Cannabis use in patients with schizophrenia: motivation for use and relation to clinical variables
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The most important findings of this thesis are:

- Patients with schizophrenia commonly report that their reasons for cannabis use are enhancement of positive affect, relief of dysphoria, and social enhancement. Relatively few patients report reasons related to relief of psychotic symptoms or relief of side-effects of medication. Many patients report that cannabis negatively affects positive symptoms.

- Patients with schizophrenia have similar explicit and implicit association towards the effects of cannabis as controls, but they have stronger explicit negative expectancies of cannabis.

- The Obsessive Compulsive Drug Use Scale for cannabis (OCDUS-CAN) is a valid instrument to assess craving for cannabis in patients with psychotic disorder, siblings and healthy controls.

- Patients have higher craving levels for cannabis compared to siblings and controls, which could be related to primary and secondary symptoms of their disorder and side-effects of antipsychotic medication.

- More than half of cannabis using patients ceased the use of cannabis before they were admitted to the Early Psychosis Department. Most of these patients ceased the use of cannabis after they became psychotic and after start of treatment in psychiatric services, which may well be related to the awareness of patients that cannabis use negatively affects symptoms and to psycho-education by health care workers.

- Age at onset of psychosis was 1.8 years earlier in cannabis users compared to non-users, corrected for gender and the use of other illicit drugs. This could be explained by cannabis use precipitating the onset of psychotic illness in vulnerable subjects.

- We did not find evidence that co-morbid obsessive-compulsive symptoms are a protective factor against the use of nicotine and other substances in patients suffering from non-affective psychotic illness.

- Current cannabis use was associated with poorer performance on immediate verbal learning, processing speed and working memory, and lifetime cannabis use was associated with better performance on acquired knowledge and social cognition. Findings suggest that cannabis using patients have a higher cognitive potential compared to non-users, but the (sub)acute effects of cannabis impair cognitive functioning.

- Cannabis naïve patients showed reduced white matter integrity in the splenium of the corpus callosum, compared to patients with early-onset cannabis use. This finding indicates a more vulnerable brain structure in cannabis naïve schizophrenia patients.
Motivation for use and relation to clinical variables

Nienke Dekker

CaNNabis use in patients with Schizophrenia
Cannabis use in patients with schizophrenia

Motivation for use and relation to clinical variables
Cannabis use in patients with schizophrenia. Motivation for use and relation to clinical variables.

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Motivation for use and relation to clinical variables

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ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. D.C. van den Boom

ten overstaan van een door het college voor promoties ingestelde

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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 admission 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 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 $\Delta^9$-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 that 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 (Atha 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, Andreasson 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).
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 at 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 drivers 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 cognition 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, KoIowski and Wilkinson 1987, Kozlowski et al 1989, Pickens and Johanson 1992, Altman et al 1996, Verheul et al 1999, Sayette et al 2000, Rosenget al 2009), craving is regarded as 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 noncollinear 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, Szesko 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.
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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Linszen DH, Dingemans PM, Lenior ME: Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 1994; 51: 273-279.


PART I

Motivation for cannabis use, affective associations toward cannabis use, and craving for cannabis use in recent-onset schizophrenia
CHAPTER 1.1

Reasons for cannabis use and effects of cannabis use as reported by patients with psychotic disorders: a review

N. Dekker, D.H. Linszen, L. de Haan
Abstract

Background. Cannabis is one of the most commonly used substances in patients with a psychotic disorder and is associated with a higher risk of psychotic relapses. Identifying reasons for cannabis use and subjective effects in patients with psychotic disorders can provide insight in the functions of cannabis use, and this may lead to targeted interventions.

Methods. A literature search of the PubMed and PsycInfo databases for articles published from 1985 till 2008 was carried out to review studies that examined self-reported reasons for cannabis use and self-reported effects of cannabis use in patients with psychotic disorders.

Results. Only a few studies were found that specifically assessed reasons for and effects of cannabis use. Despite the heterogeneity in the study samples and methodology, patients commonly reported that their reasons for cannabis use were enhancement of positive affect, relief of dysphoria, and social enhancement. Fewer patients reported reasons related to relief of psychotic symptoms or relief of side-effects of medication. Frequently reported positive effects of cannabis were positive changes in affect and relaxation. A large amount of patients reported that cannabis negatively affected positive symptoms.

Conclusions. Patients suffering from psychotic disorder report using cannabis mainly for affect regulation and socialization, despite awareness that cannabis has a negative effect on positive symptoms. In spite of the heterogeneity of the studies, results turned out to be broadly comparable and support the external validity of this review to a broad range of cannabis using patients with psychotic disorder.
Introduction

Cannabis is one of the most commonly used substances in patients presenting to psychiatric services with their first episode of schizophrenia (Hambrecht and Häfner 1996, Cantwell et al 1999, Van Mastrigt et al 2004, Barnes et al 2006). Based on treatment sample data, prevalence rates for 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). Several studies demonstrate that co-morbid cannabis abuse is associated with a higher risk of psychotic relapses (Linszen et al 1994) and worsens the outcome of schizophrenia (Caspari 1999, Bühler et al 2002, Van Os 2002). Further, patients who abuse cannabis have been found to have a greater number of positive psychotic symptoms (Negrete et al 1986). D’Souza et al (2005) showed that in patients with schizophrenia ∆9-tetrahydrocannabinol (∆9-THC), the principal active component of cannabis, exacerbates psychotic symptoms, cognitive impairment and medication side effects in patients with schizophrenia. Rates of cannabis use and misuse are generally higher in schizophrenia patients than in the general population (Green et al 2005). There has been considerable debate about this co-morbid association (Mueser et al 1998, Blanchard et al 2000, Degenhardt et al 2003, Degenhardt et al 2006, Gregg et al 2007). Most authors conclude that cannabis use is a component cause of psychosis (Henquet et al 2005a, Moore et al 2007). Another explanation is based on the self-medication hypothesis, which proposes that substance use is a consequence of patients’ attempts to decrease symptoms accompanying the disease or to alleviate underlying distressing emotional states (Khantzian 1985, Khantzian 1997). Previous reviews on self-report literature regarding reasons for substance use and effects of drug use in people with psychosis have also tried to give a better understanding of the relationship of schizophrenia and substance use (Gregg et al 2007, Dixon et al 1990). In this review we will give an overview of the self-reported reasons for use of cannabis and the perceived effects of cannabis use in individuals with psychotic disorders, to obtain more insight in the drives and motivation that patients have for using cannabis. This insight may be useful in the treatment of patients with both psychotic and cannabis use disorders, and it may give a better understanding of how to encounter this group of patients.

Methods

Literature search

Relevant articles were searched in PubMed and PsycINFO with the following keywords: ‘schizophrenia’, or ‘psychosis’, or ‘psychotic disorders’ combined with ‘cannabis’, or ‘marijuana’, or ‘marihuana’, or ‘hashish’, or ‘substance use’, combined with ‘motivation’, or ‘reasons’ or ‘subjective effects’. English-language and non-English language articles (with abstracts in English) were selected. We used articles published from 1985 till 2008. Articles were included if they described studies in which patients with psychosis, schizophrenia-spectrum disorders or schizophrenia were assessed with a (semi)structured interview or questionnaire about their current reasons for the use of cannabis and/ or subjective effects of cannabis use. Studies in which effects expectancies of cannabis (beliefs that are hold about the effects of cannabis) were measured were also used. Both open and closed question data were used. We included studies that had assessed general reasons for substance use or general effects of substance use, on the condition that cannabis was among the two most used substances, and used by at least one third of the interview sample. Case reports were not used.
Analysis of prevalence data

To obtain an overall idea of the frequency of self-reported reasons for cannabis use, we pooled the results of studies that provided prevalence data on self-reported reasons for specifically cannabis use. Based on our literature review we grouped reasons for cannabis use into four main categories, namely (1) enhancement of positive feelings (e.g. to enhance pleasure, to feel good), (2) to relieve dysphoria (e.g. to relieve boredom, to improve depression, to relax), (3) to socialize (e.g. to go along with the group, to become more talkative), and (4) to reduce symptoms and medication side-effects (e.g. to decrease voices, to reduce paranoia, to decrease subjective unwell being caused by prescribed medication). For all studies that provided prevalence data on self-reported reasons for specifically cannabis use, two authors independently grouped the reported reasons into the above mentioned four categories. We resolved disagreement with consensus. One reported reason that caused some debate was ‘mood alteration’, which was interpreted as either ‘enhancement of positive affect’ or ‘relieve of dysphoria’. Finally we agreed that ‘mood alteration’ more closely belonged to ‘relieve of dysphoria’, because it most probably is a change from a worse to a better mood. In order to pool the frequency data, we looked at each category and each study and used the frequency of the reason reported by the highest amount of patients. For instance, if in one study both the items ‘to relax’ and ‘to relieve boredom’ were reported by respectively 86% and 79%, we used 86% for the category ‘dysphoria relief’. We then -per category- added up the numbers of subjects from each of the studies and divided the sum by the total number of subjects in the studies. If a study did not report reasons belonging to a certain category, we did not include that study in the calculation of the overall percentage for that category. Based on our literature review we also grouped self-reported subjective effects of cannabis use into categories, namely (1) affect (e.g. depression, happy, anxiety), (2) relaxation, (3) socialization (e.g. friendly, lonely), (4) energy and physical effects (e.g. feel bad physically, energetic), and (5) symptoms and medication side-effects (e.g. paranoia, suspiciousness, confused, stiffness). For each category, effects of cannabis were split up in either a positive or negative effect, according to the scales in the studies. For all studies that provided prevalence data on self-reported effects of cannabis use, we grouped the reported effects into the five main categories. Again, two authors did this independently. One effect gave some debate, namely ‘work output’ that was put in the category ‘energy and physical effects’. To pool the prevalence data, the same method as described for the reasons for use was used. In case of one study (Green et al 2004), in which reasons and effects were assessed at two time points and therefore two ratings were available, we used the highest percentage.

Results

Chapter 1.1 - Self-reported reasons and effects

Reasons for specifically cannabis use

Studies with prevalence data. Table 2 depicts self-reported reasons for cannabis use in the studies that provided prevalence data (Green et al 2004, Addington and Duchak 1997, Fowler et al 1998, Goswami et al 2003, Schofield et al 2006). According to the results, relief of dysphoria and social reasons were reported most frequently (resp. 66.3% and 61.7%), followed by enhancement of positive affect (42.1%), and illness and medication related reasons (12.9%). Below we will describe the studies summarized in table 2 in more detail. Addington and Duchak (1997) examined reasons for cannabis use in 21 outpatients with dependence for cannabis. The most commonly reported reasons for the use of cannabis were ‘to increase pleasure’ (95%), ‘to get high’ (95%), ‘to relax’ (81%), ‘to relieve depression’ (81%), and ‘to go along with the group’ (71%). Use ‘to decrease slowed-down feeling caused by medication’, and ‘to decrease voices’ were reported by lower percentages, respectively 19%, 38% and 40% of the patients. Fowler et al (1998) examined reasons for use of substances in a larger sample of 194 patients with schizophrenia, with over one third having a lifetime diagnosis of cannabis abuse or dependence. All self-reported reasons were grouped into four main categories, namely (1) drug intoxication effects, (2) dysphoria relief, (3) social effects, and (4) illness and medication-related effects. Users of cannabis (n=58) used for intoxication effects (41%), to relieve dysphoria (62%), and a small proportion (6.9%) used for illness and medication-related reasons. Only cannabis abusers (rather than users) reported this last reason. Ratings related to sociality were not provided. In a small study at least four of the five schizophrenia patients reported using cannabis ‘to increase pleasure’, ‘to get high’, ‘to relax’, and ‘to satisfy curiosity’ (Goswami et al 2003). Green and colleagues (2004) compared reasons for cannabis use in individuals with (n= 49) and without (n=47) psychotic disorder. For patients, the five most important reasons for use at baseline and 4-week follow up were social activity reasons (resp. 37.8 % and 28.9%), positive mood alteration (resp. 35.6 and 42.1%), coping with anxiety/ depression (resp. 26.7 and 28.9%), availability (resp. 24.4 and 28.9%) and boredom (resp. 22.2 and 31.1%). Compared to controls, patients were less likely to use cannabis for relaxation, out of habit, and for social reasons. Patients were more likely to use cannabis to reduce anxiety/ depression, and to reduce boredom. An important question in another study with 49 patients who recently used cannabis, was whether discomfort of experienced side-effects of medication is consciously self-medicating with cannabis (Schofield et al 2006). According to the results, psychological (mental) side-effects (other than neurologic, autonomic or other undifferentiated side-effects) were most distressing and more frequently associated with the motivation to use cannabis use. Almost 50% of patients having inner unrest/agitation or difficulty sleeping, and at least 25% of patients having side effects like sleepiness/sedation, muscle tension and lack of emotions, reported to reduce these symptoms and signs with cannabis. Analysis of reported general reasons showed that cannabis was most commonly used ‘to relax’ (86%), ‘as something to do with friends’(81%), and to ‘relieve boredom’ (79%). Lambert and colleagues (1997) interviewed 56 patients with both schizophrenia and a cannabis use disorder about their motivation for the use of cannabis, and provide prevalence data for the most important reason patients have for the use of cannabis. Relaxation was the reason reported by the largest part (17.9%) of patients, followed by expansion of consciousness/awareness (16.1%), improvement of mood (14.3%), and improvement of contact with others (10.7%). Using cannabis to
<table>
<thead>
<tr>
<th>Author</th>
<th>Total study sample</th>
<th>Diagnosis and in-/ outpatient</th>
<th>Inclusion criteria for cannabis or other substance use</th>
<th>Self-reported reasons</th>
<th>Self-reported subjective effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addington and Duchak (1997)</td>
<td>41</td>
<td>DSM-III-R schizophrenia and schizoaffective disorder; outpatients</td>
<td>DSM-III-R substance abuse or dependence</td>
<td>Inspection of a list adapted from Dixon et al (1991)</td>
<td>Yes 21 Inspection of a list, responses based on increasing or decreasing effect</td>
</tr>
<tr>
<td>Goswami et al (2003)</td>
<td>22*</td>
<td>DSM-IV schizophrenia; outpatients</td>
<td>DSM-IV cannabis or other substance abuse/dependence at least one month prior to intake</td>
<td>Questionnaire (Stated Reasons Scale), adapted from Dixon et al (1993)</td>
<td>Yes 5 Questionnaire (Perceived Effects Scale, adapted from Dixon et al (1991), responses based on increased/ decreased/no effects on mood, thoughts and behaviour</td>
</tr>
<tr>
<td>Green et al (2004)</td>
<td>45*</td>
<td>DSM-IV schizophrenia and schizoaffective disorder</td>
<td>Used 3 cones of cannabis (eq. 1/4 g of cannabis) a week for a month in last 3 months</td>
<td>Open-ended questions</td>
<td>Yes 45 Interview with open-ended questions</td>
</tr>
<tr>
<td>Lambert et al (1997)</td>
<td>200</td>
<td>ICD-10 schizophrenia (F20); inpatients</td>
<td>ICD-10 lifetime or recent diagnosis of Alcohol use disorder (F10.1 or F10.2) Cannabis use disorder (F12) Polydrug use disorder (F19)</td>
<td>Interview about motives (from Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (AMDP: 1981))</td>
<td>Yes** 56 X</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Mean Age (SD)</td>
<td>Diagnostic Criteria</td>
<td>Method of Data Collection</td>
<td>Measures</td>
</tr>
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<tr>
<td>Spencer et al (2002)</td>
<td>69</td>
<td>31</td>
<td>DSM-IV psychotic disorder; in- and outpatients</td>
<td>Questionnaire adapted from Drinking Motives Questionnaire (Cooper 1994), responses based on a 5-point Likert scale</td>
<td>Yes**</td>
</tr>
<tr>
<td>Dixon et al (1991)</td>
<td>83</td>
<td>30.6 (8.5)</td>
<td>DSM-III-R schizophrenia, schizoaffective disorder, and schizofreniform disorder; inpatients</td>
<td>Inspection of a list</td>
<td>No</td>
</tr>
<tr>
<td>Auger et al (1995)</td>
<td>53</td>
<td>29.3 (9.5)</td>
<td>DSM-III-R schizophrenia, inpatients</td>
<td>Interview (schizophrenia/substance abuse interview schedule) designed by authors with open-ended questions</td>
<td>No</td>
</tr>
<tr>
<td>Mueser et al (1995)</td>
<td>70</td>
<td>36.7 (8.7)</td>
<td>DSM-III-R schizophrenia and schizoaffective disorder; in- and outpatients</td>
<td>Drug Use Motives Measure (DUMM), adapted from the Drinking Motives Measure (Cooper et al 1992), responses based on a 4-point Likert scale</td>
<td>No</td>
</tr>
</tbody>
</table>
Continuation table 1

<table>
<thead>
<tr>
<th>Test et al (1989)</th>
<th>29*****</th>
<th>Schizophrenia and schizoaffective disorder according to Research Diagnostic Criteria (Spitzer et al 1978), DSM-III Schizotypical personality disorder; outpatients</th>
<th>Use of alcohol or cannabis or some other street drug several times a week or daily during past 6 months</th>
<th>Free response and inspection of a list</th>
<th>No</th>
<th>27</th>
<th>Inspection of list, responses based on increasing/decreasing/no effect on certain symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gearon et al (2001)</td>
<td>25******</td>
<td>DSM-IV schizophrenia and schizoaffective disorder; outpatients</td>
<td>DSM-IV Drug abuse or dependence within 6 months before assessment</td>
<td>Questionnaire (Inventory of Drug Taking Situations) (Annis et al 1989), and Self-Medication Questionnaire developed by authors</td>
<td>No</td>
<td>25</td>
<td>X</td>
</tr>
</tbody>
</table>

* only males; ** not used in table 2 because only prevalence data of most important reason are reported; *** not used in table 2 because percentage of participants reporting a certain reason not available due to instrument used; **** not used in table 3 because percentage of participants reporting a certain perceived effect not available due to instrument used or otherwise; ***** total study sample was larger, but the interview sample was restricted to 29 significant users; ****** total study sample was larger (including patients with major affective disorders), but separate analysis was made for 25 patients that had both schizophrenia and drug use disorder.

have less symptoms of psychotic symptoms was only reported by 1 patient (1.8%). This study is not
used in table 2 because only prevalence data of the most important reason are reported.

Studies that used a qualitative measure. Spencer and colleagues (2002) assessed 69 patients with
psychotic disorders with the ‘Drinking Motives Measure’ (DMM: Cooper 1994), a validated self-
report instrument that was adapted by the authors to assess motives for alcohol and cannabis use.
The DMM contains four underlying factors, namely enhancement, coping, social motives and
conformity motives. The authors added more items to explore the use of substances to alleviate
psychotic symptoms and medication side effects. For each item, patients rated how often they had
used their most frequent substance on a five-point scale (from never/almost never, to almost/
always/almost always). A factor analysis revealed the same factor structure as revealed by Cooper (1994). A
fifth factor, namely relief of positive symptoms and side effects demonstrated limited reliability.
Overall, users of cannabis gave the subscale enhancement of positive effect the highest mean rate,
followed by social motives and coping with unpleasant affect. They were less frequently to use for
conformity purposes and rarely for relief of positive symptoms and medication side-effects.

Reasons for substance use with cannabis as one of the main substances

Studies with prevalence data. Five studies provided prevalence data on self-reported reasons for
1994, Baigent et al 1995, Gearon 2001). Many reported reasons were recognizable from the four
categories depicted in table 2. Across all five studies, relieve of dysphoria (e.g. ‘to relieve boredom’,
‘to relieve depression’, ‘to relax’) was among the five most frequently reported reasons, and was reported by up to 80% of patients. For three studies, social reasons were also in top
five of most frequently reported reasons, reported by up to 75% of patients. In two studies, reasons
related to enhancement of positive feelings (e.g. ‘to increase pleasure’, ‘to get high’) were in the top
five of most frequently reported reasons. Reasons related to illness or medication were reported in
not belong to the top five of most frequently reported reasons. Relief of side-effects as a reason to
use was reported by 4-48%, and relieve of positive and negative symptoms by 4-36%.

Studies that used a qualitative measure. Like Spencer et al (2002), Mueser et al (1995) also used the
‘Drinking Motives Measure’ (DMM: Cooper et al 1992), but an earlier version. They adapted the DMM
for assessing motives for drug use and developed the ‘Drug Use Motives Measure’ (DUMM). Mean
scores were reported separately for different groups of drug abusing patients, ranging from groups
with no abuse to recent drug abuse. Results are comparable with the study of Spencer et al 2002.
Across all groups, the motive pleasure enhancement scored higher than the other two motives (social
and coping motives). Patients with a history of drug use disorder tended to endorse motives more
strongly than did patients with no substance use disorder history.

Subjective effects of specifically cannabis use

Studies with prevalence data. Table 3 depicts subjective effects of cannabis reported in the studies
that provided prevalence data (Dixon et al 1991, Addington and Duchak 1997, Goswami et al 2003,
Green et al 2004). According to the results of pooling, positive effects on affect and relaxation (resp.
75.5% and 59.6%) are reported by far more patients than negative effects on these dimensions
(resp. 17% and 8.2%). Positive effects on energy and socialization (33% and 35.2%) are reported
slightly more than negative effects on these domains (23.4% and 30.8%). Up to 45% of the patients
report that cannabis has a negative effect on symptoms and side-effects, as opposed to only less
than 10% who report relieving effects of cannabis on symptoms and side-effects. Dixon et al (1991) evaluated effects of cannabis use on mood and symptoms in 23 cannabis abusing patients. Cannabis use decreased both anxiety and depression as reported by most of the patients (at least 80%). Increased energy and calmness due to cannabis use was reported by at least 66% of the patients. An increase in symptoms like suspicion and hallucinations was reported by much more patients than a decrease of those symptoms. In Addington and Duchak’s study (1997) most of the 21 patients reported that cannabis increased feelings of happiness (91%), relaxation (71%) and being friendly (67%). Other notable ratings were a decrease of boredom and energy (both rated by approximately 70%), and a decrease of feeling sad and angry (resp. 43% and 57%). More than half of the cannabis users reported an increase of positive symptoms. Goswami et al (2003) used an adapted version of Dixon and co-workers questionnaire (Dixon et al 1991), and reported that four of the five cannabis abusing patients reported an increase of energy. In another study 45 patients were interviewed; the most important positive effect of cannabis was mood alteration (42.2 at baseline and 62.2% at 4-week follow up), followed by relaxation (26.7 at baseline and 48.9% follow up) (Green et al 2004). ‘Psychotic symptoms’, particularly paranoia, was the most frequently reported negative effect (24.4% at baseline and 8.5% at follow up). In comparison with the healthy control group, patients were significantly less likely to report relaxation as the most important positive effect, and patients were significantly more likely to report psychotic symptoms as negative effect. Warner and co-workers (1994) asked 55 patients what symptoms they experienced recently and for each, whether use of their most typical substance generally made the symptoms worse, better or caused no change. Most subjects that reported anxiety, depression, insomnia, or physical discomfort perceived cannabis as reducing those symptoms. Very few experienced a reduction of side effects, paranoia or hallucinations, when using cannabis. This study is not included in table 3 because the total of participant that reported effects of cannabis is not provided.

Studies that used a qualitative measure. Four studies assessed the effects of cannabis use with a Likert scale (Baigent et al 1995, Mueser et al 1995, Busquets et al 2005, Schofield et al 2006). Baigent et al (1995) asked 35 patients about the perceived effect of cannabis on 10 dimensions of feelings and symptoms. Responses were based on 5-point equal interval scales. The dimension ‘mood’ had the highest mean score of 3.7, meaning cannabis had a neutral to slightly cheerful effect on mood. Further, positive symptoms had a mean score of 3.6, meaning neutral to slightly more, and negative symptoms were rated by a mean of 3.2, meaning neutral to slightly more. The other dimensions (energy, anxiety, hostility, suspicion, thought clarity, distractibility and group attachment) perceived a neutral score. Mueser et al (1995) asked 63 patients’ expectancies of the effects of cannabis use with the use of the Marijuana Effect Expectancy Questionnaire (MEEQ: Schafer and Brown 1991), a validated self-report instrument. The MEEQ contains items describing common effects of marijuana and subjects can agree or disagree according to their own current thoughts, feelings, and beliefs about the effects of cannabis. Across the groups of different histories of drug use and alcohol use there was a variation in mean scores of the scales, but the subscale ‘cognitive and behavioural impairment’ perceived the highest mean score across all groups. Patients with a history of drug use disorder tended to endorse expectancies more strongly than did patients with no substance use disorder history. Schofield et al (2006) used the ‘Cannabis Use Effects Survey’, an adaptation of the ‘Assessment of Cannabis Use’ (Rolfe et al 1999), in 49 cannabis using patients. Detailed information on ratings were not provided, but the authors did report that on average, subjects reported that cannabis usually reduced their anxiety. Cannabis made them feel good, sleep better, experience less
Table 2. Self-reported reasons (%) for cannabis use in patients with psychotic disorders

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Enhancement of positive feelings</th>
<th>Relieve of dysphoria</th>
<th>Social reasons</th>
<th>Illness- and medication-related reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addington and Duchak (1997)</td>
<td>21</td>
<td>95</td>
<td>95</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to increase pleasure</td>
<td></td>
<td>to go along with group</td>
<td>to decrease voices</td>
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<tr>
<td></td>
<td></td>
<td>to get high</td>
<td></td>
<td>to become more talkative</td>
<td></td>
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<tr>
<td>Goswami et al (2003)</td>
<td>5</td>
<td>100</td>
<td>80</td>
<td>40</td>
<td>40</td>
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<tr>
<td></td>
<td></td>
<td>to increase pleasure</td>
<td></td>
<td>to go along with group</td>
<td>to decrease hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to get high</td>
<td></td>
<td></td>
<td>to decrease suspiciousness</td>
</tr>
<tr>
<td>Green et al (2004)</td>
<td>45</td>
<td>15.6</td>
<td>42.2</td>
<td>42.2</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>entertainment</td>
<td>mood alteration</td>
<td>interaction</td>
<td>psychotic symptoms</td>
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<td></td>
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<td>anxiety/depression</td>
<td>social activity</td>
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<td>boredom</td>
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<td>to cope other neg</td>
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<td></td>
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<td>mood</td>
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<td>relaxation</td>
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<td></td>
<td>to feel good about oneself</td>
<td>to relax</td>
<td>to decrease voices</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>relieve boredom</td>
<td>to reduce paranoia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>reduce anxiety</td>
<td>to reduce medication side-effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n)</td>
<td>178</td>
<td>42.1</td>
<td>66.3</td>
<td>61.7^</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Self-reported reasons that could not be assigned to one of the four groups of reasons were as follows; from Addington and Duchak (1997): to give one more interests 62%, to give one more thoughts 57%, to concentrate better 33%, to increase energy 29%, to decrease tiredness 29%, to increase one's sexual interest 24%, to increase voices 55%, from Goswami et al (2003): to satisfy curiosity 80%, to increase energy 40%, to be more creative 40%, to increase concentration 40%, to work/study better 40%, to increase confidence 40%, to increase sleep 40%, to increase appetite 20%, from Green et al (2004): availability 28.9%, wanted to 30%, addiction 17.8%, cognitive enhancement 11.1%, habit 11.1%, physical enhancement 11.1%, preferred alternative 6.7%, perceptual change 2.1%, and from Schofield et al (2006): to improve sleep 58%.

^ number of studies pooled to obtain total sample size is 4 (n= 120)
Table 3. Self-reported effects of cannabis use in patients with psychotic disorders

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Affect</th>
<th>Relaxation</th>
<th>Energy / Physical effect</th>
<th>Socialization</th>
<th>Symptoms and medication side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>better %</td>
<td>worse %</td>
<td>better %</td>
<td>worse %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>relaxation</td>
<td>physical effect</td>
<td>socialization</td>
<td>side-effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>better %</td>
<td>worse %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dixon et al (1991)</td>
<td>23</td>
<td>anxiety depression</td>
<td>96.4 3%</td>
<td>78.3 8.7%</td>
<td>65.2 21.7%</td>
<td>X X</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addington and Duchak (1997)</td>
<td>21</td>
<td>happy</td>
<td>91 10%</td>
<td>71 10%</td>
<td>14 62%</td>
<td>67 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sad</td>
<td>24 52%</td>
<td>52 43%</td>
<td>67 29%</td>
<td>38 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38 29%</td>
<td>29 38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>43 14%</td>
<td>14 62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33 19%</td>
<td>19 38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>57 14%</td>
<td>14 62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71 0</td>
<td>0 14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green et al (2004)</td>
<td>45</td>
<td>mood alteration</td>
<td>62.2 8.9%</td>
<td>48.9 8%</td>
<td>11.1 6.7%</td>
<td>20.0 6.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>depression</td>
<td>26.7 13.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>entertainment</td>
<td>11.1 6.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.7</td>
<td>2.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.7</td>
<td>2.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample size</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average of highest prevalences</td>
<td>75.5 17</td>
<td>59.6 8.2%</td>
<td>33.0 23.4</td>
<td>15.2 30.8</td>
<td>8.5 44.7</td>
<td></td>
</tr>
</tbody>
</table>

Self-reported effects of cannabis use that could not be assigned to one of the five groups of effects were as follows (% better vs. % worse): from Addington and Duchak (1997): slowed down (mentally) (29% vs 43%), restless (38% vs 38%), interested in sex (33% vs 34%), without purpose (34% vs 24%), from Goswami et al (2003): speech (40% vs 0%), and from Green et al (2004): addiction (better 2.2%), cognitive enhancement (better 20.0%), perceptual change (better 13.1%), preferred alternative (better 4.4%), lack of cannabis due to have consumed cannabis (worse 8.5%), impaired cognition (worse 2.2%).

Number of studies pooled to obtain total sample size is 3 (n=49); number of studies pooled to obtain total sample size is 3 (n=71); number of studies pooled to obtain total sample size is 2 (n=26).
feelings of depression and relieve boredom between usually and often. In contrast, subjects also reported that sometimes cannabis actually made them feel anxious and depressed. Subjects reported that sometimes cannabis helped them socialise. Busquets et al (2005) used the Spanish version of the Addiction Research Center Inventory (ARCI: Lamas et al 1994), which is a questionnaire developed for the assessment of subjective states produced by psychoactive drugs. It has 5 scales that all measure the intensity of a certain effect, with Likert scales from a minimum of 0 to a varying maximum of 11 to 15. The authors compared scores between patients with a cannabis use disorder and patients who had tried cannabis but had no diagnosis of cannabis use disorder. It was found that patients with a cannabis use disorder showed higher scores on the euphoria scale and no differences in other scales were found. Both groups had highest scores on the scale measuring sedation.

**Subjective effects of substances with cannabis as one of the main substances**

One study did not make a specification in type of substance when asking about the perceived effects on recently experienced symptoms (Test et al 1989), but overall results were comparable with results from the above mentioned studies. For five (anxiety, sleep problems, depression, voices and side effects) of eight symptoms, the number of patients who reported positive changes was much greater than the number who reported negative consequences. For two of the symptoms (feel paranoid and feel bad physically) the number of people that reported negative changes was greater than the number that reported positive effects.

**Discussion**

An important finding of this review is that patients with psychotic disorders have various reasons to use cannabis, but –irrespective of the method used– most of the self-reported reasons can be categorized into four main categories, namely enhancement of positive feelings, relief of dysphoria, social reasons, and reasons related to the illness and side-effects of medication. Studies assessing prevalence of reasons for specifically cannabis use indicate that relieve of dysphoria is reported by most patients, followed by social reasons and enhancement of positive affect. Reasons related to the illness and side-effects are reported by a minority of the patients. One study that used a qualitative self-report measure showed that patients are most likely to use cannabis for enhancement purposes, followed by social and coping purposes (Spencer et al 2002). They confirm the finding that patients rarely use cannabis for relief of symptoms and side-effects. A possible explanation could be that patients are not aware that symptoms could be a reason for use. Patients may not be aware of the distinction between primary dysphoria and secondary dysphoria due to positive or negative symptoms and side-effects (Spencer et al 2002), or due to other symptoms or signs of the disorder like cognitive impairment or decline in social functioning. In this line of thought, the concept ‘self-medication’ can cover “use to specifically reduce positive or negative symptoms or side-effects” or “use to reduce secondary dysphoria related to the disease”. Similarly to our results, longitudinal studies showed no clear evidence for self-medication effects (Arsenault et al 2002, Van Os 2002, Stefanis et al 2004, Fergusson et al 2005, Henquet et al 2005b) however Ferdinand et al (2005) reported bidirectional association between cannabis and psychosis. More specifically, they found that cannabis use predicted future psychotic symptoms in individuals who did not have psychotic symptoms before they began using cannabis, but they also found that psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use.
Reported subjective effects of cannabis are in line with the reasons patients report for using cannabis. According to our results, improvement of affect and increased relaxation are very important reported subjective effects of cannabis. Another important finding is that patients are aware of negative effects of cannabis use, and are able to report them. They especially report negative effects on positive symptoms. From the patient’s perspective there are advantages of using cannabis that apparently outweigh potential hazards or the affective consequences of not using cannabis (Cox and Klinger 1988). In an experience sampling study in patients with psychotic disorders, Henquet and co-workers found that the mood-enhancing properties of cannabis were acute, whereas psychosis-inducing effects were subacute (Henquet et al 2006). The immediate positive effects could outweigh the delayed negative effects and explain the continuation of cannabis use. More insight into this could be obtained by using an instrument such as used by Stirling et al (2008) that distinguishes between concurrent and after effects of cannabis use. Enhancement, coping and social motives for the use of cannabis are also commonly found among individuals in the general population (Newcomb et al 1988, Simons et al 1998, Simons et al 2000, Chabrol et al 2005, Zvolensky et al 2007). However, research in the general population that used validated self-report instruments has revealed two additional reasons, namely conformity (to avoid social censure or rejection), and expansion (enhancement of perceptual and cognitive experience) (Simons et al 1998, Simons et al 2000, Chabrol et al 2005, Zvolensky et al 2007). One of the few studies in our review that used a validated instrument, also established conformity as a separate factor in patients with psychotic disorder (Spencer et al 2002). Most probably, other studies in our review did not assign reasons related to conformity into a separate group, because they included them among social reasons (like we did in table 2). Items related to expansion are rarely assessed in studies focussing on reasons for cannabis use in individuals with psychoses. Spencer and co-workers’ study (2002) did not include items related to expansion. Further, in only four other studies looking at reasons for specifically cannabis use, expansion motives were brought to light (Addington and Duchak 1997, Lambert et al 1997, Goswami et al 2003, Green et al 2004 ). One study that assessed effects expectancies of cannabis, used an instrument (the MEEQ) that contains items related to expansion (Mueser et al 1995). In the MEEQ expansion is incorporated into the factor ‘perceptual and cognitive enhancement’. This factor was rated with a mean score lying in between scores of other factors. Notably, in Lambert and colleagues’ study (Lambert et al 1997) , 16.1% of patients reported that they use cannabis for expansion of consciousness/awareness. The only case controlled study comparing patients with healthy controls showed that patients were less likely to use cannabis for relaxation, for social activity or out of habit, and more likely to use cannabis to reduce anxiety, depression or boredom (Green et al 2004). Additionally, in the same study patients were significantly less likely to report relaxation as positive effect. However, within the group of patients, relaxation – after mood alteration - was the second most frequently reported positive effect. Furthermore in our other reviewed studies, relaxation was a frequently reported reason and seemed to be an important positive effect. According to a review of self-reported cannabis effects in the general population, the most frequently reported effect appeared to be relaxation (Green et al 2003).

This review has several limitations. First, we found a relatively small number of studies, and most of them used interviews and instruments that have not been psychometrically evaluated. Only three studies used validated instruments (Mueser et al 1995, Spencer et al 2002, Busquets et al 2005). Further, there were differences in methodology (e.g. different types of questionnaires), and differences in patient samples (e.g. different inclusion criteria for psychotic disorder, different criteria...
for substance use, inpatients vs. outpatients. The size of the patient samples also varied. One study had only 5 patients who reported reasons and effects of cannabis use, therefore the validity of this study could be questioned (Goswami et al 2003). Although studies were heterogeneous in many ways, we addressed this in our review by making a distinction in studies that assessed reasons for/effects of specifically cannabis use and studies that assessed reasons for/effects of substance use. Further, we made a distinction in prevalence studies and qualitative studies. In spite of the heterogeneity of the studies, results turned out to be broadly comparable and support the external validity of this review to a broad range of cannabis using patients with psychotic disorder. Another limit is that the studies reviewed were published over a 17-year period. It could be argued that the older studies were undertaken at a time when the amount of THC in cannabis was lower and thus that self-reported effects may have been different. However, across older and newer studies, reasons and effects appeared broadly similar. Further, retrospective self-report data are subject to general biases of recall, probably even more when these reports depend on memories of experiences that occur while individuals are actually under the influence of cannabis. Also patient’s explanations of cannabis use may have been post hoc rationalizations for symptoms caused by cannabis use. A limitation of our method of pooling the results of prevalence studies is that we included both studies with closed-questions and studies with open-ended questions. Further, reasons that we excluded from the four main categories of reasons, could be interpreted as not being important to patients. However, that is not our intention. For instance, we could not assign ‘improving sleep’ to one of the four categories, but in one of the reviewed studies it was reported by up to almost 60%, and from our clinical point of view we know it is an important reason, at least in part of the patients. Although there were differences in the reviewed studies on various aspects, we found convergent results on reasons for cannabis use and subjective effects reported by a variety of patients with a psychotic disorder. Notwithstanding the methodological heterogeneity and weaknesses we think that enough data were available to have a thorough overview of the most commonly reported explicit reasons and subjective effects of cannabis use. Identifying reasons for cannabis use and subjective effects in patients with psychotic disorders provides us with insight in the role of cannabis use. This insight may lead to targeted interventions.

References


Linszen DH, Dingemans PM, Lenior ME: Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 1994;51:273-279.


Implicit and explicit affective associations toward cannabis use in patients with recent-onset schizophrenia and healthy controls


Abstract

Background. Cannabis use is common in patients with recent-onset schizophrenia, and this is associated with poor disease outcome. More insight in the cognitive-motivational processes related to cannabis use in schizophrenia may inform treatment strategies. The present study is the first known to compare implicit and explicit cannabis associations in individuals with and without psychotic disorder.

Methods. Participants consisted of 70 patients with recent-onset psychotic disorder and 61 healthy controls with various levels of cannabis use. Three Single-Category Implicit Association Tests (SC-IAT) were used to assess 'relaxed', 'active' and 'negative' implicit associations toward cannabis use. Explicit expectancies of cannabis use were assessed with a questionnaire using the same words as the SC-IAT.

Results. There were no differences in implicit associations between patients and controls, however patients scored significantly higher on explicit negative affect expectancies than controls. Both groups demonstrated strong negative implicit associations toward cannabis use. Explicit relaxed expectancies were the strongest predictors of cannabis use and craving. There was a trend for implicit active associations to predict craving.

Conclusions. The findings indicate that patients suffering from schizophrenia have associations toward cannabis similar to controls, but they have stronger negative explicit cannabis associations. The strong negative implicit associations toward cannabis could imply that users of cannabis engage in a behaviour they do not implicitly like. Explicit relaxing expectancies of cannabis might be an important mediator in the continuation of cannabis use in patients and controls.
Chapter 1.2 - Implicit and explicit affective associations toward cannabis

Introduction


If we obtain more insight into the cognitive-motivational processes related to cannabis use in patients with psychotic disorder, by assessing self-reported motives for cannabis use, self-reported effects of cannabis use, and effect expectancies of cannabis use (e.g. Dixon et al 1990, Mueser et al 1995, Addington and Duchak 1997, Fowler et al 1998, Spencer et al 2002, Green et al 2004, Schofield et al 2006, Reviewed in Dekker et al 2009, Hides et al 2008). Overall, these studies find that patients with schizophrenia use cannabis to enhance positive affect, to relieve dysphoria, to socialize with peers, and - to a lesser extent- to relieve psychotic symptoms or side-effects of medication. Further, these studies find that patients not only report positive effects, but also negative effects of cannabis use, like cognitive impairment. All of the above mentioned studies relied on self-report from the patient. Self-report measures, however, 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). Moreover, several studies have found that implicit and explicit alcohol- and cannabis related cognitions predict unique variance in alcohol and cannabis use (Stacy 1997, Wiers et al 2002, Wiers et al 2005, Ames et al 2007).

Implicit measures are intended to assess relatively automatic associations that are difficult to gauge with explicit self-report measures. In general, these 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 often used to assess alcohol or drug-related memory associations is the Implicit Association Test (IAT; Greenwald et al 1998). 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. During the past decade, varieties of the IAT have been applied in the field of addiction research (e.g. Wiers et al 2002, Wiers et al 2005, De Houwer et al 2004, Wiers et al 2007a, Wiers et al 2007b). To date, two studies have used a cannabis-IAT to assess implicit associations toward cannabis. Field et al (2004) found more negative associations for marijuana related words in non-users compared to users, which could be interpreted as indicating that non-users associated unpleasant words more strongly with cannabis compared to users. No significant differences were found between non-users and users for positive marijuana associations. Ames et al (2007) reported that implicit excitement associations toward cannabis predicted cannabis use when
controlled for explicit cognition measures. Determining the predictive value of implicit measures after controlling for explicit measures is often used to determine the unique predictive power of implicit measures beyond commonly used explicit questionnaires. Implicit associations toward cannabis have not been investigated in patients with schizophrenia or related disorders. Also, few studies have been reported on craving for cannabis in psychotic disorder, although craving is regarded as a central phenomenon in drug dependence (Robinson and Berridge 1993, Franken et al 2003).

In the current study, one of our questions was whether patients with recent-onset schizophrenia and healthy controls differ on implicit and explicit cannabis-related cognitions. Secondly, we were interested in the extent to which explicit and implicit cannabis-related cognitions predict craving and cannabis use. We included participants with varying levels of cannabis exposure in order to determine whether the differences between patients and controls would depend on their cannabis use status, and secondly for a proper variance in cannabis use patterns and craving levels in the prediction model. Our study may contribute to more insight in the underlying processes in addictive behaviour in cannabis using patients suffering from schizophrenia.

Methods

Participants
We included male in- and outpatients from the Adolescent Clinic of the Psychiatric Department of the Academic Medical Centre in Amsterdam. This clinic is specialized in the treatment of young patients with schizophrenia spectrum disorders. In general, two third of patients are admitted for psychosis for the first or second time (Dekker et al 2008), and most of the patients use antipsychotic medication (De Haan et al 2003). Patients were included in the study if they had a diagnosis of schizophrenia or related disorder (schizoaffective disorder, schizophreniform disorder, or psychosis not otherwise specified), according to the Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association 1994) and were between 16 and 30 years old. Other inclusion criteria were that patients should be able and willing to give written informed consent, and be able to understand, speak and read Dutch. Exclusion criteria were diagnosis of a primary alcohol- or drug-related psychosis, a demonstrable brain or neurological or endocrine disease, or mental retardation. Male healthy controls were recruited from the community, and matched with respect to age and level of education. In a first recruitment phase, a larger proportion of controls had never used cannabis compared to patients. To ensure comparable levels of cannabis use in both participant groups, we later recruited controls more strictly on the basis of their level of cannabis use. Only males were included. Males generally have an earlier age at onset of psychosis, more often need intensive psychiatric care and more often use cannabis compared to females. Therefore males are overrepresented at our clinic. Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder. After complete description of the study, written informed consent was obtained from all participants. The study was approved by the human subject review board of our institution.

Materials and measures

Drug use
Drug use was assessed with the Composite International Diagnostic Interview (CIDI, WHO 1994) section L. Participants with lifetime cannabis use of 5 times or less were considered to be ‘non users’.
Participants who had used cannabis more than 5 times lifetime were subdivided in ‘past users’ (those who had used cannabis more than 12 months ago) and ‘recent users’ (those who had used cannabis in the recent 12 months). Recent use was further subdivided into ‘infrequent use’ (less than weekly use in the past year) and ‘frequent use’ (daily or weekly use in the past year). In ‘recent users’, we estimated total amount of cannabis joints used in the past year by multiplying total weeks of cannabis use in the past year by average amount of cannabis joints used per week in the period that cannabis was used. Although there is a variety in percentage of delta-9-tetrahydrocannabinol ($\Delta^9$-THC) and cannabidiol (CBD) in different cannabis products (Niesink et al 2007), one cannabis joint was considered to contain 1/2 gram of cannabis product (e.g. hash, weed etc.).

**Craving for cannabis**

The Obsessive Compulsive Drug Use Scale (OCDUS; Franken et al 2002) was used in past and recent cannabis users to measure craving for cannabis in the past 7 days. It is a self-rating scale consisting of 12 items with a 5-point, Likert-type rating that measures drug craving in the past 7 days. The 12 items were summed to create a total craving score (Cronbach’s alpha = 0.85).

**Implicit association test**

Implicit affective associations toward cannabis were assessed with three unipolar Single Category Implicit Association Tests (SC-IATs; Karpinski and Steinman 2006). Each SC-IAT measured a different affective association toward the use of cannabis; ‘active’ for positive arousal, ‘negative’ for negative affect, and ‘relaxed’ for positive sedation. Other IAT studies in addiction research have also used these subscales (e.g. Ames et al 2007, Wiers et al 2007b), because they represent the three main types of expectancies (Goldman and Darkes 2004, Wiers 2008a). Each affective category was compared with a neutral category labelled ‘neutral’. In the SC-IAT, participants have to categorize words as quickly as possible into different categories by pressing a left or right response-button. Each SC-IAT consisted of four phases that came in a fixed order (see table 1). For someone who has a very strong association between cannabis and one of the affective categories (e.g. active), the combination block where cannabis and active are on the same side will be significantly easier (and thus faster) to perform than the reversed combination block where cannabis and active are on different sides. Each combination phase consisted of 40 words. The three SC-IATs were presented in a fixed order. The IAT-tasks were programmed in Inquisit 2.0 (by Millisecond Software). Stimulus words were presented in blue font (34-point) in the middle of the screen. The affective label words were always presented at the top of the screen, appropriately positioned on the left or the right side of the screen, depending on the required response (as in Greenwald et al 1998). Feedback appeared in green letters (34-point) below the stimuli words: in case of a wrong response the words ‘try again’ appeared on the screen. The words used (see Appendix) were matched on number of letters, syllables, familiarity, and on valence and arousal values. The valence and arousal values of stimulus words were matched on group level (positive-arousal, positive sedation, negative and neutral words) by using student word ratings. As main outcome measure for the IAT, we chose one of the recently recommended new “D-algorithms” as main reaction time measure (D2SD, Greenwald et al 2003). In this algorithm all trials (including the practise phases) are included, an error-penalty to the reaction times on erroneous responses is given, and the outcome is divided by a personalized standard deviation of the combination phases (so the measure is not influenced by differences in response speed between participants, which is optimal for comparison between clinical and non-clinical groups).
Table 1. Schematic overview of the block sequence in the Active, Relaxed and Negative Single Category- Implicit Association Tests.

<table>
<thead>
<tr>
<th>Block 1</th>
<th>Block 2</th>
<th>Block 3</th>
<th>Block 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practise phase</td>
<td>Combination phase</td>
<td>Reversed practise phase</td>
<td>Reversed combination phase</td>
</tr>
<tr>
<td>Active SC-IAT</td>
<td>active</td>
<td>neutral</td>
<td>neutral</td>
</tr>
<tr>
<td></td>
<td>cannabis</td>
<td>active</td>
<td>neutral</td>
</tr>
<tr>
<td>Relaxed SC-IAT</td>
<td>relaxed</td>
<td>neutral</td>
<td>relaxed</td>
</tr>
<tr>
<td></td>
<td>cannabis</td>
<td>neutral</td>
<td>relaxed</td>
</tr>
<tr>
<td>Negative SC-IAT</td>
<td>negative</td>
<td>neutral</td>
<td>neutral</td>
</tr>
<tr>
<td></td>
<td>cannabis</td>
<td>neutral</td>
<td>negative</td>
</tr>
</tbody>
</table>

Note: The following explanation is for the Active SC-IAT (for an explanation of the Relaxed SC-IAT, replace active with relaxed, for an explanation of the Negative SC-IAT, replace active with negative). During the practice phase (block 1), participants press the left key when the stimulus word that comes up in the middle of the screen is an active word (e.g. energetic), and press the right key when the stimulus word is neutral (e.g. standard). In the Combination task (block 2), participants press the left key when the stimulus word is an active or a cannabis word (e.g. hash), and press the right key when the stimulus word is neutral. During the Reversed practise phase (block 3), participants press the left key when the stimulus word is neutral, and press the right key when the target word is an active word. During the Reversed combination task, participants press the left key when the stimulus word is a neutral or a cannabis word, and press the right key when the stimulus word is an active word. Note that during the Combination phase and the Reversed Combination phase, cannabis is paired with one of the affective categories (e.g. active) or the neutral category respectively. The difference score between the reaction times of these two combined blocks is the so-called IAT-effect and gives an indication of strength of the association between the target (e.g. cannabis) and the affective category (e.g. active) (Greenwald et al 1998).

Expectancy questionnaire

The explicit cannabis expectancy measure was a questionnaire with 18 unipolar items, each consisting of a statement on using cannabis and an affective outcome (for example: ‘Smoking cannabis makes me relaxed’). Participants indicated the extent to which they agreed or disagreed with each item on an unmarked Visual Analogue Scale (VAS). The questionnaire consisted of an active (positive-arousal) scale, a negative outcome scale, and a relaxed (positive-sedation) scale, with the same affective words as used in the implicit test. Internal consistencies were as follows: VAS-active 0.81; VAS-relaxed 0.86; and VAS-negative 0.82.

Procedure

After signing the informed-consent form, drug use was assessed with the CIDI. Next, participants performed the cannabis SC-IATs on a computer, and subsequently the explicit expectancy questionnaire and craving questionnaire were filled out.

Data screening

IAT effects were calculated in such a way that higher IAT scores reflected a stronger association between cannabis and the affective dimension. The total amount of cannabis joints used in the past year scores and total craving scores were positively skewed, and log_{10} transformations addressed this problem satisfactorily. Of two participants, the score of total cannabis joints used in the past year were missing.

Statistical analysis

For comparisons between patients and controls on explicit and implicit measures, we used multivariate analysis of variance (MANOVA) with the three explicit variables and three implicit variables as dependent variables. In order to assess the relative contribution to multivariate differences, a discriminant analysis was performed that focused on the structure coefficients.
In the comparisons between patients and controls we first took all participants into account, second only past and recent cannabis users, third only recent infrequent and frequent users, and last only recent frequent cannabis users. We used multiple hierarchical regression analysis to evaluate the predictive utility of the explicit and implicit measures for craving and cannabis use (total cannabis joints used in past year). In the regression models we entered participant group into step 1, and highest achieved level of education into step 2 of the regression equation as background variables. In step 3, we added measures of explicit expectancies, and finally in step 4 we added measures of implicit associations. The implicit measures were entered last to evaluate their predictive value added, above and beyond that of the other (explicit) variables. The alpha level was set at .05 for all analysis to ensure an optimal trade-off between completeness (not leaving out possible interesting effects) and correctness (restricting Type-II error) given the exploratory nature of the data.

Results

Sample characteristics

Table 2 gives the sample characteristics. The patient group and the control group did not significantly differ in age, level of education, cannabis use (i.e. non use, past use only, recent infrequent use, and recent frequent use), total cannabis joints used in the past year, craving, and cannabis use disorder in the past year.

Table 2. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=70)</th>
<th>Controls (n=61)</th>
<th>χ²</th>
<th>df</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (sd) range</td>
<td>23.0 (3.5)</td>
<td>22.8 (3.9)</td>
<td>1.14</td>
<td>1</td>
<td>0.29</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>70 (100)</td>
<td>61 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia, n (%)</td>
<td>50 (71.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder, n (%)</td>
<td>12 (17.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophreniform disorder, n (%)</td>
<td>4 (5.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis NOS, n (%)</td>
<td>4 (5.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education: highest achieved level (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1 = Lower secondary prof. education/ Intermediate vocational education, 2 = Higher general secondary education/ higher vocational education, 3 = Pre-university education/ university</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non use</td>
<td>9 (12.9)</td>
<td>15 (24.6)</td>
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<td>3.00</td>
<td>0.08</td>
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<tr>
<td>Past use only</td>
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<td>6 (9.8)</td>
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<td>3.25</td>
<td>0.07</td>
</tr>
<tr>
<td>Recent infrequent use†</td>
<td>10 (14.3)</td>
<td>13 (21.3)</td>
<td></td>
<td>1.11</td>
<td>0.29</td>
</tr>
<tr>
<td>Recent frequent use‡</td>
<td>36 (51.4)</td>
<td>27 (44.2)</td>
<td></td>
<td>0.67</td>
<td>0.41</td>
</tr>
<tr>
<td>Age at onset of cannabis use, mean (sd) range</td>
<td>15.4 (2.6)</td>
<td>15.0 (1.4)</td>
<td>2=-0.17</td>
<td>0.87</td>
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</tr>
<tr>
<td>Cannabis use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Non use</td>
<td>461.9 (611)</td>
<td>339.9 (518)</td>
<td>2= -1.06</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Past use only</td>
<td>1.3388</td>
<td>1.2048</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent infrequent use†</td>
<td>20.5 (8.0)</td>
<td>20.5 (8.5)</td>
<td>2= -0.29</td>
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<tr>
<td>Recent frequent use‡</td>
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<td>12.36</td>
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<td>Cannabis use disorder in past year, n (%)</td>
<td>33 (47.1)</td>
<td>28 (45.9)</td>
<td>0.021</td>
<td>1</td>
<td>0.89</td>
</tr>
</tbody>
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Sample characteristics

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* 1 = Lower secondary prof. education/ Intermediate vocational education, 2 = Higher general secondary education/ higher vocational education, 3 = Pre-university education/ university
† weekly or daily use in past 12 months
‡ in recent (past 12 months) cannabis users
§ in past and recent cannabis users
¶ in past and recent cannabis users
Figure 1. Means on the explicit (a) and implicit (b) measures in all past and recent cannabis users by participant group. a) Means on the explicit (Visual Analogue Scale) measures (61 patients and 46 controls). b) Mean IAT effects (D-2SD, milliseconds) separately for each SC-IAT in all past and recent cannabis users by participant group (56 patients and 44 controls).

Comparison between patients and controls on explicit cannabis-related cognitions

MANOVA performed in all patients (n = 70) and controls (n = 61) indicated that patients differed significantly on their explicit cannabis use expectancies from healthy controls, $F(3, 127) = 5.58$, $p = 0.001$, Wilks’ Lambda = 0.88, partial eta squared 0.12. Relative contributions to this multivariate difference were (in descending order, with structure coefficients in parentheses): negative (0.87), active (0.10 ), relaxed (0.04 ). An inspection of the mean scores indicated that patients had higher scores on the negative scale ($M = 4.74, SD = 2.35$) than controls ($M = 3.35, SD = 2.07$).
MANOVA performed in all past and recent users of cannabis (61 patients and 46 controls) also indicated that patients and controls scored significantly different on the explicit scale, $F(3, 103) = 4.81$, $p = 0.004$. Wilks' Lambda = 0.88, partial eta squared = 0.12, with relative contributions: negative (0.85), active (0.15), relaxed (-0.03). See figure 1a for mean scores on the explicit expectancy measure for all past and recent users of cannabis. MANOVA performed in the group of recent users (46 patients, 40 controls) and recent frequent users (36 patients, 27 controls) also indicated that patients and controls scored significantly different on the explicit scales (resp. $F(3, 82) = 3.39$, $p = 0.02$, Wilks' Lambda 0.89, partial eta squared = 0.11, and $F(3, 59) = 3.17$, $p = 0.03$, Wilks' Lambda 0.86, partial eta squared = 0.14), with highest relative contributions for this multivariate difference on the negative scale. Relative contributions in all recent users: negative (0.83), active (0.25), relaxed (-0.13). Relative contributions in recent frequent users: negative (0.89), relaxed (-0.19), active (0.14).

Comparison between patients and controls on implicit cannabis-related cognitions

Prior to conducting analysis on the SC-IAT, we detected outliers and excluded them from the dataset: five participants (4 patients, 1 control) were excluded from further analysis because they had an percentage of response errors on the SC-IAT that was more than three standard deviations from the mean, and two participants (1 patient, and 1 control) were excluded because more than 10% of their reaction times were faster than 300 ms on the SC-IAT (see Greenwald et al 2003). MANOVA performed in all patients (n=65) and controls (n=59) indicated that patients did not differ significantly from healthy controls on their implicit cannabis use associations, $F(3,120) = 1.16$, $p = 0.327$, Wilks’ Lambda = 0.97, partial eta squared 0.03. Additionally, no significant differences emerged between patients and controls when all past and recent users (56 patients, 44 controls), $p = 0.25$, when only recent users (42 patients, 38 controls), $p > 0.30$, or when recent frequent users (33 patients, 25 controls), $p > 0.80$, were taken into account. See figure 1b for mean scores on the SC-IATs for all past and recent users of cannabis.

Factors predicting craving and cannabis use

Prior to conducting regression analysis, we determined that no participant exceeded Cook’s distance >1. The regression models were evaluated on the basis of the results of bivariate analyses (see table 3); only the explicit and implicit variables that were significantly correlated with craving or cannabis use were included in the multiple regression models.

Table 3. Pearson Correlations between explicit expectancies and implicit associations, and cannabis use variables in all past and recent cannabis users (n=100: 56 patients and 44 controls)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Expl Negative</td>
<td>-0.31**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Expl Relaxed</td>
<td>0.30**</td>
<td>-0.43**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. SC-IAT Active</td>
<td>0.13</td>
<td>-0.01</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. SC-IAT Negative</td>
<td>-0.03</td>
<td>0.12</td>
<td>0.20*</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. SC-IAT Relaxed</td>
<td>-0.19</td>
<td>-0.11</td>
<td>0.08</td>
<td>0.02</td>
<td>0.11</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7. Craving</td>
<td>0.26**</td>
<td>0.11</td>
<td>0.36**</td>
<td>0.20*</td>
<td>-0.22*</td>
<td>-0.04</td>
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<td></td>
</tr>
<tr>
<td>8. Cannabis use</td>
<td>0.03</td>
<td>-0.12</td>
<td>0.47**</td>
<td>0.06</td>
<td>-0.11</td>
<td>0.31</td>
<td>0.57**</td>
<td></td>
</tr>
</tbody>
</table>

Note. Expl. Active = Explicit Positive-Arousal cannabis use expectancies; Expl Negative = explicit Negative cannabis use expectancies; Expl Relaxed = Explicit Positive-Sedation cannabis use expectancies; SC-IAT = Single Category Implicit Association Test; SC-IAT Active = D (standardized difference score) - 2SD score for the positive-arousal SC-IAT; SC-IAT Negative = D - 2SD score for the negative SC-IAT; SC-IAT Relaxed = D - 2SD score for the positive-sedation SC-IAT; Craving = total OCDUS score; Cannabis use = total cannabis joints used in past year in participants that have used cannabis in the past year. * $p < 0.05$, ** $p < 0.01$.  # $p \leq 0.10$.  * $p < 0.05$.  ** $p < 0.01$.  

Craving as dependent variable

Craving was best predicted by the explicit relaxed measure ($\beta = 0.25$, $p = 0.017$), adjusted for the other predictors (see Table 4). The implicit measures (as a group) showed a trend toward significance in the prediction of craving ($\Delta R^2 = 0.05$, $p = 0.06$) above and beyond the background variables and explicit measures. Overall, the full model explained 20.9% of the variance in the total craving score, $R^2$ adjusted $= 0.15$, $F(7, 92) = 3.47$, $p < 0.005$. In subsequent analysis we evaluated a trimmed regression model for craving, which included all (borderline) significant ($p < 0.10$) predictor variables (see Table 5). This overall trimmed regression model was statistically significant, $F(3, 96) = 6.97$, $p < 0.005$ explaining 18% of the variance in craving, $R^2$ adjusted $= 0.15$. Again, craving was best predicted by the explicit relaxed measure ($\beta = 0.31$, $p = 0.001$), adjusted for the other implicit predictors. The implicit measure of active associations predicted craving borderline significantly ($\beta = 0.17$, $p = 0.068$).

Cannabis use as dependent variable

Explicit relaxed expectancies significantly predicted cannabis use ($\Delta R^2 = 0.21$, $p < 0.0001$) above and beyond the background variables (see Table 4). Overall, the full model explained 24.6% of the variance in total cannabis joints used in the past year, $R^2$ adjusted $= 0.21$, $F(4, 73) = 5.96$, $p < 0.0005$.

Table 4. Summary of hierarchical multivariate regression analysis for variables predicting craving and cannabis use (cross-sectional)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative</th>
<th>Simultaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$\Delta R^2$</td>
</tr>
<tr>
<td>Participant group</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Education 1</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Education 2</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Expl. Active</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Expl. Relaxed</td>
<td>0.16</td>
<td>0.14*</td>
</tr>
<tr>
<td>SC-IAT Active</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>SC-IAT Negative</td>
<td>0.21</td>
<td>0.06*</td>
</tr>
</tbody>
</table>

Cannabis use $n=78$

| Participant group   | 0.01       | -0.23       | 0.20    | -0.12  |
| Education 1         | 0.14       | 0.25        | 0.07    |        |
| Education 2         | 0.03       | 0.02        | 0.23    | 0.10   |
| Expl. Relaxed       | 0.35       | 0.31**      | 0.25    | 0.06   | 0.46**  |

Note. Craving = total OCDUS score; Education 1 = lower secondary prof. education/ intermediate vocational education; Education 2 = higher general secondary education/ higher vocational education; Expl. Active = explicit positive-arousal cannabis use expectancies; Expl. Relaxed = explicit positive-sedation cannabis use expectancies; SC-IAT Active = D (standardized difference score)- 2SD score for the Positive-Arousal SC-IAT; SC-IAT Negative = D – 2SD score for the negative SC-IAT; Cannabis use = total cannabis joints used in past year (in participants that have used cannabis in the past year). $^* p \leq 0.10$; $^* p < 0.05$; $^{**} p < 0.01$

Table 5. Trimmed regression model for craving

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<tr>
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<td>0.18</td>
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Note. Craving = total OCDUS score; Education 1 = lower secondary prof. education/ intermediate vocational education; Education 2 = higher general secondary education/ higher vocational education; Expl. Relaxed = explicit positive-arousal cannabis use expectancies; SC-IAT Active = D (standardized difference score)- 2SD score for the Positive-Arousal SC-IAT; SC-IAT Negative = D – 2SD score for the negative SC-IAT; $^* p \leq 0.10$; $^* p < 0.05$; $^{**} p < 0.01$
Discussion

In this study we found that patients with recent-onset psychotic disorder and controls did not differ in implicit affective cannabis associations. In contrast, patients scored significantly higher on explicit negative cannabis expectancies than healthy controls, irrespective of their level of cannabis use. An explanation for this finding could be that all patients received education in our clinic about how cannabis use can deteriorate symptoms and course of the disease. Additionally, patients might have experienced more severe negative effects of smoking cannabis. Some evidence for this comes from Green et al (2004), who found that a larger proportion of individuals with psychosis reported psychotic symptoms as negative effect of cannabis, compared to healthy controls. Peters et al (2009) found that patients with schizophrenia reported more often than controls to have felt depressed, anxious, suspicious and to have experienced more psychotic symptoms during cannabis intoxication. Additionally, an experimental study showed that patients with schizophrenia, compared to healthy controls, were more sensitive to the cognitive effects of Δ9 THC on learning and recall (D’Souza et al 2004, D’Souza et al 2005). However, Henquet et al (2006) did not replicate this finding, but found that differential Δ9 THC sensitivity was restricted to subjects homozygous for the catechol-O-methyltransferase (COMT Val158Met) Valine (Val) allele and that this was in part conditional on psychometric psychosis liability.

Both patients and controls had strong explicit relaxed outcome expectancies of cannabis use. Relaxation is a consistently reported effect of cannabis in both people with and without psychosis (Green et al 2003, Pencer and Addington 2008, Dekker et al 2009). Relaxation might be an important motivator for use of cannabis in both participant groups. Our regression analysis showed that the explicit relaxed subscale was the strongest predictor for craving and level of cannabis use. Ames et al (2007) also found that explicit relaxed expectancies strongly predicted cannabis use in a high school population. Possibly, people that experience relaxing effects may eventually smoke more cannabis, and consequently develop more craving for cannabis. Another notable association among patients and controls was the strong implicit negative association toward cannabis. This finding 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). However, another cannabis IAT study (Field et al 2004) found that negative associations were present in non-users of cannabis, but not in users of cannabis. Usage of a different IAT may explain differences between their and our findings: Field et al (2004) used a bipolar IAT, were positive associations were measured relative to negative associations.

There are some plausible explanations for the strong implicit negative cannabis associations. It might be that users of cannabis engage in a behaviour they do not implicitly like, and go along with their cannabis use behaviour more on the explicit rather than on the implicit level. Other explanations have to do with concerns about the validity of the IAT effect. One concern is that strong negative implicit associations may partly reflect general associations that are present in a culture instead of someone’s personal associations (Karpinski and Hilton 2001). Houben and Wiers (2007a, 2007b) examined this by using personalized alcohol-IATs (where the labels ‘positive’ and ‘negative’ were replaced by the labels ‘I like’ or ‘I dislike’). They found implicit positive associations toward alcohol and weaker negative attitudes toward alcohol, which is in line with the hypothesis that the standard alcohol-IAT may to some extent reflect negative general associations with alcohol. However, in one of their studies (2007b), the personalized IAT did not show evidence for implicit positive attitudes toward alcohol.
Another concern is that the IAT measures associations at the level of the category, and not at the level of the individual words from this category (De Houwer, 2001). People might associate ‘cannabis’ (the category label in our study) with negative consequences because of usage of this word in the media and associate words like ‘weed’ or ‘stoned’ with more pleasant effects. Houven and Wiers (2006a) found that this ‘label effect’ indeed may play a role in the IAT, however in all IAT versions they found strong negative alcohol associations, suggesting they reflect something ‘real’ in memory rather than an IAT artefact. Lastly, it has been argued that IAT effects could reflect non-associative factors based on salience, rather than on implicit associations (Rothermund and Wentura, 2004). Salience could facilitate IAT performance: when two salient categories have to be categorised under the same key, this will be easier than categorising under two different keys. A previous alcohol-IAT study showed that this salience asymmetry could only partly explain the results found for the negative associations, and not at all for the positive and arousal associations (Houben and Wiers 2006b). Additionally, many studies (e.g. Thush et al 2007a, Thush et al 2007b, Ames et al 2007) show that the IAT predicts behaviour and it correlates with explicit measures on less controversial themes (Hofmann et al 2005), implying that the IAT encompasses personal associations, at least in part. Also, in our study implicit associations correlated significantly with craving, so extrapersonal contamination is not likely to completely account for the effects with the cannabis SC-IAT. In the present study there was a trend for implicit active associations to predict craving. Wiers et al (2002) hypothesized that their finding of implicit arousal associations in heavy drinkers is in line with the incentive-sensitization theory (Robinson and Berridge 1993) according to which addictive behaviours are related more to ‘wanting’ (sensitized arousal), than to liking of substances. This sensitized arousal or intensively wanting of substances may be transformed in craving (Robinson and Berridge 1993), and thereby explain our finding.

As opposed to craving, cannabis use was unrelated to implicit associations. This is in contrast with another cannabis IAT study (Ames et al 2007) who revealed that implicit excited associations predicted cannabis use. Differences between the present study and previous findings of Ames et al (2007) might be contributed to differences in the study population, outcome variables and differences in the IATs used. In summary, there is reason to doubt the validity of the strong negative substance-associations found here and in many other studies (extrapersonal associations, saliency effects), but the active and relaxation associations appear to be more valid and related to meaningful other constructs including craving.

Limitations and strengths
A limitation of this study is that the percentages of THC en CBD in cannabis products used by the participants was unknown. THC is thought to give psychotomimetic effects (D’Souza et al 2004) and CBD has anxiolytic and antipsychotic properties (Zuardi et al 2006, Leweke et al 2000). Although it is likely that the variation of cannabis ingredients was equally distributed among patients and controls, we do not know the different contributions of THC and CBD to explicit and implicit cannabis associations. Another limitation is that we did not have self-reports on cannabis intoxication at the time of testing and we did not use urinary screens to confirm that subjects were not intoxicated at the time of testing. To control for possible slower reaction times and response errors due to cannabis intoxication, we resp. used the D2SD reaction time measure (Greenwald et al 2003) which is not influenced by differences in response speed between participants, and we excluded IAT data of five participants who had a percentage of response errors on the SC-IAT that were more than three standard deviations from the mean. Lastly, our study had a cross-sectional nature and many of the
observed relationships were relatively weak. A prospective study examining relations between cannabis associations and cannabis use variables might overcome these limitations. However, this study does provide additional information for the role of cannabis-related cognitions in patients with recent-onset schizophrenia spectrum disorders. Strengths of this study were that we had a relatively large sample of recent-onset schizophrenia patients, and a matched control group. To our knowledge, this is the first study that assessed implicit cannabis associations in both patients with psychosis and controls.

Conclusions and practical implications

Our findings indicate that patients suffering from schizophrenia have associations toward cannabis similar to controls, but they have stronger negative explicit cannabis associations. The finding of strong negative implicit associations toward cannabis in both patients and controls could imply that they engage in a behaviour they do not implicitly like. Explicit relaxed associations toward cannabis were the strongest predictor of cannabis use and craving, which might imply that the perceived relaxing effects of cannabis is an important mediator in the continuation of cannabis use. Therefore, intervention and prevention strategies aimed at reducing cannabis use should target the explicit cognitions related to the relaxing effects of cannabis that may be due to the CBD compound in cannabis. Further, because implicit positive arousal cognitions were associated with craving, an important intervention would be to challenge these cognitions in order to prevent relapse into cannabis use. Although researchers have begun to study whether it is possible to change implicit alcohol associations (Wiers et al 2008b), future research is needed to indicate how automatic cannabis associations could be changed, and if so, how this affects the use of cannabis.

Appendix

<table>
<thead>
<tr>
<th>IAT word stimuli (translated from Dutch)</th>
<th>Neutral stimuli (neutral words)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive arousal stimuli (active words)</td>
<td>Indefinite (neutral words)</td>
</tr>
<tr>
<td>creative</td>
<td>general</td>
</tr>
<tr>
<td>energetic</td>
<td>usual</td>
</tr>
<tr>
<td>cheerful</td>
<td>standard</td>
</tr>
<tr>
<td>motivated</td>
<td>impartial</td>
</tr>
<tr>
<td>talkative</td>
<td></td>
</tr>
<tr>
<td>Positive sedation stimuli (relaxed words)</td>
<td>Neutral stimuli (neutral words)</td>
</tr>
<tr>
<td>relaxed</td>
<td>accompanying</td>
</tr>
<tr>
<td>calming</td>
<td>preceding</td>
</tr>
<tr>
<td>contented</td>
<td>supplementary</td>
</tr>
<tr>
<td>comforting</td>
<td>frequent</td>
</tr>
<tr>
<td>reassuring</td>
<td>additional</td>
</tr>
<tr>
<td>Negative stimulus (negative words)</td>
<td>Neutral stimuli (neutral words)</td>
</tr>
<tr>
<td>miserable</td>
<td>central</td>
</tr>
<tr>
<td>suspicious</td>
<td>daily</td>
</tr>
<tr>
<td>listless</td>
<td>middle</td>
</tr>
<tr>
<td>anxious</td>
<td>common</td>
</tr>
<tr>
<td>confused</td>
<td>customary</td>
</tr>
<tr>
<td>Target (cannabis words)</td>
<td></td>
</tr>
<tr>
<td>weed</td>
<td></td>
</tr>
<tr>
<td>hash</td>
<td></td>
</tr>
<tr>
<td>cannabis</td>
<td></td>
</tr>
<tr>
<td>stoned</td>
<td></td>
</tr>
<tr>
<td>blow</td>
<td></td>
</tr>
</tbody>
</table>
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Wiers RW: Alcohol and drug expectancies as anticipated changes in affect: negative reinforcement is not sedation. Substance Use & Misuse 2008a; 43, 429-444


Zuardi AW, Crippa JAS, Hallak JEC, Moreira FA, Guimarães FS: Cannabidiol, a cannabis sativa constituent, as an antipsychotic drug. Brazilian journal of medical and biological research 2006; 39, 421-429.
CHAPTER 1.3

Craving for cannabis in patients with psychotic disorder, their non-affected siblings and healthy controls: psychometric analysis of the Obsessive Compulsive Drug Use Scale


Cannabis use is more common in individuals with non-affective psychotic disorder and their siblings compared to healthy controls. As cannabis use is associated with a greater risk to develop psychotic disorder and an adverse outcome in those who already developed psychosis, it is important to know the role of craving in continued cannabis use and relapse in these vulnerable subjects. Therefore, we examined 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 who all used cannabis in the past year. Simultaneous component analysis (SCA) was used to determine component weights that optimally explained the (co)variance of the OCDUS-CAN variables in these different populations simultaneously. A three-component SCA solution explained 74.2% of the total variance, and consisted of well-interpretable subscales that could be best described as craving/urge, resistance, and impact. Reliability of the subscales was good. The three subscales significantly discriminated between frequent and infrequent cannabis users. Patients scored higher on the craving/urge and impact scale than siblings and controls, which could be related to primary and secondary symptoms of their disorder. The OCDUS-CAN is well suitable for people with or without vulnerability for psychotic disorder.
Introduction

Cannabis is one of the most frequently used substances in patients with schizophrenia (Hambrecht and Hafner 1996, Cantwell et al 1999, Barnes et al 2006) and cannabis use is more common in people with psychosis than in the general population (Regier et al 1990, Hall and Degenhardt 2000). Moreover, cannabis use in patients with a psychotic illness is associated with increased relapse and rehospitalisation and with decreased treatment adherence (Linszen et al 1994, Zammit et al 2008). Non-psychotic siblings of individuals with schizophrenia also have higher rates of cannabis use than healthy controls (Smith et al 2008), which is an important finding since cannabis abuse is associated with a greater risk of developing psychosis (Moore et al 2008), and siblings of individuals with schizophrenia have a greater genetic vulnerability to develop schizophrenia like disorders (Gottesman 1991, GROUP 2010, Van Winkel et al 2010). Little is known about underlying mechanisms that lead to continued cannabis use in high risk subjects and patients with psychotic disorder, and about the role of craving in continuous use and relapse after initial abstinence. Craving is regarded as 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).

Measuring craving for cannabis in individuals with a vulnerability for psychotic illness and in patients with a psychotic disorder is important both from a clinical and scientific point of view. A valid measure of craving for cannabis could help health care providers and scientists understand the different elements that compose craving. Also, a valid cannabis craving measure could be used for monitoring urges for cannabis use, which is important, because craving predicts relapse into drug use (Doherty et al 1995, Anton et al 1996, Robbins and Ehrman 1998, Roberts et al 1999, Hartz et al 2001). In addition, monitoring craving for cannabis before, during and after pharmacological or psychological treatment may improve our understanding of how treatment affects craving. Only a few studies on craving for cannabis in patients with psychotic disorder are available (Potvin et al 2006, Akerele and Levin 2007, Van Nimwegen et al 2008, Dekker et al 2009a). These studies focused on the relation between craving and the effects of antipsychotic treatment and underlying associations towards the use of cannabis, and used self-report questionnaires for cannabis craving, like a modified version of the Penn Alcohol Craving Scale (PACS; Potvin et al 2006), the Marijuana Craving Report (Akerele and Levin 2007), and the Obsessive Compulsive Drug Use Scale for cannabis use (OCDUS-CAN; Van Nimwegen et al 2008, Dekker et al 2009a). To our knowledge, there are no reports about the validity of these measurement specifically for cannabis craving, nor in patients with psychotic disorder. In addition, no studies of cannabis craving in siblings of individuals with psychotic disorder have been reported. We are aware of one validated self-report questionnaire measuring subjective craving for cannabis, namely the Marijuana Craving Questionnaire (MCQ; Heishman et al 2001, Singleton et al 2002), but the MCQ has not been validated in a population with psychotic disorder.

The first aim of our study was to assess whether the Obsessive Compulsive Drug Use Scale (Franken et al 2002) for cannabis use (OCDUS-CAN) is a valid cannabis-craving scale that can be used for both research and clinical purposes. More specifically, we assessed 1) whether a common factor structure of the OCDUS-CAN can be found in patients with psychotic disorder, their non-affected siblings and
healthy controls; 2) whether this common factor structure is dependent on frequency of cannabis use; and 3) whether the OCDUS-CAN subscales are internally consistent. The second aim of the study was to assess whether the OCDUS-CAN subscale scores differentiate between patients, siblings and controls and between low and high frequent cannabis users.

Methods

Participants

Participants took part in the Genetic Risk and Outcome of Psychosis (GROUP) study, a multi site longitudinal cohort study in The Netherlands that focuses on vulnerability and resilience factors for variation in expression and course of non-affective psychotic disorders (for details, see Korver and Quee et al submitted). Inclusion criteria for patients were the following: (1) age range 16 to 50 years, (2) diagnosis of non-affective psychotic disorder according to DSM-IV (APA, 1994) and (3) good command of Dutch language. Inclusion criteria for siblings and controls were age 16-50 years, and good command of Dutch language. Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder. Patients were recruited from mental health centres covering more than 75% of the mental health institutes in the Netherlands, including both inpatient and outpatient clinics. Participating siblings with a lifetime or current diagnosis of non-affective psychotic disorder were considered as patients. Healthy controls were recruited by advertisements and by mailings in the local area. All participants gave written informed consent after complete description of the study. The study was approved by the human subject review boards of all four Academic Centres. To increase the size of the control group, research data of 36 healthy male controls were added from another observational study in which the OCDUS-CAN was used as well (described in Dekker et al 2009a). This study applied the same inclusion and exclusion criteria for healthy controls as the GROUP study, and - as in the current study- used the Composite International Diagnostic Interview (CIDI; WHO 1994) to measure substance use patterns.

Measures

Diagnosis

To establish DSM-IV (APA, 1994) diagnosis of psychotic disorder, three sites of the GROUP study used the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al 1992) and one site used the SCAN Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1; Wing et al 1990). Age at first occurrence of positive symptoms was taken as age of onset of the illness. The Positive and Negative Syndrome Scale (PANSS; Kay et al 1987) was used to assess symptoms in patients.

Substance use

Substance use was assessed with a short version of the CIDI (WHO 1994) sections B (tobacco use), J (alcohol use) and L (drug use). It contains items on the quantity of tobacco use and alcohol use in the past year, and items on the quantity and severity of use of drugs like cannabis and cocaine in the past year and lifetime. Frequency of drug use is categorised in daily, weekly, or less than weekly use. Current cannabis use was defined as cannabis use in the last month. Nicotine use was defined as daily use of cigarettes for at least one month in the past 12 months. Alcohol use in the past year was defined as having consumed more than 12 alcoholic drinks in the past 12 months. One alcoholic drink was considered to be equal to approximately 10 grams of ethanol. Illicit substance use (other than
cannabis) in the past year was defined as having used any hard drug (using terms like stimulants, speed, amphetamines, hallucinogens, opiates, cocaine or ecstasy) in the past year.  
In order to have biological validation concerning about recent use of cannabis, urinalysis for the presence of tetrahydrocannabinol (THC) was carried out using immunoassays with a cut off of 50ng/ml. Cannabis urine screening has a detection window up to 30 days, but the detection time has been documented in literature to be even longer (up to three months), depending on intensity of cannabis use (Musshoff and Madea 2006). Given the relatively high cut-off level of 50ng/ml, a conservative detection window of one month can be inferred. Urinalysis was not available for the 36 healthy controls from the observational study (see above, Dekker et al 2009a).  

**Craving for cannabis**  
Cannabis craving was measured with the OCDUS-CAN (see appendix), which is a cannabis-specific version of the original OCDUS (Franken et al 2002). It is a self-rating scale with a 5-point, Likert-type rating that measures drug craving in the past 7 days. Higher scores indicate higher craving for cannabis. The original OCDUS is based on the Obsessive Compulsive Drinking Scale (OCDS: Anton et al 1996), which has been translated into Dutch by Schippers et al (1997). Franken et al (2002) reported good reliability and validity for the original OCDUS in 102 heroin dependent patients. In this study, three underlying factors were found using exploratory Principal Component Analysis (PCA) and Varimax rotation: ‘thoughts and interference’, ‘desire and control’, and ‘resistance to thoughts and intention’. The first two factors showed substantial correlations with a measure of instant (now) craving. As suggested by the authors (Franken et al 2002) one item about becoming anxious or upset if one was prevented from using, was deleted because of the low factor loading of this item on the first factor, resulting in an OCDUS-CAN with 12 items.  

**Statistical analysis**  
Participants were divided into 6 groups according to subject type (patient, non-affected sibling or control) and frequency of consumption (frequent = at least weekly cannabis use in the past year, infrequent = less than weekly cannabis use in the past year). To compare the three subjects groups (patients, non-affected siblings, controls) and the two frequency groups (frequent use, infrequent use) on demographics and substance use characteristics, chi-square tests were used for categorical variables and one-way between-groups analyses of variance were conducted for continuous variables. 
To assess whether the OCDUS-CAN has a common factor structure in all three subject groups and in the two frequency groups Simultaneous Component Analysis (SCA) was used. To ensure sufficient variance in levels of cannabis use and craving, the SCA was restricted to those participants that had used cannabis in the preceding 12 months. Only data from subjects who had fully completed the OCDUS-CAN were included in the analyses. Components are linear combinations of the OCDUS-CAN items. Separate principal component analysis (PCA) in each population leads to component weights that, by definition, explain the maximum amount of variance of the OCDUS items. These component weights, however, generally result in a different component structure in each population. SCA on the other hand tries to find component weights that optimally explain the variance of the variables in different populations simultaneously (Millsap and Meredith 1988). The variance accounted for by SCA can be compared with the variance accounted for by the optimum solution in explained variance terms (i.e. separate PCA). If the explained variance of the OCDUS-CAN items by the subpopulation specific PCA components is comparable to that of the SCA components it can be concluded that the common
component solution adequately describes the (co)variance of the OCDUS-CAN items in the different populations. In other words, it can then be stated that the component structure is invariant over these populations. However, when a common component structure is found, this does not automatically mean that these components have the same meaning in the different populations. This can be assessed by comparing the factor loadings of components in the different populations.

In this study, the component weights resulting from a PCA solution of the mean correlation matrix (i.e. the correlation matrix based on the pooled populations) were used as a starting point. Since a three factor solution was reported in the original OCDUS study (Franken et al 2002), we started our analysis with a three-component solution. The resulting SCA weight matrix was transformed into a more simple structure by Varimax rotation. This weight matrix was further transformed into a simple weight matrix using only 1 and 0 as weights. The latter transformation is based on the values of the component weights in the Varimax rotated weight matrix. This caused only minimal loss of variance explained and greatly increased interpretability of the resulting components. Since we used only 1 and 0 as weights (i.e. binary weights) subscale scores could be calculated by simple adding the scores of the items of a subscale. All analysis were performed with the SCA computer program (Kiers 1990).

To assess whether the OCDUS-CAN subscales are internally consistent, Cronbach’s alphas of the subscales were determined. Correlations between the subscales were expressed as Pearson PM correlation coefficients.

To assess whether the OCDUS-CAN subscale scores were able to differentiate between the subject groups and frequency groups, we used linear regression analysis. For each of the subscale scores, we used a regression model with the component score as the dependent variable, and subject group, frequency group, and the interaction between subject and frequency groups as independent variables. To control for age, gender, nicotine use in the past year, alcohol use in the past year and hard drug use in the past year, these variables were included in the regression model as covariates. To take intra-family correlation into account (data from patients and siblings are not independent), we used a mixed model regression analysis with family as a random factor and a compound symmetry covariance matrix.

Results

Sample characteristics

OCDUS-CAN and CIDI data were available for 621 subjects: 346 patients, 165 non affected siblings and 110 controls. Of the patients, 232 (67.1%) were diagnosed with schizophrenia, 29 (8.4 %) with schizoaffective disorder, 39 (5.5 %) with schizophreniform disorder, 39 (11.3 %) with psychotic disorder NOS, and 27 (7.8 %) with another psychotic disorder. Means of PANSS subscales in patients were as follows: positive syndrome scale 2.0 (SD 0.8), negative syndrome scale 2.1 (SD 0.9), and general psychopathology scale 1.8 (SD 0.5). Mean duration of illness in patients was 3.7 (SD 3.8) years. Of all 346 patients, 284 (82.1 %) were currently using antipsychotic medication.
### Table 1. Participants’ demographic and substance use characteristics stratified to subject type and frequency of cannabis use in the past 12 months.

<table>
<thead>
<tr>
<th></th>
<th>Patients-frequent users</th>
<th>Patients-infrequent users</th>
<th>Siblings-frequent users</th>
<th>Siblings-infrequent users</th>
<th>Controls-frequent users</th>
<th>Controls-infrequent users</th>
<th>All groups</th>
<th>( \chi^2 ) or ( F )</th>
<th>df</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>92.7 (259)</td>
<td>86.2 (87)</td>
<td>76.0 (96)</td>
<td>87.1 (62)</td>
<td>75.0 (48)</td>
<td>83.4 (62)</td>
<td>55.6 (621)</td>
<td>5.715</td>
<td>5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>25.5 (6.2)</td>
<td>25.4 (6.0)</td>
<td>23.9 (6.2)</td>
<td>23.4 (4.8)</td>
<td>24.4 (6.3)</td>
<td>22.0 (5.5)</td>
<td>24.6 (6.1)</td>
<td>4.05</td>
<td>5</td>
<td>.001</td>
</tr>
<tr>
<td>Education *</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1 (%)</td>
<td>55.7 (476)</td>
<td>49.5 (40.5)</td>
<td>39.4 (18.4)</td>
<td>48.4 (7.3)</td>
<td>32.6 (6.4)</td>
<td>48.2 (7.1)</td>
<td>29.9 (10)</td>
<td>5.715</td>
<td>5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 (%)</td>
<td>22.8 (31.7)</td>
<td>26.9 (34.8)</td>
<td>33.9 (32.6)</td>
<td>27.9 (22.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (%)</td>
<td>21.3 (20.7)</td>
<td>23.7 (25.8)</td>
<td>17.7 (17.7)</td>
<td>47.8 (47.8)</td>
<td></td>
<td></td>
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<tr>
<td>Ethnicity, Caucasian (%)</td>
<td>72.5 (82.4)</td>
<td>83.3 (83.3)</td>
<td>70.7 (81.3)</td>
<td>91.3 (80.7)</td>
<td>91.3 (80.7)</td>
<td>86.7 (87.0)</td>
<td>16.7 (5)</td>
<td>5.41</td>
<td>5</td>
<td>.005</td>
</tr>
<tr>
<td>Nicotine use in past year, yes (%)</td>
<td>96.5 (90.8)</td>
<td>77.1 (61.8)</td>
<td>79.0 (50.0)</td>
<td>83.7 (83.7)</td>
<td>98.4 (98.4)</td>
<td>96.1 (98.1)</td>
<td>0.5 (5)</td>
<td>5.90</td>
<td>5</td>
<td>.003</td>
</tr>
<tr>
<td>Alcohol use past year, yes (%)</td>
<td>83.0 (92.0)</td>
<td>91.7 (93.5)</td>
<td>93.5 (93.5)</td>
<td>89.0 (89.0)</td>
<td>18 (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks per week, mean (SD)</td>
<td>9.8 (14.4)</td>
<td>10.8 (20.0)</td>
<td>9.0 (9.4)</td>
<td>12.4 (14.4)</td>
<td>11.9 (10.9)</td>
<td>10.0 (7.2)</td>
<td>10.3 (12.3)</td>
<td>0.75 (5)</td>
<td>5</td>
<td>.617</td>
</tr>
<tr>
<td>Current cannabis use, yes (%)</td>
<td>55.4 (78.0)</td>
<td>83.7 (59.1)</td>
<td>86.9 (76.1)</td>
<td>61.7 (79.5)</td>
<td>79.5 (79.5)</td>
<td>79.5 (79.5)</td>
<td>0.5 (5)</td>
<td>5.90</td>
<td>5</td>
<td>.003</td>
</tr>
<tr>
<td>Urine test for THC, positive (%)</td>
<td>49.8 (13.3)</td>
<td>65.9 (10.8)</td>
<td>54.3 (8.6)</td>
<td>40 (40)</td>
<td>96.4 (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other illicit substance use in past year *</td>
<td>34.0 (32.2)</td>
<td>32.3 (18.8)</td>
<td>40.3 (31.6)</td>
<td>22.9 (9.8)</td>
<td>98.5 (98.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.08</td>
</tr>
</tbody>
</table>

* 1 = Lower secondary professional education / intermediate vocational education
  2 = Higher general secondary education / higher vocational education
  3 = Pre-university education / university

*Other illicit substances = stimulants (speed, amphetamines), hallucinogens, opiates, cocaine, ecstasy

Figures in bold have adjusted standardised residuals > 3.0; figures underlined have adjusted standardised residuals < -3.0.
Table 1 shows the similarities and differences in sociodemographic and substance use variables between the six groups. Mean age of all subjects was 24.6 (SD 6.1) years, with a statistically significant difference in age between the subgroups \((P = 0.001)\), but post-hoc comparisons between subgroups did not survive Bonferroni correction. The sample was predominantly male (83.4%), with frequent cannabis using males even stronger overrepresented (92.7%), and infrequent cannabis using male siblings being under-represented (58.0%).

In the subgroup of patients with frequent cannabis use in the past year there was an under-representation of Caucasians and users of alcohol and an over-representation of nicotine users. Finally, in the group of infrequent cannabis using controls, subjects with a relatively low education and nicotine users were underrepresented. Urine tests for THC were available in 525 (84.5%) of all 621 subjects, with highest proportion of available urine tests results in frequent cannabis using patients (96.2%), and lowest proportion of available urine tests in frequent cannabis using controls (56.4%). Frequent cannabis using siblings had highest proportion of positive THC urine test results (65.9%). According to the CIDI, frequent cannabis using siblings and controls had the highest proportion of current cannabis users (83.7% resp. 86.9%).

**Underlying factor structure of the OCDUS-CAN**

Table 2 shows that a three-component SCA solution using binary component weights explained a mean of 74.2% of the total variance in the three subject groups (patients: 73.6%, siblings: 69.6%, controls: 79.3%) compared to a mean of 74.7% when using separate PCA’s (patients: 74.4%, siblings 70.0%, controls 79.5%). In addition, table 3 shows that a three-component SCA solution using binary component weights explained a mean of 72.1% of the total variance in the two groups defined by frequency of cannabis use (frequent 70.5%, infrequent 73.7%) compared to a mean of 72.7% when using separate PCA’s (frequent 71.2%, infrequent 74.2%). The small differences between the SCA and PCA solutions indicate the existence of a common component structure that adequately describes the covariance between the OCDUS-CAN items. Furthermore, there were no substantial differences in the factor loading of components in the three subject groups or the two frequency groups.

The first component can be labelled ‘craving/urge’ and includes items related to time spend on thoughts/urges and frequency of thoughts/urges related to cannabis use, and intensity of the experienced urge. The second component can be labelled ‘resistance’ and comprises two items related to how much an effort is made to resist thoughts and use of cannabis. The third component can be labelled ‘impact’ and includes items that relate to interference of thoughts and urge related to cannabis use on social and work functioning, the distress these thoughts cause, and how much control people have to stop thoughts or to not use cannabis.
# Chapter 1.3 - Craving for cannabis

<table>
<thead>
<tr>
<th>OCDUS Item</th>
<th>Patients</th>
<th>Siblings</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How much of your time (when you are not using) is occupied by ideas, thoughts, impulses, or images related to cannabis use? 0.85</td>
<td>0.84</td>
<td>0.93</td>
<td>0.79</td>
</tr>
<tr>
<td>2. How frequently do these thoughts related to cannabis occur? 0.88</td>
<td>0.91</td>
<td>0.90</td>
<td>0.74</td>
</tr>
<tr>
<td>3. When you do not use, how much time of the day do you feel the urge or drive to use cannabis? 0.91</td>
<td>0.71</td>
<td>0.71</td>
<td>0.76</td>
</tr>
<tr>
<td>4. When you do not use, how often do you fear the urge or drive to use cannabis? 0.90</td>
<td>0.64</td>
<td>0.64</td>
<td>0.76</td>
</tr>
<tr>
<td>5. How strong was the drive to use cannabis in the past week? 0.88</td>
<td>0.91</td>
<td>0.90</td>
<td>0.75</td>
</tr>
<tr>
<td>6. How much of an effort do you make to resist these thoughts related to cannabis or try to disregard or turn your attention away from these thoughts? 0.47</td>
<td>0.40</td>
<td>0.54</td>
<td>0.47</td>
</tr>
<tr>
<td>7. How much of your time (when you are not using) is occupied by ideas, thoughts, impulses, or images related to cannabis use? 0.85</td>
<td>0.88</td>
<td>0.93</td>
<td>0.79</td>
</tr>
<tr>
<td>8. How much of an effort do you make to resist the use of cannabis? 0.47</td>
<td>0.40</td>
<td>0.54</td>
<td>0.47</td>
</tr>
<tr>
<td>9. How much does the urge to use cannabis interfere with your social or working functioning? 0.66</td>
<td>0.61</td>
<td>0.72</td>
<td>0.88</td>
</tr>
<tr>
<td>10. How much does the urge to use cannabis interfere with your social or working functioning? 0.66</td>
<td>0.61</td>
<td>0.72</td>
<td>0.88</td>
</tr>
<tr>
<td>11. How much does the urge to use cannabis interfere with your social or working functioning? 0.66</td>
<td>0.61</td>
<td>0.72</td>
<td>0.88</td>
</tr>
<tr>
<td>12. How much control did you have over your cannabis use in the past week? 0.53</td>
<td>0.64</td>
<td>0.68</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Subscale's internal consistency and total variance explained by the three components based on SCA with binary weights:

- **SCA Total variance explained by the three components based on SCA with binary weights:** 73.6%
- **Total variance explained by the three components based on subject type specific PCA's:** 74.4%
### Table 3. Simultaneous component analysis factor loadings (three-factor solution) and variance explained of the OCDUS stratified on frequency type

<table>
<thead>
<tr>
<th>OCDUS item</th>
<th>Frequent users</th>
<th>Infrequent users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>craving/urge</td>
<td>resistance</td>
</tr>
<tr>
<td>1. How much of your time—when you are not using—is occupied by ideas, thoughts, impulses, or images related to cannabis use?</td>
<td>0.84</td>
<td>0.26</td>
</tr>
<tr>
<td>2. How frequently do these thoughts related to cannabis occur?</td>
<td>0.87</td>
<td>0.27</td>
</tr>
<tr>
<td>7. When you do not use, how much time of the day do you feel the urge or drive to use cannabis?</td>
<td>0.89</td>
<td>0.31</td>
</tr>
<tr>
<td>8. When you do not use, how often do you feel the urge or drive to use cannabis?</td>
<td>0.88</td>
<td>0.32</td>
</tr>
<tr>
<td>11. How strong was the drive to use cannabis in the past week?</td>
<td>0.85</td>
<td>0.33</td>
</tr>
<tr>
<td>5. How much of an effort do you make to resist these thoughts related to cannabis or try to disregard or turn your attention away from these thought?</td>
<td>0.27</td>
<td>0.86</td>
</tr>
<tr>
<td>10. How much an effort do you make to resist the use of cannabis?</td>
<td>0.33</td>
<td>0.86</td>
</tr>
<tr>
<td>3. How much do these thoughts related to cannabis interfere with your social or work functioning?</td>
<td>0.62</td>
<td>0.14</td>
</tr>
<tr>
<td>4. How much distress or disturbance do these thoughts related to cannabis cause?</td>
<td>0.61</td>
<td>0.11</td>
</tr>
<tr>
<td>6. How successful are you in stopping or diverting these thoughts related to cannabis?</td>
<td>0.60</td>
<td>0.33</td>
</tr>
<tr>
<td>9. How much does the urge to use cannabis interfere with your social or work functioning?</td>
<td>0.65</td>
<td>0.14</td>
</tr>
<tr>
<td>12. How much control did you have over your cannabis use in the past week?</td>
<td>0.53</td>
<td>0.30</td>
</tr>
<tr>
<td>Subscale’s internal consistency</td>
<td>0.91</td>
<td>0.64</td>
</tr>
<tr>
<td>SCA Total variance explained by the three components based on SCA with binary weights</td>
<td>70.5%</td>
<td>73.7%</td>
</tr>
<tr>
<td>Total Variance explained by the three components based on frequency of use type specific PCAs</td>
<td>71.2%</td>
<td>74.2%</td>
</tr>
</tbody>
</table>
Table 4. Subscale correlation matrix for the OCDUS for the total pooled population with Cronbach’s alpha on diagonal (n = 621)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving/Urges</td>
<td>0.92**</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance</td>
<td>0.62**</td>
<td>0.36**</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Impact</td>
<td>0.87**</td>
<td>0.78**</td>
<td>0.29**</td>
<td>0.85</td>
</tr>
</tbody>
</table>

** Correlation is significant at 0.01 level (2-tailed)

Table 4 shows that for the pooled population of patients, siblings and controls (N=621), Cronbach’s α of the subscales were as follows: 0.93 for the component ‘craving/urge’, 0.69 for the subscale ‘resistance’, and 0.85 for the subscale ‘impact’. Cronbach’s α of the subscales in the different subject and frequency groups are displayed in tables 2 and 3. Table 4 also shows the subscale correlation matrix for the pooled population, indicating moderate positive correlations between the second subscale and first and third subscale (r=.36 and r=.29 receptively), and a strong positive correlation between the first and third subscale (r=.78). These overall correlations are very similar to the subscale correlations in the various subgroups (patients, siblings, controls; frequent users, infrequent users) [data not presented]. Given the relatively low internal consistency and the small number of items in the second subscale (‘resistance’), we also examined a two-component SCA solution. However, this two-component SCA solution did not solve the problem. It resulted in the same ‘resistance’ component with the same two items and another component with all other items. In addition, the two component solutions explained less variance than the three factor solution: 67.7% vs. 74.7%.

Differences in OCDUS-CAN scale scores between subgroups

As the interaction effect between subject type and frequency type was not statistically significant in predicting each of the component scores, we present the results of the regression analysis with only the main effects of subject group and frequency of cannabis use group (table 5). After controlling for frequency of cannabis use, age, gender, nicotine use in the past year, alcohol use in the past year, hard drug use in the past year, and intra-family correlation, mean OCDUS-CAN subscale scores were significantly different between the subject group, in all three subscales (see table 5 for details). Patients scored significantly higher on the subscale ‘craving/urge’ than siblings (B= -0.16, SE B= 0.07, t=-2.2, P=0.028) and controls (B= -0.19, SE B= 0.08, t=-2.3, P=0.021). Patients also scored significantly higher on the subscale ‘impact’ than siblings (B= -0.19, SE B= 0.06, t=-3.0, P=0.003) and controls (B= -0.25, SE 0.06, t=-3.6, P<0.001). Using the same control variables, siblings and controls scored higher on the subscale ‘resistance’ than patients (B= 0.31, SE B=0.13, t=3.4, P=0.002, resp. B=0.5, SE B=0.15, t=3.5, P=0.001). When controls were used as reference category, there were no significant differences in subscale scores between siblings and controls. Frequent users had significantly higher scores on all three subscales (‘craving/urge’ subscale B=0.71, SE B= 0.06, t=11.0, P <0.001: ‘resistance’ subscale B=0.72, SE B=0.12, t=6.3, P <0.001, ‘impact’ subscale B=0.42, SE B= 0.54, t= 7.8, P < 0.001) compared to infrequent cannabis users even after controlling for subject type, age,
In this study we found a three component structure of the OCDUS-CAN that was both invariant over subject type (patients with non-affective psychotic disorder, unaffected siblings, and healthy controls) and over cannabis frequency type (frequent, infrequent cannabis user). The three components were interpreted as 'craving/urge', 'resistance' and 'impact'. This means that these OCDUS-CAN subscales can be applied and can be easily interpreted in patients with non-affective psychotic disorder, their siblings, and healthy controls who used cannabis recently (in the past year) in various amounts. The first ('craving/urge') and third ('impact') subscale had good internal consistency, with an overall Cronbach’s α of 0.93 and 0.85 respectively. The second subscale ('resistance') consisted of only two items and consequently had a somewhat lower but still acceptable internal consistency with an overall Cronbach’s α of 0.69. This three-factor solution also corresponds very well with the factor solution of the original OCDUS in heroin dependent patients (Franken et al 2002). Our component 'resistance' was the same as their factor 'resistance to thoughts and intention'. In addition, our component 'urge/craving' was similar to their factor 'desire and control' with an overlap of three of the five items. Finally, our 'impact' component is very similar to their 'thoughts and interference' scale with an overlap of four of the five items. Differences in the assignment of specific items to components/factors were found in only three items: two items about time spend on thoughts and frequency of thoughts related to cannabis use and one item about control on use. These differences may be accounted for by differences in the type of drug for which craving was measured, and differences in subject types. Furthermore, differences may be attributable to methodological differences in the two studies; Franken et al (2002) used PCA, and the present study used SCA. As mentioned in the introduction, the 47-item MCQ (Heishman et al 2001, Singleton et al 2002) is another validated self-report questionnaire measuring subjective craving for cannabis. The MCQ contains items that were drawn from theoretical conceptualizations of craving with four aspects: compulsivity (inability to control cannabis use), emotionality (cannabis use in anticipation of relief from withdrawal or negative mood), expectancy (cannabis use in anticipation of positive outcomes).
and purposefulness (intention and planning to use cannabis for positive outcomes). It is difficult to compare the OCDUS with the MCQ on the content of their scales, because the MCQ has a different approach to the measurement of craving than the OCDUS. This is understandable, because craving is a broad concept of which there is no agreement on how it should be defined and measured (e.g. Sayette et al 2000). It would be interesting to assess the concurrent validity of the OCDUS-CAN and the MCQ or the short 12-item version of the MCQ (Heishman et al 2009). To obtain more information about construct validity of the OCDUS-CAN, subscale scores of the OCDUS-CAN could be correlated to other underlying constructs of addiction, such as attentional bias for cannabis or implicit (automatic) associations toward cannabis. The OCDUS-CAN has not been related to attentional bias, but in heroin and cocaine research the OCDUS showed high correlations with attentional bias for cocaine and heroin cues and with a single-item for craving (Franken et al 2000a) (Franken et al 2000b). Finally, a recent study in patients with psychotic disorder and healthy controls found a trend for the relationship between (implicit) positive arousal associations toward cannabis use and craving for cannabis measured with the OCDUS-CAN (Dekker et al 2009a). These studies provide some early evidence for construct validity of the OCDUS.

In the present study, we found that patients scored significantly higher on the ‘craving/urge’ and ‘impact’ scale than siblings and controls after controlling for frequency of use and other potential confounders. This means patients experience higher craving levels compared to siblings and controls and that it causes more distress, independent of their level of cannabis use. One may speculate that this higher craving in patients could be related to symptoms of their disease. Perhaps positive and negative symptoms or secondary dysphoria associated with the psychotic disorder is related to more severe craving for cannabis in patients. Although longitudinal studies generally do not show evidence for self medication effects (Arsenault et al 2002, Stefanus et al 2004, Fergusson et al 2005, Henquet et al 2005, Van Os et al 2002) except Ferdinand et al (2005), and self-medication as reason to use cannabis is reported only in a minority of patients (Dekker et al 2009b), no study has examined these specific disease related motivations for cannabis use in relation to craving. Another explanation of higher craving in patients could be the use of antipsychotic medication. However, the exact effect of antipsychotic medication on craving is not known. Although some efficacy studies of antipsychotics in patients with schizophrenia and comorbid substance use disorder suggest that conventional antipsychotics may induce or worsen substance use disorders, some atypical antipsychotics have shown a role in alleviating comorbid substance abuse (Green 2005, Van Nimwegen et al 2008).

Further, studies concerning self-reported reasons for cannabis use in patients with psychotic illness have shown that cannabis use to relieve side effects of medication is indeed reported by patients, but only in 15 to 38% (Dekker et al 2009b). The finding that patients with a non-affective psychosis experience more craving may (partly) explain the increased rates of cannabis use in people with psychotic illness (Hall and Degenhardt 2000, Regier et al 1990). However, the exact mechanism to the development of more craving in these patients, i.e. how it relates to use of antipsychotic medication and to primary and secondary symptoms of psychotic disorders, is still unknown and needs further investigation. It is important to note that siblings did not report higher craving levels on the OCDUS-CAN scales than controls, suggesting that higher craving levels are not related to the underlying vulnerability for psychosis but rather to the presence of psychosis-related symptoms or the use of antipsychotic medication. Although we found that patients reported higher craving levels than siblings and controls, a much larger effect was found for the difference in OCDUS-CAN scores between frequent and infrequent cannabis users; frequent cannabis users had significantly higher scores on all OCDUS-CAN subscales than infrequent cannabis users. This is in line with the findings of
another study (Dekker et al 2009a) reporting a positive correlation between scores on the OCDUS-CAN and the level of cannabis use. However, more precise information on dose-response relationships could be provided by comparing craving levels among more refined categories of frequency of cannabis use than the ones used in the current study.

A limitation of the current study is that we have no information on test-retest reliability of the OCDUS-CAN. However, Franken et al (2002) reported that the original OCDUS had good test-retest reliability in heroin dependent patients with interclass correlations coefficients (ICC) for the three subscales ranging from 0.72 to 0.79 over a period of 48 hours. Another limitation is that we have no data on the predictive validity of the OCDUS-CAN. This needs further investigation. Lastly, this study population was predominantly male. Although gender was used as covariate in the regression analysis, we did not investigate whether the OCDUS-CAN scales differentiate between males and females. Although males are more prone to use cannabis than females in psychosis samples (e.g. Gonzales-Pinto et al 2008, Foti et al 2010) as well as in normal population samples (Cotto et al 2010), reports about effects of gender on cannabis craving are needed.

Strengths of the present study are (1) the use of the same craving instrument (OCDUS-CAN) in a large sample of patients, their unaffected siblings and normal controls, (2) the use of simultaneous component analysis (SCA) to study the underlying structure of the OCDUS-CAN, and (3) the correction of the relationship between group status and craving levels for a large number of potential confounders.

The key focus of the current study was the search for a common factor or component structure of the OCDUS-CAN in different groups of psychosis vulnerability and different levels of cannabis use. This is the first study providing evidence that the OCDUS-CAN is a valid instrument to assess craving for cannabis in clinical and research samples of patients with psychotic disorder, but also in siblings and individuals without a (family) history of psychotic illness. The three subscales score can be easily estimated using a summed scoring approach, and thus, scoring the OCDUS in terms of these three subscales is simple. The resulting subscales have good internal consistency and clearly discriminate between frequent and infrequent cannabis users, independent of their psychosis vulnerability status. We recommend that the second subscale “resistance” is expanded with newly generated items to establish an even better internal consistency. More research is needed on the underlying mechanisms related to the different aspects of craving, and the effectiveness of substance use disorder treatments in cannabis using individuals who are vulnerable for psychotic disorder. In these studies, the OCDUS-CAN can be recommended as a valid indicator for one of the most crucial predictors and outcome parameters.
Appendix

OCDUS-CAN (translated)

Directions: The questions below ask you about your cannabis use and your attempts to control your cannabis use. The questions refer to the past week. If you have never used cannabis, and/or if you never considered using it, you do not have to fill in this instrument. Could you then mark the following box:

□ Never used cannabis and never considered cannabis use

Note: The following questions are about thoughts (images, ideas, impulses) related to cannabis in the past week.

1. How much of your time–when you are not using–is occupied by ideas, thoughts, impulses, or images related to cannabis use?
   1. None
   2. Less than 1 hour a day
   3. 1-3 hours a day
   4. 4-8 hours a day
   5. Greater than 8 hours a day

2. How frequently do these thoughts related to cannabis occur?
   1. Never: I have not had these thoughts related to cannabis in the past week
   2. Seldom: No more than 8 times a day
   3. Sometimes: More than 8 times a day, but most hours of the day are free of these thoughts
   4. Often: More than 8 times a day and during most hours of the day
   5. Always: An hour rarely passes without several such thoughts occurring

3. How much do these thoughts related to cannabis interfere with your daily functioning (e.g. work, contact with family and friends)?
   1. Not at all: Thoughts related to cannabis never interfere – I can function normally
   2. Mild: Thoughts related to cannabis slightly interfere with my social or occupational activities, but my overall performance is not impaired
   3. Moderate: Thoughts related to cannabis definitely interfere with my social or occupational performance, but I can manage
   4. Severe: Thoughts related to cannabis cause substantial impairment in my social or occupational performance
   5. Extreme: Thoughts related to cannabis interfere completely with my social or work performance

4. How much distress or disturbance do these thoughts related to cannabis cause?
   1. Not at all: These thoughts do not cause distress
   2. Mild: Thoughts related to cannabis are not too disturbing
   3. Moderate: Thoughts are disturbing, but still manageable
   4. Severe: Thoughts are very disturbing
   5. Extreme: Thoughts cause nearly constant disabling distress

5. How much of an effort do you make to resist these thoughts related to cannabis or try to disregard or turn your attention away from these thoughts? Rate your effort made to resist these thoughts, not your success or failure in actually controlling them.
   1. Always: My thoughts are so minimal, I don’t need to actively resist, or; If I have these thoughts, I make an effort to always resist
   2. Most of the time: I try to resist most of the time
   3. Sometimes: I make some effort to resist
   4. Seldom: I give in to such thoughts without attempting to control them, but I do so with some reluctance
   5. Never: I complete and willingly give in to all such thoughts

6. How successful are you in stopping or diverting these thoughts related to cannabis?
   1. Always: I am completely successful in stopping or diverting such thoughts
   2. Most of the time: I am usually able to stop or divert such thoughts with some effort and concentration
   3. Sometimes: I am sometimes able to stop or divert such thoughts
   4. Seldom: I am rarely successful in stopping such thoughts and can only divert such thoughts with difficulty
   5. Never: I am rarely able to divert such thoughts even momentarily
Note: the following questions are not about thoughts related to cannabis, but about the urge or drive to use cannabis in the past week.

7. If you do not use cannabis, how much time of the day do you feel the urge or drive to use cannabis?
   1. Not at all
   2. Less than 1 hour a day
   3. 1-3 hours a day
   4. 4-8 hours a day
   5. Greater than 8 hours a day

8. When you do not use, how often do you feel the urge or drive to use cannabis?
   1. Never: I have not had the urge or drive to use cannabis in the past week.
   2. Seldom: Less than 8 times a day.
   3. Sometimes: More than 8 times a day, but most hours of the day are free of those urges or drives.
   4. Often: More than 8 times a day and during most hours of the day
   5. Always: An hour rarely passes without such urges or drives occurring

9. How much does the urge to use cannabis interfere with your daily functioning (e.g. work, contact with family and friends)?
   1. Not at all: This urge does not cause no distress.
   2. Mild: This urge is not too disturbing.
   3. Moderate: This urge is disturbing, but I can still manage.
   4. Severe: This urge is very disturbing.
   5. Extreme: This urge causes extreme, nearly constant disabling distress.

10. How much of an effort do you make to resist the use of cannabis? (Only rate the effort to resist, not your success or failure in actually controlling the drinking).
    1. Always: I use so little (or no) cannabis, I don’t need to actively resist, or, I always try to resist the use of cannabis.
    2. Most of the time: I try to resist the use of cannabis most of the time.
    3. Sometimes: I make some effort to resist the use of cannabis.
    4. Seldom: I give in to the use of cannabis without attempting to control it, but I do so with some reluctance.
    5. Never: I complete and willingly give in to cannabis use.

11. How strong was the drive to use cannabis in the past week?
    1. Not at all: I have not felt the drive to use cannabis.
    2. Mild: I have felt a mild drive to use cannabis.
    3. Moderate: I have felt a moderate drive to use cannabis.
    4. Severe: I have felt a strong drive to use cannabis.
    5. Extreme: The drive to use cannabis is completely involuntary and overpowering.

12. How much control did you have over use of cannabis in the past week?
    1. Very much: I have complete control over my cannabis use.
    2. Reasonably much: I am usually able to exercise voluntary control over my cannabis use.
    3. Moderate: I can control my cannabis use only with difficulty.
    4. Hardly: I must use cannabis and can only delay using cannabis with difficulty.
    5. None: I am rarely able to delay using cannabis even momentarily.
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Chapter 1.3 - Craving for cannabis


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CHAPTER 1.4

Cessation of cannabis use by patients with recent-onset schizophrenia and related disorders

N. Dekker, L. de Haan, S. van den Berg, M. de Gier, H. Becker, D.H. Linszen
Abstract

Background. Cannabis abuse has been found to be a component risk factor for the onset and poor outcome during the early course of schizophrenia and related disorders. Cannabis use has become a target for prevention and treatment of schizophrenia patients. Therefore, knowledge of factors that influence continuation and cessation of cannabis use is crucial. However, little is known about factors associated with cessation of cannabis use in young schizophrenia patients.

Sampling and methods. We examined medical records of 206 consecutively admitted young patients with schizophrenia or related disorders, to explore factors associated with cessation of cannabis use.

Results. Of all patients that had used cannabis (167) in the past, more than half (87) ceased the use of cannabis before they were admitted to our clinic. Most patients ceased the use of cannabis after they became psychotic and after their first contact with psychiatric services. According to the urinalysis, only 5 patients seemed to have lied about their time of cessation. No differences in patient characteristics were found between patients that ceased their use of cannabis and patients that continued their use.

Conclusions. The results suggest that start of treatment for psychosis is related to the cessation of cannabis use, at least in part of the patients.
Introduction

Several studies indicate that the prevalence of substance use disorders among individuals with psychotic disorders is higher than in the general population, with lifetime estimates of more than 40% (Fowler et al 1991, Dixon 1999, Green 2005). Patients with first-episode schizophrenia are also likely to have a high rate of co-morbid substance use disorders, with cannabis being a prominent drug of abuse (Green 2005, Buhler et al 2002, Van Mastrigt et al 2004). In a first episode sample of 357 patients, 78% misused substances and 35% had a diagnosis of cannabis abuse or dependence (Van Mastrigt et al 2004). In another sample of 232 patients at first admission, 14.2% had a lifetime history of drug abuse, with 88% reporting the use of cannabis (Buhler et al 2002). In schizophrenia patients, cannabis use has been associated with an early age of onset of the disease (Van Mastrigt et al 2004, Veen et al 2004, Barnes et al 2006), and more and earlier psychotic relapses (Linszen et al 1994). For the prevention and treatment of cannabis use among schizophrenia patients, not only knowledge of factors which influence the initiation and continuation of cannabis use is crucial, but also of the factors associated with cessation of cannabis use are important.

As opposed to the numerous studies that have been conducted investigating self-reported reasons for cannabis use in patients with psychotic disorders (Fowler et al 1991, Test et al 1989, Dixon et al 1991, Warner et al 1994, Baigent et al 1995, Addington and Duchak 1997, Spencer et al 2002) little is known about self-reported reasons for cessation of cannabis use among these patients. Also, there are limited data on the course of cannabis use in young schizophrenia patients, the proportion of patients that cease the use of cannabis and the time of cessation.

A few studies have examined the course of cannabis use in first episode psychosis patients. Wade et al (2006) examined the course of substance misuse in 103 individuals treated for first-episode psychosis. Between baseline and 15-month follow up, there was a significant reduction in the rate of cannabis misuse from 63.1% to 41.7%. Patients who continued substance misuse were more likely to be younger, male and single, less likely to have completed secondary school and more likely to be heavy cannabis users prior to entry to treatment compared to patients who ceased substance use. Reasons for cessation were not examined. Another prospective study of first-episode psychosis (Addington and Addington 2001) found a lower rate of cannabis misuse during the first year of treatment compared to the pre-treatment period. Of the initial 30 patients (32% of total) that met the criteria for current cannabis abuse, 7 still abused cannabis after 1 year, which was a significant drop. Baseline predictors and reasons for cessation were not examined.

In chronic psychosis, two prospective longitudinal studies of the course of substance misuse have been reported (Cuffel and Chase 1994, Bartels et al 1995). Cuffel and Chase (1994) reported 1-year rates of substance abuse and dependence remission and relapse in a sample of schizophrenic patients taken from the Epidemiologic Catchment Area study. They found that individuals who developed abuse or dependence over the year were younger, male, and showed increases in depression and risk for hospitalisation. Individuals who remitted from abuse or dependence were older, female and showed decreases in depression over the year. Another prospective naturalistic study (Bartels et al 1995) of 148 outpatients with chronic psychosis found that those patients with initial drug abuse had a higher rate of remission (54 %) than those with initial drug dependence (31 %) at the 7 year follow up.

In the general population, several studies have identified factors associated with cessation of cannabis use. Earlier studies (Kandel and Raveis 1998, Hammer and Vaglum 1990) have found that
cessation of cannabis use was significantly related to the establishment of an adult social role as a partner or as a parent, and negatively correlated to long-term unemployment. These findings support the role incompatibility theory (Thornton and Nordi 1975), which implicates that the role of a cannabis user is incompatible with the acquisition of typical and normative adult roles. Goodstadt et al (1984) found in a large high school sample that those students who started to use cannabis at a very young age were less likely to quit than those who tried it later. A more recent one year prospective study (Van den Bree et al 2005) among 13718 adolescents found that three risk factors influenced all stages of development of cannabis use (including failure to discontinue use): own and peer involvement with substances, delinquency and school-related problems. Sussman and Dent (2004) found in a five year prospective study among 339 teenage marijuana users that light users, those who obtained a conventional adult role, those who had relatively few friends that used marijuana and those who were female were relatively likely to quit. Chen and Kandel (1995), who investigated factors associated with cessation of cannabis use from adolescence to adulthood in a sample of 706 marijuana users, found that the two most important predictors of stopping marijuana use were frequency of marijuana use and age. Infrequent users and individuals in their late twenties were most likely to stop using. Early onset into cannabis use and using illicit drugs other than marijuana delayed cessation.

The aim of this study was to examine factors associated with the cessation of cannabis use in a clinical sample of consecutively admitted adolescent and young adult patients with recent onset schizophrenia and related disorders. We tried to answer the following four questions:

What is the proportion of patients that cease cannabis use prior to treatment in our clinic for young schizophrenia patients?

What are the differences between patients that ceased cannabis use and patients that continued their use?

When did patients stop using cannabis in relation to their psychiatric history?

Are patients honest about their reported cannabis cessation?

Methods

Subjects and procedure

We examined 206 medical records of consecutively admitted patients with schizophrenia or related disease (schizoaffective disorder, schizophreniform disorder, psychosis due to cannabis use and psychosis NOS) who were consecutively admitted to the inpatient and day-care unit of the Adolescent Clinic of the Psychiatric Department of the Academic Medical Center in Amsterdam from 2002 to 2005. This clinic is specialized in the treatment of young schizophrenia patients aged between 16 and 28 years. Patients are referred to the program by outpatient and inpatient care facilities in the region.

Data collection and measures

For this study data were retrieved from medical records. Shortly before and after admission in the clinic all patients are asked routinely about their psychiatric history, prior and current symptoms and past and current substance use. Clinical discharge diagnoses according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV: APA 2000), were made with the use of all available diagnostic information (systematic interviews with patients and parents and previous medical records) by two clinical psychiatrists and two residents, after which the diagnoses were
reviewed by a research psychiatrist (Spitzer and Williams 1995). Besides self-report measures, a laboratory test (urinalysis) is conducted routinely for detection of drug use (cannabis, cocaine and amphetamines) in the first week of admission.

We collected data of the psychiatric treatment history, data about the onset of the first positive psychotic symptoms (hallucinations, delusions, and disorganisation). We also used quantitative data of past drug use and recent drug use that patients reported shortly after admittance. We determined whether the patient had used cannabis, in what average amount and at what age patients started using cannabis. Patients that had used cannabis less than 5 times in their lives were counted as never users.

All patients that had ceased the use of cannabis before admittance to our clinic were counted as those patients that had ceased their use. Of all those patients, we looked at what age they had done this and whether reasons or certain occurrences during cessation of cannabis use had been reported in the medical records. We also determined whether patients had ever used hard drugs (ecstasy, cocaine, lsd, amphetamines/speed, opiates). For a more complete description of characteristics of drug use in this population, we made a comparison between males and females. Furthermore, results of the urinalysis for cannabis use were used.

Data analysis

For analysis of the data we used SPSS 12.0.1. To assess group differences on categorical drug use variables among males and females, and among patients that ceased cannabis use and patients that continued their use, we conducted chi-square tests for independence. To compare means on continuous variables we used independent-sample t-tests. To relate the time of cessation of cannabis use to the psychiatric history, we divided the time of cessation in four periods: prior to onset of psychotic symptoms, after onset of psychotic symptoms but before first outpatient care, during or after first outpatient care, during or after prior admittance for psychosis. According to the time (month-year) of cessation that was reported by the patient and the timeframe of his psychiatric history, patients were assigned to one of these groups. We performed a chi-square goodness of fit test to determine whether these different groups were equally represented among those patient that had ceased their cannabis use.

Validity of self-reported cannabis use was established by its correspondence with urinalysis test results. The laboratory of the Academic Medical Center uses the enzyme immunoassay method for detecting tetrahydrocannabinol (THC) metabolites in urine samples, with a cut-off level of 50 ng/ml. Cannabis has a detection window up to 30 days, but the detection time has been documented in literature to be even longer (up to three months) and more variable in populations of heavier cannabis users (Mushoff and Madea (2006). However, given the relatively high cut-off level of 50 ng/ml we chose a detection window of one month. Of those patients that said they stopped using cannabis, but had positive urine for THC- we determined whether the time of cessation was in the detection window of one month.
Results

Baseline Characteristics

Table 1 shows baseline characteristics of the 206 patients of whom the medical records were reviewed. Most patients were male (86%). The average age at admission was 21.8 years (SD 3.0). Almost two thirds of the patients was diagnosed with schizophrenia. One third of patients had never been admitted for psychosis before, the rest was admitted once or more times. Every patient had had contact with a psychiatric caregiver before admittance to our clinic.

Table 1. Baseline characteristics of 206 patients with schizophrenia or related disorders

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Patients (%)</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Age at admission, mean (SD)</th>
<th>Diagnosis according to DSM-IV</th>
<th>Prior admissions</th>
<th>Prior contact with psychiatric caregiver (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>206 (100)</td>
<td>177 (86)</td>
<td>29 (14)</td>
<td>21.8 (3.0)</td>
<td>Schizophrenia, (%) 132 (64.1)</td>
<td>None (%)</td>
<td>206 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schizoaffective disorder (%) 34 (16.5)</td>
<td>One (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schizophreniform disorder (%) 9 (4.4)</td>
<td>Two (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cannabis-induced psychotic disorder (%) 10 (4.9)</td>
<td>Three or more (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Psychotic disorder NOS (%) 21 (10.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug use

Drug use characteristics are shown in table 2. Cannabis was the most used substance; 81% had used cannabis. Males were more likely than females to have used cannabis ($p < 0.001$). The average age of first cannabis use was 15.6 years. The average amount of joints used per week was 16.2. Almost all patients who ever used hard drugs, also had used cannabis.

Table 2 Characteristics of drug use of 206 patients with schizophrenia or related disorders

<table>
<thead>
<tr>
<th>Drug use before current admission</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=206</td>
<td>n=177</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td>No drug use (%)</td>
<td>37 (18.0)</td>
<td>23 (13.0)</td>
<td>14 (48.3)</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Cannabis (%)</td>
<td>167 (81.1)</td>
<td>153 (86.4)</td>
<td>14 (48.3)</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Only cannabis (%)</td>
<td>72 (35.0)</td>
<td>65 (36.7)</td>
<td>7 (24.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cannabis + hard drugs* (%)</td>
<td>95 (46.1)</td>
<td>88 (49.7)</td>
<td>7 (24.1)</td>
<td>$p &lt; 0.05$</td>
</tr>
<tr>
<td>Age of first cannabis use, mean (SD)</td>
<td>15.6 (2.4)</td>
<td>15.5 (2.5)</td>
<td>15.4 (1.5)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. = not significant
* ever used hard drugs: ecstasy, cocaine, lsd, amphetamines/speed, opiates
Proportion of patients that ceased cannabis use prior to treatment in our department

Of all patients that had used cannabis (n = 167), more than half (n = 87) ceased their use before they were admitted to our clinic. The average age of cessation in the group of patients that stopped using cannabis was 20.4 years (see table 2).

Comparison of patients that ceased cannabis use and patients that continued their use

In table 3, patient characteristics are given from patients that ceased cannabis use and patients that continued their use. We found no differences between these groups.

Table 3 Comparison of patient characteristics between patients that ceased cannabis use and patients that continued their use

<table>
<thead>
<tr>
<th>Total of cannabis users</th>
<th>Patients who ceased cannabis use</th>
<th>Patients who continued cannabis use</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=167</td>
<td>n=87</td>
<td>n=80</td>
<td></td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>153/14</td>
<td>78/9</td>
<td>75/5</td>
</tr>
<tr>
<td>Age of first cannabis use, mean (SD)</td>
<td>15.6 (2.4)</td>
<td>15.7 (2.3)</td>
<td>15.5 (2.5)</td>
</tr>
<tr>
<td>Age of first psychiatric care for psychosis, mean (SD)</td>
<td>20.3 (3.2)</td>
<td>20.5 (2.9)</td>
<td>20.1 (3.9)</td>
</tr>
<tr>
<td>Age at admission in our clinic, mean (SD)</td>
<td>21.9 (2.9)</td>
<td>21.9 (2.9)</td>
<td>21.9 (2.9)</td>
</tr>
<tr>
<td>Drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only cannabis (%)</td>
<td>72 (43)</td>
<td>36 (41.4)</td>
<td>36 (45.0)</td>
</tr>
<tr>
<td>Cannabis + hard drugs* (%)</td>
<td>95 (57)</td>
<td>51 (58.6)</td>
<td>44 (55.0)</td>
</tr>
<tr>
<td>Joints used per week, mean (SD)</td>
<td>16.2 (14.8)</td>
<td>17.2 (16.1)</td>
<td>15.2 (13.2)</td>
</tr>
</tbody>
</table>

n.s. = not significant
* ever used hard drugs: ecstasy, cocaine, lsd, amphetamines/speed, opiates

Time of cessation in relation to psychiatric history

In figure 1 the moment of cessation is related to the psychiatric history. Overall, the greatest part of all cannabis users that ceased the use of cannabis, did so after they became psychotic. One third of patients stopped using cannabis during or after a prior admittance for psychosis. There was a significant difference between the numbers of patients in the different groups representing time of cessation (chi square value 18.920, \( p = 0.001 \)).

Reliability of self-reported cannabis use cessation

Of all 87 patients who reported they had ceased the use of cannabis, 73 (83%) had their urine analysed. Of those, 11 (15%) tested positive for cannabis. Five of them were tested outside the detection window, because their self-reported moment of cessation was more than one month before the urine test date. Four of the 11 patients that tested positive for cannabis had said that they had ceased the use of cannabis less than one month before, so they were tested in the detection window period. Of two of the 11 patients the time of cessation was not available, so we cannot determine whether they were tested in the detection window or not.
Discussion

The main finding of this retrospective cohort study of young patients with recent onset schizophrenic disorders was that more than 50% of those who had used cannabis in the past had ceased the use of cannabis before they were admitted to a clinic specialized in the treatment of early schizophrenia. Of all patients that had ceased the use of cannabis, one third did so during or after a prior admittance for psychosis and a quarter did so during or after first outpatient care for psychosis. Moreover, a prior admittance was reported most frequently as the reason for cessation. The exact motivation for cessation during this treatment for psychosis is unknown, but perhaps outpatient care and admittance for psychosis have an effect on this motivation. Further, it may well be that motivation to receive treatment is related to motivation to stop using cannabis. Two other studies (Wade et al 2006, Addington and Addington 2001) have examined the course of substance use of young patients treated for first episode psychosis. They both show a significant drop in cannabis use between baseline and follow up (up to 15 months), supporting the idea that treatment and the motivation for ceasing the use of cannabis are related, at least in part of the patients.

We found no differences in patient characteristics between patients that ceased the use of cannabis, and patients that continued their use. Two prospective naturalistic studies (Cuffel and Chase 1994, Bartels et al 1995) in chronic psychosis have examined factors associated with remission of substance
use. Bartels et al (1995) found that those patients with initial drug abuse had a higher rate of remission (54 %) than those with initial drug dependence (31 %) at the 7 year follow up. Cuffel and Chase (1994) found that individuals who remitted abuse or dependence over the year were older, female and showed decreases in depression over the year. A distinction in type of drug was not made in these studies, so the specific course of cannabis use is not known. Additionally, whether these findings generalize to patients with first-episode psychosis is not known. In contrast to our results, studies in the general population (Goodstadt et al 1984, Sussman and Dent 2004, Chen and Kandel 1998) did find that people that ceased their use of cannabis were more likely to be female, older, started use of cannabis at an older age and used less amounts of cannabis. Limited variance in age and gender in the cohort we studied probably precluded finding differences between patients that ceased cannabis use and those that didn’t. The reasons patients described for cannabis cessation were in concordance with the only other study we are aware of (Addington and Duchak 1997) that assessed reasons for stopping drugs in patients with both schizophrenia and drug abuse or dependence. A total of 21 cannabis using patients were asked to give reasons why they might stop drug use. As in our study, reasons related to symptoms (confusion 67%, becoming paranoid 71%, hallucination 48%) and hospitalization (38%) were reported. Also disapproval of others (of a doctor 71%, of parents/relatives 86%) was important. The two most reported reasons were disapproval of parents/relatives and costs (both 86%).

Cannabis was the most used substance in our study population, which is in agreement with other studies among patients with recent onset schizophrenic disorders (Green 2005, Buhler et al 2002, Van Mastrigt et al 2004, Barnes et al 2006). In the Dutch general population, cannabis is also the most commonly used drug (Abraham et al 2001). Eighty-one percent of our study population had used cannabis, in agreement with other studies finding a high prevalence of cannabis use in patients with schizophrenia (Regier et al 1990, Hambrecht and Häfner 1996, Degenhardt and Hall 2001). This percentage is substantially higher than in the general population: a survey in The Netherlands in 2001 shows that the percentage of people that ever used cannabis in a comparable age group (16-29 years old) is between 30 and 40 (Abraham et al 2001). In our study population men were more likely to have used cannabis than females. In literature, more studies describe that substance use disorders are seen more frequently in men with schizophrenia than in women with schizophrenia (Buhler et al 2002, Hambrecht and Häfner 1996). In the general population, cannabis use is also more prevalent among men than among women (Abraham et al 2001).

Urinary tests for cannabinoids can be positive for days to weeks after ceasing cannabis, complicating the interpretation of positive results (Musshoff and Madea 2006). However, of the 73 patients that had stopped using cannabis and had their urine analysed, 5 (6.9 %) patients did have positive urinalysis outside a detection window of 1 month. They seemed to have lied about their current use of cannabis. Overall, when we look at the concordance between self-report and the urine test result in our population, it seems that most patients are honest about their current use of cannabis. A few studies have described the concordance between self-report of substance use and results of urinalysis in patients with psychosis. In a Norwegian study Helseth et al (2005) found, like we did, that psychotic inpatients were reliable in reporting their substance use. Out of 35 patients that had reported having used one or more substances for intoxication during the month prior to admittance, only one patient tested positively for a drug not reported in the interview. In contrast, Claassen et al (1997) found in a population of psychotic patients seeking treatment in an urban American emergency room, that self- reported use of substances was uncommon among patients with positive results. A country’s drug policy probably has an influence on the reliability of self-report data of
substance use. In The Netherlands cannabis use is not illegal, so self-report data may be less biased than in some other countries.

This study has several limitations. First, all data were retrieved from medical records. We were dependent on what medical staff had asked the patients and what they had reported in the records. However, in all our medical records a structured way of reporting is used by every psychiatrist and resident. Cannabis use is an important topic of the diagnostic interview at admission. However, reasons for cessation of cannabis were only reported in 52% of cases. A prospective study design with structural interviews may yield a more complete insight in this topic. Asking for reasons for cessation, may give an estimation of the risk that patients will restart their habit of using cannabis in the future. Second, concerning past drug use and time of onset of symptoms there may have been recall bias by patients. However, we used correspondence of prior psychiatric caregivers and information retrieved by the parents as well, to check the self-reported data of patients. Third, because of the retrospective design of this study, we were only able to describe data concerning cessation in the group that did actually stop using cannabis in the past. It would be interesting to follow the course of cannabis use in the patients that did not cease their use of cannabis before the diagnostic interview at admission. Additionally, it would be interesting to know whether patients that had stopped using cannabis prior to admittance in our clinic could sustain this abstinence. Fourth, in the comparison between patients that ceased the use of cannabis and those who continued the use of cannabis, we were not able to look at differences in characteristics of symptoms and symptoms severity. For prevention and treatment strategies, it is important to know whether this is related to cessation of cannabis.

Conclusions

In conclusion, this retrospective study of consecutively admitted patients with recent onset schizophrenic disorders found that a substantial part of cannabis users ceased their cannabis use during or after first contact with psychiatric services. Admittance to a psychiatric hospital was the most frequently reported reason for cessation of cannabis use. Treatment for psychosis seems to be related to the motivation to cease the use of cannabis, at least in part of the patients. On the whole, patients were honest about their current use of cannabis, which is probably related to our country’s liberal drug policy. A prospective study with a structured interview concerning past and current motivation for cessation of cannabis use may contribute to a better and more complete understanding of predictors for cessation in a population of young schizophrenia patients.
References


Musshoff F, Madea B: Review of biologic matrices (urine, blood, hair) as indicators of recent or ongoing cannabis use. Ther Drug Monit 2006; 28: 155-163.


PART II

Cannabis use in relation to clinical variables
CHAPTER 2.1

Age at onset of non-affective psychosis in relation to cannabis use, other drug use and gender


Submitted for publication.
Abstract

Background: Cannabis use is associated with an earlier age at onset of psychotic illness. The aim of the present study was to examine whether this association is confounded by gender or other substance use in a large cohort of patients with non-affective psychotic disorder.

Methods: In 785 patients with a non-affective psychotic disorder, regression analysis was used to investigate the independent effects of gender, cannabis use, and other drug use on age at onset of first psychosis.

Results: Age at onset was 1.8 years earlier in cannabis users compared to non-users, controlled for gender and other possible confounders. Use of other drugs did not have an additional effect on age at onset when cannabis use was taken into account. Up to 64% of cannabis using patients had used cannabis most intensively before the onset of psychosis. In males, mean age at onset was 1.3 years lower than in females, controlled for cannabis use and other confounders.

Conclusion: Cannabis use and gender are independently associated with an earlier onset of psychotic illness. Further, our findings support that cannabis use may precipitate psychosis. More research is needed to clarify the neurobiological factors that make people vulnerable for this precipitating effect of cannabis.
Introduction
Since early age at onset of psychotic illness is associated with poor outcome (Lauronen et al 2007) and with more frequent hospitalizations over the course of illness (Rabinowitz et al 2006), better insight in factors that are associated with an early age of onset of psychotic disorders is important. One of the factors associated with an earlier age at first psychotic episode is cannabis use (Buhler et al 2002, Veen et al 2004, Barnes et al 2006, Mauri et al 2006, Addington and Addington 2007, González-Pinto et al 2008, Barrigon et al 2009, Ongur et al 2009, Sugranyes et al 2009, Foti et al 2010, Pelayo-Terán et al 2010, De Hert et al 2010, Large et al 2011). In a recent meta-analysis, the mean age at onset of psychosis was 2.70 years lower in cannabis users compared to non-users (Large et al 2011). However, some studies did not find differences in age at onset of psychosis between cannabis users and non-users (Bersani et al 2002, Goldberger et al 2010, De Rosse et al 2010).

A second factor associated with age at onset of psychosis is gender: males are 3 to 4 years younger at illness onset compared to females (Hambrecht et al 1992, Castle et al 1998, Szymanski et al 1995, Leung and Chue 2000, Häfner 2003). As cannabis use is more prevalent among male patients with schizophrenia (e.g. Hambrecht and Häfner 1996, Gonzales Pinto et al 2008, Sevy et al 2010), some studies investigated the relation between cannabis use and age at onset of first psychosis after correction for gender. These studies showed that cannabis use remained an independent predictor of an earlier age at first psychotic episode after correction for gender (Veen et al 2004, Barnes et al 2006, Gonzalez Pinto 2008, Barrigon et al 2009, Sugranyes et al 2009, Ongur et al 2009, De Hert 2010). In only one of these studies (Barnes et al 2006) gender remained an independent predictor for age at onset of psychosis after adjusting for cannabis use. This suggests that the frequently reported relation between gender and age at onset is spurious or might be the consequence of a lack of power in the studies that did not find this relationship, since most of these studies included a relatively small number of female patients (range of number of included females was 36-99). Lack of power was not an issue in the one study that did include a relatively large number (n=236) of females (De Hert et al 2010). However, this study used age at onset of admission as a proxy for age at onset of psychosis. Since males have a longer treatment delay than females (e.g. Wunderink et al 2006, Thomas et al 2009), age at onset of admission might not be gender-independent and thus not an accurate proxy for the age at onset of psychotic illness. A third factor that could confound the relation between cannabis use and age at onset of psychosis, is use of other illicit drugs that have been reported to precipitate psychotic symptoms, such as stimulants (Brady et al 1991, Satel et al 1991, Landabaso et al 2002, McKetin et al 2006), and hallucinogens (Vardy and Kay 1983). Although these drugs have not yet been shown to have an additional affect on age at onset of psychosis (Barnes et al 2006, Barrigon et al 2009, Gonzalez Pinto et al 2008), the non significant relation between these other illicit drugs and age of onset might also be the result of insufficient power. This study assesses the independent effects of gender, cannabis use, and the effect of additional drug use on age at onset of first psychosis in a large sample of patients receiving treatment for non-affective psychotic illness, including a relatively large sample of females, and users of drugs other than cannabis.
Methods

Participants
Patients took part in the Genetic Risk and Outcome of Psychosis (GROUP) study, a multi-site longitudinal cohort study in The Netherlands and Belgium that focuses on vulnerability and resilience factors for variation in expression and course of treatment seeking patients with non-affective psychotic disorders (Korver and Quee et al submitted). Inclusion criteria for patients were: (1) age between 16 and 50 years, (2) a diagnosis of non-affective psychotic disorder according to DSM-IV (APA 1994), and (3) good command of the Dutch language. In selected representative geographical areas in the Netherlands, patients were identified through clinicians working in regional or academic psychosis centres whose caseloads were screened for inclusion criteria (prevalence sample). In addition, all consecutive patients presenting at these services - either as out- or inpatients - were recruited for the study (incidence sample). All participants gave written informed consent after complete description of the study. The study was approved by the human subject review boards of all four academic centres.

Measures
Clinical measures
To establish a DSM-IV (APA 1994) diagnosis of psychotic disorder, two different structured diagnostic instruments were used in the four GROUP study sites: three sites used the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al 1992) and one site used the Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1; Wing et al 1990). All raters had completed training in one of these instruments.

Age at onset of psychosis
Age at onset of first psychosis was defined by the age of the patient at the time of onset of the first psychotic episode. A psychotic episode was defined by the occurrence of at least one of the following psychotic symptoms during at least a week; 1) hallucinations, 2) delusions, and/or 3) formal thought disorders.

Substance use
Substance use was assessed with a short version of the Composite International Diagnostic Interview (CIDI; WHO, 1994) sections B (tobacco use), J (alcohol use) and L (drug use). It comprises items on the quantity of tobacco use and alcohol use in the past year, and items on the quantity and severity of illicit drug use over the past year and lifetime. According to the CIDI, patients were considered drug users if they had used a particular drug five or more times. Nicotine use was defined as daily use of cigarettes for at least one month in the past 12 months. Alcohol use in the past year was defined as having consumed more than 12 alcoholic drinks in the past 12 months. Heavy alcohol use in the past year was defined as having consumed more than 21 alcoholic units per week. In contrast to the age at most intense cannabis use, age at onset of cannabis use was not assessed. Definition of age of most intensive cannabis use was defined as the age at which cannabis was used most intensively lifetime. To determine whether most intense cannabis use had occurred prior to psychosis onset, we subtracted age at most intensive cannabis use from age at onset of first psychosis. In addition to the structured interviews, we used urinalysis to detect current cannabis use (presence of tetrahydrocannabinol (THC) metabolite 11-nor-delta-9-THC-carboxylicacid was assessed with
immunoassays with a cut off of 50ng/ml), current amphetamine use (presence of d-
methamphetamine assessed with immunoassays using a cut off of 1000 ng/ml), and current cocaine
use (presence of benzoylecgonine assessed with immunoassays using a cut off of 300 ng/ml).

We defined three subgroups based on drug use history:

a) a subgroup of patients who never used drugs (NO DRUG USE), i.e. patients who 1) reported
no illicit drug use in the past year or lifetime in the CIDI, and 2) had negative urine screens for
THC, cocaine and amphetamines.

b) a subgroup of patients who had used cannabis but no other illicit drugs (ONLY CAN), i.e.
patients who 1) reported cannabis use in the past year and/or lifetime but no other drug use
in the CIDI, and 2) had negative urine screens for amphetamines en cocaine.

c) a subgroup of patients who had used cannabis and other illicit drugs that can precipitate
psychosis (CAN + OTHER DRUGS), i.e. patients who reported cannabis use and other drug use
(cocaine, ecstasy, hallucinogens and/or stimulants) in the past year and/or lifetime in the
CIDI.

Statistical Analysis
Chi-square tests were used to determine group differences for categorical variables. One-way
between-groups analyses of variance (ANOVAs) and T tests were conducted to explore group
differences for continuous variables. A linear regression model was fitted with age at onset of first
psychosis as dependent variable, and patient subgroup (NO DRUG USE, ONLY CAN, CAN + OTHER
DRUGS), gender, and patient subgroup by gender interaction as independent variables. Nicotine use
and alcohol use in the past year were entered as covariates. We used Kaplan Meier analyses to
assess the effect of drug use history (NO DRUG USE, ONLY CAN, CAN + OTHER DRUGS) on age at
onset of first psychosis. The log-rank test was used to compare the survival distributions between the
different subgroups. Since the survival curves of the different subgroups crossed, we decided not to
perform Cox-regression analysis (because the proportional hazards assumption implies non crossing
survival curves). Separate Kaplan Meier analyses were performed for males and females.

Results
Sample characteristics
In 785 patients (599 males (76.3%) and 186 females (23.7%)), inclusion criteria for one of the
subgroups according to drug use history (NO DRUG USE, ONLY CAN, and CAN + OTHER DRUGS) were
met. The numbers of patients per subgroup were: NO DRUG USE 281 (35.8%), ONLY CAN 223
(28.4%), CAN + OTHER DRUGS 281 (35.8%). In the CAN + OTHER DRUG group (n= 281), lifetime
prevalence was 51.6% for stimulant use, 52.7% for cocaine use, 48.8% for hallucinogens use, and
66.9% for ecstasy use.

DSM-IV diagnoses of the patients were: schizophrenia (n=528, 67.3%), schizoaffective disorder (n=93,
11.8%), schizophreniform disorder (n=44, 5.6%), psychotic disorder NOS (n=79, 10.1%), and other
psychotic disorders (n=41, 5.2%). Sample characteristics stratified by drug use history and gender are
shown in table 1a and 1b. For 457 patients (398 males and 59 females), the age at most intensive
cannabis use was available, (mean 19.5, SD 4.4; table 1). Age at most intensive cannabis use did not
statistically differ (p = 0.148) between males (mean 19.4, SD 4.4) and females (mean 20.5, SD 5.6). In
63.5% of the patients, age at most intensive cannabis use preceded the age at onset of first
psychosis. There were no statistically significant differences between males and females in this percentage (64.3\% resp. 57.6\%, $\chi^2$ 1.0, $p = 0.319$).

Table 1. Sample characteristics of total study sample (n = 785), stratified by drug use history (a), and stratified by gender (b)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>No drug use</th>
<th>Only cannabis</th>
<th>Cannabis and other drugs</th>
<th>$\chi^2$ or $F$</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>599 (76.3)</td>
<td>159 (66.6)</td>
<td>180 (80.7)</td>
<td>260 (92.5)</td>
<td>103.7</td>
<td>2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>27.2 (7.2)</td>
<td>26.8 (8.5)</td>
<td>26.8 (6.9)</td>
<td>26.1 (5.7)</td>
<td>10.9</td>
<td>2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Illness duration, years</td>
<td>4.1 (3.7)</td>
<td>4.2 (3.8)</td>
<td>4.3 (4.2)</td>
<td>3.9 (3.3)</td>
<td>1.1</td>
<td>2</td>
<td>0.343</td>
</tr>
<tr>
<td>Ethnicity, Caucasian (%)</td>
<td>616 (78.5)</td>
<td>233 (82.9)</td>
<td>161 (72.2)</td>
<td>222 (79.0)</td>
<td>8.5</td>
<td>2</td>
<td>0.014</td>
</tr>
<tr>
<td>Nicotine use past year, yes (%)</td>
<td>508 (65.0)</td>
<td>85 (30.6)</td>
<td>178 (79.8)</td>
<td>245 (87.5)</td>
<td>228.8</td>
<td>2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcohol use past year, yes (%)</td>
<td>579 (74.2)</td>
<td>155 (59.7)</td>
<td>172 (77.8)</td>
<td>241 (85.8)</td>
<td>51.7</td>
<td>2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcoholic heavy use past yr, yes (%)</td>
<td>55 (7.0)</td>
<td>5 (1.8)</td>
<td>20 (9.0)</td>
<td>30 (10.7)</td>
<td>18.9</td>
<td>2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age most intensive cannabis use, mean (SD)</td>
<td>19.5 (4.4)</td>
<td>19.7 (4.8)</td>
<td>19.4 (4.0)</td>
<td>2.9</td>
<td>455</td>
<td>0.456</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>$\chi^2$ or $t$</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>599 (76.3)</td>
<td>599 (77.5)</td>
<td>164 (81.7)</td>
<td>1.5</td>
<td>1</td>
<td>0.217</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>26.7 (6.6)</td>
<td>29.0 (8.9)</td>
<td>24.2 (6.5)</td>
<td>3.3</td>
<td>3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Illness duration, years</td>
<td>4.1 (3.7)</td>
<td>4.4 (4.0)</td>
<td>3.7</td>
<td>0.7</td>
<td>783</td>
<td>0.460</td>
</tr>
<tr>
<td>Ethnicity, Caucasian (%)</td>
<td>616 (78.5)</td>
<td>646 (77.5)</td>
<td>152 (81.7)</td>
<td>1.5</td>
<td>1</td>
<td>0.217</td>
</tr>
<tr>
<td>Nicotine use past year, yes (%)</td>
<td>508 (65.0)</td>
<td>421 (70.6)</td>
<td>82 (47)</td>
<td>34.6</td>
<td>1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcohol use past year, yes (%)</td>
<td>579 (74.2)</td>
<td>462 (77.5)</td>
<td>117 (63.6)</td>
<td>14.3</td>
<td>1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcoholic heavy use past yr, yes (%)</td>
<td>55 (7.0)</td>
<td>50 (8.3)</td>
<td>5 (2.7)</td>
<td>7.0</td>
<td>1</td>
<td>0.008</td>
</tr>
<tr>
<td>Age most intensive cannabis use, mean (SD)</td>
<td>19.5 (4.4)</td>
<td>19.4 (4.1)</td>
<td>20.5 (5.6)</td>
<td>1.5</td>
<td>67.6</td>
<td>0.148</td>
</tr>
</tbody>
</table>

Figures in bold have adjusted standardised residuals > 3.0; figures underlined have adjusted standardised residuals < -3.0. Percents in the columns and means are sometimes based on less than n presented in the top row, because of missing data in the CIDI data.

Post-hoc Bonferroni test: no drug use > only can, no drug use > can + other drugs
equal variances not assumed
Comparison of age at onset of first psychosis between subgroups according to drug use history.

Figure 1 shows mean age at onset of first psychosis with 95% confidence intervals, stratified for subgroups according to drug use history and gender. Since no statistically significant gender by drug use history interaction was found in the prediction of age at onset of first psychosis, only main effects without the gender by drug use history interaction are presented (table 2).

Males: mean age (95% CI) NO DRUG USE 23.2 (22.0-24.3), ONLY CAN 21.8 (21.0-22.5), CAN + OTHER DRUGS 21.7 (21.0-22.3)

Females: mean age (95%CI) NO DRUG USE 25.3 (23.7-26.8), ONLY CAN 22.6 (20.5-24.8), CAN + OTHER DRUGS 21.1 (19.4-22.9)

Figure 1. Mean ages at onset of psychosis with 95% confidence intervals, stratified for subgroups according to drug use history and gender.
Table 2. Summary of general linear regression analysis, with total patient sample (n= 785) a,b

<table>
<thead>
<tr>
<th></th>
<th>Age at onset of psychosis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>t</td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>25.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug use history, only cannabis compared to no drug use</td>
<td>-1.7</td>
<td>0.6</td>
<td>-2.6 **</td>
<td></td>
</tr>
<tr>
<td>Drug use history, cannabis and other drugs compared to no drug use</td>
<td>-1.8</td>
<td>0.7</td>
<td>-2.7 **</td>
<td></td>
</tr>
<tr>
<td>Gender, male/ female</td>
<td>-1.3</td>
<td>0.6</td>
<td>-2.3 *</td>
<td></td>
</tr>
<tr>
<td>Covariates</td>
<td>-0.2</td>
<td>0.6</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>Alcohol use, yes/no</td>
<td>-0.4</td>
<td>0.5</td>
<td>-0.8</td>
<td></td>
</tr>
</tbody>
</table>

* General linear regression analysis, with age at onset of psychosis as dependent variable and drug use history and gender as independent variable. The covariance structure is unstructured. The B coefficient indicates the individual contribution of each predictor to the model. This value indicates that as the predictor increases by one unit, age at onset of psychosis increases by the B value. A positive B value means that compared to the reference category, the component score increases. A negative sign means that compared to the reference category, the component score decreases. The t indicates whether the predictor is making a significant contribution to the model. The larger the value of t, the greater the contribution to the model.

**Bold is reference category

* p < .05, ** p < .01

After controlling for gender, nicotine use and alcohol use in the past year, mean age at onset of psychosis was significantly different between patients from the NO DRUG USE, ONLY CAN and CAN + OTHER DRUGS subgroups (F (2, 772)= 4.3, p = 0.014). Mean age at onset of first psychosis in patients from the ONLY CAN group was significantly lower than mean age at onset of psychosis in patients from the NO DRUG USE group (adjusted difference of 1.7 years; B = -1.7, SE B 0.6, t = -2.6, p = 0.009). Further, mean age at onset of first psychosis in patients from the CAN + OTHER DRUGS group was also significantly lower than the mean age at onset of psychosis in patients from the NO DRUG USE group (adjusted difference 1.8 years; B = -1.8, SE 0.6, t = -2.7, p = 0.008). There was no significant difference in age at onset between the ONLY CAN and CAN + OTHER DRUGS group.

**Comparison of age at onset of first psychosis between males and females**

Gender was significantly related to age at onset of psychosis, above and beyond illicit drug use, nicotine use and alcohol use. Mean age at onset of psychosis was significantly lower in males than in females (adjusted difference 1.3 years; F (1,772) = 5.6, p = 0.018).

Figure 2a and 2b show Kaplan-Meier survival curves for onset of first psychosis stratified by drug use history for male and female patients, respectively. Log-rank tests showed that both in males and in females, age at onset of psychosis was significantly different between the NO DRUG USE, ONLY CAN and CAN+ OTHER DRUGS subgroups (males: log rank $\chi^2$=11.40, df 2, p=0.003, females: $\chi^2$=11.05, df 2, p = 0.004). As shown in figure 2 and 3, differences in age at onset of first psychosis between the NO DRUG USE group and the ONLY CAN and CAN+OTHER DRUGS are most pronounced in the later onset group, i.e. onset of first psychosis after the age of 23 for males and after the age of 20 for females.
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Figure 2. Kaplan Meier survival curves for age at first psychosis stratified by drug use history for a) males (n= 599) and b) females (n=186)

Figure 2. Kaplan Meier survival curves for age at first psychosis stratified by drug use history for a) males (n= 599) and b) females (n=186)
Discussion

This large cohort study of patients treated for non-affective psychotic illness confirms previous findings that a history of cannabis use is associated with a lower age at onset of first psychosis, independent of the effects of gender or use of other drugs. Further, males had an earlier age at onset of psychotic illness compared to females irrespective of the use of cannabis, and the majority of both males and females that had used cannabis, had done so most intensively prior to onset of psychotic illness.

Our finding that cannabis use was associated with earlier age at onset of psychotic illness, independent of the effect of gender, is in line with the results of a recent meta-analysis on this topic (Large et al 2011). We speculate that earlier onset of first psychosis in cannabis using patients could be explained by (early) cannabis use precipitating the onset of psychotic illness in vulnerable subjects. Support for this hypothesis comes from studies in which age at onset of cannabis use is positively associated with age at onset of high risk symptoms for psychosis (Dragt et al 2010) and with age at onset of psychotic illness (Barnett et al 2007, Estrada et al 2010). Interestingly, the difference in age of onset between the cannabis users and non-cannabis users seem to manifest itself most pronouncedly in the group with a relatively late age of onset, i.e. onset after the age of 23 for males and 20 for females (figure 2a and 2b). The survival curve from the study of Gonzales-Pinto et al. (2008), with comparable subgroups of patients, shows a similar pattern. 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 age range where differences occurred in our study (De Rosse et al 2010, Bersani et al 2002, Goldberger et al 2010). It may also explain why the absolute differences in age at onset between cannabis users and non-users substantially differ across studies. Studies with a later age at onset than in our study will probably find a larger difference in age at onset between users of cannabis and non-users. This corresponds with the finding of a meta-analysis on cannabis use and age at onset of psychosis (Large et al 2011) that the use of an upper age limit (< 45 years of age) as inclusion criterion inflated effect sizes. However, in the meta-analysis, the finding of an association between the proportion of cannabis users and earlier age at onset was statistically independent of age inclusion criteria.

Our finding that cannabis-related differences in age at onset of psychosis seem to manifest itself only in the group with a relatively late age of onset, could be explained by recent findings from a genetic study (Pelayo- Terán et al 2010). In this study, age of onset of first psychosis in non-users of cannabis was significantly later in the COMT Met/Met genotype carriers than in the COMT Val/Val and COMT Val/ Met genotype carriers, while this association was absent in users of cannabis. The authors suggest that use of cannabis could exert a modulator effect on the genotype, suppressing the delay effect for the age of onset in the case of the Met allele patients. Although this could be an explanation for our findings, further studies are needed to confirm our preliminary findings and to clarify possible other neurobiological mechanisms that make people vulnerable for the precipitating effects of cannabis on psychotic illness.

We did not find a significant difference in age at onset between patients who had used only cannabis and patients who had used both cannabis and other illicit drugs. Our findings suggest that the additional use of other drugs has no independent effect on age at onset of psychosis when adjusted for cannabis use.
We found that male patients had a lower age of onset of first psychotic episode compared to female patients, irrespective of the use of cannabis or other illicit drugs. This is similar to findings of Barnes et al (2006), but in contrast to findings of other studies (Veen et al 2004, Gonzales Pinto et al 2008, Ongur et al 2009, Sugranyes et al 2009, Barrigon et al 2009, De Hert et al 2010), which may be explained by the low power due to small groups of female patients in most of these studies. Later age at onset of psychosis in females has been related to the modulating effect of estrogen, which is thought to play a protective role in the disease process of schizophrenia, resulting from a hypothesized anti-dopaminergic effect that could delay the development of the disease (Szymanski et al 1995). Another explanation might be that psychosis in females is later recognized by the environment resulting in treatment delays (Aleman et al 2003). Although we found significant gender differences in age at onset of psychosis irrespective of the use of cannabis, we did not find gender differences for the mean age at most intensive use of cannabis (males 19.4 and females 20.5 years of age). Although other studies on gender and age at most intensive cannabis use are lacking, there are a few studies comparing age at onset of first cannabis use between males and females. Those studies did not find a difference between age at first use of cannabis between male and female patients (mean 15.5 and resp. 15.4 years; Dekker et al 2008), or found a trend towards earlier first use of cannabis in males (mean 15.6 years) than females (mean 17.9 years) (Barnett et al 2007).

In the current study, 64% of cannabis users had used cannabis most intensively prior to the onset of first psychosis, with no statistical difference in proportion of males and females. As many patients from both sexes use cannabis prior to first psychosis and cannabis effects age at onset of first psychosis in both males and females, treatment interventions for cannabis use in prodromal and ultrahigh risk populations should focus on both males and females. Finally, as the largest proportion of patients used cannabis most intensively before the onset of psychosis, the self-medication hypothesis is not supported in this study, at least not in the majority of patients. A limitation of the current study is that the age of first cannabis use was not assessed. A comparison between patients that started cannabis use prior to the onset of psychosis versus non using patients might have provided more robust conclusions about the possible contribution of cannabis use to the onset of psychotic illness. However, many of the cannabis using patients (64%) in the current study had used cannabis most intensively prior to onset of psychosis, which corresponds with previous first-episode studies reporting that 62-98% of cannabis using patients had started using cannabis before the onset of the first psychosis (Linszen et al 1994, Buhler et al 2002, Mauri et al 2006, Barnett et al 2007, Seyv et al 2010, Goldberger et al 2010). Further, studies in comparable patient populations have reported a mean age at first cannabis use of 15.6 and 15.4 years (Dekker et al 2009, Dekker et al 2010), which is at least 5 years earlier than the mean age at onset of psychosis in the current sample.

Strengths of our study are: (1) the large study sample, (2) the fact that we included patients presenting consecutively either as out-patients or in-patients, reflecting a sample of treated patients which enhances the generalizability of our findings, (3) a larger number of females than in most of the previous studies, which enables us to perform a sufficiently powered regression analysis in which the independent effect of gender on age at onset of psychosis was tested, and (4) the fact that we checked urine for the presence of drugs in addition to self reported drug use.

In summary, this study shows that both cannabis use and gender are independently associated with an earlier age at onset of psychotic illness, above and beyond the effect of possible confounders, and that the difference in age at onset between cannabis users and never users seems to manifest itself in the subgroup with a relatively late age of onset, i.e. from the age of 23 in males and 20 in females.
Our findings do not support the self-medication theory, but point toward cannabis as a precipitating factor in the development of psychosis. Future studies are needed to clarify the neurobiological factors that make people vulnerable for the precipitating effects of cannabis use on age at onset of psychotic illness.

Acknowledgement

We are grateful for the generosity of time and effort by the patients and their families, healthy subjects, and all researchers who make this GROUP project possible. The infrastructure for the GROUP study is funded through the Geestkracht programme of the Dutch Health Research Council (ZON-MW, grant number 10-000-1002) and matching funds from participating universities and mental health care organizations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Centre and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven, GGZ Midden-Brabant, GGZ Oost-Brabant, GGZ Noord-Midden Limburg, Mondriaan Zorggroep, Prins Clauscentrum Sittard, RIAGG Roermond, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekeren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Diment, Mediant, GGZ De Grote Rivieren and Parnassia psycho-medical centre (The Hague). Utrecht: University Medical Centre Utrecht and the mental health institutions Altrecht, Symfona, Meerkanten, Riagg Amersfoort, en Delta.)

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CHAPTER 2.2

Substance use in a large sample of patients with schizophrenia or related disorders and co-morbid obsessive-compulsive symptoms


Submitted for publication.
Abstract
This study examined relationships between obsessive compulsive symptoms (OCS) and substance use in patients with a non-affective psychotic disorder. We found no significant differences in substance use between patients without OCS (n=777), patients with mild OCS (n=143), and patients with more severe OCS (n=85). 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.
Introduction

Obsessive compulsive symptoms (OCS) and obsessive compulsive disorder (OCD) are common in patients with schizophrenia and related disorders, with prevalence rates ranging from 7.8 to 55% for OCS (Berman et al. 1998), and a mean prevalence rate of 12.1% for OCD (Achim et al. 2009). This is considerably higher than the prevalence of OCS and OCD in the general population in the Netherlands, which is estimated at 5.8% and 0.9% respectively (De Bruijn et al. 2010). The higher prevalence of OCS/OCD in schizophrenia suggests a relation between the two disorders.

Prevalence rates of substance use disorders (including nicotine use) are higher in patients with schizophrenia compared to the general population (Mueser et al. 1990, Dixon et al. 1991, Buckley 1998, De Leon et al. 2002, McCreadie et al. 2003, Roick et al. 2007). A co-morbid prevalence rate of 47.0% for abuse or dependence of substances has been found in schizophrenia patients in the Epidemiologic Catchment Area Study (Regier et al. 1990). In contrast, studies showed that the prevalence of substance use disorders is lower in OCD patients compared to the general population. For example, Denys et al. (2004) found a current prevalence of 4.3% of substance use disorders in 420 Dutch OCD patients, compared to 5.8% in the Dutch general population (Bijl et al. 1998). Further, Bejerot and Humble (1999) found that smoking rates were lower in OCD patients, compared to smoking rates in the general population (14.5% vs. 25.4%). In contrast, one study found that lifetime prevalence of substance use disorders was higher in people with OCD (40.1%), compared to people without OCS (17.8%: De Bruijn et al. 2010). Overall, prevalence of substance use disorders in OCD seems to be lower than in schizophrenia. In sum, OCS occur relatively frequent in schizophrenia, schizophrenia patients show elevated rates of substance use as compared to the general population, but most studies in OCD patients show lower rates of nicotine and substance use compared to the general population. It would be interesting to know whether schizophrenia patients with OCS might have lower substance use rates than schizophrenia patients without OCS. So far, studies that compared smoking rates between schizophrenia patients with and without co-morbid OCS found no significant differences (Dome et al. 2006, Fawzi et al. 2007). Additionally, Poyurovsky and colleagues (Poyurovsky et al. 1999, Poyurovsky et al. 2008) found that substance abuse rates did not differ between schizophrenia patients with and without OCD. In comparison with OCD patients without co-morbid psychotic illness, prevalence of illicit substance use in patients with OCD and co-morbid psychotic illness was found to be higher (3.8% vs 15.4%; De Haan et al. 2009).

The aim of this study was to explore the relationship between OCS and substance use in patients with schizophrenia or related disorders, in a large cohort study of schizophrenia patients. We hypothesized that patients suffering from schizophrenia and co-morbid OCS had lower substance use rates than schizophrenia patients without OCS. Bejerot and Humble (1999) suggested that symptoms linked to OCD (e.g. fear of bodily harm and diseases) may keep subjects from using substances, and substance use may deteriorate OC symptoms by further overactivating the frontal cortex, thus withholding patients of substance use. Therefore, having OCS might be a protective factor for substance use in schizophrenia.
Methods

Participants
Patients took part in the Genetic Risk and Outcome of Psychosis (GROUP) study, a multi-site longitudinal cohort study in The Netherlands that focuses on vulnerability and resilience factors for variation in expression and course of non-affective psychotic disorders (for details, see Korver and Quee et al submitted for publication). All participants gave written informed consent after complete description of the study. The study was approved by the human subject review boards of all four Academic Centres.

Measures
Clinical measures
The Y-BOCS (Goodman et al 1989a, Goodman et al 1989b) was used to measure the severity of OCS over the previous week. For more details on the Y-BOCS and its reliability as used in schizophrenia patients, see Boyette et al (2010). Patients were categorized into three groups according to their level of OCS; one group without obsessions or compulsions, one group with OCS but Y-BOCS total scores between 1 and 15, and one group with total Y-BOCS scores that equaled or exceeded 16. The threshold of 16 was also used by two other studies on the relation between smoking and OCS in schizophrenia (Dome et al 2006, Fawzi et al 2007). Furthermore, this threshold is typically used for inclusion in drug trials, and typical scores for patients with OCD are in the 16 to 30 range (Blacker 2009).

Substance use measures
Use of nicotine, alcohol, cannabis and hard drugs (stimulants, opiates, hallucinogens, cocaine, and ecstasy) was assessed with the Composite International Diagnostic Interview (CIDI) (WHO 1994) section B, J and L. Nicotine use was defined as daily use of cigarettes for at least one month in the past 12 months. Alcohol use in the past year was defined as having consumed more than 12 alcoholic drinks in the past 12 months. Heavy alcohol use in the past year was defined as having consumed more than 21 alcoholic units per week. Diagnosis of cannabis- or hard drug abuse or dependency at present state (= in the past year) and lifetime was made according to DSM-IV (APA 1994). In order to have objective knowledge about recent use of cannabis, urinalysis for the presence of the tetrahydrocannabinol (THC), amphetamines and cocaine was carried out using immunoassays with a cut off of resp. 50 ng/ml, 1000 ng/ml and 300 ng/ml. The total score of Obsessive Compulsive Drug Use Scale (OCDUS) was used as a measure for cannabis craving in the past week (Dekker et al, in press).

Statistical Analysis
The chi-square test for independence was used to determine whether two categorical variables were related to each other. A one-way between-groups analysis of variance (ANOVA) was conducted to explore differences between the three groups in one dependent variable. The Kruskal-Wallis test was conducted to explore differences between the three groups in one dependent variable, in case data were not normally distributed.
Chapter 2.2  - Substance use in relation to obsessive-compulsive symptoms

Results

Of 1005 patients in whom the Y-BOCS was assessed, 777 patients did not have OCS, 143 patients had OCS with a total Y-BOCS score between 1 and 15 (mean 11.0, SD 2.5), and 85 patients had a total Y-BOCS score that equaled or exceeded 16 (mean 19.4, SD 3.6). DSM-IV diagnoses were: schizophrenia (66.2%), schizoaffective disorder (11.1%), schizophreniform disorder (5.5%), psychotic disorder NOS (10.2%), and other psychotic disorders (7.0%).

There were no significant differences between the three patients groups on substance use variables (table 1), except for a statistically different score for cannabis craving in the past week (Kruskal-Wallis test: $\chi^2 = 6.2, p = 0.045$), however post hoc comparisons with Mann-Whitney Tests did not survive Bonferroni correction. Further, there was a trend for the mild OCS group to be more likely to have a lifetime diagnosis of a cannabis use disorder use ($p = 0.08$) and to use alcohol heavily ($p = 0.07$), compared to the other groups (no OCS, or Y-BOCS $\geq 16$).

Table 1. Substance use variables in patients with a total Y-BOCS score 1-15, $\geq 16$, and patients without OCS

<table>
<thead>
<tr>
<th></th>
<th>Without OCS (n=777)</th>
<th>Y-BOCS 1-15 (n=143)</th>
<th>Y-BOCS $\geq 16$ (n=85)</th>
<th>$\chi^2$ or $F$</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (S.D.)</td>
<td>28.0 (8.3)</td>
<td>27.4 (7.3)</td>
<td>25.8 (7.8)</td>
<td>2.9</td>
<td>2</td>
<td>0.053</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>597 (76.8)</td>
<td>109 (76.2)</td>
<td>64 (75.3)</td>
<td>0.01</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Nicotine use in past year, yes (%)</td>
<td>500 (65.6)</td>
<td>97 (68.8)</td>
<td>58 (69.0)</td>
<td>0.8</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Cigarettes per day, mean (SD)</td>
<td>17.4 (8.6)</td>
<td>17.8 (8.7)</td>
<td>18.3 (10.0)</td>
<td>0.2</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Alcohol use in past year, yes (%)</td>
<td>568 (74.8)</td>
<td>105 (73.9)</td>
<td>53 (63.1)</td>
<td>5.4</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>Heavy alcohol use past year, yes (%)</td>
<td>56 (7.2)</td>
<td>18 (12.6)</td>
<td>5 (5.9)</td>
<td>5.3</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>Alcoholic drinks per week, mean (S.D.)</td>
<td>8.8 (11.5)</td>
<td>11.1 (13.8)</td>
<td>9.9 (16.5)</td>
<td>3.4</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>DSM-IV cannabis use disorder present state, yes (%)</td>
<td>152 (19.9)</td>
<td>31 (21.7)</td>
<td>16 (19.0)</td>
<td>0.3</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>DSM-IV cannabis use disorder lifetime, yes (%)</td>
<td>292 (38.3)</td>
<td>69 (48.3)</td>
<td>32 (38.1)</td>
<td>5.1</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>DSM-IV hard drug use disorder present state, yes (%)</td>
<td>44 (5.8)</td>
<td>13 (9.1)</td>
<td>4 (4.8)</td>
<td>2.6</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>DSM-IV hard drug use disorder lifetime, yes (%)</td>
<td>136 (17.8)</td>
<td>32 (22.4)</td>
<td>16 (19.0)</td>
<td>1.7</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Urine test for THC, positive (%)</td>
<td>116 (16.9)</td>
<td>26 (19.8)</td>
<td>8 (11.8)</td>
<td>2.1</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Urine test for cocaine, positive (%)</td>
<td>9 (1.3)</td>
<td>4 (3.0)</td>
<td>0 (0)</td>
<td>3.4</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Urine test for amphetamines, positive (%)</td>
<td>6 (0.9)</td>
<td>2 (1.6)</td>
<td>0 (0)</td>
<td>1.2</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Craving for cannabis (OCDUS-CAN score), mean (SD)</td>
<td>1.56 (0.66)</td>
<td>1.73 (0.77)</td>
<td>1.68 (0.74)</td>
<td>6.2</td>
<td>2</td>
<td>0.045*</td>
</tr>
</tbody>
</table>

*p < 0.05

Percents in the columns and means are sometimes based on less than n presented in the top row, because of missing data; CIDI data of 19 patients (1.9%) were missing, urine data of 118 patients (11.7%) were missing. Craving for cannabis data were available for 439 patients from the group without OCS, 98 patients from the Y-BOCS 1-15 group, and 48 patients from the Y-BOCS $\geq 16$ group.
Discussion
We found no differences in substance use between patients with mild OCS (Y-BOCS score 1-15), patients with more severe OCS (Y-BOCS score ≥ 16) and patients without OCS. Patients with more severe OCS were less likely to use alcohol in the last 12 months. However, this difference was small and non-significant. Taken together, our results suggest co-morbid OCS is not a protective factor against the use of nicotine and other substances in patients suffering from non-affective psychotic illness.

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. Because of the small differences, it is questionable whether this non-significant finding is clinically relevant. However, speculative explanations for our findings might be 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.

In concordance with our results, previous studies did not find differences in prevalence rates of nicotine and substance use in schizophrenia patients with or without OCS (Poyurovsky et al 1999, Dome et al 2006, Fawzi et al 2007, Puyorovsky et al 2008). Our large study sample and more detailed comparison of substance use rates strongly adds to the evidence that schizophrenia patients with OCS do not differ in prevalence of substance use compared to patients without OCS.

Funding/acknowledgement
We are grateful for the generosity of time and effort by the patients and their families, healthy subjects, and all researchers who make this GROUP project possible. The infrastructure for the GROUP study is funded through the Geestkracht programme of the Dutch Health Research Council (ZON-MW, grant number 10-000-1002) and matching funds from participating universities and mental health care organizations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Centre and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven, GGZ Midden-Brabant, GGZ Oost-Brabant, GGZ Noord-Midden Limburg, Mondriaan Zorggroep, Prins Clauscentrum Sittard, RIAGG Roermond, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekenen Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGZ De Grote Rivieren and Parnassia psycho-medical centre (The Hague). Utrecht: University Medical Centre Utrecht and the mental health institutions Altrecht, Symfora, Meerkanten, Riagg Amersfoort, en Delta).

References
Chapter 2.2 - Substance use in relation to obsessive-compulsive symptoms


Korver N, Quee PJ (Korver and Quee are combined first authors), Boos H, Simons C, G.R.O.U.P. authors: Genetic Risk and Outcome of Psychosis (GROUP), a multi site longitudinal cohort study focused on gene-environment interaction: Objectives, Sample Characteristics, Recruitment, Assessment Methods and validity of diagnostic categories. Submitted for publication.


CHAPTER 2.3

Cannabis and cognitive performance in psychosis: a cross-sectional study in patients with non-affective psychotic illness and their unaffected siblings


Submitted for publication.
Abstract

Background. The relationship between cannabis use and cognitive functioning in patients with psychosis has yielded contradictory findings. In individuals at genetic high risk for psychosis, information is sparse. The aim of this study was to assess the association between recency and frequency of cannabis use and cognitive functioning in patients with psychosis and their unaffected siblings.

Method. Cross-sectional study in 956 patients with non-affective psychosis, 953 unaffected siblings, and 554 control subjects. Participants completed a cognitive test battery including assessments of verbal learning, set shifting, sustained attention, processing speed, working memory, acquired knowledge, reasoning and problem solving and social cognition. Cannabis use was assessed by urinalysis and by the Composite International Diagnostic Interview. Using mixed-model analyses, the main effects of Cannabis (recency and frequency) and the interaction with Status (patient, sibling, control) on cognitive functioning were assessed.

Results. Current cannabis use was associated with poorer performance on immediate verbal learning, processing speed and working memory (Cohen’s d -0.20 to -0.33; p<0.005). Lifetime cannabis use was associated with better performance on acquired knowledge, facial affect recognition and face identity recognition (Cohen’s d +0.17 to +0.33; p<0.005). There was no significant interaction between Cannabis and Status on cognitive functioning.

Conclusion. Lifetime cannabis using individuals might constitute a subgroup with a higher cognitive potential. The residual effects of cannabis may impair short term memory and processing speed.
Chapter 2.3  - Cannabis use and cognitive performance in psychosis

Introduction
Cognitive impairment is recognized as a core feature of schizophrenia (Green 1996, Palmer et al 2009). Mild cognitive alterations are also observed in unaffected relatives of patients who are at increased risk to develop a psychotic disorder (Snitz et al 2006). In both patients with psychosis and their unaffected siblings, cannabis use is more prevalent than in the general population (Barnes et al 2006, Smith et al 2008). In patients with psychosis, cannabis use has been associated with worse disease outcome (Linszen et al 1994). In unaffected siblings the psychotomimetic effect of cannabis is increased compared to control subjects, suggesting that familial liability to psychosis is associated with sensitivity to cannabis (van Winkel 2011, Genetic Risk and Outcome of Psychosis (GROUP) Investigators 2011). Whether cannabis use is also associated with cognitive alterations in patients with psychosis and their unaffected relatives is however still a matter of debate.

Acute administration of the major psychoactive component in cannabis (Δ9-tetrahydrocannabinol; THC) has been shown to cause impaired attention and memory in schizophrenia patients and their unaffected siblings (D’Souza et al 2005, Henquet et al 2006). These impairments in patients and siblings were larger compared to those in healthy controls, suggesting an increased sensitivity to the adverse cognitive effects of acute cannabinoid administration. On the contrary, better cognitive functioning has also been reported in cannabis using patients in contrast to non-using patients with a psychotic disorder on tasks of planning and reasoning, visual memory, processing speed, global cognition and working memory (Coulston et al 2007a, Potvin et al 2008, Loberg and Hugdahl 2009, Yucel et al 2010). This superior cognitive functioning in cannabis using patients seems counterintuitive given the deleterious acute and long-term effects that have been reported in cannabis using subjects without psychotic illness (Solowij and Michie 2007, Morrison et al 2009). Two hypotheses attempt to explain these results. First, it has been suggested that cannabis improves cognition, either by counteracting a putative neurotoxic process related to schizophrenia, or by stimulating prefrontal neurotransmission (Verrico et al 2003, Jockers-Scherubl et al 2007, Coulston et al 2007a, Coulston et al 2007b, Potvin et al 2008, Cohen et al 2008). Secondly, it has been suggested that causality is the other way around. In this view, patients with psychotic disorder and lifetime cannabis use may form a subgroup with a relatively lower genetic vulnerability for psychosis and better premorbid functioning compared to patients who have never used cannabis (Schnell et al 2009, de la Serna et al 2010, Yucel et al 2010).

Elucidating the association between cannabis use and cognitive functioning in patients and individuals at genetic high risk for psychosis is of both theoretical and clinical relevance (Loberg and Hugdahl 2009). Whilst spared cognitive functioning through cannabis use would be relevant for the development of cognitive enhancing medication, a further cognitive decline associated with cannabis use should stimulate development of interventions aiming at a reduction of cannabis use.

It is essential to account for the recency of cannabis use in studies on the association between cannabis and cognition, since contradictory findings between acute administration and lifetime cannabis use have been found (D’Souza et al 2005, Henquet et al 2006, Coulston et al 2007a, Potvin et al 2008, Loberg and Hugdahl 2009, Yucel et al 2010). In addition, the frequency of cannabis use should be taken into account in order to investigate dose-response relationships (Coulston et al 2007a). Thus, the aim of the present study was to investigate if cognitive performance differs between cannabis users and non-users depending, on the recency and frequency of use. The second aim was to investigate whether these associations are different in patients with non-affective psychosis, their unaffected siblings, and control subjects.
Methods

Study design and population
Data were derived from the first assessment in the Genetic Risk and Outcome of Psychosis (GROUP) study. The GROUP study is a population based cohort study with a six year follow-up of patients with non-affective psychotic disorders, their unaffected siblings and parents, and control subjects. Data were gathered by four academic schizophrenia research centres and their affiliated mental health care institutions in the Netherlands and Belgium. The main objective of the GROUP study is to investigate the dynamic interaction between genetic and environmental factors that contribute to the expression and course of psychosis over time. The procedure of recruitment, criteria of inclusion and exclusion, informed consent, assessments, and population characteristics have been described previously (Köver et al submitted). For the current study we included subjects from the GROUP study that had performed cognitive testing and from whom both self-report on cannabis use and a drug urine screening were available, leading to a study sample of 2463 subjects (956 patients, 953 non-affected siblings, 554 controls).

Substance use and clinical symptoms
Substance use was assessed with a short version of the Composite International Diagnostic Interview (CIDI; World Health Organization, 1990) sections B (tobacco use), J (alcohol use), and L (substance use), and with urinalysis. Urine was screened for the presence of THC with a cut off of 50ng/ml, in order to infer a detection window of one month. Cannabis Recency was categorized as current (urinalysis positive for THC), lifetime (urinalysis negative AND cannabis use ≥ 5 times lifetime based on the CIDI), and never (urinalysis negative and cannabis use < 5 times lifetime based on the CIDI). Although this latter group may have included subjects who had limited experience with cannabis, for simplicity this group is referred to as ‘never-users’. Cannabis Frequency was categorized as daily, weekly, or less than weekly, based on the CIDI. Severity of positive and negative symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS) with total scores for positive, negative and general symptoms (Kay et al 1987).

Cognitive assessment
Subjects were administered 10 cognitive tasks that yielded 13 outcome parameters which were used as dependent variables in the analyses. The cognitive assessment took 90 to 120 minutes and included the Word Learning Task (WLT; assessing verbal learning with outcome parameters of Immediate Recall and Retention Rate after 20 minutes), the Response Shifting Task (RST; assessing set shifting ability with outcome parameters of Reaction Time and Accuracy), the Continuous Performance Task-HQ (CPT-HQ; assessing sustained visual attention with outcome parameters of Reaction Time and Accuracy), WAIS-III Digit-symbol Coding (processing speed), WAIS-III Arithmetic (working memory), WAIS-III Information (acquired knowledge), WAIS-III Block Design (reasoning and problem solving), the Degraded Facial Affect Recognition Task (DFAR; assessing recognition of neutral, happy, fearful and angry emotions), the Benton Face Recognition Task (BFRT; assessing visuospatial discrimination of unfamiliar faces), and the Hinting Task (assessing theory of mind). For a further description of the abovementioned tasks we refer to the baseline description of cognitive functioning in GROUP (Meijer et al submitted).
Statistical analysis
Statistical analyses were performed using SPSS 17.0 for Windows. Differences in demographic and substance use characteristics among patients, siblings, and controls were assessed using one way analysis of variance (ANOVA) and $\chi^2$ tests. Demographic and clinical characteristics in current and lifetime cannabis using patients were compared to those in never using patients using independent t-tests and $\chi^2$ tests. Tests were two-tailed with a significance level of 0.05.

In the entire study sample (n=2463), separate linear mixed-model regression analyses for each of the 13 outcome parameters were conducted to assess the main effects of Status (patient, sibling, control), Cannabis Recency (current, lifetime and never) and Status x Cannabis Recency. For subjects with cannabis use during the year prior to inclusion of the study (n=612), the same analysis was conducted, with the variable Cannabis Frequency (daily, weekly, less) instead of Cannabis Recency.

Although not a primary aim of this study, the main effects of Status are presented in the results section to facilitate interpretation. Cannabis effects have been assessed in regression analyses together with the main effect of Status. Any effects of Cannabis should thus be interpreted in addition to existing cognitive differences between the Status groups.

To control for intra-family correlation, family was used as a random factor with a random intercept regression model. Potential confounders that have been mentioned previously (Coulston et al. 2007b; Potvin et al. 2008) were entered separately into the regression model as covariates. If a potential confounder changed the effect estimates by 10% or more it was kept as covariate in the final model. The following covariates were entered: age, gender, heavy alcohol use (>14 units weekly for women and >20 units weekly for men), a history of illicit substance use other than cannabis over the past year (cocaine, amphetamines, XTC, opiates, inhalants, hallucinogens), and highest parental educational degree. Since the Dutch educational system already differentiates after primary school, a coding system was used that goes from lowest (1=primary school) up to highest (8=university). In the analyses for the Degraded Facial Affect Recognition task, scores on the Benton Face Recognition Task were used as an extra covariate to adjust for non-emotional facial processing skills. If the interaction term was not statistically significant, it was removed from the model and the analysis was repeated with the main effects and relevant confounders. To correct for multiple comparisons, alpha was set to 0.005. Due to the increased power caused by the large n, effect sizes (Cohen’s $d$) were calculated to facilitate the interpretation of the statistical significant effects.

Normality of the cognitive parameters was checked visually with histograms and box plots and confirmed if the test-statistic $W$ in the Shapiro Wilk test exceeded 0.90. Parameters for CPT accuracy and the Hinting Task were not normally distributed due to ceiling effects. Data transformations did however not substantially improve normality. Therefore these two tasks were analyzed by differing methods. Besides conducting mixed-model regression analyses, a second analysis was performed by splitting subjects into two similar sized groups of ‘affected’ and ‘unaffected’ individuals. “Affected” for the CPT accuracy (range 0-100%) was defined as <100% accurate responses (=51.6% of total sample) and for the hinting task (range 0-20) as a score <20 (=57.8% of total sample). This dichotomous outcome was analyzed using a generalized estimating equations (GEE) approach (Hanley et al 2003). The regression model and procedures were the same as in the mixed-model regression analyses. To minimize the risk of type I errors, the analyses yielding the most conservative results were selected for the discussion.
**Results**

**Characteristics of the study sample**

As presented in table 1, control subjects were older (30.2 years) than patients (27.3 years) and siblings (27.9 years). Males were overrepresented in the patient group (76.4%) compared to siblings (45.4%) and controls (45.5%). Parental educational degree and subject educational degree was lowest in patients. Of all subjects, 38.3% (n=943) had used cannabis lifetime, and 10.5% (n=258) were current cannabis users. Patients and siblings were more likely to be current or lifetime cannabis users compared to controls. Regarding the frequency of cannabis use over the past year, patients and siblings were more likely to be daily users compared to controls. Patients were more likely to be nicotine users (66.4%) or users of illicit substances (20.4%) compared to siblings (37.5% and 7.8% respectively) and controls (25.5% and 6.0%, respectively). Groups did not differ in the proportion of heavy alcohol users.

Table 1. Demographic variables in patients, siblings and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Siblings</th>
<th>Controls</th>
<th>F (df)</th>
<th>( \chi^2 ) (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>27.3 (7.4)</td>
<td>27.9 (8.3)</td>
<td>30.2 (10.5)</td>
<td>21.6 (2, 2459)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Gender, % male</td>
<td>76.4</td>
<td>45.4</td>
<td>45.5</td>
<td>229.0 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Education, % lowest (% highest)</td>
<td>12.3 (4.3)</td>
<td>7.1 (12.0)</td>
<td>2.2 (9.4)</td>
<td>244.5 (16)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Parental education, % lowest (% highest)</td>
<td>6.7 (18.3)</td>
<td>5.1 (18.8)</td>
<td>4.3 (16.1)</td>
<td>35.22 (16)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Nicotine use, %</td>
<td>66.4</td>
<td>37.5</td>
<td>25.5</td>
<td>282.4 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Heavy alcohol use, %</td>
<td>10.9</td>
<td>9.0</td>
<td>7.7</td>
<td>4.6 (2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Other substance use, %</td>
<td>20.4</td>
<td>7.8</td>
<td>6.0</td>
<td>97.09 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Cannabis Recency (n=2463)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current, %</td>
<td>16.3</td>
<td>7.9</td>
<td>4.9</td>
<td>60.16 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Lifetime, %</td>
<td>49.8</td>
<td>33.4</td>
<td>26.9</td>
<td>93.82 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>33.9</td>
<td>58.7</td>
<td>68.2</td>
<td>200.49 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Cannabis Frequency past year (n=612)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily, %</td>
<td>48.3</td>
<td>25.6</td>
<td>19.5</td>
<td>38.71 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Weekly, %</td>
<td>26.6</td>
<td>28.3</td>
<td>30.5</td>
<td>0.57 (2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Less, %</td>
<td>25.1</td>
<td>46.1</td>
<td>50.0</td>
<td>32.12 (2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Test statistic: F for continuous data, \( \chi^2 \) for categorical variables, NS=not significant

Table 2 shows that patients with current or lifetime cannabis use were 2.3 years younger than never users and more often male (86.1% vs. 57.4%). Current or lifetime cannabis using patients had lower functioning on the GAF disability scale (52.9 vs. 58.3), higher PANSS positive symptoms (14.6 vs. 12.4), but similar PANSS negative symptoms compared to patients who had never used cannabis. In both groups around 85% of patients received treatment with antipsychotics.
## Table 2. Demographic and clinical variables of patients with and without a lifetime history of cannabis (CB) use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifetime CB use</th>
<th>Never CB use</th>
<th>t (df)</th>
<th>χ² (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>26.5 (6.4)</td>
<td>28.9 (8.7)</td>
<td>4.9 (954)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Gender, % male</td>
<td>86.1</td>
<td>57.4</td>
<td>97.5 (1)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Education, %lowest (%highest)</td>
<td>15.2 (3.0)</td>
<td>6.8 (6.8)</td>
<td>34.1 (8)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Parental education, %lowest (%highest)</td>
<td>7.1 (19.0)</td>
<td>5.9 (17.0)</td>
<td>11.9 (8)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GAF - disability, mean (SD)</td>
<td>52.9 (16.0)</td>
<td>58.3 (15.5)</td>
<td>4.8 (919)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>PANSS Positive Scale, mean (SD)</td>
<td>14.6 (6.7)</td>
<td>12.4 (5.7)</td>
<td>-4.9 (930)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>PANSS Negative Scale, mean (SD)</td>
<td>15.2 (6.6)</td>
<td>14.7 (6.4)</td>
<td>-1.2 (930)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic treatment, % yes</td>
<td>86.3</td>
<td>84.9</td>
<td>2.0 (2)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Current and lifetime cannabis using patients combined.

**test statistic: T for continuous data, χ² for categorical variables, NS=not significant

### Cannabis Recency

For none of the cognitive outcome variables the interaction Status (patients, sibling, control) x Cannabis Recency (current, lifetime, never) was statistically significant and therefore the interaction term was removed from the regression models. Figure 1a demonstrates that patients performed worse than controls on all cognitive parameters except RST reaction time, while siblings performed intermediate to patients and controls on selected tasks. In the model including Status, Cannabis Recency and relevant confounders, current -but not lifetime- cannabis users performed significantly worse compared to never users on immediate verbal learning (d=-0.20), WAIS-III Digit Symbol Coding (d=-0.22) and WAIS-III Arithmetic (d=-0.20) (figure 1b). Lifetime cannabis users performed better than never users on WAIS-III Information (d=+0.17), Degraded Facial Affect Recognition task (d=+0.33), and Benton Face Recognition Task (d=+0.21). In addition, current cannabis users performed significantly better than never users on the WAIS-III Information task (d=+0.19). GEE analyses confirmed the mixed-model regression results for the not normally distributed data. For CPT-accuracy, the proportion of ‘affected’ individuals was not significantly different within current (58.8%), lifetime (53.1%), and never users (49.0%), Wald χ²(2)=0.98, p=0.61. Also for the Hinting task, the proportion of ‘affected’ individuals was not significantly different within current (64.0%), lifetime (60.0%), and never users (54.8%), Wald χ²(2)=0.35, p=0.84.

### Cannabis Frequency

For none of the cognitive outcome variables the interaction term Status x Cannabis Frequency was statistically significant. In the resulting model, including Status, Cannabis Frequency, and relevant confounders, there was no significant effect of Cannabis Frequency on any of the cognitive parameters (Figure 1c). GEE analyses confirmed the mixed-model regression results for the not normally distributed data. For CPT-accuracy, the proportion of ‘affected’ individuals was not significantly different within daily (57.1%), weekly (59.6%), and less frequent users (52.6%), Wald χ²(2)=1.87, p=0.39. For the Hinting task, the proportion of ‘affected’ individuals was not significantly different within daily (70.7%), weekly (60.5%), and less frequent users (60.9%), Wald χ²(2)=1.74, p=0.42.
Figure 1. Main effects of Status (Figure 1a), Cannabis Recency (Figure 1b, see following page), and Cannabis Frequency (Figure 1c, see following page) on cognitive functioning.

WLT IR: Word Learning Task Immediate Recall; WLT RR: Word Learning task Retention Rate; RST RT: Response Shifting task Reaction Time; RST Acc: Response Shifting Task Accuracy; CPT RT: Continuous Performance Task-HQ Reaction Time; CPT Acc: CPT-HQ Accuracy; DS Coding: WAIS-III Digit-symbol Coding; Arithmetic: WAIS-III Arithmetic; Information: WAIS-III Information; Block: WAIS-III Block Design; Affect Rec: Degraded Facial Affect Recognition total score; Face Rec: Benton Face Recognition; Hinting: Hinting Task; F: Test statistic from mixed-model regression analyses; df: degrees of freedom. Effects that remained significant after correction for multiple comparisons (p<0.005) in current/lifetime users compared to never users are circled in Figure 1b.
Figure 1b)

Figure 1b)
Figure 1c)

WLT IR: Word Learning Task Immediate Recall; WLT RR: Word learning task Retention Rate; RST RT: Response Shifting task Reaction Time; RST Acc: Response Shifting Task Accuracy; CPT RT: Continuous Performance Task-HQ Reaction Time; CPT Acc: COP-HQ Accuracy; DS Coding: WAIS-III Digit-symbol Coding; Arithm: WAIS-II Arithmetic; Inform: WAIS-III Information; Block: WAIS-III Block Design; Affect Rec: Degraded Facial Affect Recognition total score; Face Rec: Benton Face Recognition; Hinting: Hinting Task; F: Test statistic from mixed-model regression analysis; df: degrees of freedom. Effects that remained significant after correction for multiple comparisons (p<0.005) in current/lifetime users compared to never users are circled in Figure 1b.
Discussion

The aim of this cross-sectional study was to investigate how recency and frequency of cannabis use are associated with cognitive performance in patients with non-affective psychosis, their unaffected siblings, and control subjects. Our findings indicate worse performance on immediate verbal learning, processing speed and working memory in current cannabis users. Furthermore, lifetime cannabis use was associated with better performance on acquired knowledge, affect recognition and face identity recognition. The effect sizes of these associations were in the small range which may explain why previous studies that included smaller sample sizes have found contradictory results (Coulston et al 2007b). Of those subjects who had used cannabis over the past year, daily or weekly users did not perform significantly different compared to subjects who had used less than weekly. Finally, associations between cannabis use and cognitive functioning were not significantly different in patients, siblings and controls. The interpretation of these findings is discussed here. As the comparison of cognitive performance between patients, siblings and controls (figure 1a) was not the primary aim of this study, we refer to our baseline study on cognitive assessment in GROUP for further interpretation of these results (Meijer et al submitted).

A negative association between cognitive functioning and current- but not lifetime- cannabis use is likely to result from a residue of cannabinoids in the central nervous system. Worse immediate verbal learning in current cannabis users is in agreement with other studies for patients with psychotic illness (Liraud and Verdoux 2002, Pencer and Addington 2003, D’Souza et al 2005, Sevy et al 2007, Jockers-Scherubl et al 2007, Coulston et al 2007a, Yucel et al 2010). Also in healthy controls, immediate verbal learning is one of the most consistently impaired cognitive functions after acute cannabis administration, and congruent with our results, this effect appears to be transient after a four-week abstinence (Grant et al 2003, Solowij and Michie 2007).

In contrast with our finding of worse processing speed in current users, the majority of studies in schizophrenia patients reported either absent, or even positive effects of both current and lifetime cannabis use on visual processing speed (Sevy et al 2007, Jockers-Scherubl et al 2007, Coulston et al 2007a, Schnell et al 2009, DeRosse et al 2010). Positive associations in those studies might have been driven by higher premorbid cognitive functioning in cannabis using patients (Fried et al 2005, Schnell et al 2009). Worse processing speed performance in current- but not lifetime- cannabis users is in agreement with evidence from studies in control subjects (Ehrenreich et al 1999, Fried et al 2005).

Similar to our findings, recent cannabis use in schizophrenia patients has been associated with worse working memory (Ringen et al 2010), but absent or positive associations have also been reported (Sevy et al 2007, Mata et al 2008, Scholes and Martin-Iverson 2010). Opposite findings may have resulted from differing samples sizes or the heterogeneity of working memory measures that have been used. WAIS-III Arithmetic may be regarded as a relatively complex measure of working memory, with split loadings on processing speed and verbal comprehension (Tellegen 2003). Our findings are supported by studies in control subjects that reported impaired working memory following intravenous THC administration and cannabis smoking (Ilan et al 2004, Morrison et al 2009), while lifetime cannabis use was not associated with working memory impairments (Scholes and Martin-Iverson 2010).

With regard to the effects of Cannabis Frequency, findings that daily and weekly users did not perform significantly different from less frequent users are corroborated by the literature in schizophrenia patients (Rodriguez-Sanchez et al 2010) and in healthy subjects (Pope Jr. et al 2002).
Tolerance for the adverse cognitive effects of cannabis in more frequent users might have accounted for the absence of a dose-response relationship on cognition (Ramaekers et al. 2009). We found that lifetime cannabis users performed better than never users on tasks of acquired knowledge, facial affect recognition, and face identity recognition. Research on the association between cannabis use and performance on facial affect and identity processing is sparse in both patients and controls. One study reported that patients who had used cannabis prior to psychosis onset showed a relative sparing of face identity recognition at 10-12 year follow-up, but this difference was lost after co-varying for age at psychosis onset (Stirling et al. 2005). In non-psychotic polysubstance users, cannabis use was not associated with quality of facial affect recognition, but this association might have been confounded by differing effects of other substances (Fernandez-Serrano et al. 2011).

A positive association between lifetime cannabis use and cognitive functioning may seem counterintuitive given the detrimental effects in acute administration studies (D’Souza et al. 2005, Morrison et al. 2009). It has been suggested that substance using patients might need better cognitive and social skills in order to maintain an illicit substance use (Joyal et al. 2003, Potvin et al. 2005), but in the Netherlands cannabis is not illegal and can be purchased with lesser restrictions. In other words, subjects do not need superior social functioning to obtain cannabis. Our findings are however 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). Our results support the hypothesis that cannabis using patients might constitute a subgroup of patients that is 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 may be less severe than a psychotic illness that is predominantly due to inherent genetic vulnerability. This developmental model has been supported by various studies that investigated the order in which cannabis use and psychosis occur. Three studies found that cognitive functioning was specifically preserved in patients who had started cannabis consumption before disease onset (Stirling et al. 2005, Rodriguez-Sanchez et al. 2010) or before the age of 17 (Jockers-Scherubl et al. 2007). These studies suggest that it is not the cognitive effects of cannabis per se, but the contribution of cannabis to disease onset that explains better cognitive functioning in cannabis using patients. Secondly, evidence from follow-up studies suggests that acutely admitted psychiatric patients using cannabis have a higher recovery potential for both cognitive and clinical parameters, especially after cessation of cannabis use (Loberg and Hugdahl 2009, Gonzalez-Pinto et al. 2009). Thirdly, studies focusing on neurodevelopmental and genetic factors have added credibility to the vulnerability hypothesis. Cannabis use before psychosis onset has been associated with less neurological soft signs after transition to psychosis, which is thought to reflect a lower genetic loading in those patients (Ibersani et al. 2002, Stirling et al. 2005, Ruiz-Veguilla et al. 2009).

It should however be stressed that lifetime cannabis use in our patients was associated with a lower educational degree. In healthy individuals adolescent cannabis use is known to increase the risk of poor school performance, and in particular early school leaving (Lynskey and Hall 2000). Cannabis use is also known to impact negatively upon later employment in control subjects (Fergusson and Boden 2008), and the impact may be even more severe in a cognitively vulnerable population of psychotic patients.
Other than in patients with psychosis and healthy controls, evidence on the association between cannabis use and cognition in genetic high risk subjects is sparse. In agreement with our results, Henquet et al (2006) found that acute THC administration in unaffected siblings and control subjects was associated with a decline in domains of verbal memory and processing speed. In addition, preliminary evidence suggested that sensitivity to the cognitive effects of THC might be moderated by a functional polymorphism in the catechol-O-methyltransferase (COMT) gene that is also known to moderate the risk to develop psychosis in reaction to cannabis use (Henquet et al 2006). The present study is to our knowledge the first observational study to assess the relationship between daily-life cannabis use and cognitive functioning in genetic high risk subjects.

Finally, patient or sibling status did not moderate the association between recency or frequency of cannabis use and cognitive functioning. Although there have been suggestions of an increased vulnerability to the cognitive adverse effects of acute THC administration in patients and their siblings (D’Souza et al 2005, Henquet et al 2006), we did not replicate this finding. A first explanation might be that such an interaction effect is restricted to the first hours following acute intoxication of cannabis and not applicable to effects resulting from a residue of cannabinoids in the brain. A second difference in study methodologies is the psychoactive substance of use. While previous studies found an interaction effect on cognitive functioning between psychosis vulnerability and THC, we assessed associations with current, daily-life cannabis use. Contrary to cannabis, THC is a synthetic preparation that is devoid of cannabidiol, which is a potential inhibitor of pharmacological effects of CB1 agonists (Pertwee 2008). Further research needs to clarify the association between individual cannabis components and cognitive functioning in individuals with psychosis and their unaffected relatives. Despite the absence of an interaction effect, our findings do not imply that campaigns to discourage cannabis use are without merit. The adverse effects of cannabis use on psychotic symptomatology are well acknowledged in both patients (Linszen et al 1994, Macleod 2007, Castle, 2008) and individuals at genetic risk for psychosis (Caspi et al 2005, Genetic Risk and Outcome of Psychosis (GROUP) Investigators2011).

The following limitations should be taken into account. First, the cross-sectional design restricts the drawing of causal inferences between cannabis use and cognitive functioning. Second, we cannot fully exclude the possibility that some of the current users in our study were tested within less than 24 hours after cannabis consumption so that the effects measured were those of acute intoxication. However, instructing frequent users to abstain from cannabis use before testing could cause negative cognitive effects as well, similar to those of acute intoxication (Pope Jr. et al 2002). The strength of this study is that due to the comprehensive database of the GROUP study we were able to address recommendations that have been made in prior studies (Coulston et al 2007b, Yucel et al 2010), such as investigating both recency and frequency of cannabis use, the inclusion of a cannabis-using control group, biological validation of self-report cannabis measures by urine drug screening, the assessment of a broad range of cognitive measures, and controlling for a range of possible confounders. Furthermore, the current study expanded on existing studies by the inclusion of unaffected siblings, so that we were able to draw conclusions on the association between cannabis and cognition in people at genetic high risk for psychosis.

Our findings implicate that cannabis use in patients, siblings, and controls is associated with differences in cognitive performance, depending on the recency of use. Current cannabis users perform worse on task of short-term memory and processing speed which may reflect residual effects. Lifetime cannabis users perform better on social cognition and acquired knowledge, which is more likely to be a result from a lower genetic vulnerability rather than an effect of cannabis itself.
This discrepancy between potential and actual performance is clinically relevant for those patients whose cannabis use might complicate a potentially less severe course of psychosis. Future studies are needed to test the validity of the vulnerability hypothesis. A longitudinal, prospective design may optimally address this issue, as it permits within-patient comparisons of cognitive performance before initiation and after cessation of cannabis use. These studies should also include subjects at genetic high risk, to elucidate if indeed the better functioning individuals only develop psychosis following a late environmental risk factor such as cannabis use.

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PART III

Cannabis use in relation to white matter
CHAPTER 3.1

Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia

Abstract

Adolescent-onset cannabis use, compared to adult onset use, has been associated with a higher risk for developing symptoms of schizophrenia-like psychotic disorders. To test the hypothesis that onset of cannabis use in early adolescence in male schizophrenia patients is associated with abnormalities in white matter structure and integrity, we used high resolution structural and diffusion-tensor brain images to compare three groups of patients: those who started regular use of cannabis (1) before the age of 15 years (early-onset cannabis users, n=10), (2) at the age of 17 years or later (late-onset cannabis users, n=8), and (3) those who were cannabis naïve (n=8). To verify patient findings we also compared white matter integrity of the three patients groups to a healthy control group (n=10). Cannabis naïve patients showed reduced white matter density and reduced fractional anisotropy, an indicator for white matter integrity, in the splenium of the corpus callosum, compared to patients with early-onset cannabis use. In the same brain area, cannabis naïve patients showed reduced fractional anisotropy compared to healthy controls. Our results suggest that the age of onset of cannabis use is not identifying for white matter abnormalities in schizophrenia patients, however, our results might indicate a more vulnerable brain structure in cannabis naïve schizophrenia patients.
Introduction

Cannabis is one of the most commonly used substances in patients presenting to psychiatric services with their first episode of schizophrenia (Hambrecht and Hafner 1996, Van Maastricht et al 2004, Barnes et al 2006). Cannabis use is known to be related to an earlier age of onset of psychotic disorders (Veen et al 2004, Barnes et al 2006, Gonzalez-Pinto et al 2008), and to an increased risk of developing psychotic outcomes independently of confounding and transient intoxication effects (Moore et al 2007). Stefanis and co-workers (2004) have shown that early-onset cannabis use conferred the greatest risk for developing positive and negative dimensions of psychosis. Caspi et al (2005) reported that adolescent-onset cannabis use, compared to later use, is associated with a higher risk of developing symptoms of schizophrenia in carriers of the COMT val 158 allele. One explanation for this increased risk could be 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). Schneider and Koch (2003) suggested that the endogenous cannabinoid system is highly susceptible to the effects of cannabinoid administration during pubertal development. In addition to this, there is evidence that a dysregulation in the endogenous cannabinoid system is associated with the pathogenesis of schizophrenia (Dean et al 2001, Leweke et al 1999, Giuffrida et al 2004). However, a clear biological explanation for the increased risk for psychosis in individuals who use cannabis in adolescence is not yet available (DeLisi 2008). Some MRI studies in non-psychotic cannabis users have examined the effect of early-onset cannabis use on brain structure. De Lisi et al (2006) suggested that the establishment of new cortical connections and growth of axons that normally occur during adolescence could be disrupted by frequent cannabis use; however, Diffusion Tensor Imaging (DTI) findings in non-psychotic individuals were not conclusive.

In line with De Lisi’s study, Tsilos et al (2005) investigated the effects of early cannabis-use on brain morphology in non-psychotic individuals and reported no significant differences in measures of brain volume between groups of different ages of onset of cannabis use. However, Wilson et al (2000) reported early-onset cannabis users to have smaller whole brain, smaller percent gray matter (GM) and larger percent white matter (WM) volumes, compared to late onset cannabis users.

Some MRI studies investigated the effects of cannabis use on brain morphology in patients with schizophrenia (Cahn at al 2004, Szekszol et al 2007, Potvin et al 2007, Rais et al 2008, Bangalore et al 2008), but these studies did not specifically focus on the timing of onset of cannabis use.

In schizophrenia, abnormalities in WM connectivity have been reported as a crucial neurobiological marker, which is 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. However, results from DTI studies are not conclusive (Kanaan et al 2005). To date, no DTI study reported on schizophrenia patients using cannabis. To test the hypothesis that cannabis use during adolescence may disrupt WM integrity in patients with schizophrenia, we compared WM structure and FA employing optimized voxel based morphometry (VBM)- in early and late onset cannabis users, and cannabis naïve patients with recent onset schizophrenia. Cannabis use before the age of 15 was considered early onset cannabis use. Cannabis use at age 17 or later was considered as late onset cannabis use, as neurodevelopment, including development of the dopamine and endocannabinoid system, undergoes major maturation in puberty and is largely concluded by the age of 16 (Sundram 2006, Shaw et al 2006, Schneider 2008). Cannabis use before...
15 years of age might therefore have a different impact on brain structure and function than cannabis use at age 17 or later. Adverse cognitive consequences of cannabis use in humans before the age of 17 have already been reported (Ehrenreich et al 1999, Pope et al 2003). To verify patient findings we also compared white matter integrity of the patients groups to those of healthy controls.

Materials and methods

Subjects and clinical measures

We included 26 male patients with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association 1994) diagnosis of schizophrenia from the open-ward inpatient and day-care units of the Adolescent Clinic of the Academic Medical Centre, University of Amsterdam. The clinic is specialized in the treatment of young patients with schizophrenia-like disorders aged between 16 and 28 years.

Clinical diagnoses of patients were made according to DSM-IV criteria by two psychiatrists with the use of all available information, including a patient history provided by a close relative or friend (most often the parents) at admission (Longitudinal Expert Assessment of Diagnosis procedure, Spitzer and Williams 1995). An estimate of the duration of illness, defined as the time between the start of the first psychotic episode (hallucinations, delusions and/or disorganisation) and MRI scanning, and estimates of total duration of antipsychotic medication was based on a detailed history taken from the patient and the parents, and all available clinical information (including case records and information from previous mental health professionals). The Clinical Global Impression-Severity of Illness (CGI-S; Guy 1976) was used for assessing the severity of the disease (state), and the Global Assessment of Functioning (GAF; American Psychiatric Association 1994) was used for assessing psychosocial functioning. Information about substance use, including cannabis use, was retrieved with the use of a detailed history taken from the patient on present and lifetime substance use and frequency of use. Further we used all available clinical information on substance use, such as case records, information from parents and information from previous mental health professionals.

Patients were included in the study if they had either started the regular use of cannabis before the age of 15 years (early onset cannabis users, n=10), if they had started the regular use of cannabis at the age of 17 years or later (late onset cannabis users, n=8), or if they had never used cannabis (cannabis naïve patients, n=8). Patients eligible for the early and late onset cannabis group were included into the study if their cannabis use consisted of at least weekly use during at least six months of their lives. All patients were receiving antipsychotic neuroleptics and chlorpromazine equivalents were calculated (Woods et al 2003). Male healthy control subjects were recruited through local advertisements and were matched for age.

Exclusion criteria for all subjects were a history of a demonstrable neurological or endocrine disease which may affect brain structure, and a history of a head trauma with loss of consciousness for more than 15 minutes. Additional exclusion criteria for healthy controls were: a personal or family history of a major psychiatric illness, or a lifetime diagnosis of alcohol or other substance abuse or dependence. After complete description of the study, written informed consent was obtained from all participants. The study was approved by the human subject review board of our institution. For baseline demographics and clinical variables, see table 1.
### Table 1. Sample characteristics

<table>
<thead>
<tr>
<th>Schizophrenia Patients</th>
<th>Healthy controls</th>
<th>( F )</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early-onset cannabis use</strong></td>
<td><strong>Late-onset cannabis use</strong></td>
<td><strong>Cannabis naive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( n=10 )</td>
<td>( n=8 )</td>
<td>( n=8 )</td>
<td>( n=10 )</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>20.9 (2.9)</td>
<td>22.2 (2.3)</td>
<td>20.4 (2.3)</td>
<td>21.1 (2.8)</td>
</tr>
<tr>
<td><strong>Education (years), mean (SD)</strong></td>
<td>10.1 (1.5)</td>
<td>10.5 (0.9)</td>
<td>10.8 (1.2)</td>
<td>13.8 (1.5)</td>
</tr>
<tr>
<td><strong>Age of disease onset (years), mean (SD)</strong></td>
<td>18.6 (3.0)</td>
<td>20.2 (1.7)</td>
<td>19.3 (2.5)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Duration of illness (years), mean (SD)</strong></td>
<td>2.3 (2.1)</td>
<td>1.9 (1.5)</td>
<td>1.2 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Number of previous hospitalizations for psychosis, mean (range)</strong></td>
<td>0.60 (0-2)</td>
<td>0.9 (0-1)</td>
<td>0.5 (0-2)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia, paranoid type</td>
<td>8 (80%)</td>
<td>7 (87.5%)</td>
<td>5 (62.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Schizophrenia, disorganized type</td>
<td>1 (10%)</td>
<td>1 (12.5%)</td>
<td>3 (37.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Schizophrenia, undifferentiated type</td>
<td>1 (10%)</td>
<td>1 (12.5%)</td>
<td>3 (37.5%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Antipsychotic medication at time of scanning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Atypical</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication dose (chlorpromazine equivalents, mg/day), mean (SD)</strong></td>
<td>360 (110)</td>
<td>336 (106)</td>
<td>355 (178)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Duration of antipsychotic medication (weeks), mean (range)</strong></td>
<td>54.3 (3-208)</td>
<td>25.8 (16-39)</td>
<td>44.8 (8-103)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Characteristics positive symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusions</td>
<td>10 (100%)</td>
<td>8 (100%)</td>
<td>6 (75%)</td>
<td>-</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>6 (60%)</td>
<td>7 (87.5%)</td>
<td>5 (62.5%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Global Assessment of Functioning, mean (SD)</strong></td>
<td>49.5 (9.8)</td>
<td>48.1 (12.2)</td>
<td>40.8 (10.2)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Clinical Global Scale, mean (range)</strong></td>
<td>4.9 (4-6)</td>
<td>5.0 (4-6)</td>
<td>5.5 (4.7)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Age of onset cannabis use (years), mean (range)</strong></td>
<td>12.9 (10-14)</td>
<td>18.3 (17-21)</td>
<td>-</td>
<td>-3.63*</td>
</tr>
</tbody>
</table>

*\( P \) score ANOVA, \( \chi^2 \) chi-quadrate in Kruskal Wallis test, FE=Fisher’s Exact value, *Z score of Mann-Whitney U test

**F= F score ANOVA, \( \chi^2 \)=chi-quadrate in Kruskal Wallis test, FE=Fisher’s Exact value, *Z score of Mann-Whitney U test**
There were no significant patient group differences in age at onset of schizophrenia, age at time of scanning, duration of illness, duration of antipsychotic medication, previous hospitalization for psychosis, GAF and CGI score.

Eight of the 10 patients from the early onset group had used cannabis on a daily basis for one or more years during adolescence. The other two patients from the early onset group had respectively used cannabis 2-3 times a week for several years during adolescence, and used cannabis daily to weekly for at least six months during adolescence. Six of the 8 patients from the late onset group had used cannabis on a daily basis for one or more years. The other two patients from the late onset group were daily heavy users for at least six months of their lives. All patients from the early and late onset groups received a DSM-IV diagnosis of cannabis use disorder, of which some were in remission;

in the early onset group 3 patients had a current diagnosis of cannabis abuse, 4 patients had a current diagnosis of cannabis dependence and 3 patients had a cannabis use disorder in early remission; in the late onset group one patient had a current diagnosis of cannabis abuse, 6 patients had a cannabis use disorder in early remission, and one patient had a cannabis use disorder in sustained remission. Two patients in the early onset group had a DSM-IV diagnosis of alcohol use disorder (alcohol abuse 1 and alcohol dependence 1), and four patients in the late onset group had a DSM-IV diagnosis of alcohol abuse disorder in remission. One patient in the early onset group had a DSM-IV diagnosis of cocaine abuse.

As expected, the groups differed in education years ($F=16.65;df=3; P<0.0001$) with healthy controls having on average more years of education than the patient groups.

**Neuroimaging protocol**

All participants were scanned with a 3 Tesla MRI system (Philips Medical System, Best, The Netherlands). Individuals were introduced to the scanning procedure before assessment. All images were acquired in the same session.

**Structural imaging**

3D T1-weighted gradient-echo images served (TR/TE 9.8/4.6 ms; axial orientation; 120 continuous slices; slice-thickness 1.2 mm; flip angle 8°; 224 mm FOV; acquisition matrix 256x256; voxel size 1.20 x 0.8 x 0.8 mm) to identify morphometric differences of WM density on a voxel-by-voxel basis and for anatomical localization of FA maps in standard space.

**Diffusion tensor imaging**

DTI data were acquired using 3D multi-slice spin echo single shot echo-planar imaging (EPI) with: TR/TE: 8872/94 diffusion sensitivities of $b=0$ and $b=1000$ s/mm$^2$; and sixteen non collinear directions, each direction was scanned twice. We took 48 continuous slices, slice-thickness 2.2 mm, 224 mm field of view (FOV); acquisition matrix 256 x 256 voxel size 3 x 3.5 x 2.2 mm. The DTI data were post processed to create FA value maps. FA maps are a representation of the directional density of WM fibre tracts and are an indicator of WM integrity. Additionally, 3D T2-weighted turbo-spin-echo images (TR/TE: 4741/80 ms; axial orientation; 48 continuous (no inter-slice gap) slices; slice-thickness 3 mm, 224 mm FOV; acquisition matrix 448x448; acquisition voxel size 0.5 x 0.5 x 3 mm) were acquired for an anatomical FA map co-registration and template creation.
Quantitative neuroimaging analysis and voxel based comparisons
All data were processed using SPM2 (Wellcome-Department of Cognitive Neurology, London, UK) modified for optimized VBM on a MATLAB platform (The MathWorks Inc., USA; version 7.4). All images were pre-processed and checked for artefacts and image corruption before entering statistical analysis.

We used optimized VBM (Good et al., 2001) implemented in SPM2 (Institute of Neurology, Queen’s Square, London, (www.fil.ion.ac.uk)), to identify regional differences in WM concentration (density). Automated optimizations (Department of Psychiatry, University of Jena, Germany) in SPM2 were used to spatially normalize and segment all T1-weighted images, based on the customized T1-template. The prior images of GM, WM and cerebrospinal fluid (CSF) were used for segmentation. All standard presets in SPM2 were maintained. For statistical comparison WM segments were smoothed with a 10 mm FWHM isotropic Gaussian-kernel, which renders the data more normally distributed to achieve optimal outcome in parametric statistical comparisons.

Also, we used a modified optimized VBM procedure to analyse FA images: We matched structural to DTI images by using the contrast level of the images’ WM map, hence, individual 3D T2-weighted images were used in the process to create a customized template of the b=0 images. The T2-weighted template was created to fit the same standards space as the T1-weighted template, with voxel dimension of 1x1x1 mm. All b=0 images were thereafter spatially normalized using the customized (DTI) template. A T2-weighted WM mask was created to remove non brain tissue from the FA images. The FA images were co-registered (write normalized) to the spatially normalized b=0 image of the corresponding subject. The images were then smoothed with 10 mm FWHM preceding statistical analyses (Eriksson et al., 2001).

Statistical analysis
ANOVA was carried out using the SPM2 platform, to investigate group differences on a voxel-by-voxel basis for WM segments and FA value maps of the three patient groups. Two way ANOVA for group comparisons were thresholded in a successive order, starting at (i) at p<0.001, uncorrected for multiple comparisons with height threshold (t) at zt=4.02 at voxel level, with a minimal cluster size (cluster extend threshold at p=0.001) of 50 voxels; then, (ii) individual significant clusters (p<0.05 at cluster level, P_c); and (iii) false discovery rate (FDR) and family wise error (FWE) corrections of multiple voxel comparisons were applied. Voxels and clusters were localized using the Montreal-Neuroligical-Institute (MNI) space and transformed into Talairach and Tournoux (T&T) co-ordinates. For results in the WM segments, T&T* co-ordinates are given as an indication of the voxel location in a standardized brain. Additionally, resulting voxel and cluster maps of FA images were overlaid on corresponding T1-weighted images for anatomical assessment. To verify our patient findings we compared FA values of cannabis naïve, early onset and late onset cannabis using schizophrenic patients to healthy controls using the same procedure as above.
Table 2: Neuroimaging findings in cannabis naïve, early onset and late onset cannabis use schizophrenia patients and control subjects.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Brain area</th>
<th>Talairach and Tournoux (T&amp;T) Coordinates</th>
<th>T value</th>
<th>P value at voxel level</th>
<th>Pc (corrected for multiple comparisons at cluster level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) cannabis naïve (CN) vs early onset (EO) cannabis users</td>
<td></td>
<td>Left posterior corpus callosum: -14 -46 27</td>
<td>5.53</td>
<td>P&lt;0.00001</td>
<td>Pc&lt;0.005</td>
</tr>
<tr>
<td>FA value differences (FA)</td>
<td>WM density differences (WM)</td>
<td>Left posterior corpus callosum: -13 -46 28</td>
<td>5.34</td>
<td>P&lt;0.00001</td>
<td>Pc&lt;0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right occipital lobe: 20 -77 29</td>
<td>5.25</td>
<td>P&lt;0.00001</td>
<td>Pc&lt;0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left temporal lobe: -30 -1 -30</td>
<td>5.21</td>
<td>P&lt;0.00001</td>
<td>Pc&lt;0.001</td>
</tr>
<tr>
<td>2) CN vs late onset (LO) cannabis users</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) EO vs LO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients vs controls:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) CN vs Controls (FA)</td>
<td></td>
<td>Left posterior corpus callosum: -13 -42 21</td>
<td>4.98</td>
<td>P&lt;0.00002</td>
<td>Pc&lt;0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right posterior corpus callosum: 12 -47 10</td>
<td>4.27</td>
<td>P&lt;0.00001</td>
<td>Pc&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left temporal lobe: -27 -16 17</td>
<td>3.59</td>
<td>P&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>2) EO vs Controls (FA)</td>
<td></td>
<td>Left temporal lobe: -31 -2 3</td>
<td>1.67</td>
<td>P&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>3) LO vs Controls (FA)</td>
<td></td>
<td>Left temporal lobe: -59 -29 11</td>
<td>1.69</td>
<td>P&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Fractional anisotropy (FA), White matter (WM), cannabis naïve (CN), early onset cannabis use (EO), late onset cannabis use (LO), P = P values at <0.001, Pc = P values corrected for multiple comparisons at cluster level, Pc<0.05, T value = standard deviation score, T&T= Talairach and Tournoux co-ordinates (estimated for WM).
**Results**

*Neuroimaging findings in patient comparisons*

We identified reduced FA values ($P_c < 0.005$ corrected) and WM density ($P_c < 0.009$, corrected) in the left posterior corpus callosum (splenium) in cannabis naïve individuals with schizophrenia, compared to early-onset cannabis users with schizophrenia (figure 1, see the Color figure section at the end of this book), table 2. Additionally, cannabis naïve schizophrenia patients, compared to early cannabis users, show significant WM density reduction in the right occipital lobe ($P < 0.008$ corrected), and the left temporal (limbic) lobe ($P < 0.001$, corrected) (figure 1b, see the Color figure section at the end of this book). We did not find increased WM density and FA values. We also did not find structural or diffusion difference, surviving correction for multiple comparisons in any of the other patient group comparisons.

*Neuroimaging findings in patient-control comparisons*

Cannabis naïve schizophrenic patients, compared to healthy controls showed significantly ($P_c < 0.03$, corrected) reduced FA values of the left posterior corpus callosum (table 2, figure 2, see the Color figure section at the end of this book) and the fronto-temporal junction ($P > 0.001$, uncorrected) (table 2). Early onset and late onset cannabis using schizophrenic patients, compared to healthy controls showed significantly ($P < 0.001$, uncorrected) reduced FA values in the left temporal lobe. These findings are not corrected for multiple comparisons and need to be considered as preliminary (table 2). We did not find increased FA values.

**Discussion**

Our main findings were that cannabis naïve schizophrenia patients showed brain abnormalities in the splenium of the corpus callosum, compared to early onset cannabis users. No morphological differences were found between early onset cannabis users and late onset cannabis users. Compared to healthy controls, cannabis naïve patients also showed reduced FA values in the splenium. Furthermore, all patient groups, compared to control subjects showed reduced temporal lobe FA values, however, these temporal lobe findings did not survive a correction for multiple comparisons and should therefore be considered as preliminary findings. Our findings are partly contrasting with findings of Bangalore et al (2008). The authors reported brain abnormalities of reduced GM density in the posterior cingulate cortex (PCC) in cannabis using schizophrenia patients, compared to cannabis naïve patients. We identified congruent anatomical and diffusion abnormalities manifesting in the posterior corpus callosum, a brain area adjacent to the PCC, in cannabis naïve schizophrenia patients. Other MRI studies also investigated the effects of cannabis use on brain morphology in patients with schizophrenia (Cahn et al 2004, Potvin et al 2007, Szesko et al 2007, Rais et al 2008). They revealed that in cannabis using schizophrenia patients, GM volume of the anterior cingulate cortex was decreased (Szesko et al 2007), and brain volume reduction was more pronounced over a 5-year follow-up (Rais et al 2008) in comparison with patients with no cannabis use. Potvin et al (2007) found increased striatal GM densities in schizophrenia patients with substance use disorder (most of them used cannabis) compared to patients without substance abuse and compared to controls. However, Cahn et al (2004) found no differences in brain structure between schizophrenia patients who did and did not use cannabis. These studies did not specifically focus on patients who used cannabis in adolescence. De Lisi and co-
workers (2006) did focus on adolescent cannabis users, and their findings are in line with our results. The authors reported higher FA values in frequent adolescent cannabis users compared to cannabis naïve individuals. However, FA differences were found in parts of the brain other than the corpus callosum, and they conducted their study in non-psychotic individuals.

Our combined findings of WM density and FA reduction in the splenium of cannabis naïve schizophrenic patients are an indicator for reduced WM integrity in this part of the corpus callosum, maybe due to a disruption of axonal integrity, or myelin dysfunction (Beaulieu 2002). Lower FA values in the splenium may have a neuro-developmental origin. In our group of cannabis naïve patients we also found reduced WM density in the occipital and temporal lobes compared to early-onset cannabis use patients. Inter-hemispheric fibres from the temporal and occipital lobes transverse the splenium (Hofer and Frahm 2006). It is therefore possible that the lower FA values in the splenium may have resulted from a focal disruption of the cortical neurons or axons of adjacent brain areas.

Furthermore, reduced FA values in the splenium of the corpus callosum have been reported in a number of DTI studies in patients with schizophrenia (Foong et al 2000, Agartz et al 2001, Ardekani et al 2003, Rotarska-Jagiela et al 2008). In line with these findings, morphological, electrophysiological and neuropsychological studies suggest that callosal connections are altered in patients with schizophrenia (Innocenti et al 2003, Arnone et al 2008).

Increased FA values have been found in schizophrenia patients who experience auditory hallucinations (Hubl et al 2004, Shergill et al 2007, Seok et al 2007). Regions with higher FA were the anterior corpus callosum, the arcuate fasciculus, the superior longitudinal fasciculus, and the anterior cingulum. However, in our study auditory hallucinations were experienced by an equal amount of patients across the patient groups.

The results presented here are of preliminary nature since our sample size is limited and the study has an exploratory character, however our findings may indicate that cannabis naïve individuals who develop schizophrenia have a more vulnerable brain structure, compared to cannabis users developing the disease. Cannabis use before the age of 15 may be an environmental trigger and interact as a partial causal risk factor with a less vulnerable brain. Early cannabis users who develop schizophrenia might belong to a patient subgroup with better pre-morbid adjustment (Arndt et al 1992), fewer negative symptoms (Bersani et al 2002), and better neurocognitive functions (Stirling et al 2005, Coulston et al 2007). On the other hand, several studies reported that co-morbid cannabis abuse was associated with poor outcome of schizophrenia with respect to relapse and exacerbation (Linszen et al 1994, Martinez-Arevalo et al 1994, Grech, 2005), poorer compliance with antipsychotic medication and rate of employment (Bühler et al 2002), and poorer psychosocial functioning (Caspari, 1999). Future studies relating neuroimaging findings to variation in susceptibility risk for schizophrenia are needed to further test our hypothesis.

When interpreting our findings, certain limitations have to be considered: We only included male individuals in our study, and our sample size was relatively small. However, our group was homogeneous for age at time of MRI scanning, diagnosis and disease duration. Another limitation is that we had to rely on a cross-sectional study design. It would be of interest to investigate the development of white matter structure and integrity differences in cannabis naïve patients and those who use cannabis.
Furthermore, we had to rely on the patient’s self-reports of cannabis use. Nevertheless, these self-reports are likely to be a valid since the Dutch drug policy is liberal and cannabis use is discussed freely. However, the reports of cannabis use may have been prone to recall bias. Another shortcoming of this study is that we have not included subjects with cannabis use disorder who do not have schizophrenia. The question whether WM structure and integrity in patients with cannabis use is changed because of cannabis use or because of having a dual diagnosis, remains unanswered. Future brain imaging studies focussing on substance use in schizophrenia patients should consider this issue. Lastly, since some patients in the early–onset group had a current DSM-IV diagnosis of alcohol abuse (n=1), alcohol dependence (n=1), or cocaine misuse (n=1), and four patients in the late-onset group had a diagnosis of alcohol abuse disorder in remission, it is possible that substance use other than cannabis use could have accounted for part of the findings. However, both alcohol and cocaine use have been associated with decreased FA values (Sullivan and Pfefferbaum 2005, Moeller et al 2007). In our study, we did not find evidence for decreased FA values in the group of early-onset cannabis users, so it is unlikely that alcohol and cocaine use can explain the difference in FA between cannabis naive patients and early onset cannabis use patients. Still, for better understanding the effects of cannabis use on WM structure, future studies should preferably exclude patients with other substance abuse.

In conclusion, our results may suggest that the age of onset of cannabis use is not identifying for WM abnormalities in schizophrenia patients, or otherwise our results might indicate a more vulnerable brain structure in cannabis naive schizophrenia patients. Further studies with a longitudinal design and studies integrating neuroimaging and gene environment interaction are necessary to put our results in perspective.

References


Caspari D: Cannabis and schizophrenia: results of a follow-up study. European Archives of Psychiatry and Clinical Neuroscience 1999; 249: 45-49.


CHAPTER 3.2

Letter to the editor: Reply to Fan and Hart


Letter to the editor

We thank Fan and Hart (2011) for their comments on our paper (Dekker et al. 2010). We agree that using the term ‘brain abnormalities’ could be seen as less appropriate. We twice use this term in the discussion when we state that ‘cannabis naïve schizophrenia patients showed brain abnormalities in the splenium of the corpus callosum, compared to early onset cannabis users’, and later when we state that ‘we identified congruent anatomical and diffusion abnormalities manifesting in the posterior corpus callosum, a brain area adjacent to the PCC- in cannabis naïve schizophrenia patients.’ As Fan and Hart suggest, the word ‘abnormality’ should only be used when there is a difference from the normal. Therefore, in future papers, we agree that it is better not to use the word ‘abnormalities’, but ‘reduced fractional anisotropy (FA) values’ or ‘reduced white matter density’ when we refer to comparisons within patient groups. However, we do not agree with their argument that the naïve group’s fractional anisotropy integrity appears to be within the normal range of healthy male adolescents, with reference to Ashtari et al (2007). For the current study we used Voxel Based Morphometry (VBM) methods to discriminate between the FA voxel intensities on a voxel by voxel basis (Ashburner and Friston 2000). We refrained from calculating the mean FA values or extracting a tensor since we were interested in the whole brain response of our study sample. Therefore, our data cannot necessarily be compared with Ashtari et al 2007. Furthermore, Voxel Based Analysis (VBA) does not allow to generate responses about ‘normal ranges’ of FA values, it serves as a comparison of numerical values between 0 and 1 without a unit, with a higher FA value implying a higher degree of anisotropic motion of water molecules. Fan and Hart argue that our title ‘cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia’ would imply that there was an effect of cannabis on the onset of schizophrenia and brain abnormalities in the current participants, while our data did not demonstrate an effect of cannabis use. Indeed, we did not find an effect of cannabis use. However, in our opinion the title is neutral. The title captures two important topics in our article namely cannabis and the corpus callosum, and therefore informs the reader -at a single glance- what our article is about. We do hope and think, that casual readers who – at any chance- will misinterpret the findings of our study by only reading the title, will later be correctly informed about our results and conclusions by reading the abstract.

References

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
Discussion

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 (Jiensen 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
ingredient and 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 summed 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 practise 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 is 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
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 use at 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=85). 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-morbid (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
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 effects 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.

**Reference List**


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DeRosse P, Kaplan A, Burdick KE, Lencz T, Malhotra AK: Cannabis use disorders in schizophrenia: effects on cognition and symptoms. Schizophr Res 2010; 120: 95-100.


This thesis is about cannabis use in patients with schizophrenia. Schizophrenia is a serious mental illness that is characterized by psychosis, apathy, social withdrawal, and cognitive impairment, causing impaired functioning in everyday living. Cannabis is one of the most commonly used substances in schizophrenia patients, and is more common in people with psychosis than in the general population. Cannabis use has been associated with the development of psychotic disorder and once it has developed with a poorer course of the disease. Studies presented in this thesis were performed in patients with (recent-onset) schizophrenia, who were receiving treatment in outpatient or inpatient clinics. In some studies, data of patients were compared to data of siblings and/or healthy controls. Self-reported reasons for cannabis use, effects of cannabis use, implicit and explicit associations toward cannabis use, craving for cannabis use, and cessation of cannabis use are described in part I. Cannabis use in relation to other clinical variables such as age at onset of schizophrenia, obsessive compulsive symptoms and cognitive functioning are studied in part II. Adolescent cannabis use in relation to white matter in the brain of patients with schizophrenia is studied in part III. The following pages give a summary of findings and limitations of the studies described in this thesis.

Part I

Motivation for cannabis use, affective associations toward cannabis use, and craving for cannabis use in recent-onset schizophrenia

Chapter 1.1 Reasons for cannabis use and effects of cannabis use as reported by patients with psychotic disorders

Findings:
In this literature review of 14 studies that examined self-reported reasons for cannabis use and self-reported effects of cannabis use in patients with psychotic disorders, it was found that patients commonly report that their reasons for cannabis use are enhancement of positive affect (42.1%), relief of dysphoria (66.3%), and social enhancement (61.7%). Fewer patients report reasons related to relief of psychotic symptoms or relief of side-effects of medication (12.9%). Frequently reported positive effects of cannabis are positive changes in affect and relaxation. Many patients reported that cannabis negatively affected positive symptoms. This review shows that patients suffering from psychotic disorder report using cannabis mainly for affect regulation and socialization, despite awareness that cannabis may have a negative effect on positive symptoms.

Limitations:
- A few studies were found with relatively small sample sizes, and most of these studies used interviews and instruments that have not been psychometrically evaluated.
- The retrospective self-report data are prone to recall bias.
Chapter 1.2  Implicit and explicit affective associations toward cannabis use in patients with recent-onset schizophrenia and healthy controls

Findings:
In this study implicit and explicit cannabis associations were compared between individuals with (n=70) and without (n=61) psychotic disorder, with use of three Single-Category Implicit Association Tests (SC-IAT) and a pen and paper questionnaire using the same words as the SC-IAT. There were no differences in implicit associations between patients and controls. However, patients scored significantly higher on explicit negative affect expectancies than controls. Both groups demonstrated strong negative implicit associations toward cannabis use, which might be explained by cannabis users not implicitly liking their cannabis use behaviour. Explicit relaxed expectancies were the strongest predictors of cannabis use and craving. There was a trend for implicit active associations to predict craving. The findings indicate that patients suffering from schizophrenia have associations toward cannabis similar to controls, but they have stronger negative explicit cannabis associations.

Limitations:
- The strong implicit negative associations toward cannabis could partly be due to extra personal associations (like general associations that are present in a culture instead of someone's personal associations) or saliency effects.
- Different contributions of THC and CBD to explicit and implicit cannabis associations are unknown.
- The study had a cross-sectional nature and many of the observed relationships were relatively weak. A prospective study examining relations between cannabis associations and cannabis use variables at follow-up might overcome these limitations.

Chapter 1.3  Craving for cannabis in patients with psychotic disorder, their non-affected siblings and healthy controls: psychometric analysis of the Obsessive Compulsive Drug Use Scale

Findings:
In this study, Simultaneous Component Analysis (SCA) was used to compare the factor structure of the Obsessive Compulsive Drug Use Scale for cannabis (OCDUS-CAN) in patients with non-affective psychotic disorder, their siblings, and healthy controls who all used cannabis in the past year. A three-component SCA solution explained 74.2 % of the total variance, and consisted of well-interpretable subscales that could be best described as craving/urge, resistance, and impact. Reliability of the subscales was good. The three subscales significantly discriminated between frequent and infrequent cannabis users. Patients scored higher on the craving/urge and impact scale than siblings and controls, which could be related to primary and secondary symptoms of their disorder. This is the first study providing evidence that the OCDUS-CAN is a valid instrument to assess craving for cannabis in clinical and research samples of patients with psychotic disorder, but also in siblings and individuals without a (family) history of psychotic illness.

Limitations:
- The test-retest reliability and the predictive validity of the OCDUS-CAN were not assessed in this study.
The study population was predominantly male. Although gender was used as covariate in the regression analysis, we did not investigate whether the OCDUS-CAN scales differentiate between males and females.

Chapter 1.4  Cessation of cannabis use by patients with recent-onset schizophrenia and related disorders

Findings:
In this study, medical records of 206 consecutively admitted patients at the Early Psychosis Department in the AMC were examined for data on cessation of cannabis use. Of all patients that had used cannabis (n=167) in the past, more than half (87) ceased the use of cannabis before they were admitted to our clinic: most of these patients (73%) ceased the use of cannabis after they became psychotic and after their first contact with psychiatric services. A prior psychiatric admittance was reported most frequently as the reason for cessation. No differences in patient characteristics were found between patients that ceased their use of cannabis and patients that continued their use. The results suggest that start of treatment for psychosis is related to the cessation of cannabis use, at least in part of the patients. It may well be, that giving patients psycho-education about the negative effects of cannabis on the course of the illness and therefore motivate them stop the use of cannabis, is effective in a substantial part of cannabis using patients.

Limitations:
- All data were dependent on what medical staff had asked the patients and what they had reported in the records.
- There may have been recall bias by patients.
- Reasons for cessation of cannabis were reported in only 52% of cases.
- Because of the retrospective design of this study, we do not know the course of cannabis use in those patients who had not ceased their use, and we do not know whether patients that had stopped using cannabis were able to sustain this abstinence.

Part II
Cannabis use in relation to clinical variables

Chapter 2.1  Age at onset of non-affective psychotic disorder in relation to cannabis use, other drug use and gender

Findings:
In this cross-sectional study of 785 patients with a non-affective psychotic disorder, we used regression analysis to assess the independent effects of gender, cannabis use, and other drug use on the age at onset of first psychosis. Age at onset was 1.8 years earlier in lifetime cannabis users compared to non-users, irrespective of gender or the use of others drugs. Additional use of other drugs did not have an effect on age at onset. From the Kaplan Meier survival curve, differences in age at onset of psychosis between the cannabis users and non users seem to manifest from the early twenties. Age at onset was 1.3 years earlier in males compared to females, irrespective the use of
cannabis or other drugs. Up to 64% of cannabis using patients had used cannabis most intense before the onset of psychosis.

Limitations:
- The age of first cannabis use was not assessed. A comparison between patients that started cannabis use prior to the onset of psychosis versus non using patients might have provided more robust support about the possible contribution of cannabis use to the onset of psychotic illness.

Chapter 2.2 Substance use in a large sample of patients with schizophrenia or related disorders and co-morbid obsessive-compulsive symptoms

Findings:
In this study we examined the relationship between obsessive compulsive symptoms (OCS) and substance use in patients with a non-affective psychotic disorder. We found no significant differences in substance use variables between patients without co-morbid OCS (n=777), patients with mild OCS (n= 143), and patients with more severe OCS (n=85). 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. The results suggest co-morbid OCS is not a protective factor against the use of nicotine and other substances in patients suffering from non-affective psychotic illness.

Limitations:
- Although the Y-BOCS was used as measurement for the severity of OCS, DSM-IV diagnosis of obsessive compulsive disorder was not screened for.
- 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.

Chapter 2.3 Cannabis and cognitive performance in psychosis: a cross-sectional study in patients with non-affective psychotic illness and their unaffected siblings

Findings:
In chapter 2.3, mixed-model regression analysis was used to assess the effect of cannabis recency (current, lifetime, never), and cannabis frequency (daily, weekly, less) and the interaction between cannabis x status (patient, sibling, control) on cognition in patients with non-affective psychosis (n=956), unaffected siblings (n=953) and controls (n=554). Current cannabis use was associated with worse performance on immediate verbal learning, processing speed and working memory compared to never users. Lifetime cannabis use was associated with better scores on acquired knowledge, affect recognition and face identity compared to never-users. Findings 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-morbid (social) functioning, rather than an effect of cannabis itself.

Limitations:
- The cross-sectional design restricts the drawing of causal inferences between cannabis use and cognitive functioning.
Part III  
Cannabis use related to brain white matter

Chapter 3.1  Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia

Findings:
In this study, high resolution structural and diffusion-tensor brain images were used to compare three groups of patients: patients who started regular use of cannabis before the age of 15 years (n=10), at the age of 17 years or later (n=8), and patients who were cannabis naïve (n=8). To verify patient findings white matter integrity of the three patients groups were also compared to a healthy control group (n=10). 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 cannabis use. In the same brain area, cannabis naïve patients showed reduced fractional anisotropy compared to healthy controls. Our results suggest that the age of onset of cannabis use is not identifying for white matter abnormalities in schizophrenia patients, however, our results might indicate a more vulnerable brain structure in cannabis naïve schizophrenia patients.

Limitations:
- Only males were included
- The sample size was relatively small.
- The crossectional study design. It would be of interest to investigate the development of white matter structure and integrity differences in cannabis naïve patients and those who use cannabis.

Chapter 3.2  Reply to Fan and Hart

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 our article presented in chapter 3.1. Fan and Hart (2011) 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 'brain abnormality'.

Dit proefschrift gaat over cannabisgebruik bij patiënten met schizofrenie. Schizofrenie is een ernstige psychiatrische aandoening die wordt gekenmerkt door symptomen als hallucinaties, wanen, apatie, sociaal terugtrekgedrag en cognitieve stoornissen, die kunnen leiden tot verminderd functioneren in het alledaags leven. Bij patiënten met schizofrenie is cannabis een van de meest gebruikte drugs, en cannabisgebruik komt onder hen meer voor dan bij de algemene bevolking. Van cannabisgebruik is inmiddels bekend dat het een verhoogd risico geeft op de ontwikkeling van psychotische stoornissen, en – als de psychotische stoornis zich eenmaal heeft ontwikkeld - op een slechter beloop van de ziekte.

De onderzoeken uit dit proefschrift zijn uitgevoerd bij patiënten met (recent ontstane) schizofrenie, die werden behandeld in een poliklinische of klinische setting. Bij sommige studies werden de gegevens van patiënten vergeleken met die van hun zussen en broers en/of met die van gezonde controles (individuen zonder een (familie-)voorgeschiedenis met een psychotische stoornis).

Deel I van dit proefschrift beschrijft de zelfgerapporteerde redenen voor cannabisgebruik, de effecten van cannabisgebruik, impliciete en expliciete associaties voor cannabis, craving voor cannabis en het stoppen met cannabisgebruik. Deel II van dit proefschrift gaat over cannabisgebruik in relatie tot andere klinische variabelen, zoals de beginleeftijd van schizofrenie, obsessieve-compulsieve symptomen (OCS) en cognitief functioneren. Deel III tenslotte behandelt cannabisgebruik tijdens de adolescentie en jong volwassenheid in relatie tot de witte stof in het brein van patiënten met schizofrenie. Op de volgende bladzijden wordt een samenvatting gegeven van de bevindingen en beperkingen van de onderzoeken uit dit proefschrift.

**Deel I**

*Motivatie voor cannabisgebruik, affectieve associaties voor cannabis en craving voor cannabis in recent ontstane schizofrenie*

Hofdstuk 1.1 Redenen voor cannabisgebruik en effecten van cannabisgebruik zoals gerapporteerd door patiënten met psychotische stoornissen

**Bevindingen:**

In een literatuuroverzicht van 14 studies waarin zelfgerapporteerde redenen voor cannabisgebruik en effecten van cannabisgebruik bij patiënten met psychotische stoornissen werden onderzocht, kwam naar voren dat patiënten over het algemeen aangeven dat ze cannabis gebruiken om positieve emoties te versterken (42,1%), om negatieve emoties te verlichten (66,3%), en om sociale redenen (61,7), zoals het gevoel te hebben ‘erbij te horen’. Relatief weinig patiënten rapporteren dat ze cannabis gebruiken om psychotische symptomen of bijwerkingen van medicatie te verlichten (12,9%).

Frequent gerapporteerde positieve effecten van cannabisgebruik zijn ontspanning en positieve veranderingen in emoties. Veel patiënten rapporteren dat cannabisgebruik positieve symptomen van een psychose negatief beïnvloedt.

**Beperkingen:**

- Er werden weinig studies gevonden met relatief kleine steekproefgroottes.
- In de meeste studies werden niet gevalideerde interviews en meetinstrumenten gebruikt.
Zelfgerapporteerde data die retrospectief zijn verzameld zijn gevoelig voor recall bias (herinneringsvertekening).

Hoofdstuk 1.2 Impliciete en expliciete affectieve associaties voor cannabisgebruik bij patiënten met recent ontstane schizofrenie en gezonde controles

Bevindingen:
Bij deze studie werden impliciete en expliciete associaties voor cannabis vergeleken tussen individuen met (n=70) en zonder (n=61) een psychotische stoornis, met behulp van drie Single-Category Impliciete Associatie Testen (SC-IAT) en een vragenlijst waarin dezelfde woorden werden gebruikt als in de SC-IAT. Er werden geen verschillen gevonden in impliciete associaties tussen patiënten en controles. Echter, patiënten scoorden significant hoger op de expliciete negatieve verwachtingen dan controles. Beide groepen vertoonden sterke negatieve impliciete associaties voor cannabis, waarbij een verklaring zou kunnen zijn dat cannabisgebruikers hun gedrag wat betreft cannabisgebruik impliciet niet aangenaam vinden. Expliciete verwachtingen van cannabis betreffende ontspanning waren de sterkste voorspellers van cannabisgebruik en craving. Er werd een trend gevonden voor de voorspellende waarde van de impliciete ‘actieve’ associaties voor craving. De bevindingen wijzen erop dat patiënten die lijden aan schizofrenie associaties voor cannabis hebben die vergelijkbaar zijn met die van gezonde controles, maar dat ze wel sterkere expliciete negatieve verwachtingen hebben van cannabisgebruik.

Beperkingen:
- De sterke impliciete negatieve associaties voor cannabis zouden te wijten kunnen zijn aan niet-persoonlijke associaties (bijvoorbeeld door algemene attitudes in een cultuur) of door salience effecten, door de opvallendheid van de woorden.
- De verschillende bijdragen van THC en CBD op expliciete en impliciete associaties voor cannabis zijn nog onbekend.
- De studie was cross-sectioneel van aard en veel van de gevonden relaties waren relatief zwak. Een prospectieve studie waarbij wordt gekeken naar de relatie tussen associaties voor cannabis en cannabisgebruik tijdens follow-up zouden deze beperkingen kunnen overkomen.

Hoofdstuk 1.3 Craving voor cannabis bij patiënten met een psychotische stoornis, hun niet-aangedane zussen en broers en gezonde controles: psychometrische analyse van de Obsessive Compulsive Drug Use Scale

Bevindingen:
Bij dit onderzoek werd Simultane Component Analyse (SCA) gebruikt om de factorstructuur van de Obsessive Compulsive Drug Use Scale voor cannabis (OCDUS-CAN) te vergelijken tussen patiënten met een non-affectieve psychotische stoornis, hun zussen en broers en gezonde controles – die allemaal cannabis hadden gebruikt in het afgelopen jaar. Een drie-componentenoplossing van de SCA verklaarde 74,2 % van de totale variatie, en bestond uit subschalen die goed te interpreteren waren. Deze subschalen kunnen het best worden beschreven als hunkering/drang, weerstand, en impact. De betrouwbaarheid van de subschalen was goed. De drie subschalen maakten significant onderscheid tussen frequente en infrequente cannabisgebruikers. Patiënten scoorden hoger op de
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hunkering/drang- en impactschaal dan zussen, broers en gezonde controles, wat mogelijk verklaard kan worden door de primaire en secundaire symptomen van hun ziekte. Dit is de eerste studie die bewijst dat de OCDUS-CAN een valide instrument is om craving voor cannabis vast te stellen bij klinische en onderzoekspopulaties van patiënten met een psychotische stoornis, maar ook bij hun zussen en broers en bij gezonde controles.

Beperkingen:

- De test-hertestbetrouwbaarheid (test-retest reliability) en de voorspellende waarde van de OCDUS-CAN zijn niet vastgesteld in deze studie.
- De studiepopulatie bestond voornamelijk uit mannen. Alhoewel geslacht als covariaat was gebruikt in de regressie-analyse, hebben we niet onderzocht of de schalen van de OCDUS-CAN kunnen differentiëren tussen mannen en vrouwen.

Hoofdstuk 1.4 Het stoppen met cannabisgebruik door patiënten met recent ontstane schizofrenie en verwante stoornissen

Bevindingen:

In dit onderzoek werden medische statussen bekeken van 206 patiënten die achtereenvolgend waren opgenomen op de Zorglijn Vroege Psychose van het AMC, waarbij werd gekeken naar data betreffende het stoppen met cannabisgebruik. Van alle patiënten die cannabis hadden gebruikt in het verleden (n=167), was meer dan de helft (n=87) gestopt met het gebruik van cannabis voordat ze in behandeling kwamen bij onze kliniek: de meeste van deze patiënten (73%) stopten met cannabis nadat ze psychotisch waren geworden en nadat psychiatrische zorg was ingezet. Een eerdere psychiatrie opname werd het meest genoemd als reden voor het stoppen met cannabis. Er werden geen verschillen gevonden tussen patiënten die gestopt waren met cannabisgebruik en patiënten die doorgegaan waren met cannabisgebruik.

De resultaten suggereren dat de start van behandeling voor psychose is gerelateerd aan het stoppen met cannabisgebruik, in ieder geval bij een deel van de patiënten. Het zou best kunnen dat psychoeducatie over de negatieve effecten van cannabisgebruik op het beloop van de ziekte (een mogelijke motivatie om te stoppen met cannabisgebruik) effectief is in een substantieel deel van de patiënten.

Beperkingen:

- Alle data waren afhankelijk van wat de medewerkers van de afdeling hadden gevraagd aan de patiënten en wat zij hadden gerapporteerd in de status.
- Er kan recall bias zijn opgetreden bij patiënten.
- Redenen voor het stoppen met cannabisgebruik waren maar in 52% van de gevallen gerapporteerd in de status.
- Wegens de retrospectieve opzet van de studie weten we het beloop van cannabisgebruik niet van de patiënten die niet waren gestopt met cannabisgebruik, en weten we niet of de patiënten die wel waren gestopt in staat waren dit vol te houden.
Deel II
Cannabisgebruik in relatie tot klinische variabelen

Hoofdstuk 2.1 De beginleeftijd van de non-affectieve psychotische stoornis in relatie tot cannabisgebruik, ander druggebruik en geslacht

Bevindingen:
In deze cross-sectionele studie bij 785 patiënten met een non-affectieve psychotische stoornis gebruikten we regressie-analyse om de onafhankelijke effecten van geslacht, cannabisgebruik en ander druggebruik op de beginleeftijd van de eerste psychose vast te stellen. De beginleeftijd van de eerste psychose bij cannabisgebruikers was 1,8 jaar eerder dan de beginleeftijd bij niet-gebruikers, ongeacht het geslacht of het gebruik van andere drugs. Zoals te zien in de Kaplan Meier-overlevingscurve, lijken verschillen in de beginleeftijd tussen cannabisgebruikers en niet-gebruikers zich te openbaren in de leeftijd van begin twintig jaar. De beginleeftijd was 1,3 jaar eerder bij mannen vergeleken met die bij vrouwen, ongeacht het gebruik van cannabis of andere drugs. Van de cannabisgebruikende patiënten had 64% cannabis het meest intensief gebruikt voor het ontstaan van de eerste psychose.

Beperkingen:
De beginleeftijd van cannabisgebruik was niet vastgesteld. Een vergelijking tussen niet-gebruikende patiënten en patiënten die waren begonnen met cannabisgebruik voor het ontstaan van psychotische verschijnselen zou mogelijk hebben voorzien in een robuustere ondersteuning voor de hypothese dat cannabisgebruik van invloed is op het ontstaan van psychotische stoornissen.

Hoofdstuk 2.2 Middelengebruik bij een grote populatie van patiënten met schizofrenie en verwante stoornissen en comorbide obsessieve-compulsieve symptomen

Bevindingen:
In dit onderzoek werd de relatie tussen OCS en middelengebruik onderzocht bij patiënten met een non-affectieve psychotische stoornis. We vonden geen significante verschillen in middelengebruikvariabelen tussen patiënten zonder comorbide OCS (n=777), patiënten met milde OCS (n=143), en patiënten met ernstigere OCS (n=85). Er werd een trend gevonden dat het percentage patiënten dat zwaar alcohol gebruikte groter was bij patiënten met milde OCS dan bij de andere twee patiëntengroepen. Tevens werd er een trend gevonden dat bij patiënten met milde OCS het percentage met een lifetime-diagnose van een stoornis in het gebruik van cannabis groter was dan bij de andere groepen. De resultaten suggereren dat comorbide OCS bij patiënten die lijden aan een non-affectieve psychotische stoornis niet een beschermende factor is voor het gebruik van nicotine en andere middelen.

Beperkingen:
Alhoewel de Y-BOCS gebruikt werd als meetschaal voor de ernst van OCS, werd er niet gescreend voor de DSM-IV-diagnose obsessieve-compulsieve stoornis.
De subtypes van OCS werden niet meegenomen in de analyse. Het zou interessant zijn om uit te vinden of er een relatie bestaat tussen de subtypes OCS en alcohol- en cannabisgebruik.

Hoofdstuk 2.3 Cannabis en cognitieve prestatie bij psychose: een cross-sectioneel onderzoek bij patiënten met een non-affectieve psychotische stoornis en hun niet-aangedane zussen en broers

Bevindingen:
In hoofdstuk 2.3 werd mixed-model regressie-analyse gebruikt om de effecten van 1) cannabis use recency (ofwel recentheid van cannabisgebruik: huidig, lifetime of nooit), 2) frequentie van cannabisgebruik (dagelijks, wekelijks of minder), en 3) de interactie tussen cannabis en status (patiënt, zus of broer, controle) op cognitie vast te stellen bij patiënten met een non-affectieve psychose (n=956), niet aangedane zussen of broers (n=953) en controles (n=554). Huidig cannabisgebruik was geassocieerd met slechtere prestaties op het verbaal kortetermijngeheugen, verwerkingssnelheid en werkgeheugen in vergelijking met nooit-gebruikers. Lifetime cannabisgebruik was geassocieerd met betere scores op verworven kennis, emotieherkenning en gezichtsherkenning in vergelijking met nooit-gebruikers. De bevindingen suggereren dat cannabisgebruikende patiënten een hogere cognitieve potentie hebben, terwijl de (sub)acute effecten van cannabis het cognitief functioneren kunnen beperken. Lifetime cannabisgebruikers presteren beter op sociale en algemene intelligentietaken, wat verklaard kan worden door hun betere premorbide (sociaal) functioneren, in plaats van door het effect van cannabis zelf.

Beperkingen:
De cross-sectionele opzet beperkt het maken van causale gevolgtrekkingen over cannabis en cognitief functioneren.

Deel III
Cannabisgebruik in relatie tot witte stof in het brein

Hoofdstuk 3.1 Cannabisgebruik en de structuur en integriteit van witte stof in het corpus callosum bij recent ontstane schizofrenie

Bevindingen:
In deze studie werden structurele en diffusion tensor afbeeldingen van het brein gebruikt om drie patiëntgroepen te vergelijken: patiënten die waren gestart met regelmatig cannabisgebruik voor de leeftijd van 15 jaar (n=10), op de leeftijd van 17 jaar of later (n=8), en cannabis-naïeve patiënten (n=8). Om de resultaten van dit onderzoek te verifiëren, werd de integriteit van de witte stof bij de drie patiëntgroepen vergeleken met die van een gezonde controlegroep (n=10). De cannabis-naïeve patiënten vertoonden een verminderde dichtheid van de witte stof en verminderde fractionele anisotropie in het splenium van het corpus callosum in vergelijking met patiënten met vroeg cannabisgebruik (voor het 15e jaar). In vergelijking met gezonde controles vertoonden cannabis-naïeve patiënten in hetzelfde hersengebied verminderde fractionele anisotropie. Onze resultaten

1 Deel van de grote witte stof bundel die de linker en rechter hersenhelften met elkaar verbindt
suggereer dat de beginleeftijd van cannabisgebruik niet bepalend is voor wittestofafwijkingen. Echter, onze resultaten zouden kunnen wijzen op een kwetsbaardere hersenstructuur bij cannabis-naieve patiënten.

**Beperkingen:**
- Deze studie bestond alleen uit mannelijke deelnemers.
- De steekproefgrootte was relatief klein.
- De cross-sectionele onderzoekssopzet. Het zou interessant zijn om verschillen tussen cannabis-naieve patiënten en cannabisgebruikende patiënten in de ontwikkeling van witte stof structuur en integriteit te onderzoeken.

**Hoofdstuk 3.2 Reactie op Fan en Hart**

Hoofdstuk 3.2 is een brief gericht aan de redacteur van het tijdschrift *Psychiatry Research: Neuroimaging*, waarin we een reactie geven op Fan en Hart (2011). Fan en Hart hadden een brief geschreven aan dezelfde redacteur, waarin ze verwijzen naar ons artikel dat we gepresenteerd hebben in hoofdstuk 3.1 van dit proefschrift. Fan en Hart (2011) richtten onze aandacht op het feit dat de manier waarop studieresultaten worden beschreven, kan leiden tot discussie over hoe ze kunnen worden ge(mis)interpreteerd. Alhoewel we het niet eens waren met al hun punten van kritiek, realiseren we ons dat we voorzichtig moeten blijven met het gebruik van sommige woorden zoals "afwijking in het brein" (*brain abnormality*).

List of publications
List of publications

Articles

Dekker N, Swets M, GROUP investigators (Kahn RS, Linszen DH, Van Os J, Wiersma D, Bruggeman R, Cahn W, De Haan L, Krabbendam L, Myin-Germeyi I). Substance use in a large sample of patients with schizophrenia or related disorders and co-morbid obsessive-compulsive symptoms. Submitted for publication.


**Book chapters**

**Dekker N**, De Haan L. Mijn eten is vergiftigd door de duivel (Casus 29). In Probleemgeoriënteerd denken in de Psychiatrie. Onder redactie van Van Balkom AJLM en Hengeveld MW, De Tijdstroom, tweede geheel herziene druk, 2009

Color figures
All color figures belong to chapter 3.1 ‘Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia’
Legends of Figure 1:

**Figure 1a**
FA differences in cannabis naïve patients, compared to patients with early-onset cannabis use. Coronal view: FA reduction of the cannabis naïve patients, compared to the patients with early-onset cannabis use in the splenium of the corpus callosum (Talairach and Tournoux [T&T] co-ordinates: -14, -46, 27)

**Figure 1b**
Morphological differences in cannabis naïve patients, compared to patients with early-onset cannabis use. Coronal view: WM reduction of cannabis naïve patients, compared to patients with early-onset cannabis use in the splenium of the corpus callosum (T&T: -13, -46, 28), occipital lobe (T&T: 20, -77, 29) and temporal lobe (T&T: -30, -01, -10)
Figure 2

Legend figure 2:

FA value differences in cannabis naïve patients, compared to healthy controls. Coronal view: FA reduction in cannabis naïve patients, compared to healthy controls in the splenium of the corpus callosum, bilaterally (Talairach and Tournoux (T&T) co-ordinates: -13, -42, 21/12, -47, 10).