Cannabis use in patients with schizophrenia: motivation for use and relation to clinical variables
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General discussion
This thesis focuses on 7 research questions pertaining to cannabis use in patients with schizophrenia. In chapter 1 to 3, the results of several studies focusing on different aspects of cannabis use in patients with schizophrenia were presented, that were used to find answers to these questions. The studies were conducted in patients receiving treatment in inpatient and outpatient clinics for non-affective psychotic disorder. Some studies included siblings and/or healthy controls as well. Studies were performed at the Adolescent Clinic of the Psychiatry Department of the AMC, and some studies were part of the GROUP (Genetic Risk and Outcome of Psychosis)-project. In this final chapter of the thesis we will - for each research question - discuss the main findings of the studies, relate them to the findings of relevant other articles that have been published recently, and discuss their main clinical and research implications. Next, we will discuss the strengths and limitation of the presented studies. The chapter ends with some general concluding remarks.

Main findings, interpretation and implications

Part I

1. What do patients with schizophrenia report as reasons for cannabis use and effects of cannabis use, what are their explicit and implicit associations toward cannabis use and what are their reasons for cessation of cannabis use?

In chapter 1.1 a literature overview is presented of 14 studies that examined self-reported reasons for cannabis use and self-reported effects of cannabis use in patients with psychotic disorders. Reasons for use could be categorized into four main categories: enhancement of positive feelings, relief of dysphoria, social reasons, and reasons related to the illness and side-effects of medication. Reasons for cannabis use most frequently mentioned by the patients were: enhancement of positive affect (42.1% according to pooled data), relief of dysphoria (66.3%), and social enhancement (61.7%). Fewer patients reported reasons related to relief of psychotic symptoms or relief of side-effects of medication (12.9%). These results are in line with a recently published overview of the literature on the self-reported reasons for cannabis use among patients with psychosis (Kolliakou et al 2010). Based on this overview the authors conclude that patients with psychosis use cannabis for the same reasons as the general population, namely for its enhancing effects, to relieve dysphoria, and with social reasons following closely. In the same article they conclude that patients with psychosis rarely use cannabis to relieve illness-related symptoms or medication side effects, thus providing little support for the self-medication hypothesis.

Concerning the self-reported effects of cannabis, our literature overview revealed that frequently reported positive effects of cannabis were positive changes in affect (75.5%) and relaxation (59.6%), based on pooled data. Many patients reported that cannabis negatively affected positive symptoms (44.7%), against only a few who reported that cannabis positively affected positive symptoms (8.5%). In summary, our literature review showed that patients suffering from psychotic disorders report to use cannabis mainly for affect regulation and social reasons, despite awareness that cannabis has a negative effect on positive symptoms. This awareness in patients of the potential negative effects of cannabis use was also found in chapter 1.2. A comparison between patients and healthy controls on explicit associations toward cannabis
revealed that patients scored significantly higher on explicit negative affect expectancies than controls. Negative affect expectancies were for example feeling miserable, confused or suspicious. However, patients had highest explicit scores on ‘relaxed’ effect expectancies, like feeling relaxed, feeling contented or comforting. These explicit relaxed expectancies were the strongest predictors of level of cannabis use and craving, suggesting that relaxed expectancies are important mediators in the continuation of cannabis use. A recently published experience sampling study of Henquet et al (2010) gives further insight in the temporal relation between cannabis use and experienced effects: increases in positive affect after smoking cannabis were observed in the short term rather than the long term. In contrast, increases in hallucinatory experiences were observed only in the long term and not in the short term. This suggests that the association between cannabis use and hallucinatory experiences was most prominent after a longer period of time compared to its shorter-term mood-enhancing effects. This gives evidence for the hypothesis that the immediate positive effects could outweigh the delayed negative effects, which can explain the continuation of cannabis use. However, for some patients, the negative effects may be a reason for cessation of the use of cannabis. In chapter 1.4 results of a file study were presented, which revealed that the most reported reason for cessation in patients that had stopped using cannabis before they were admitted at the Early Psychosis Department, was a prior admittance for psychosis and worsening of their psychotic symptoms. For these patients the negative effects of cannabis and its consequences probably outweighed the positive effects.

In summary, we conclude that 1) patients are aware of negative effects of cannabis, 2) for some patients this results in cessation of cannabis, but 3) in other patients, the (long term) negative effects like increase of positive symptoms may not outweigh the (short term) positive mood enhancing and relaxation effects, resulting in continued cannabis use. It must be mentioned though, that other factors like biological drives for cannabis use and sociocultural and environmental influences may also influence the continuation or cessation of cannabis use. Longitudinal studies are needed to further explore and test these hypotheses.

Besides obtaining data from patients’ self-report, the study described in chapter 1.2 also assessed the more underlying (implicit) associations toward cannabis use in patients with psychotic disorder (n=70) and healthy controls (n=61), with the use of three Single-Category Implicit Association Tests (SC-IAT). We found no differences in implicit associations between patients and controls. Both groups displayed ‘IAT effects’ for all three dimensions (‘negative’, ‘relaxed’, and ‘active’) reflecting implicit associations between cannabis and these dimensions. Interestingly, both groups demonstrated strong negative implicit associations toward cannabis use. This is in line with previous research on implicit associations toward alcohol use (Wiers et al 2002, De Houwer et al 2004, Wiers et al 2005) and toward smoking (Swanson et al 2001), but contradicts with another cannabis IAT study (Field et al 2004) that found negative associations in non-users of cannabis, but not in users of cannabis. This contradictory finding may be explained by the fact that they used a bipolar IAT, where positive associations are measured relative to negative associations. Plausible explanations for the strong implicit negative cannabis associations have been discussed in chapter 1.2. In short, one explanation is that users of cannabis engage in a behavior they do not implicitly like, but go along with their cannabis use because of other positive associations as discussed above. Other explanations have to do with concerns about the validity of the IAT effect, for example that strong negative implicit associations may partly reflect: 1) general associations that are present in a culture instead of someone’s personal associations (Karpinski and Hilton 2001), or 2) a ‘label effect’ (De Houwer 2001) which means that people might associate the label ‘cannabis’ with negative
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consequences because of usage of this word in the media, but associate words like ‘weed’ or ‘stoned’ with more pleasant effects, or 3) non-associative factors based on salience (when two salient categories have to be categorized under the same key, this will be easier than categorizing under two different keys) (Rothermund and Wentura 2004). Thus, there is reason to doubt the validity of the strong negative substance-associations found here and in many other studies. However, the active implicit associations appear to be more valid and related to meaningful other constructs including craving, because we found a trend for implicit active associations to predict craving for cannabis, which may be explained by sensitized arousal or intensively wanting of substances (Robinson and Berridge 1993), being transformed in craving.

Clinical implications and suggestions for further research

One of the conclusions of a recently published systematic review on treatment of cannabis use among people with psychotic disorders (Baker et al 2010) was that effectively treating the mental health disorder with standard pharmacotherapy may reduce cannabis use, and that ‘specific recommendations regarding the type and length of specific psychological treatments cannot be made at this time, although motivational interviewing and cognitive-behavioral therapy approaches appear most promising’. For these interventions, health care workers need to have insight in the reasons patients have to use cannabis and the effects they experience. Schizophrenia patients in out- or inpatient departments who use cannabis should be interviewed in an openly manner about how cannabis affects their emotional state, how it affects relaxation and how it affects their social life. Although patients do not report often that cannabis is used to decrease positive symptoms, they may be motivated to use cannabis to relieve secondary dysphoria.

As we showed in chapter 1.1 and 1.2 patients are aware of the negative effects of cannabis use. It is important to ask what kind of negative effects they experience and how this relates to the timing of smoking cannabis. Besides the anamnesis of motivation and expected effects of cannabis use, psycho-education about the short and long term effects of cannabis is essential: the short term effects might seem positive, but the long term effects can be deterioration of positive symptoms and relapse into psychosis. Further, as shown in chapter 3.3, acute intoxication of cannabis worsens cognitive performance, such as verbal learning, working memory, and visual processing speed. Together with the patient, alternative ways to achieve relaxation, and/or relieve of dysphoria are important components of treatment. However, there may be patients who use cannabis infrequently and experience mainly positive effects of cannabis, for example relaxation. It is interesting to discuss what to answer when such patients ask whether they should cease their use.

Cannabis use is associated with a poorer disease outcome and there is evidence for a dose-response association between cannabis use and increased relapse of psychosis, and a strong association between cannabis misuse and relapse (Linszen et al 1994, Zammit et al 2008). Thus, patients who use less cannabis and do not misuse are less at risk for relapse. However, for each individual case, also in patients who use cannabis infrequently, discussing the functions cannabis has in the patient and psycho-education about the short and long term effect is still essential, including the effects on cognitive performance (see chapter 2.3). Additionally, it is important to look for alternative ways to achieve effects that cannabis establishes. Follow-up meetings with the patient are then necessary to follow their use/non use and how this relates to symptomatology.

Something that needs more attention, both on the work floor and in research, is the type of cannabis used. As mentioned in the general introduction, the principal constituents of cannabis are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The former is the main psychoactive constituents of cannabis are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The former is the main psychoactive.
In experimental studies it produces transient psychotic symptoms and impaired memory in a dose dependent manner (D’Souza et al. 2004). In contrast, CBD does not induce hallucinations or delusions, and seems to antagonize the cognitive impairment and psychotogenic effects caused by THC (Bhattacharyya et al. 2010). People with psychosis tend to smoke higher potency cannabis that controls (Di Forti et al. 2009). Thus, asking patients what kind of cannabis they use and psycho-education about the risks of high-potency cannabis is important. Further, investigating the distinct subjective effects of THC and CBD on patients could increase our knowledge about how different the compounds of cannabis effect patients. Research on motivation and expected effects of cannabis should focus on this issue.

Another research implication is that longitudinal studies are needed that investigate the relationship between motivation for cannabis use and symptomatology. This would help to increase insight in the (temporal) relationship between primary and secondary symptoms of psychotic disorder and motivation to use cannabis. Also, exploring to what extent motivation relates to changing cannabis use in patients with psychosis and developing instruments to measure their readiness to change is possible in longitudinal studies.

We end the discussion of chapter 1.2 by mentioning that because implicit positive arousal cognitions were associated with craving, an important intervention could be to challenge these cognitions in order to prevent relapse into cannabis use. However, research on changing implicit associations towards substance use was scarce at that time. Recently, Houben and colleagues (2010) demonstrated that behavioral change in alcohol consumption can be achieved by changing implicit attitudes via evaluative conditioning. In a student sample, participants were randomly assigned to an experimental condition -were they were subjected to an evaluative conditioning procedure that consistently paired alcohol related cues with negative stimuli-, and to a control condition were alcohol related cues were consistently paired with neutral stimuli. Following the evaluative conditioning procedure, the experimental group showed stronger negative implicit attitudes and consumed less alcohol compared to the control group. The authors conclude that evaluative conditioning may be a useful new intervention tool to reduce alcohol misuse. Although this intervention seems promising, research is still needed to indicate if automatic cannabis association can be changed with this intervention as well, and how this effects the use of cannabis.

2. What is the validity of the Obsessive Compulsive Drug Use Scale for cannabis (OCDUS-CAN) in patients with non-affective psychotic disorder, their siblings, and healthy controls, and how is craving for cannabis related to vulnerability for psychotic illness and level of cannabis use?

In chapter 1.3, we concluded that the OCDUS-CAN is a valid instrument to assess craving in patients with psychotic disorders, but also in siblings and individuals with a (family) history of psychotic illness. Simultaneous Component Analysis (SCA) proved a common three factor structure of the OCDUS-CAN in these subject groups. This three-component SCA solution explained 74.2% of the total variance, and resulted in three well-interpretable and reliable subscales that can be labeled craving/urge, resistance, and impact. This three-factor solution corresponds well with the factor solution of the original OCDUS in heroin dependent patients (Franken et al. 2002). Further comparison with other studies is difficult because only few articles on cannabis craving in patients with psychotic disorder are available (Potvin et al. 2006, Akerele and Levin 2007, Van Nimwegen et al. 2008), and these focused mainly on the relation between craving and the effects of antipsychotic...
treatment. To our knowledge, our study is the first to validate a self-report measure for craving in individuals vulnerable for psychotic illness.

Another finding in chapter 1.3 was that mean total scores on all three OCDUS-CAN subscales were higher in frequent (at least weekly use) cannabis users than in infrequent (less than weekly) users, irrespective of subject status (patient, sibling or control). Further, patients scored higher on the craving/urge and impact scale than siblings and controls, irrespective of the level of cannabis use (frequent or infrequent). This means that patients experienced higher craving levels compared to siblings and controls and that this caused more distress, independent of the level of cannabis use. Although we did not assess the relation between symptoms of psychosis or use of antipsychotic medication with level of craving, we speculate that this higher craving in patients could be related to primary or secondary symptoms of psychotic disorder or side-effects of antipsychotic medication. In chapter 1.2 we showed that relaxed effect expectancies of cannabis use were positively related to the total score on the OCDUS-CAN in patients. So, it might be that feeling tense or anxious as a result of symptoms or side-effects, makes patients urge for cannabis because of its relaxing effects.

Clinical implications and suggestions for further research

Recently, in the study of Machielsen et al (in press), use of antipsychotic medication was related to craving measured with the OCDUS-CAN in part of our GROUP sample. Cannabis dependent patients treated with risperidone reported significantly more craving compared to patients treated with clozapine or olanzapine. This association between use of a specific type of antipsychotic and increased craving supports our hypothesis that the increased craving in patients compared to siblings and controls could be due to use of antipsychotic medication. However, this should be corroborated by a direct comparison between patients, siblings and controls, controlling for use of antipsychotic medication.

A way to test the hypothesis that patients have higher craving levels due to symptoms of the disease is to assess the relation between craving for cannabis and subclinical symptoms of psychosis. As non-affected siblings and healthy controls do not have primary symptoms of psychosis, but may have subclinical psychosis symptoms, these symptoms can be related to craving in all subject groups in future studies.

The OCDUS-CAN can be used both in clinical and research samples and is easy to use. It takes a few minutes for patients to fill in and the three subscales score can be easily estimated using a summated scoring approach. By assessing the OCDUS, patients and health care workers can understand the different elements that compose craving. Further, using the OCDUS-CAN can be used in practice for monitoring urges for cannabis use, which is important, because craving predicts relapse into drug use. However, longitudinal studies are needed that assess the predictive validity of the OCDUS for relapse into cannabis use.

3. What the timing of ceasing cannabis use in relation to the psychiatric history of patients with schizophrenia?

In chapter 1.4, we showed that of all patients that used cannabis (n=167) in the past, more than half (n=87) ceased the use of cannabis before they were admitted to the Early Psychosis Department of the Psychiatry Department of the AMC. Most (73%) of these 87 patients ceased the use of cannabis after they became psychotic and after they started having contact with psychiatric services. The exact motivation for cessation during treatment for psychosis is not known, but since the
majority of the patient that ceased their cannabis use did so after contact with psychiatric services, outpatient care and admittance for psychosis may have had an effect on this motivation.

Clinical implications and suggestions for further research
Our findings give some support for the hypothesis that giving patients psycho-education in the first phase of the illness about the negative effects of cannabis on the course of the illness, is effective in a substantial part of cannabis using patients in that they cease the use of cannabis. As shown in chapter 1.1 and 1.2, patients are aware of negative effects, but discussing these with patients and emphasizing that these negative effects may not be obvious on the short term, will increase their insight in the harmful effects of cannabis and may help them to decide to stop their cannabis use. Even though this sounds plausible, there are also indications that giving psycho-education about the negative effects in individuals who already know the negative effects is counter effective. Because of the cross-sectional design of our study, we do not know the course of cannabis use in those patients who had not ceased their use, neither do we know whether patients that had stopped using cannabis could sustain this abstinence. A prospective study design would enable us to assess the course of cannabis use in people with recent-onset schizophrenia. Such a study was recently conducted by Foti et al (2010). In their longitudinal study they followed 225 patients for 10 years. Although the lifetime prevalence of cannabis use was 66.2%, the baseline prevalence was only 10%. This current prevalence rate of 10% cannabis use remained stable over the course of schizophrenia. Although patterns of cannabis use tended to persist, a fair number of individuals stopped or started over the course of the follow-up period. In fact, of the 62 (28%) individuals who were using at any of the waves, only seven were using cannabis continuously. From this study it can be interpreted that a substantial part of the patients that cease the use of cannabis restarts the use of cannabis, but in a pattern of waves with stopping and restarting, and only a very small proportion of patients (3%) used cannabis continuously.

Part II
4. What is the relationship between cannabis use and age at onset of first psychosis?
This issue was addressed in chapter 2.1. In a sample of 785 patients with a non-affective psychotic disorder lifetime cannabis use was associated with an earlier age at onset of psychosis, irrespective of gender or the use of other drugs: age at onset of psychotic illness was 1.8 years earlier in cannabis users compared to non-users. This is in line with many previous reports (for a meta-analysis see Large et al 2011). In contrast to previous smaller studies with relatively smaller number of females (Veen et al 2004, Gonzales Pinto et al 2008, Ongur et al 2009, Sugranyes et al 2009, Barrigon et al 2009), age at onset in our sample was 1.3 years earlier in males compared to females, irrespective of the use of cannabis of other drugs. Although we did not know the age at onset of cannabis use, a substantial part (up to 64%) of the cannabis using patients in our sample had used cannabis most intense before the onset of their psychosis. We speculate that earlier onset of psychosis in cannabis using patients could be explained by cannabis use precipitating the onset of psychotic illness in vulnerable subjects. The pattern (from the Kaplan Meier survival curve) of the differences between the cannabis users and non users seem to manifest from the early twenties. This may also explain why some studies in schizophrenia patients did not find differences in age at onset between cannabis users and non-users: the age at onset of psychosis in these studies was around 20 years, which is earlier than the
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The age range where differences occurred in our study (Bersani et al 2002, De Rosse et al 2010, Goldberger et al 2010). This may also explain why the absolute differences in age at onset between cannabis users and non-users varied considerably between studies; studies with a relatively older sample than our study will probably find a larger difference in age at onset between users of cannabis and non-users.

Clinical implications and directions for future research

Results of our study in combination with comparable results of a recent meta-analysis on cannabis use and age at onset of psychosis (Large et al 2011), provide strong evidence that reducing cannabis use could delay psychotic illness in part of patients. By reducing cannabis use and thereby delaying illness onset, outcome of psychosis might be improved, as earlier onset of schizophrenia is associated with a worse prognosis (Rabinowitz et al 2006, Lauronen et al 2007). Although the 1.8 year difference in age at onset between cannabis users and non-users does not seem large, this might be crucial years in adolescence and early adulthood, in which certain milestones can be achieved, for example graduation from education, starting a working carrier and developing a social life. Therefore, patients vulnerable for the development of psychotic illness should be warned for the potential detrimental effects of cannabis. It is important though, to get insight in what kind of people are vulnerable. Therefore, future studies are needed to clarify the neurobiological factors that make people vulnerable for the precipitating effects of cannabis on age at onset of psychotic illness. Recently, results from some of these studies, e.g. the study of Pelayo Teran et al (2010) which was discussed in chapter 2.1, have been published. Further, Decoster et al (2011) investigated brain derived neurotrophic factor (BDNF) Val66Met genotype with respect to cannabis use and age at onset of psychotic illness. In this genetic study, BDNFVal66Met genotype and cannabis use before illness onset were retrospectively assessed in a large sample (n=585) of patients with schizophrenia and their association with age at onset was evaluated. In females, cannabis use was associated with earlier age at onset in BDNF Met carriers, but not in Val/Val genotypes. In males, cannabis use was associated with earlier age at onset irrespective of BDNF Val66Met genotype. This study showed that BDNF excretion could be a neuronal adaptive response to the psychotogenic effects of THC, although this could only be demonstrated in female and not in male patients. This study helps to gain insight into the interaction of cannabis use and important genetic factors operating in the crucial phase of transition from vulnerability to onset of psychotic disorder, but more studies are needed.

5. What is the relationship between substance use and obsessive compulsive symptoms in patients with schizophrenia?

In chapter 2.2 we found no significant differences in substance use variables between patients without obsessive compulsive symptoms (OCS) (n=777), patients with mild OCS (n= 143), and patients with more severe OCS (n=185). These results did not support our hypothesis that co-morbid OCS are a protective factor against the use of nicotine and other substances in patients suffering from non-affective psychotic illness. In line with our findings, previous studies did not find differences in nicotine use an substance use rates between schizophrenia patients with and without OCS (Dome et al 2006, Fawzi et al 2007, Puyurovsky et al 2008). Speculative explanations for our finding that there was a trend for patients with mild OCS to be more likely to use alcohol heavily and to have a lifetime diagnosis of cannabis use disorder, is the possibility of mild OCS mediating the tendency to use cannabis and alcohol as self-medication.
(relaxation), or cannabis and alcohol use mediating mild OCS. However, as the differences were small, it is questionable whether this non-significant finding is clinically relevant.

Clinical implications and directions for future research
Health care workers should be aware that schizophrenia patients with OCS have the same probability of using nicotine and other substances as patients without OCS. Patients with OCS should also be interviewed about usage of drugs, the motivation for drug use and the expectancies of the effects. As subtype of OCS was not included in the analysis, it would be interesting to find out whether there is a relationship between type of OCS and alcohol and cannabis use. Additionally, future studies are needed that relate the occurrence of OCS to patients' reasons and expectancies of cannabis. This could increase insight in the function cannabis use has in patients with OCS and whether this differs from patients without OCS.

6. What is the relationship between cannabis use and cognitive performance in patients with schizophrenia, their unaffected siblings and healthy controls?

In chapter 2.3, we found that current cannabis use was associated with worse performance on immediate verbal learning, processing speed and working memory compared to never users. On the other hand, lifetime cannabis use was associated with better scores on acquired knowledge, affect recognition and face identity compared to never-users. Our findings demonstrate that cannabis use in patients, siblings and controls is associated with differences in cognitive performance and that this effect depends on how recently cannabis has been used.

Our findings also suggest that cannabis using patients have a higher cognitive potential than non-users, while the (sub)acute effects of cannabis may impair cognitive functioning. Lifetime cannabis users perform better on social and general intelligence tasks which may be explained by better pre-morbidity (social) functioning, rather than an effect of cannabis itself. This is in correspondence with a recent meta-analysis reporting that superior neuropsychological functioning in cannabis using schizophrenia patients was largely driven by studies that included lifetime users rather than current or recent users (Yucel et al 2010). This supports the hypothesis that cannabis using patients might belong to a subgroup of patients who might be intrinsically less vulnerable for schizophrenia than patients who have never used cannabis (Mueser et al 1998). This so-called vulnerability hypothesis postulates that a psychotic illness triggered by an environmental stressor such as cannabis use may be less severe than a psychotic illness that is predominantly due to inherent genetic vulnerability.

Frequency of use was not related to cognitive performance: daily or weekly cannabis users did not perform significantly different than more infrequent users. This is in agreement with literature in schizophrenia patients (Rodriguez-Sanchez et al 2010) as well as in healthy subjects (Pope Jr et al 2002). Tolerance for the adverse cognitive effects of cannabis in more frequent users could have accounted for the absence of a dose-response relationship (Ramaekers et al 2009).

Clinical implications and directions for future research
The discrepancy between potential and cognitive performance in cannabis using patients is clinically relevant for patients, in whom cannabis use might thus complicate an otherwise less severe course of psychosis. Cannabis using patients should be educated about the negative effects of cannabis intoxication on cognitive performance, such as verbal learning, working memory, and visual processing speed. Further, as our results suggest that ceasing the use of cannabis will probably result
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in improvement in these cognitive domains, this should be educated as well. However, as effect sizes were small in this study, one may question the clinical relevance of the effects of cannabis recency on cognitive performance. Still, as this effect adds to the cognitive impairments that are already present in patients, it does seem of clinical relevance.

Longitudinal studies focusing on the cognitive effects of both initiation and cessation of cannabis use in psychotic patients and controls are needed to support our hypothesis that cannabis using patients have a higher cognitive potential, unless they are intoxicated. Thereby, assessing age at onset of cannabis use is crucial.

Part III

7. What is the relationship between adolescent cannabis use in patients with schizophrenia and brain white matter structure and integrity?

In chapter 3.1, with high resolution structural and diffusion-tensor brain images we found that cannabis naïve patients showed reduced white matter density and reduced fractional anisotropy in the splenium of the corpus callosum, compared to patients with early-onset (<17 years of age) cannabis use. In the same brain area, cannabis naïve patients showed reduced fractional anisotropy compared to healthy controls. This suggests that the age of onset of cannabis use is not identifying for/related to white matter abnormalities in schizophrenia patients, however, our results might indicate a more vulnerable brain structure in cannabis naïve schizophrenia patients. Early cannabis users who develop schizophrenia might belong to a patient subgroup that is (in some ways) different than a patient group that never used cannabis and develop schizophrenia, like we mentioned above in the discussion of research question 6.

Interestingly, Peters et al (2009) found even higher FA values in schizophrenia patients with cannabis use before age 17 compared to controls in other white matter areas of the brain (the bilateral uncinate fasciculus, anterior internal capsule and frontal white matter), but confounding effects of other illicit drugs could not be excluded. The authors suggest that patients who start using cannabis during early adolescence may represent a subgroup of schizophrenia patients with increased white matter directional coherence, which may reflect structural hyper connectivity. The authors discuss that although this may reflect an effect of cannabis or illicit hard drugs use on the brain, it may as well be that young adults with adolescent cannabis or hard drug use represent a distinct group of patients, like we suggested above.

Another explanation why effects of cannabis use on the brain were not identified in our DTI study, is that the effects of cannabis use may be not be detectable with DTI, or are that they are only detectable at a later stage of the disease. In a review on DTI studies in recent-onset schizophrenia, Peters et al (2010) discuss that because DTI abnormalities in first-episode patients are less robust than in chronic patients, progression to more extensive abnormalities occurs after illness onset. This underscores the need for longitudinal studies, and the relative weakness of cross-sectional DTI studies in recent-onset schizophrenia patients. Recently, Rais et al (2010) published the results of a structural MRI study, in which it was indeed shown that effects of cannabis might not be detectable at baseline in patients with first episode psychosis, but are detectable years later, e.g. after the first five years of schizophrenia. Patients who used cannabis during the scan interval showed a more pronounced cortical thinning than non-using patients in areas known for their high density of CB1 receptors, such as the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex.
After we published our results, Fan and Hart (2010), in a letter to the editor, put our attention on the fact that the way study results are described or put in certain words can lead to discussion about how they can be (mis)interpreted. Although we did not agree with all their points, we do realize that we have to remain cautious with using some words such as ‘abnormality’.

**Clinical implications and directions for future research**

No specific clinical implications emerge from or DTI study. However, suggestions for further research are that our findings need to be replicated in a larger sample, and the above finding of Rais et al (2010) stress the need for longitudinal studies in which the development of white matter structure and integrity in cannabis naïve patients and those who use cannabis is compared. To further test the vulnerability hypothesis, neuroimaging findings should be related to variation in susceptibility risk for schizophrenia.

**Strengths and limitations**

In each chapter of this thesis, methodological strengths and limitations were already discussed. Therefore we will now restrict ourselves to the most important ones.

**Strengths**

First, study samples in most studies were relatively large. For example, chapter 2.1 about the age at onset of psychosis in relation to cannabis use comprised the largest sample published to date. Second, the number of included females was relatively large in samples derived from the GROUP study, this enabled us to enter gender as independent variable or as covariate in the regression analyses (chapters 1.3, 2.1 and 2.2). Third, in four studies we used urinalysis for the presence of THC to validate self-report about cannabis use, and/or to create subgroups according to drug use history as valid as possible (chapters 1.3, 2.1, 2.2, 2.3). Fourth, in three studies, unaffected sibling and/or healthy controls were included to compare their data with data of patients (chapters 1.2, 1.3, 2.3, 3.1). Fifth, we corrected for possible confounders in regression analyses in chapters 1.3, 2.1, 2.3, such as age, gender, nicotine and alcohol use.

**Limitations**

First, all studies had a cross-sectional study design. Therefore, robust conclusion of the effects of cannabis use on clinical variables could not be drawn. Future, longitudinal studies could give more insight in 1) how craving for cannabis is related to relapse into cannabis use, 2) how self-reported reasons for cannabis use, and explicit and implicit associations toward cannabis predict cannabis use, and how they are related to symptoms of schizophrenia, 3) what the course is of cannabis use after being treated at an early psychosis department, 5) how cannabis use effects brain white matter. Second, although a relatively large number of females were included in three studies, in three other studies on associations toward cannabis and brain white matter, the study population was predominantly male or only males were included (chapter 1.2, 1.3, 3.1). Generalization of our findings to females was therefore not possible in these studies. Third, age at onset of cannabis use was not assessed in the GROUP study. A comparison between patients that started cannabis use prior to the onset of psychosis versus non using patients could have provided more robust support for hypothesis that cannabis precipitates onset of psychotic illness. Fourth, we did not know the different proportions of THC and CBD in cannabis used by the patients. If we had known this, we could have given insight in the different contributions THC and CBD to explicit and implicit cannabis
associations, reasons for cannabis and craving for cannabis. Di Forti and colleagues (2009) showed that an assessment of the specific type of cannabis used (by asking the patient) is certainly possible.

Concluding remarks

This thesis focused on cannabis use in patients with schizophrenia. We found that patients mainly use cannabis to regulate their affect and social life. We also found that patients are aware of the negative effects of cannabis and this can be a motivation to stop using cannabis. However for some patients, the relaxing effects of cannabis and associated craving levels may be mediators for continuation of cannabis use. Mental health care workers should discuss patients' experiences with cannabis use and how it affects their affect, social life and their symptoms of psychosis. Psycho-education about how cannabis affects the course of the disease and symptoms may have an effect on some patients who will consequently cease their cannabis use. Together with the patient, alternative ways to achieve relaxing or mood enhancing effects and/or achieving coping-skills can be important components of treatment. Future longitudinal studies are needed to relate motivation, craving and symptoms to the course of cannabis use and to assess whether evaluative conditioning can change implicit attitudes toward cannabis and consequently can reduce cannabis use. Further, our findings provide indirect evidence that reducing cannabis use in individuals who have not developed psychotic illness yet, could delay psychotic illness in part of them. However, future studies are needed that identify neurobiological factors that make patients vulnerable for the precipitating effects of cannabis on psychotic illness.

Findings of the studies on cannabis and cognition, and cannabis and white brain matter integrity in patients with schizophrenia support the hypothesis of less vulnerable brain structure and higher cognitive potential in patients with cannabis use compared to patients who develop a psychotic disorder without using cannabis. However, as co morbid cannabis abuse is associated with poor outcome of schizophrenia with respect to relapse of psychotic episodes, reducing cannabis use in patients with schizophrenia remains necessary.

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