Cannabis use in patients with schizophrenia: motivation for use and relation to clinical variables

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General introduction
Introduction

This thesis focuses on cannabis use in people with schizophrenia. The presented findings are based on studies conducted at the Early Psychosis Department of the Psychiatry Department of the Academic Medical Centre (AMC), and on data obtained in the Genetic Risk and Outcome Project (GROUP). GROUP is a longitudinal observational study that investigates the dynamic interaction over time between genetic and environmental factors that contribute to the expression and course of psychotic illness. This introductory chapter starts with a brief overview of schizophrenia and related disorders, and the psychological effects of cannabis. Next, general epidemiological information is presented about cannabis use in patients with schizophrenia followed by the main topics of this thesis: motivation for cannabis use and expected effects of cannabis in people with schizophrenia, craving for cannabis, cognitive functioning in relation to cannabis use, and brain white matter in relation to cannabis use. Thereafter, a short explanation on GROUP will be given. The chapter ends with the research question followed by the outline of the thesis.

Schizophrenia

Schizophrenia is a serious mental illness that is characterized by psychosis, apathy, social withdrawal, and cognitive impairment, causing impaired functioning in everyday living. The annual incidence of schizophrenia is 0.2-0.4 per 1000, with a lifetime prevalence of about 1% (Mueser and McGurk 2004). Schizophrenia is more prevalent in men than in women (Aleman et al 2003). Age at onset of schizophrenia lies between 16 and 35. Women have a later onset than men, and a more benign course of illness, reflected in fewer hospital admissions and better social functioning. For the diagnosis of schizophrenia, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) requires an illness duration of at least 6 months, with at least 1 month of active symptoms. Further, during at least 1 month, two positive symptoms are required, like hallucinations, delusions, disorganized speech, or grossly disorganized or catatonic behavior, or a combination of one of these positive symptoms and negative symptoms like affective flattening, alogia, or avolition. The DSM-IV also requires that for a significant proportion of the time since the onset of the disturbance, one of the major areas of functioning such as work, interpersonal relations, or self-care is markedly below the level achieved prior to onset (APA 1994). Other disorders in the spectrum of schizophrenia are brief psychotic disorder, schizophreniform disorder, delusional disorder, schizoaffective disorder, and psychotic disorder not otherwise specified. They all share the occurrence of psychotic symptoms, but have different DSM-IV criteria than schizophrenia, for example another illness duration, occurrence of affective symptoms during psychosis, or less occupational dysfunction. These disorders are also called ‘non-affective’ psychosis, because they are characterized by few affective symptoms, in contrast to ‘affective’ psychosis in for example bipolar disorder or psychotic depression in which mood dysregulation is more prominent. Besides positive and negative symptoms, impairment in neurocognition (difficulties in memory, attention, and executive functioning) is also a characteristic of schizophrenia.

Both genetic and environmental factors play a role in the etiology of schizophrenia (Van Os et al 2010). The rate of schizophrenia is higher among relatives of patients than in the general population. This increased risk is genetic, with a tenfold increase in risk associated with the presence of an affected first degree family member. The genetic transmission does not follow simple Mendelian single-gene inheritance patterns, but multiple polymorphisms and copy number variants have been
identified that are associated with schizophrenia (Van Winkel et al. 2010). Environmental risks for schizophrenia include biological and psychosocial factors, for example obstetric complications, growing up in an urbanized area, being part of a minority group, developmental trauma and cannabis use (Van Os et al. 2010).

**Cannabis and its acute psychological effects**

Cannabis sativa is an annual plant that has been used by humans for centuries, largely for its psychological effects. The flowers contain psychoactive and physiologically active compounds known as cannabinoids. Preparation of flowers (marijuana) and leaves and preparations derived from resinous extract (hashish) are consumed by smoking, vaporizing and oral ingestion. After alcohol and tobacco, cannabis is the most popular recreational drug in the world, with an estimated 162 million users worldwide in 2006 (UNODC World Drug Report). The major psychoactive ingredient of cannabis is Δ9-tetrahydrocannabinol (THC) (Mechoulam and Gaoni 1965). THC elicits its psychological effects by stimulation the cannabinoid 1 (CB1) receptor (Huestis et al. 2001), which is expressed at high levels in the hippocampus, the cerebellum, the basal ganglia and the neocortex (Reggio 2006), consistent with the major psychological and motor effects of THC administration. Another compound of cannabis is the cannabinoid cannabidiol (CBD; Mechoulam and Shvo 1963). CBD is not hallucinogenic, and in contrast to THC, CBD appears to have anxiolytic effects. Further, it has been considered to have antipsychotic effects (Leweke et al. 2000). The precise molecular mechanism of action of CBD is unclear and may involve a wide variety of mechanisms (Mechoulam et al. 2007). In cannabis products, the percentage of CBD is much lower than the percentage of THC. For example, in Dutch weed the percentage of CBD is 0.2% and the percentage of THC is 17.8% (Rigter and Niesink 2010).

A survey among regular cannabis users (Athar and Blanchard 1997) reported that the positive benefits of cannabis use they most frequently mentioned were relaxation and relief from stress (26%), insight and personal development (9%) and a positive effect on mood (5%). One fifth reported adverse effects of cannabis use, like impaired memory (6%), apathy/laziness (5%), and paranoia (6%). In early studies, it has already been described that cannabis has the ability to produce paranoia (Ames 1958, Chopra and Smith 1974). In a more recent double blind placebo-controlled study, acute administration of THC in healthy individuals produced transient psychotic symptoms that were dose dependent, and a broad range of other transient symptoms, like altered perception, increased anxiety, euphoria, and cognitive deficits such as disrupted immediate and delayed word recall and working memory (D’Souza et al. 2004).

**Cannabis and the risk of psychosis**

As there were many early reports of psychotic episodes triggered by cannabis consumption in otherwise healthy individuals, Andreassen and colleagues (1987) investigated the association between the level of cannabis consumption and the development of schizophrenia during a 15-year follow up in more than 45000 Swedish conscripts. Their study demonstrated a convincing dose response relationship between early cannabis use and later admission for schizophrenia in men. Since 2000, more longitudinal studies in the general population have been carried out in which cannabis use was related to subsequent onset of psychosis. A recent systematic review of these studies reported an increased risk of any psychotic outcome in individuals who had ever used cannabis (odds ratio 1.41), and a dose-response effect, with greater risk in people who used cannabis most frequently (odds ratio 2.09) (Moore et al. 2007).
Introduction

Besides cannabis as a causal factor in the development of schizophrenia, an alternative explanation for the relation between and psychosis is that people vulnerable for psychosis are more likely to start using cannabis to self-medicate their distress. This self-medication hypothesis states that substance use is a consequence of patients’ attempts to decrease symptoms accompanying the disease or to alleviate underlying distressing emotional states (Khantzian 1997). So, cannabis might be used in an attempt to self-medicate against symptoms of schizophrenia. However, longitudinal studies in population-based samples in which the relation between cannabis use and development of psychosis was assessed, provided no clear evidence to support the self-medication hypothesis (Fergusson et al 2005, Henquet et al 2005a). For example, in the study of Henquet et al (2005a), cannabis use at baseline increased the cumulative incidence of psychotic symptoms at follow up, but baseline predisposition for psychosis did not significantly predict cannabis use at follow up. However, one longitudinal cohort study reported a bidirectional association between cannabis and psychosis: cannabis use predicted future psychotic symptoms, and psychotic symptoms predicted future cannabis use (Ferdinand et al 2005). Regarding the causal and self-medication hypothesis finality has not yet been reached. However, evidence suggests that cannabis is a component cause (a risk factor that acts in combination with some other factor or factors to have a causal effect on the risk for a disease) for the development of psychosis (Henquet et al 2005b), with ‘psychosis-prone’ individuals (individuals with psychosis liability) especially at risk to develop psychotic symptoms after using cannabis (Verdoux et al 2003, Henquet et al 2005a).

Cannabis use in people with schizophrenia

Cannabis is one of the most commonly used substances in patients presenting to psychiatric services with their first episode of schizophrenia (e.g. Cantwell et al 1999, Barnes et al 2006), and is more common in people with psychosis than in the general population (Regier et al 1990). Based on treatment sample data, prevalences of cannabis use and abuse in people with psychosis are estimated to be 42.1% (range 19.2-89.1%) and 22.5% (range 5.5-54.9%) respectively (Green et al 2005). Male patients are more at risk to use cannabis and other drugs of abuse than female patients (Hambrecht and Hafner 1996).

If cannabis is a component cause of psychotic disorders, it is also likely that using cannabis once a psychotic disorder has developed may maintain and aggravate the disorder. Indeed, several studies have shown that cannabis has a detrimental effect on the course of the illness. In 1994, Linszen and colleagues were the first to report a study in which cannabis use was related to outcome variables in recent-onset schizophrenia patients. Cannabis was associated with poorer outcome over a 1 year period: significantly more and earlier psychotic relapses occurred in cannabis-abusing patients compared to non-users (Linszen et al 1994). In line with these findings, other longitudinal studies in schizophrenia patients showed that using cannabis is associated with increased relapse or rehospitalisation, decreased treatment adherence (Zammit et al 2008), and an increased level of positive symptoms (e.g. hallucinations, delusions) (Van Os et al 2002, Grech et al 2005). In addition to an impaired course of the disease, acute THC administration in schizophrenia patients can cause transient exacerbation of a range of positive and negative symptoms, perceptual alterations, learning and memory deficits, and medication side effects (D’Souza et al 2004).

Motivation for cannabis use in patients with schizophrenia

As cannabis use is so popular in patients with schizophrenia and has been shown to have a detrimental effect on the course of the illness, researchers have tried to understand what drives people with psychotic disorders to use cannabis. This is important to be able to develop
psychological and pharmacological treatment strategies for reducing cannabis use, and for a better understanding in health care workers who treat patients with psychotic disorder. Many factors have to be considered when trying to understand what patients drive to use cannabis. For example, biological drives for cannabis use, genetic influences, sociocultural influences, personality variables and coping strategies, and dependence (Spencer et al 2002). It is argued, that the final common pathway to use cannabis is the expectancy of the direct and indirect effect cannabis use will have on affect (Spencer et al 2002).

The empirical studies that have examined reasons and motivations for drug use typically focussed on two related areas: motivation/reasons to use substances, and expectations of the effects of substances, which are related to each other. Motives refer to reasons for using substances to attain a desired outcome, and expectancies refer to a personal belief regarding the effects of using substances, even if these effects are not desirable (Cox and Klinger 1988, Cooper 1994, Cooper et al 1995, Agrawal et al 2008). Motives are thought to be more proximate to actual substance use behavior than expectancies (Cooper et al 1994). Research in the general population on motives for cannabis use found five overall motives: enhancement, conformity, expansion, coping and social motives (Simons et al 1998). Expectancies of cannabis use have also been assessed in the general population and compromise cognitive and behavioral impairment, relaxation, social and sexual facilitation, perceptual and cognitive enhancement, global negative effects and physical effects (Schafer and Brown 1991).

In people with psychotic disorders, expectancies, reasons and motivation for cannabis use have been investigated in a variety of studies using self-report questionnaires. The first report dates from 1989 (Test et al 1989). In the last two decades other studies followed. Although reviews of hypotheses for the increased risk of substance use and cannabis use in patients with psychotic illness have been published (Blanchard et al 2000, Degenhardt 2003, Gregg et al 2007), a review of the self-report literature was lacking at the time this thesis started. Further, although numerous studies have investigated self-reported reasons for cannabis use in patients with psychotic disorders, little is known about self-reported reasons for cessation of cannabis use among these patients. In addition there is limited data available on the course of cannabis use in young schizophrenia patients, the proportion of these patients that cease the use of cannabis and the time of cessation.

All of the studies on motivation and expectancies of cannabis in patients with schizophrenia relied on patient self-report. However, self-report measures have been criticized because of their susceptibility to self-presentation biases (e.g. Holtgraves 2004) and the possibility that cognitive processes mediating substance abuse are not accessible through introspection (McCusker 2001, Stacy 1997). For these reasons, Greenwald and Banaji (1995) proposed the use of more implicit (indirect) measures in addition to the use of explicit measures, which may tap different underlying cognitive-motivational processes (Stacy 1997, Wilson et al 2000). In one of the studies presented in this thesis, both explicit measures and implicit measures were used to assess expectations of cannabis use. For the implicit measure, we used the Implicit Association Task (IAT; Greenwald et al 1998).

**Implicit association task**

Greenwald and Banaji (1995) defined implicit cognition as ‘the introspectively unidentified (or inaccurately identified) trace of past experience that mediates a response’. Implicit measures are intended to assess relatively automatic associations in memory that are difficult to gauge with explicit self-report measures. In general, implicit measures intend to make a participant react fast and spontaneous without self-reflection or introspection. Explicit measures assess cognitions that are
related to slower deliberate processes that may inhibit more automatic, impulsive thinking and behaviour (Greenwald and Banaji 1995, Kahneman 2003). A test used to assess alcohol or drug-related memory associations is the IAT (Greenwald et al 1998). Although the IAT will be explained, the reader can try the IAT at https://implicit.harvard.edu/implicit/. The IAT assesses the relative strength of associations indirectly, without asking people to reflect and report motivations for their behaviour. It is a computerized categorization task based on the principle that people find it easier to categorize stimuli together if those stimuli are strongly associated rather than if the stimuli are not associated. The following explanation is derived from Wiers et al 2007a:

The IAT is a timed classification test, where 2 target categories (e.g. alcoholic drinks vs. soft-drinks) are sorted in different combinations with two attribute-categories (e.g. positive vs. negative valence). Participants’ task is to classify stimuli (words or pictures) as fast as they can, using two classification rules with two opposing response buttons. Participants first learn one rule (e.g. press left when the stimulus presented is an alcoholic drink and right when the stimulus is a soft-drink). They then learn the other classification rule (e.g. press left when the stimulus presented is a negative word and right when it is a positive word). Then the two rules are combined: press left when the stimulus is either an alcoholic drink or a negative word and right when the stimulus is either a soft-drink or a positive word. After this first combination phase, participants learn a reversed version of one rule (e.g., press left when the stimulus presented is positive and right when it is negative), followed by the other combination (press left when the stimulus is either an alcoholic drink or a positive word and right when the stimulus is either a soft-drink or a negative word). The IAT-effect is the difference in reaction time between the one sorting condition (i.e. alcohol/negative vs. soft-drink/positive) and the other sorting condition (alcohol/positive vs. soft-drink/negative).

In the study described in chapter 1.2 we use a slightly modified IAT, with a single attribute and single category, but the underlying principle is the same. When the IAT is used in addiction research, different affective associations toward the use of substances can be used. In our study we used three affective associations, namely positive arousal, negative affect, and positive sedation, because they represent the three main types of expectancies (Goldman and Darkes 2004, Wiers 2008). Although varieties of the IAT have been applied in the field of alcohol research (e.g. Wiers et al 2002, Wiers et al 2005, De Houwer et al 2004, Wiers et al 2007a, Wiers et al 2007b), and cannabis research (Field et al 2004, Ames et al 2007), implicit associations toward cannabis have not been investigated in patients with schizophrenia or related disorders. Investigating both implicit and explicit associations toward cannabis is interesting, since several studies found that implicit and explicit alcohol- and cannabis related cognitions predict unique variance in alcohol and cannabis use in the general population (Stacy 1997, Wiers et al 2002, Wiers et al 2005, Ames et al 2007).

Craving
As mentioned above, many factors may explain why people with psychotic disorder maintain the use of cannabis. One of those is dependence. Despite a lack of consensus regarding the concept of craving (Rankin et al 1979, Kozlowski and Wilkinson 1987, Kozlowski et al 1989, Pickens and Johanson 1992, Altman et al 1996, Verheul et al 1999, Sayette et al 2000, Rosenberg 2009), craving is regarded a central phenomenon of drug dependence (Robinson and Berridge 1993, Franken 2003). The WHO defines craving as ‘a very strong desire for a psychoactive substance or for the intoxicating effects of that substance, and further states that craving develops as a result of conditioned associations that evoke conditioned withdrawal responses, and that it may also be induced by the provocation of any physiological arousal state resembling an alcohol or drug withdrawal syndrome (WHO, 2008).’
Craving can be measured by self-report measures or by non-verbal measures of craving such as drug self-administration, psychophysiological responding, neurobiological responding, and cognitive processing (Sayette et al 2000). Sayette et al (2000) suggest that interpretation of these responses depends on one’s theory of craving, and there is no such thing as the best way to measure craving. A self-report measure to assess craving for drugs is the Obsessive Compulsive Drug Use Scale (OCDUS; Franken et al 2002). The OCDUS is the drug analogue to the Obsessive Compulsive Drinking Scale (OCDS; Anton et al 1996) and measures drug craving within a timeframe of one week. The OCDS was originally derived from the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al 1989a, 1989b). It has been suggested that many aspects of craving for substances are similar to the thought patterns and behaviours of patients with obsessive-compulsive illness (Modell et al 1992). The basic similarity is thought to be the occurrence of frequently recurring thoughts which cannot be stopped and the occurrence of compulsive behaviour. Although many studies investigated the factor structure of the OCDS (Bohn et al 1996, Kranzler et al 1999, Roberts et al 1999, De Wildt et al 2005, Connor et al 2008, Cordero et al 2009) only one study (Franken et al 2002) validated the OCDUS and reported three underlying factors: ‘thoughts and interference’, ‘desire and control’, and ‘resistance to thoughts and intention’. The factor structure of the OCDUS neither resembled the original two factor structure of the OCDS (obsessions and compulsions) reported by Anton et al (1995), nor the factor structures found in other studies of the OCDS (Bohn et al 1996, Kranzler et al 1999, Roberts et al 1999, Connor et al 2008, Cordero et al 2009).

At the start of this thesis, only a few studies on craving for cannabis in patients with psychotic disorder were available (Potvin et al 2006, Akerele and Levin 2007, Van Nimwegen et al 2008). These studies focused on the relation between craving and the effects of antipsychotic treatment, and used self-report questionnaires. Further, although the OCDUS for cannabis craving was available, the validity of this instrument, nor of any other craving instrument in patients with psychotic disorder had been established.

**Cannabis use and cognitive functioning in patients with schizophrenia**

Evidence of altered neuropsychological functioning is widely documented in both schizophrenia patients and cannabis users. Most of the studies investigating the neuropsychological functioning of schizophrenia patients have found that they perform significantly worse than normal controls on many cognitive functions, including memory, attention, executive function and language skills (Riley et al. 2000, Palmer et al 2009). Cannabis use in healthy individuals can produce cognitive impairment which resembles that of schizophrenia patients (Solowij & Michie 2007). As cannabis use is highly prevalent in patients with schizophrenia and both cannabis use and schizophrenia are related to impaired cognitive functioning, several studies have investigated the association of cognitive performance and cannabis use in patients with schizophrenia. One of the first reviews (Coulston et al 2007) of these studies (only seven studies were available at the time of the review) showed that three of the seven studies under review found that cannabis use was associated with worse performance on tests of executive functions, memory, and attention, while the remaining four studies found that cannabis use was associated with better performance on tests of memory, executive functions, attention, psychomotor speed, and visual spatial construction. The authors of the review (Coulston et al 2007) concluded that these seven studies provide inconsistent evidence, which was in part attributable to methodological variability between the studies, as well as methodological limitations within each study, including poor control for confounding variables. Later, Yucel et al (2010) performed a meta-analysis comprising some of the reviewed studies by
Coulston et al (2007), and in more recent studies that addressed the relation between cannabis use on cognitive functioning in schizophrenia patients. This meta-analysis revealed that overall, schizophrenia cannabis-using patients performed moderately better than non using patients on measures of global cognition, visual memory, processing speed, working memory, planning, and reasoning. This difference was largely driven by studies that included patients with a lifetime history of cannabis use rather than those with current or recent use. In a selection of patients with first episode psychosis, cannabis using patients performed better on tests of visual memory, working memory, and executive functioning. Further, patients with early onset cannabis use had less neuropsychological impairment than patients with later onset use. The authors concluded that these findings suggest that patients with schizophrenia and patients with first episode psychosis with a history of cannabis use have better neuropsychological functioning than non using patients. This may be caused by a subgroup of ‘neurocognitively less impaired’ patients, who only developed psychosis after a relatively early initiation into cannabis use.

Diffusion tensor imaging in cannabis using schizophrenia patients

The ‘dysconnectivity’ hypothesis of schizophrenia suggests that the core pathology of schizophrenia is disturbed communication with and between brain areas. White matter alterations may form the basis for this dysconnectivity, as brain white matter consists of the axonal projections to other neurons and functional brain areas and is therefore key to neural communication (Peters et al 2010). White matter abnormalities can be calculated and visualized by diffusion tensor imaging (DTI). DTI makes use of water diffusion. DTI uses a conventional magnetic resonance imaging (MRI) scanner, but by imposing additional magnetic field gradients, the scanned images are sensitized to the diffusion of water in the direction of those gradients. If measurements in at least six noncolinear directions are acquired, along with a nondiffusion weighted image, the diffusion tensor can be calculated at each point (voxel) in the brain (Basser and Pierpaoli 1996). The tensor can be thought of as an ellipse shape that matches the distribution that water molecules placed at its center will form after diffusing. The longest axis of the ellipsoid corresponds to the direction in which the diffusion is strongest, which is called axial diffusion, and the size of the ellipsoid along the other two axes corresponds to the diffusion perpendicular to the main diffusion direction and is called radial diffusion. In this way, the diffusion tensor provides a three-dimensional direction in which the diffusion is greatest and thereby the most-likely axonal fibre orientation at each voxel (Peters et al 2010). The ratio between the amount of diffusion along the axonal fibre and the amount of diffusion perpendicular to it is called diffusion anisotropy. A DTI index called fractional anisotropy is thought to be a marker of the structural integrity of fibers (Beaulieu 2002).

In schizophrenia, abnormalities in white matter connectivity are thought to arise from myelin related and oligodendroglia dysfunction (Davis et al 2003). In schizophrenia patients, compared to healthy controls, several DTI studies reported reduced fractional anisotropy (FA) in prefrontal and temporal lobes, connecting fibres, and the corpus callosum (Kanaan et al 2005). When this thesis was started, no DTI study was available reported on schizophrenia and cannabis use. However, there were (few) reports of magnetic resonance imaging (MRI) studies available that investigated the effects of cannabis use on brain morphology in patients with schizophrenia (Cahn et al 2004, Szekso et al 2007, Potvin et al 2007, Rais et al 2008, Bangalore et al 2008), but these did not have consistent results. It must be mentioned though, that the study of Rais et al (2008) revealed that in cannabis using schizophrenia patients brain volume reduction was more pronounced over a 5-year follow-up (Rais et al 2008) in comparison with patients with no cannabis use. These studies did not specifically focus on
patients who used cannabis in adolescence, which would be of interest since there is evidence that individuals who start using cannabis during pubertal brain development are most vulnerable to its deleterious effects (Ehrenreich et al 1999, Pope et al 2003, Schneider and Koch 2003, Schneider 2008).

The GROUP study

GROUP is the abbreviation of Genetic Risk and OUtcome of Psychosis, a longitudinal observational study in The Netherlands (and part of Belgium) (www.group-project.nl). The main objective of the GROUP study was to investigate the dynamic interaction over time between genetic and environmental factors that contribute to the expression and course of psychosis. GROUP is a consortium of four academic centers in Amsterdam, Groningen, Maastricht, and Utrecht. Data were gathered by these centers and their affiliated mental health care institutions. For this population based cohort study, patients with a recent onset psychotic disorder (n=1057), siblings (n=1099), parents (n=938) and healthy controls (n=590) were included. Inclusion of participants and first assessment started in 2004. Participants will be followed after 3 and 6 years for the second and third assessments. Instruments used for this study address symptoms, vulnerability and resilience factors and course of the disease. Besides interviews and self-report instruments, neuropsychological tests (e.g. attention, working memory, executive functioning) were performed, and blood and urine samples were taken for molecular and genetic research respectively. Urinalysis for the presence of substances like THC. Population characteristics have been described previously (Korver et al 2011).

Four chapters (1.3, 2.1, 2.2, and 2.3) of this thesis are derived from data of GROUP’s first assessment. The other chapters (1.1, 1.2, 1.4, 3.1) are derived from studies performed separately from GROUP. For these studies, patients were recruited from the inpatient and outpatient clinic of the Adolescent Clinic (nowadays Department of Early Psychosis) of the Psychiatric Department of the AMC in Amsterdam. This clinic is specialized in the treatment of young patients with a diagnosis of recent onset schizophrenia or related disease aged between 16 and 28 years. In four chapters (1.2, 1.3, 2.3, 3.1) unaffected siblings of patients and/ or healthy controls were included as well.
Research questions

The questions addressed in this thesis were:

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?

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?

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

Part II

4. What is the relationship between cannabis use and age at onset of first psychosis?

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

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

Part III

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

Part I of this thesis addresses research questions 1, 2 and 3 and focuses on what patients report about the reasons for cannabis use, the effects of cannabis use, their craving for cannabis use, and when and why they cease the use of cannabis. To reduce the detrimental effect of cannabis on the illness and increase the likelihood of a better prognosis, treatment for cannabis use in patients with schizophrenia or related disorders is of major importance. To inform health care workers and develop treatment strategies, insight in factors that make patients continue or stop their cannabis use is essential. One of the ways to understand the reasons for use of cannabis in patients with psychotic illness is to ask them directly by means of self-report questionnaires. In the last two decades, many reports have been published of studies in which patients with psychotic illness were asked to report what their reasons are for using cannabis and which effects they experienced during intoxication of cannabis. A review of these studies is presented in chapter 1.1. During the review, we concluded that studies were lacking on implicit effect expectancies. As implicit associations are important predictors in other areas of addiction research, we conducted such a study (chapter 1.2) in which implicit associations toward cannabis were examined in schizophrenia patients and healthy controls. Although craving is an important risk factor for the continuation of substance use, data on craving for cannabis in patients with schizophrenia are scarce. To assess whether craving for cannabis can be reliable and validly assessed in patients with non-affective psychotic disorders, the Obsessive Compulsive Drug Use Scale for Cannabis (OCDUS-CAN) was psychometrically analyzed. Results are presented in chapter 1.3. In addition, this chapter presents the results of a comparison of craving between patients, siblings and controls and between frequent and infrequent users. Because studies on factors related to cessation of cannabis in patients with schizophrenia are lacking, and knowledge of these factors may provide further insight in how to treat patients with co morbid cannabis use, we performed a file-study (chapter 1.4) in which 206 medical records of consecutively admitted patients with recent-onset schizophrenia or related disorders were examined for information about cannabis use, cessation of cannabis use and the motivation for cessation of cannabis use.

Part II of this thesis addresses research questions 4, 5 and 6 and focuses on the relation between cannabis use and clinical variables, like age at onset of first psychosis, obsessive compulsive symptoms and cognitive performance. Studies presented in part II are derived from GROUP data. Chapter 2.1 describes the results of a study in which the relation between cannabis use, other drug use, gender and age at onset of non-affective psychotic illness is examined in patients of the GROUP study. As opposed to previous studies on the relationship between cannabis and age at onset, our study comprised a relatively large number of females which enabled us to assess the independent influence of gender on age at onset properly. As the literature on the relation between substance use and OCS in patients with schizophrenia is scarce, we performed a study in which we compared patients with or without co morbid obsessive compulsive symptoms on cannabis use and other substance use variables in patients of the GROUP study. Results of this study are presented in chapter 2.2. We extended the available literature on the association between cannabis and cognitive performance in patients with schizophrenia by investigating the relationship between cannabis use and cognitive performance in patients, sibling and controls using a wide variety of cognitive tasks. In this study we made a distinction between recency and frequency of cannabis use, and corrected for major possible confounders. Results of this study are presented in chapter 2.3.
Introduction

Part III of this thesis addresses research question 7 and describes a brain imaging study, in which structural and diffusion tensor imaging data are compared between patients who started the use of cannabis before the age of 15, patients who started the use of cannabis at the age of 17 or later, and patients who had never used cannabis (chapter 3.1). Chapter 3.2 is a letter to the editor, in which we reply to Fan and Hart (2011) who wrote a letter to the editor referring to the article presented in chapter 3.1.

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Introduction


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