between heavy cannabis users and controls. Both behavioral performance and working-memory network function in terms of strength, location, and activation amplitude did not differ significantly between heavy cannabis users and controls.

The lack of behavioral IGT and N-Back differences between heavy cannabis users and controls suggest that the level of cannabis use of the present sample does not lead to behavioral impairments in decision-making and working-memory. Moreover, it supports the idea that the neurotoxicity of cannabis may be relatively mild in humans and deficits may only be evident in dependent cannabis users. Nevertheless, these studies provide insufficient evidence to conclude that these functions are not impaired in heavy cannabis users. First, the behavioral IGT results show that on average both heavy cannabis users and controls improve but do not learn which card decks are the advantageous decks. A tentative explanation may be that the PFC may still be relatively immature in the present sample of young adults (Somerville and Casey, 2010), potentially obscuring the effect of cannabis on IGT performance. However, normal IGT performance has been repeatedly reported in student populations (Buelow and Suhr, 2009). Second, performance at the highest working-memory load of the N-Back was still 89 % correct, indicating a potential ceiling effect that may obscure any working-memory deficits in heavy cannabis users.

RISK FACTORS FOR CANNABIS ABUSE

A question central to this thesis was why some individuals develop a cannabis use disorder while others do not. There are many different factors known to contribute to SUD-risk ranging from specific genetic to social influences (Swendsen and Le Moal, 2011). In this thesis, the predictive association between brain function and prospective cannabis use was studied. Brain function was assessed in terms of behavior and brain activations related to different motivational and cognitive control functions. A potential advantage of studying brain function with neurocognitive tasks and neuroimaging techniques is that it may provide information about vulnerable intermediate-phenotypes to which social and/or genetic risk factors give rise to. For the behavioral and neural mechanisms underlying the cannabis approach bias (chapter 5 & 6), decision-making (chapter 7), and working-memory (chapter 8) the predictive relationship with quantitative cannabis use (in

grams) and cannabis problem severity (CUDIT) after six months was assessed. Although not described in chapter 4 and 5, this was also done for the neural mechanisms underlying passive cue-reactivity and implicit memory associations. Since the costs of neuroimaging techniques are high compared to self-reports and neurocognitive tasks it was important to verify whether the neurophysiological indices predicted future cannabis use and cannabis related problems severity beyond that of self-reports and neurocognitive tasks.

Based on the present findings it can de concluded that both motivational and cognitive control functions can predict future cannabis use. The AAT approach bias, neural activation patters associated with decision-making, and working-memory network function were found to predict escalation of cannabis use after six months. Moreover, the neural approach bias was found to predict cannabis use related problems over and beyond session induced craving. These findings imply that, even though behavioral performance and brain activations in heavy cannabis users may not deviate yet from controls, individual differences in brain function may be indicative of SUD-risk. Also, brain activation patterns uniquely contributed to the prediction of future cannabis use, and this was true even after correction for behavioral measures and self-reports. These novel findings are important for our understanding of SUDs in general and cannabis use disorders specifically as they highlight the importance of motivational processes and cognitive control functions in the maintenance of addictive behaviors. Importantly, they also provide new biomarkers in the prediction of cannabis abuse and new targets for prevention and treatment.

Risk factors for escalation of cannabis use

The transition from recreational substance use towards chronic use is associated with an escalation of substance use. To investigate escalation of cannabis use, weekly cannabis use (in grams) was measured at baseline and at six-month follow-up. Regarding motivational processes, it was found that the approach bias as measured with an AAT predicted cannabis use (Chapter 5). Heavy cannabis users with a stronger approach bias toward cannabis-related images used more cannabis after six months. Compulsive craving [compulsivity factor Marijuana Craving Questionnaire (MCQ; Heishman et al., 2009)] was also found to be associated with cannabis use after six months: higher craving was related to increased use. This latter effect disappeared when the approach bias entered the regression model. No predictive relationship was observed for cannabis cue-induced brain activations (Chapter 3), implicit memory associations (Chapter 4), and the neural activation patterns associated with the approach bias as measured with the SRC task (Chapter 6).

Regarding risky decision-making as measured with the IGT, it was found that win-related activity in the Superior Frontal Gyrus (SFG) and higher activity in anticipation of disadvantageous decisions in the frontal pole and ventral temporal lobe predicted an increase in cannabis use after six months (Chapter 7). Interestingly, the brain activation areas that predicted cannabis use are

known to be more generally involved in cognitive functions rather than specifically in decision-making (Bullier, 2001; Du Boisgueheneuc et al., 2006; Koechlin, 2011). Moreover, individual differences in working-memory network response, including the SFG and frontal pole, predicted weekly cannabis use six months later, after correction for the variance explained by the AAT approach bias: a stronger network response during the N-back task was related to an increase in weekly cannabis use. These findings imply that heavy cannabis users requiring greater effort to accurately complete an N-back working-memory task have a higher probability of escalating cannabis use.

Table 1 Model of cannabis escalation: Hierarchical multiple regression analysis for variables predicting weekly cannabis use (gram) at six-month follow-up in heavy cannabis users (n = 28).

	B	SE B	*β*
Step 1: Change R^2 = .42***			
Baseline weekly use	1.11	.26	.65***
Step 2: Change R^2 = .48***			
Baseline weekly use	.89	.14	.52***
Compulsive craving	.24	.08	.28**
IGT activations anticipating disadvantageous decisions in FP and VTL	5.86	1.84	.33**
Behavioral approach bias	.01	.01	.23*
Working-memory network	.54	.20	.23*

*p < .05, **p < .01 and ***p < .001. Final model R^2 = .89**, adjusted R^2 = .87.
SE: standard error. FP: Frontal Pole. VTL: Ventral Temporal Lobe

The model of cannabis escalation described in chapter 8, which included baseline cannabis use, AAT approach bias, and working-memory network function, explained a substantial 70 % of the variance in future cannabis use. In an attempt to integrate all findings into a single model of cannabis escalation and to investigate if the model described in Chapter 8 could be improved, a post hoc regression analysis was run with all the variables that were shown to have an association with future cannabis use. A model additionally including compulsive craving and IGT-related activity in anticipation of disadvantageous decisions in the frontal pole and ventral temporal lobe (average % signal change extracted from the significant clusters) explained 19 % more variance, with the final model explaining 89 % of the variance in prospective weekly cannabis use ($F_{5,22}$ = 46.57, p < .001). After correction for baseline cannabis use, the different motivational and cognitive control processes together explained an additional 48 % of the variance of future cannabis use ($F_{4,24}$ = 24.96, p < .001; Table 1). Compulsive craving, IGT activations, AAT approach

bias, and working-memory network function each significantly explained unique variance; higher compulsive craving, stronger activations anticipating disadvantageous decisions (vs. advantageous decisions) in the frontal pole and ventral temporal lobe, a stronger approach bias, and a stronger working-memory network response related to increased cannabis use after six months. The total variance that can be explained with these variables is very high, highlighting the importance of each of these factors in continued cannabis use and the potential progression towards a cannabis use disorder.

Even though motivational and cognitive control processes explained a large part of the variance, these findings should be cautiously interpreted. First, the results also confirm that risk to escalate cannabis use depends on a complex interaction between different processes, each factor contributing to a relatively small part of the variance. To estimate individual risk to escalate may then require assessing various motivational and cognitive control functions, measured at the level of behavior and at the level of brain activations. This may be difficult in practice. Second, although escalation of substance use often precedes dependence, it is important to note that escalation does not equal dependence. The link between this model of cannabis escalation and eventual development of cannabis dependence still needs to be investigated. Third, this model is based on a relatively small sample of healthy cannabis users. Only cannabis users with a limited drug history and without any history of a psychiatric disorder were included. This is not very likely to be true for the general population of heavy cannabis users.

Risk factors for cannabis problem severity

Problem severity of cannabis use was assessed with the CUDIT (Adamson and Sellman, 2003). The CUDIT is a screening-instrument for at-risk cannabis use and consists of 10 items on cannabis use-frequencies and severity of use-related problems. In the current group of cannabis users CUDIT scores ranged from 4 to 27, (mean = 12.4). Although the CUDIT does not distinguish between dependent and non-dependent cannabis use, most heavy cannabis users with a score of ≥12 probably were dependent (Adamson et al., 2010, see also Chapter 3).

The only factors found to be associated with future cannabis problem severity were session-induced craving and approach bias activations of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) measured during the SRC task (Chapter 6). Higher levels of session induced subjective craving were also associated with more problems after six months. Yet, this effect disappeared when the neural approach bias was entered in the regression model. Interestingly, higher DLPFC and ACC activity during cannabis approach trials, but lower activity during cannabis avoidance trials was associated with decreases in cannabis problem severity. The DLPFC and ACC are thought to play an important role in appropriately adjusting behavior in conflicting situations (Cohen and Cavanagh, 2011; Mansouri et al., 2009), implying that cannabis users with well-developed capacity to regulate drug use may be more likely to

reduce or control their cannabis use. These findings also support a specific role for DLPFC and ACC functionality as a biomarker in the prediction of cannabis related problem severity and as new loci for prevention (i.e., psycho-education, cognitive training) and treatments (i.e., cognitive training, pharmacological interventions, neuromodulation). Nevertheless, one should also take into account the feature-relevant paradigm that was used to measure approach and avoidance: the participants were explicitly instructed to approach cannabis in one block and avoid cannabis in the other blocks. These explicit instructions may be important for involvement of the DLPFC and ACC. Future research using an irrelevant feature paradigm like the AAT should investigate these issues. Finally, the findings indicate that the approach bias does not merely reflect bottom-up sensitized and conditioned responses. Instead, control over approach and avoidance behavior could be the primary mediator of the relation between approach bias, continued substance use and substance use-related problems.

In contrast to our hypothesis, no predictive association was found between future problem severity and other motivational measures, decision-making, and working-memory. This could be due to methodological issues. In accordance with normative trajectories of cannabis use in young adults (Schulenberg et al., 2005), average cannabis problem severity decreased in heavy cannabis users. Only 5 heavy cannabis users increased more than 1 point on the CUDIT. Cannabis-related problems may have been too low and a six-month follow-up may have been too short to observe large increases in problems. In chapter 6, a negative association was observed between DLPFC and ACC activity and cannabis related problems after six months. The relationship between DLPFC and ACC function and cannabis problem severity may then be interpreted as protective.

Alternatively, motivational biases like the approach bias, but also individual differences in decision-making and working memory as observed in the general population may play a role in the course of drug use in *earlier* stages of problematic substance use. Motivational biases, decision-making, and working memory may predict who will (start to) use more but not who will progress to problematic drug use. Only poor cognitive control, possibly compromised by substance use, may then predict the development of dependence. For example, with regard to cognitive control, favoring short term-rewards over long term rewards may generally predispose individuals to start and continue substance use, but only poor inhibitory control (possible caused by substance use) may promote the development of dependence (Diergaarde et al., 2008). With regard to motivational processes, a reduced role in later stages appears to disagree with the incentive sensitization theory of addiction (Robinson and Berridge, 2000) and seems more in line with theories where sensitization to the substance rewarding effects is mainly important during escalation of drug use and less when subsequent compulsive drug use progresses (Di Chiara, 2000; Everitt and Robbins, 2005; Koob and Le Moal, 2005; Koob and Volkow, 2010). However, these inferences are speculative and future longitudinal studies are needed to investigate these issues.

Relationships between different motivational processes

In chapters 3-6, the relationship between different implicit motivational measures and cannabis use was separately investigated. Since the different motivational processes are all suggested to be manifestations of sensitized and conditioned responses towards substance related cues, SUD theories predict a positive relationship between the measures (Robinson and Berridge, 2003; Verdejo-Garcia and Bechara, 2009; Wiers et al., 2007). In a post-hoc analysis including participants that completed the IAT, AAT, and SRC, behavioral data was correlated. Both within the group of heavy cannabis users and controls, IAT, AAT, and SRC behavioral measures did not significantly correlate with each other, indicating that all three tasks measure different processes. This also suggests that the tasks do not solemnly measure sensitized and conditioned responses towards cannabis. This view is supported by a study showing that implicit measures of motivation were not positively associated with sensitized alcohol activating effect, that is heart-rate accelerations (Van den Wildenberg et al., 2006). The lack of a significant relationship between the AAT and SRC behavioral scores is especially surprising as both tasks attempt to measure the approach bias. Only the heavy cannabis users had an approach bias for cannabis-related images during the AAT, whereas both heavy cannabis users and controls had an approach bias during the SRC, which might suggest a limitation in the construct validity of the fMRI-optimized version of the SRC. Motivational biases measured with implicit tasks are generally in the range of tens of milliseconds. Noise is known to increase reaction time and reaction time variance (Szalma and Hancock, 2011). Due to these issues measuring the behavioral approach bias inside a noisy MRI scanner may not be optimal. How to best measure the approach bias remains to be discussed: while content-relevant tasks like the SRC may be more reliable, content-irrelevant tasks like the AAT may be more likely to tap into automatic motivational processes (De Houwer, 2003; Krieglmeyer and Deutsch, 2010). The current findings add to the ongoing discussion that content-relevant and content irrelevant tasks do not measure the same. This is further strengthened by the finding that the AAT bias-score predicted escalation of cannabis use, whereas the neural correlate of the approach bias in the DLPFC and ACC measured during a SRC task predicted cannabis problem severity.

Subjective craving is also thought to be an important motivational process contributing to continued substance use and relapse (Franken, 2003). A bidirectional positive relationship could be expected between craving and other motivational biases: craving may direct attention towards substances of abuse, activate memory associations, and activate approach action tendencies, which in turn may lead to a further increase of craving (Field et al., 2009). The Marijuana Craving Questionnaire (MCQ: Heishman et al., 2009) was used to assess pre-test, post-test, and session induced craving (post-test – pre-test). The MCQ distinguishes four craving factors: compulsivity (inability to control use), emotionality (relief from withdrawal and negative affect), expectancy

(anticipation of positive outcomes), and purposefulness (planning/intention to use for positive outcomes).

In contrast to our hypothesis, cannabis cue-induced brain activation patterns in the right putamen and right DLPFC were negatively associated with average post-test craving (Chapter 3). Moreover, the AAT approach bias correlated negatively with craving in heavy cannabis users: higher approach bias was related to lower pre-test scores on the MCQ emotionality and expectancy factor (Chapter 5). On the other hand, the MCQ compulsivity factor was found to predict escalation of cannabis use, together with AAT approach bias and working-memory network function. Average session induced craving was found to predict cannabis problem severity after six months, together with approach bias activations in the DLPFC and ACC during the SRC. No correlations were observed between MCQ craving measures and implicit cannabis associations (Chapter 4), behavioral approach bias measured with the SRC (Chapter 6), and neural activation patterns underlying the approach bias (Chapter 6).

These different findings are difficult to explain and more research is needed to investigate the interaction between the different motivational processes. A detailed theoretical framework around the different MCQ craving factors is currently lacking and needs to be further developed (Heishman et al., 2009). As indicated by the negative relationship between DLPFC activation [an area involved in regulatory self-control (Miller and Cohen, 2001)] and post-test craving, the MCQ craving-scores may in part reflect the inability to control the urge to use cannabis rather than the urge itself. Moreover, these findings support the idea that craving and motivational biases share variance, but that they are not just different measures of the same underlying construct (Field et al., 2009). Nevertheless, the predictive relationship between session induced craving and future cannabis problem severity, and between the MCQ compulsivity factor and future cannabis use support an important role for craving in continued cannabis use and the potential progression towards dependence. Most importantly, these findings emphasize the importance of measuring both pre- and post-test craving and using factorial decomposition of self-reported craving.

Relationship working-memory & decision-making

Working-memory network function was found to predict cannabis use after six months in heavy cannabis users. Working-memory has been considered a central executive function (Baddeley, 2010; Kane and Engle, 2002) and the underlying network plays a role in many cognitive tasks, including decision-making (Fox et al., 2005). This raises the question if the association between working-memory network function and future cannabis use generalizes to other executive functions. If so, the network's function during other executive tasks like the IGT may also predict escalation of cannabis use. Indeed, during IGT performance activity in the SFG and frontal pole, areas part of the working-memory network (Owen et al., 2005; Wager and Smith, 2003), were also found to predict an increase in cannabis use after six months. To further explore this

hypothesis the average percent signal change when anticipating disadvantages versus advantages decisions in the working-memory network (derived from the ICA-analysis described in chapter 8) during the IGT was extracted per participant. A hierarchical multiple regression analysis indicated that, after correction for variance explained by baseline weekly cannabis use, working-memory network reactivity during the IGT explained an additional 11 % of the variance in future cannabis use (F change$_{1,27}$ = 6.41, p = .018). Stronger activity related to disadvantageous versus advantageous decisions in the working-memory network was positively associated with an increase in weekly cannabis use. After entering the AAT approach bias it was no longer a significant predictor of future cannabis use (p = .12). These results indeed indicate that working-memory network function during other executive functions like decision-making may also predict escalation of cannabis use, however, not as strong as the network's function during a working-memory task. Further, it supports the idea that the predictive association between decision-making related brain activations and cannabis use reflects individual differences in more general regulatory function networks rather than specific to decision-making. Nevertheless as shown in the previous paragraphs, individual differences in activations preceding disadvantageous decisions in the frontal pole and ventral temporal lobe explained unique variance in cannabis use, beyond the working-memory network (Table 1).

Interaction motivation & cognitive control

Going back to the SUD models discussed in the introduction of this thesis, the imbalance between strong motivations to use and compromised cognitive control has been suggested to play an important role in the development of addictive behaviors (e.g., Dawe and Loxton, 2004; Everitt and Robbins, 2005; Koob and Volkow, 2010; Robinson and Berridge, 2008; Verdejo-Garcia and Bechara, 2009; Wiers et al., 2007). Thus far, motivational processes and cognitive control functions were separately discussed in this thesis. Consequently, an imbalance could then only be interpreted as strong substance-use oriented motivations and at the same time poor cognitive control, relative to the control group. Yet, in case of the substance dependent individual, it is especially important how good cognitive control processes functions in the presence of substance-related cues.

Although motivation and control function were separately investigated they may not be separable in relation to their effects on substance use. It has repeatedly been found that the association between motivational processes and measures of substance use is moderated by executive functions (Grenard et al., 2008; Houben and Wiers, 2009; Thush et al., 2008). Similarly to the studies described in this thesis, each process was separately measured in these studies. There are indications in the present data and in recent neurocognitive research that stress the importance of an interaction between motivational and control functions (see also Gladwin et al., 2011). First, brain activity in areas though to be important in regulating and controlling behavior

(e.g., the DLPFC and ACC) during cannabis approach and avoidance responses was found to predict a reduction in cannabis-related problems six months later (Chapter 6). Second, cannabis appeared to influence decision-making processes through influencing motivational processes rather than general cognitive control processes (Chapter 7). It may well be that measuring cognitive control functions in the presence of distracting substance-related cues may even be a better predictor of SUD.

GENERAL CONCLUSIONS

In summary, the association between heavy cannabis use and brain structure is complex: differential patterns of brain structure for various cannabis use levels imply that alterations in brain structure are associated with specific cannabis use characteristics and dependence. With regard to brain function, heavy cannabis use is associated with biased motivations towards cannabis use, but there is weak evidence for cognitive control deficits. Compared to healthy matched controls, heavy cannabis users showed increased cue-reactivity in the VTA, stronger implicit positive but weaker negative associations towards cannabis, and an approach bias towards cannabis. The neural activation patterns underlying decision-making differed between heavy cannabis users and controls, but heavy cannabis users showed no signs (yet) of behavioral decision-making impairments. Similarly, working-memory performance and function of the underlying brain network did not differ between heavy cannabis users and controls. Interestingly, differences appear stronger in cannabis users with higher levels of use and problems, suggesting a threshold at which cannabis use affects motivational processes and cognitive control functions. Moreover, motivational processes may change relatively early in time during escalation of cannabis use towards dependence, compared to cognitive control deficits. Nevertheless, individual differences in motivational and cognitive control processes were found to predict future cannabis use. Significant predictors of cannabis escalation were compulsive craving, behavioral approach bias, working-memory network function, and brain activations during decision-making, each uniquely explaining variance in future cannabis use. Functioning of the DLPFC and ACC, areas involved in cognitive control, during cannabis approach and avoidance were found to predict a reduction in cannabis problems. These findings suggest similar mechanisms underlying continued cannabis use as compared to other substances of abuse. They highlight the importance of motivational and cognitive control functions in SUDs, and help understand why some individuals develop a SUD while others do not. Moreover, they point out new targets for prevention and treatment of SUDs in general, and cannabis use disorders specifically (which will be discussed below).

CHALLENGES, CLINICAL IMPLICATIONS & FUTURE DIRECTIONS

The studies described in this thesis have provided further insight in the brain processes underlying continued cannabis use. However, some limitations should be considered. First, inherent to the employed study design, one cannot differentiate between causal and consequential effects of cannabis use. Measures of cannabis use were found to correlate with brain function and measures of brain function were found to predict future cannabis use, suggesting a bidirectional relationship between cannabis use and brain function. However, only longitudinal study designs, preferably with a measurement before onset of substance use, can provide definite conclusions. Second, related to this issue one can also not differentiate between sub-acute and long-term cannabis effects as sub-acute effects of cannabis may last up to four weeks (Schweinsburg et al., 2008a). The heavy cannabis users who participated in our studies were only abstinent for 24h. This problem is general to the literature on cannabis abuse disorders; to the best of our knowledge there are no studies investigating motivational processes and cognitive control function in cannabis users with a diagnosis of cannabis dependence who have been abstinent for much more than a month. A third issue that needs to be considered is that it remains to be tested if the present findings hold for dependent cannabis users. Independently of substance specific effects, substance use disorders are associated with altered brain function (Koob and Volkow, 2010). Although the present findings support similar mechanisms underlying cannabis dependence compared to other SUDs, this cannot be confirmed. Future research should aim at elucidating these issues. Finally, there were more tobacco smokers among the cannabis users. Although the cannabis users were relatively light smokers and no associations were found between measures of tobacco smoking and measures of brain structure and function, potential confounding effects of tobacco smoking cannot be excluded. Aside from considering tobacco use as a potential confounder, it would be interesting to investigate the interaction between tobacco smoking and cannabis use. It was very difficult to recruit cannabis users who did not smoke tobacco and tobacco potentially increases effects of cannabis (McPartland et al., 2008). To investigate the effects of smoking and the interaction with cannabis use it is recommended to include a tobacco-smoking group in future studies.

An important issue emerging from these findings is the need for longitudinal studies, including measurements before and after the onset of SUDs. Compared to healthy controls, individuals with a SUD (including cannabis) often have broad cognitive impairments and comorbid psychopathologies. Which neurocognitive processes causally relate to the transition from recreational substance use towards dependence remains unknown without proper longitudinal study designs. Unfortunately, feasibility of longitudinal studies is relatively low as the general structure of scientific funding hinders longitudinal studies. Moreover, a limited number of individuals from the general population develop a SUD, which requires the study of large populations to properly investigate the transition towards dependence. An alternative approach

to overcome part of these issues is comparing individuals with and without a SUD with a similar history of substance use. It would be very interesting to investigate the specific differences between substance users who stay in control or who lose control over substance use.

From group to the individual: clinical implications

Interestingly, modification of motivational biases might be a promising new treatment options as an adjunct to standard SUD treatment. Indeed, it has been shown that retraining of the approach bias with a modified version of the AAT predicted improved treatment outcome in alcohol-dependent patients (Wiers et al., 2011). Attentional bias retraining has also been found to reduce craving in tobacco smokers (Attwood et al., 2008) and it may improve treatment outcome in alcoholics (Fadardi and Cox, 2009; Schoenmakers et al., 2010). Next to modification of motivational biases, working-memory training has been suggested as a potential new treatment for SUD: 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). The predictive relationship between the approach bias and working-memory network function and future cannabis use suggests that these new interventions may also be effective in (dependent) cannabis users. The ADAPT-lab of the University of Amsterdam currently investigates the potential effectiveness of approach bias retraining, inhibition training, and working-memory training in relation to alcohol, tobacco, and cannabis use, of which results are soon to be expected. A second clinical implication coming forward from these results is the use of motivational and cognitive control functions to screen for at-risk cannabis use. Important to note, one should first properly define a cut-off of abnormal functioning. Moreover, even though neural indices of working-memory and decision-making uniquely explained variance in future cannabis use, the costs of neuroimaging techniques relative to neuropsychological tasks should be taken into account.

Motivational and cognitive control functions are heterogeneous within SUD populations: cognitive biases towards substances of abuse and compromised regulatory functions are evident in a substantial part, but not in all individuals with a SUD (e.g., Bechara, 2005; Wiers et al., 2011). SUDs are difficult to treat and the heterogeneity of SUDs calls for personalized treatment (Oslin, 2011). Profiling brain function in individuals with a SUD may shed light on which interventions may or may not work. For example, individuals with poor working-memory may benefit most from working-memory training and individuals with an approach bias may benefit most from approach bias retraining. Additionally, working-memory capacity has also been found to moderate the association between motivational processes and substance use: The association between implicit motivational processes and substance use is strongest in individuals with relatively poor working-memory (Grenard et al., 2008; Thush et al., 2008) and response inhibition (Houben and Wiers, 2009). This could imply that individuals with good working-memory would

benefit less from both cognitive bias modification and working-memory training. Interestingly, explicit positive-arousal rather than implicit positive-arousal predicted alcohol use in individuals with relatively good working memory (Thush et al., 2008). Changing explicit substance related cognitions may be a better treatment approach in these individuals (Darkes and Goldman, 1993, 1998; Wiers et al., 2005).

Future research directions

The studies described in this thesis revealed some interesting issues for future research. What happened with the heavy cannabis users included in our studies? Who quit and who continued cannabis use? How does this relate to changes in brain structure and function? To answer these questions, a three-year follow-up on brain structure and function is currently conducted. The response rate so far is high and it appears that approximately half of the heavy cannabis users quit. Regardless of substance specific effects, substance dependence has been thought to alter brain function (Koob and Volkow, 2010). A bidirectional relationship between continued cannabis use and motivation and control could then be expected. Continued cannabis use is hypothesized to be associated with reduced cognitive performance and stronger implicit cannabis motivations, as reflected in changes in behavior and brain activations. Moreover, baseline brain function is expected to predict continued cannabis use: the heavy cannabis users who continued to use may have relatively strong automatic cannabis motivations and relatively poor cognitive control functions to start with. Important to note, this preliminary ratio between cannabis users who continued and quit indicates that from young adult heavy cannabis users, a substantial part is able to quit without treatment. This is in line with normative trajectories of substance use and abuse as they tend wane during the transition into adulthood (Bachman et al., 2002; Schulenberg et al., 2005).

An important next step in taking these finding to a clinical level is investigating if the observed predictive associations also hold for a group of dependent cannabis users. In collaboration with Brijder, a Dutch clinic specialized in SUD treatment, it is currently investigated if the approach bias for cannabis and alcohol can predict treatment outcome in cannabis and alcohol dependent youth. In addition, in a second collaborative study with Brijder, it is investigated if approach bias retraining improves treatment outcome in cannabis dependent youth. Finally, it is important to investigate these issues in older more chronically dependent cannabis users.

The predictive findings presented in this thesis suggest that changing motivational processes and boosting cognitive control may both be effective in preventing escalation of cannabis use. Besides using neurocognitive tasks like the approach bias retraining or working-memory training, various techniques may have the potency to change cognition. There is preliminary evidence that a pharmacological intervention with Modafinil improves cognitive

control functions in healthy individuals (Rasetti et al., 2010) and in individuals with a SUD (Hester et al., 2010). Moreover, non-invasive neuromodulatory techniques like Transcranial Direct Current Stimulation (tDCS) and rapid Transcranial Magnetic Stimulation (rTMS) over the DLPFC have been shown to improve cognitive control functions and reduce craving (e.g., Fecteau et al., 2010; Mishra et al., 2011; Rose et al., 2011). Given that DLPFC activity during cannabis approach and avoidance predicted problem severity after six months, it would especially be interesting to assess the effectiveness of an approach bias retraining combined with stimulation of the DLPFC. Moreover, the unique variance in prospective cannabis use explained by different measures of motivation and control suggests that a combination of different techniques may achieve better results than using a single technique.