Cannabis use, cognitive functioning and behaviour problems

Lendering, M.F.H.

Cannabis use, cognitive functioning and behaviour problems.

Proefschrift

Merel Griffith - Lendering

Cover photo: Gerard van Buurt.

Cannabis use, cognitive functioning and behaviour problems

Proefschrift

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,

op gezag van de Rector Magnificus, prof. mr. C.J.J.M. Stolker,

volgens het besluit van het College voor Promoties

te verdedigen op donderdag 28 Maart 2013

klokke 11:15 uur

door

Merel Federique Heleen Griffith – Lendering

geboren op 3 september 1983

te Curaçao.

Promotiecommisie

Promotoren: Prof. dr. H. Swaab
Prof. dr. W.A.M. Vollebergh (Universiteit Utrecht, Algemene Sociale Wetenschappen, Faculteit Sociale Wetenschappen)

Co-promotor: Dr. S.C.J.Huijbregts

Overige leden: Prof. Dr. T.F.M. ter Bogt (Universiteit Utrecht, Gedragswetenschappen, afdeling Jeugd en Gezin)
Prof. Dr. H. Van Engeland (UMC Utrecht, afd. Psychiatrie, Rudolph Magnus Instituut)
Prof. Dr. I.H.A. Franken (Erasmus Universiteit Rotterdam)
Prof. Dr. E.M. Scholte
Prof. Dr. P.H. Vedder

Content

1. General Introduction

Introduction

Since the 1960s, cannabis has gained enormous popularity. Nowadays, cannabis is the most widely used drug worldwide. It has been estimated that 78 million people (aged 15 – 64) have used cannabis at least once in European countries (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2011). Also, an estimated 23 million have used cannabis in the last year, which represents 6,7 % of all 15 – 64 year olds (EMCDDA, 2011). Cannabis use has become especially prevalent among 15-24 year olds. In 1990, it was estimated that about 5 % had used cannabis in the past year. This number has increased rapidly; based on the 2011 survey reports, about 12.1 % of 15-24 year olds have used it in the past year and 6.6 % in the past month (EMCDDA, 2011). Research in countries outside Europe, including the US, New Zealand and Canada, has shown a high prevalence among young adults as well (EMCDDA, 2011). Interestingly, despite the fact that the Netherlands is the only country where possession of up to five grams of cannabis is not legally prosecuted, prevalence rates of cannabis use are higher in other countries. For example in 2009, annual prevalence within the adult population (aged 15-64 years) was far higher in the US (11%) and Australia / New Zealand (15 %) than in the Netherlands (7%) (EMCDDA, 2011; UNODC, 2012).

Along with increasing prevalence rates, the level of delta-9-tetra-hydrocannabinol (Δ^9-THC) has increased over the past years, in particular in Dutch weed (EMCDDA 2011; Pijlman et al., 2005). THC is the primary (psycho-)active ingredient of cannabis, and it has been argued that higher levels of THC may yield stronger effects. THC concentrations in imported marijuana remained stable (Pijlman et al., 2005). In 2004, Dutch marijuana contained on average 20 % THC levels, whereas THC levels in imported marijuana was around 7 %. In 2008, THC levels in European marijuana ranged between 3 – 16 %, again with especially high levels in Dutch marijuana (EMCDDA, 2011). These higher levels of THC concentrations, in combination with an increase in prevalence rates, may contribute to cannabis abuse and dependency problems (Cooper & Haney, 2009).

Whereas this is still subject to further investigations, indications for associations with (mental) health problems are strong enough to validate further research into (risk) factors associated with (the initiation of) cannabis use. It is important to study such possible (risk) factors of cannabis use as early in life as possible, as it has been shown that early initiation of cannabis use is associated with an increased risk of escalation to heavier cannabis use, and to the use of other illicit drugs (Coffey et al., 2000; Lynskey et al., 2002; Lynskey et al., 2006). Early onset of cannabis use might also mean a longer period of heavy use, and hence, an increased risk of

experiencing any adverse health effects that cannabis use may have in later adult life (e.g. Moore et al., 2007; Patton et al., 2002). According to Hawkins, Catalano & Miller's (1992) and Petraitis, Flay & Miller's (1995) risk factor taxonomy, risk factors for the initiation of cannabis use or extent of cannabis use can be summarized into four categories: (1) Socio-environmental variables (e.g. male gender, low SES, unemployment, financial situation); (2) substance-related variables (e.g. easy availability of drugs, drug-using peers, positive attitude towards drugs, prior history of tobacco, alcohol, or other illicit drug use); (3) intrapersonal variables (e.g. mental health problems) and (4) interpersonal variables (e.g. family functioning, relationship with mother, not having been brought up by both parents) (Von Sydow et al., 2002). The focus of the present thesis is on intrapersonal variables, including vulnerability for psychosis and internalizing and externalizing behaviour problems, which may be correlates of cannabis use. In addition to factors that have been more or less established as intrapersonal risk factors, there will be an emphasis on social functioning (more specifically, lack of social skills) as a risk factor for cannabis use, its initiation and its frequency. Although social functioning in general may also be considered an interpersonal risk (or protective) factor, specific social skills appear to classify more readily as intrapersonal risk (or protective factors). Lastly, we will focus on (specific) cognitive weaknesses in cannabis users, which may also classify as intrapersonal risk factors.

Cannabis Use and Mental Health

Research reveals that regular cannabis use is strongly correlated with use of alcohol, smoking, and use of other (illicit) drugs (Fergusson, Boden & Horwood, 2006, Fergusson et al., 2002a; Lynskey et al., 2003), and is related to delinquency, unemployment, risky sexual behaviour, affiliation with delinquent peers, school dropout and reduced educational achievement (Fergusson & Horwood, 1997; Fergusson et al., 2002b; Lynskey & Hall, 2000). Also, cannabis use, in particular regular use, has been associated with a wide range of mental health problems, including psychotic disorders (Arseneault et al., 2002; van Gastel et al., 2012; Malone et al., 2010; Moore et al., 2007; van Os et al., 2002), externalizing problems (aggressive and delinquent behaviour) (Monshouwer et al., 2006), depression (Degenhardt et al., 2001; Degenhardt et al., 2003; Patton et al., 2002) and anxiety (Hayatbakhsh et al., 2007; Patton et al., 2002; van Laar et al., 2007).

Associations between cannabis use and different mental health problems, including internalizing and externalizing behaviour problems and increased risk of psychosis, need to be

examined further. One important issue to investigate is the temporal order of the associations. Different hypotheses have been put forward to try to explain these associations, including the damage hypothesis, the self-medication hypothesis, the vulnerability hypothesis and the shared causes hypothesis. According to the 'damage hypothesis', the association between cannabis and mental health problems reflects cause and effect associations in which the use of cannabis leads to the development of various mental health problems (Brook, Cohen & Brook, 1998; Kandel, Yamaguchi & Chen, 1992). For example, Moore et al. (2007) concluded that cannabis use increases the risk of psychosis by 14 %. Alternatively, the 'self-medication hypothesis' proposes that cannabis use might be the result rather than the cause of mental health problems, as adolescents with mental health problems tend to resort to drug use to 'sooth painful feelings' rather than to seek pleasure (Khantzian , 1985). Previous evidence for the self-medication hypothesis stems mostly from clinical observations of patients suffering from psychiatric disorders (e.g. Klein et al., 1994; Warner et al., 1994). However, empirical studies and clinical observations have not consistently provided evidence for either the damage- or the self-medication hypothesis. Following the lack of consistency in results supporting these hypotheses, it has been suggested that cause and effect might be moderated by particular forms of vulnerability (the 'vulnerability hypothesis'), i.e. the linkage between cannabis use and mental health problems might be particularly evident in individuals who are - due to their biological, personal or familial make-up - sensitive to the damaging effects of cannabis or more likely to use drugs for their soothing effects (Caspi et al., 2005; Henquet et al., 2005; Miller et al., 2001; Verdoux et al., 2003). It should be noted that it is not entirely clear which biological, personal or familial factors might constitute particular risk enhancers for mental health problems when present together with cannabis use. A further issue is finding the best possible measures through which such moderating risk factors express themselves. For example, Caspi and colleagues (2005) showed that carriers of the catechol-O-methyltransferase (COMT) valine158 allele were most likely to exhibit psychotic symptoms if they used cannabis. Functional polymorphisms of other genes as well as several environmental factors (e.g. stress) have also been shown to moderate the effects of cannabis considering the development of different forms of psychopathology (Henquet et al., 2008). Even though a number of these interactions were replicated (Gill et al., 2010; Rijsdijk et al., 2011), the amount of variance in mental health problems explained by single gene polymorphisms or environmental factors remains limited. Thus, it may be preferable to study intermediate cognitive phenotypes, which have generally been associated with multiple gene variants and environmental factors, in association with cannabis use. It is clear, however, that

the vulnerability hypothesis may have many different faces and should be investigated more thoroughly. Moreover, it is related-, but not entirely similar to the so-called 'shared causes hypothesis'. This last type of hypothesis implies that the linkage between cannabis use and mental health problems is largely non-causal and may be the result of several factors associated with the use of cannabis and mental health problems (simultaneously), such as disadvantaged backgrounds (including low SES; low maternal education; growing up in a single parent family; poorer parental attachment) and difficult childhood circumstances (including family dysfunction, crime, depression, anxiety, suicidal behaviours, exposure to the use of (illicit) substances) (Fergusson & Horwood, 1997; Fergusson, Horwood & Swain-Cambell, 2002a). Thus, this hypothesis states that the higher rate of mental health problems found among cannabis users arises because cannabis use is more common in individuals exposed to other possible causes of mental health problems. As with the vulnerability hypothesis, there are many different (other) factors that might play a role in the development of mental health problems. The main difference between the two types of hypotheses is that the vulnerability hypotheses state that co-occurring cannabis use and other risk factors constitute supra-additive effects on mental health, whereas the shared-causes hypotheses particularly involve mediating effects of other risk factors on cannabis-mental health associations.

Although many studies have focused on cannabis use and mental health outcomes, including psychosis and both internalizing and externalizing behaviour problems, little is known about this relationship during (early) adolescence. This seems crucial, since adolescence is a life phase characterized by significant biological changes and consecutive maturation processes, especially neurologically, which might increase vulnerability to enduring effects of external influences like such as exposure to cannabis (Bossong & Nieding., 2010; Schneider, 2008). The first aim of this dissertation is to determine the temporal order of cannabis use and mental health problems, including vulnerability for psychosis, internalizing and externalizing problems, thereby testing the damage hypothesis, the self-medication hypothesis and the shared-causes hypothesis.

Cannabis use and Social Functioning

Associations between social functioning and cannabis use have not yet been extensively investigated. This is a relevant factor to study in adolescents and young adults as individuals

in this age range generally use cannabis in social contexts (e.g. at parties, dancing clubs or on the street). Indeed, some of the most frequently reported reasons for using cannabis by young adults are of a social nature, i.e. ”to bond with friends” or to “hang out” (Lee et al., 2007). Another reason for engaging in cannabis use is conformity, in other words, “under peer pressure” or “because friends do it” (Simons et al., 1998). Taken together, cannabis can be seen as a social drug, and many of the reported motives for engaging in cannabis use are socially-driven.

There has been relatively little research focusing on possible prospective associations between social parameters and cannabis use during adolescence. Cross-sectional studies have shown that adolescents who experiment with cannabis show lower levels of social self-control and higher levels of negative self-esteem compared to non-users (Sussman et al., 2003; Veselska et al., 2009). Such results appear to indicate relatively poor social adjustment among cannabis users. Also, although being under the influence of cannabis has been associated with increases in the extent of social interactive behaviour, the quality of such behaviour (e.g. of verbal exchanges during these social interactions) has been shown to be relatively low (Foltin et al., 1987, 1988). Other studies, however, showed that cannabis users displayed higher levels of social competence (e.g. assertive behaviour) compared to non-users, without apparent differences in the quality of such behaviour (e.g. Shedler & Block, 1990; Veselska et al., 2009). Such results lead to the hypothesis that socially competent adolescents may find themselves in social contexts more often, where the probability of exposure to cannabis is higher. Other studies have found similar results, namely that those who experiment with cannabis during adolescence are socially better adjusted and have better social skills than both abstainers and heavy users (Engels & Ter Bogt; 2001; Shedler & Block, 1990). Pokhrel et al. (2007) investigated the prospective relationship between cannabis use and social self-control. Lack of social self-control refers to one’s tendency to ‘act without thinking’ (Tarter, 1988), especially in a social context. Results showed a reciprocal relationship between social self-control and cannabis use. Lack of social self-control increased cannabis use, which in turn decreased social self-control.

Studies describing social functioning in cannabis users have predominantly focused on psychopathology and associated negative effects on social behaviour. Indeed, psychosis, internalizing- and externalizing behavioural problems, which are obviously characterized by social dysfunction, have been associated with cannabis use (Moore et al., 2007; Degenhardt et al., 2003; Fergusson et al., 2002a). However, cannabis is used very frequently and by many different types of people. Most of these people do not develop serious forms of

psychopathology. These individuals could, however, still experience social problems with potential impact upon everyday life. To our knowledge, there are no studies focusing specifically on social skills as predictors of cannabis use.
Therefore, another aim of the present thesis is to study cannabis use and its relation to social parameters. More specifically, the focus will be on (lack of) different social skills (cooperation, assertion and self-control) as possible risk factors of cannabis initiation and frequency of cannabis use (chapter 4).

The above research questions on mental health (Chapter 2 and 3), social functioning (Chapter 4) and cannabis use will be studied using data from a large prospective cohort study called TRAILS (Tracking Adolescents' Individual Lives Survey), which follows Dutch adolescents biennially, starting at the age of 10-12 years at the first assessment (chapter 2-3-4). Due to a lack of available data on specific possible moderating factors such as particular gene polymorphisms and their associated cognitive profiles, (variants of) the vulnerability hypothesis were not tested in this sample. In chapter 5 and 6 of this thesis moderating effects of cognitive abilities on cannabis use predicting psychological problems are tested in a different sample, consisting mainly of undergraduate students. The TRAILS-sample was used for a related research question featuring in this thesis, i.e. whether social functioning predicts (different aspects of) cannabis use. Social functioning could be regarded as another intermediate phenotype in associations between cannabis use and mental health, and might therefore also moderate such associations. It may be argued, however, that social functioning is not a very unitary concept, i.e. it contains many subcomponents and different operationalizations as well as its own broad set of determining factors. Thus, if an interaction between cannabis use and social functioning in the prediction of psychological problems would be observed, this would not yet provide very detailed information on (constellations of) risk factors for poor mental health. Moreover, social functioning has, perhaps unfortunately, not yet been extensively studied in relation to cannabis use.

Cannabis use and Cognitive Functioning

Another important factor to study in relation to cannabis use is cognitive functioning, which may be related to both initiation and continuation of drug use, as well as transition to more serious use of cannabis or other drugs. It has proven to be difficult to pinpoint specific domains of cognitive weaknesses in cannabis users (Fernández-Serrano et al., 2011). One

reason is that cognitive weaknesses generally do not appear to be specific to cannabis use: similar weaknesses can be found among users of other substances. A second reason lies in methodological issues, i.e. the means of assessment of certain cognitive constructs, the definition of those constructs, and differing sample characteristics.

Cognitive impairments that have been associated with cannabis use involve executive function (EF), implicit cognition, episodic memory, and emotional processing (Pope et al., 2001; Solowij, 1998; Solowij et al., 2002; Stacy and Wiers, 2010; Verdejo-Garcia, Lawrence & Clark, 2008). Except perhaps episodic memory, these are all broadly defined constructs. Core EF-abilities include inhibitory control and working memory, which are multi-faceted concepts themselves (cf. Christ et al., 2010; D'Esposito et al., 1999; Nigg, 2000). Core aspects of emotional processing include social perception (e.g. emotion recognition), Theory of Mind (i.e. the ability to "mentalize"), empathy, and reward/punishment sensitivity (Adolphs, 2002; Beer et al., 2004; Dodge and Rabiner, 2004; Ochsner, 2008; Pettit and Mize, 2007). Studies investigating cognitive correlates of cannabis use have often employed task paradigms addressing combinations of different (social-) cognitive skills. Examples include decision-making and implicit cognition tasks, which require working memory, and cognitive and motivational inhibitory control (Busemeyer and Stout, 2002; Stacy and Wiers, 2010; Whitlow et al., 2004).

In this thesis, the focus will be on more specific cognitive constructs that may underlie or follow cannabis use, i.e. motivational versus cognitive inhibitory control (chapter 5) and social perception (chapter 6). Contrasting cognitive and motivational inhibitory control is based on the taxonomy of executive function proposed by Zelazo and Müller (2002). Zelazo and Müller (2002) distinguish executive functions along "hot" and "cool" dimensions. Hot EF involves affect and motivation, either inherent in the task or the context in which a task has to be performed, while cool EF does not involve such components or contexts and is more related to basic abilities. This taxonomy has been supported by neuroanatomical and developmental studies (Kerr & Zelazo, 2004; Prencipe et al., 2011; Zelazo & Müller, 2002)

Results of several (recent) studies suggest that cognitive deficits in cannabis users (particularly in "non-addicted" users) may only become apparent when a task involves an affective/motivational component or has to be performed in a context containing such elements. In order to test this hypothesis, contrasting performance on tasks with and without such components is required.

The choice to investigate social perception is based on recent research findings (Platt et al., 2010), abnormalities observed in amygdala volumes and activity of cannabis users (or

following cannabis use) ((Yucel et al., 2008), thereby taking into account the evidence for amygdale-involvement in social perception (Adolphs, 2002; Ochsner, 2008), and the central role of social perception in affective/motivational information processing. Another very important argument to investigate social perception is that this aspect of cognition (similar to other aspects of cognition associated with affect and motivation) has repeatedly been associated with the types of psychological problems that have also been associated with cannabis use, including (subclinical) levels of psychosis/schizophrenia, and internalizing and externalizing behaviour problems (Demenescu et al., 2010; Germine and Hooker, 2011; Kiehl et al., 2000; Kohler et al., 2010; Marsh and Blair, 2008; Nigg et al., 1998; Raaijmakers et al., 2008; Riggs et al., 2006; Rössler et al., 2011). As for the study of cognitive versus motivational inhibitory control, a contrast will be introduced in order to allow more specific statements on the cognitive profile of cannabis users. This contrast is provided as one of the tasks that will be used involves actual emotion recognition whereas the other task does not. Moreover, the two tasks that are used differ in the amount of working memory capacity that has to be allocated to achieve optimal performance. Again similar to the cognitive versus motivational inhibition study, interrelations between possible cognitive impairments and psychological problems will be investigated, incorporating both mediating and moderating effects.

For investigation of the above research questions on cognition and cannabis use (Chapter 5 and 6), we did not make use of the TRAILS-sample. A disadvantage of this is that the self-medication and damage-hypotheses could not be investigated, as for samples that were used here (see Samples and Methods-sections below) no longitudinal data were available. We did however add to the existing literature on cannabis and cognition by adding associations with behaviour in daily life and psychological problems. Moreover, we tested the vulnerability hypothesis by examining whether cannabis users with relatively poor cognitive skills experience more psychological problems compared to those without such difficulties.

Research questions

The first aim of this dissertation is to determine the temporal order of cannabis use and mental health problems during (early) adolescence. Secondly, we will focus on social parameters in association with cannabis use. The third aim of this thesis is to investigate cognitive correlates of cannabis use, thereby specifically investigating their roles in cannabis-behaviour associations.

The main research questions of this thesis are:

1. Is there a relationship between cannabis use and both internalizing and externalizing behaviour problems in early adolescence? And if so, what is the temporal order of these relationships?
2. Is there a relationship between cannabis use and vulnerability for psychosis, as measured by social problems, thought problems and attentional problems, in adolescence? And if so, what is the temporal order of this relationship?
3. Are the social skills cooperation, assertiveness and self-control precursors of cannabis use during early adolescence? Specifically, are these social skills precursors of (early) cannabis initiation and the frequency of use?
4. Do cannabis users experience problems with motivational inhibitory control, cognitive inhibitory control or both? Also, do cannabis users experience problems in behavioural impulsivity, and is this related to motivational and/or cognitive inhibitory control?
5. Do cannabis users experience problems with respect to social perception? Also, are cannabis users with problems in social perception more likely to experience psychological problems?

Samples en Methods

For the present thesis, three different samples were used. The first 3 research questions concerning mental health and social functioning were studied in a population-based sample, the cognitive processes (research questions #4 and #5) were studied in two samples of (mostly) undergraduate students. Details of the datasets are provided below.

1. TRAILS Sample

The study described in this thesis was embedded in the Tracking Adolescents' Individual Lives Survey (TRAILS) (de Winter et al., 2005; Huisman et al., 2008). TRAILS is a large prospective cohort study of Dutch adolescents initially aged 10-12 years, who are measured biennially at least until they are 24 years old. The key objective of TRAILS is to chart and explain the development of mental health from preadolescence into adulthood, both at the level of psychopathology and the levels of underlying vulnerability and environmental risk. For the present thesis, data from the first (2001-2002), second (2003-2004), third (2005-2007) and fourth (2008-2010) assessment waves were used. The TRAILS target sample involved young adolescents living in five municipalities in the North of the Netherlands, including both urban and rural areas.

Sample selection involved two steps. First, the municipalities selected were requested to give names and addresses of all inhabitants born between 10-01-1989 and 09-30-1990 (first two municipalities) or 10-01-1990 and 09-30-1991 (last three municipalities), yielding 3483 names. Simultaneously, primary schools (including schools for special education) within these municipalities were approached with the request to participate in TRAILS; i.e., pass on students' lists, provide information about the children's behaviour and performance at school, and allow class administration of questionnaires and individual testing (neurocognitive, intelligence, and physical) at school. School participation was a prerequisite for eligible children, before parents were approached by the TRAILS staff, with the exception of children already attending secondary schools (< 1%), who were contacted without involving their schools. Of the 135 primary schools within the municipalities, 122 (90.4% of the schools accommodating 90.3% of the children) agreed to participate in the study.

If schools agreed to participate, parents (or guardians) received two brochures, one for themselves and one for their children, with information about the study; and a TRAILS staff member visited the school to inform eligible children about the study. Approximately one week later, a TRAILS interviewer contacted them by telephone to give additional

information, answer questions, and ask whether they and their son or daughter were willing to participate in the study. Respondents with an unlisted telephone number were requested by mail to pass on their number. If they reacted neither to that letter, nor to a reminder letter sent a few weeks later, staff members paid personal visits to their house. Parents who refused to participate were asked for permission to call back in about two months to minimize the number of refusals due to temporary reasons. If parents agreed to participate, an interview was scheduled, during which they were requested to sign an informed consent form. Children were excluded from the study if they were incapable to participate due to mental retardation or a serious physical illness or handicap; or if no Dutch-speaking parent or parent surrogate was available, and if it was not feasible to administer part of the measurements in the parent's language.

Of all children approached for enrollment in the study (i.e., selected by the municipalities and attending a school that was willing to participate, N = 3145), 6.7% were excluded because incapability or language problems. Of the remaining 2935 children, 76.0% (N = 2230, mean age = 11.09, SD = 0.55, 50.8% girls) were enrolled in the study (i.e., both child and parent agreed to participate). Responders and non-responders did not differ with respect to gender, parental education, proportion of single-parent families, teacher-rated problem behaviour, or school absence; but children in the non-response group needed additional help for learning difficulties more frequently. At T2, 96.4% of these participants (N=2149) were re-assessed, mean age 13.56 years; SD 0.53; 51.0% girls. T3 was completed with 81.4 % of the original number of participants (N=1816), mean age 16.27 years old; SD 0.73 and 52.3% girls. During T3, 42 subjects were unable to participate in the study, due to mental/physical health problems, death, emigration, detention or by being untraceable. With these subjects left out, response rate increases to 83.0%. T4 was completed with 84.3% of the original sample (total n = 1881, mean age 19.1 (SD 0.60), 52.3% girls) (Nederhof et al., 2012).

The number of individuals that were included in the analyses differs for the separate chapters of this thesis (specifically chapter 2-3-4), depending on the availability of complete data on the measures that were used (and the choice to use data imputation for missing data or not).

2. Leiden Samples

The two final research questions were investigated in studies using cross-sectional designs. Two samples of (mostly) undergraduate students at Leiden University were recruited. The key objectives of these studies were to obtain greater insight into the cognitive profiles of (recreational) cannabis users, to investigate associations between possible cognitive

weaknesses and psychological or behaviour problems, and to find out whether chances of psychological or behaviour problems among cannabis users were influenced by the presence of cognitive weaknesses. Participants were classified as cannabis users when they reported using cannabis at least three times a month during the past year (they had not used cannabis 24 hours prior to testing) and as non-users when they reported the use of cannabis 0 times in the past year and less than 4 times in their lifetimes. Based on these criteria, cannabis users and non-users were recruited at two points in time (2009 and 2010). In 2009 (Wave 1), 53 cannabis users (mean age of 22.6) and 48 non-users (mean age of 22.3) were recruited. In 2010 (Wave 2), 75 cannabis users (mean age 24.6 years) and 75 non-users (mean age 24.7 years) were recruited. Participants were asked to volunteer in a study into information processing and social functioning of cannabis users. All participants signed informed consent forms.

After participants agreed to enroll in the study, an appointment was made, where participants completed (social) cognitive tasks on a computer. Furthermore, they were asked to fill out several questionnaires at home. On the day of the appointment, questionnaires were handed in.

Outline of the thesis

The first focus of this thesis is on associations between cannabis use and behaviour problems. The second focus is on cannabis use and cognitive outcomes. In Chapter 2, we examine associations between cannabis use and mental health. Specifically, we focused on internalizing behaviour problems (withdrawn behaviour, somatic complaints and depression) and externalizing behaviour problems (delinquent and aggressive behaviour). First, we investigated whether cannabis use is related to both internalizing and externalizing behaviour problems in early adolescence. Next, path analysis was used to identify the temporal order of internalizing and externalizing problems and cannabis use, thereby testing the damage hypothesis, the self-medication hypothesis and the shared-causes hypothesis. In Chapter 3, we examine associations between cannabis use and vulnerability for psychosis during adolescence. Specifically, we focused on attention problems, thought problems and social problems as indicators of vulnerability for psychosis. Again, path analysis was used to identify the temporal order of cannabis use and vulnerability for psychosis, thereby testing the damage hypothesis, the self-medication hypothesis and the shared-causes hypothesis. In Chapter 4**,** we focus on social skills as possible risk factors of cannabis use. Specifically, we used multinomial regression analyses to find out whether the social skills of cooperation, assertiveness and self-control could predict cannabis use, early onset and frequency of use during early adolescence. In Chapter 5, we examine whether recreational cannabis users and non-users differed on motivational and cognitive inhibitory control. Also, we analysed possible relations between both types of inhibitory control and impulsive behaviour in everyday life. In Chapter 6**,** we examine social perception in cannabis users. We also tested whether (relatively) weak social perception would disproportionally increase the chances of cannabis users to experience psychological problems (i.e. a variant of the vulnerability hypothesis). Finally, in Chapter 7, the main findings and conclusions of chapter 2-6 are presented and discussed. This thesis concludes with some implications for clinical practice and recommendations for future research.

References

Adolphs, R. (2002). Recognizing emotion from facial expressions: psychological and neurological mechanisms. *Behavioral and Cognitive Neuroscience Review, 1*, 21-62.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal, 325,* 1212–1213.

Beer J.S., Shimamura A.P., & Knight R.T. (2004). *Frontal lobe contributions to executive control of cognitive and social behavior*. In: Gazzaniga MS, (Ed.). The cognitive neurosciences III. 3rd ed. Cambridge, MA: MIT Press, pp. 1091–1104.

Bossong, M.G., & Niesink, R.J.M. (2010) Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Progress in Neurobiology, 92,* 370-385.

Brook, J.S., Cohen, P., & Brook, D.W. (1998). Longitudinal study of co-occurring psychiatric disorders and substance use. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*, 322–330.

Busemeyer, J.R., & Stout, J.C. (2002). A contribution of cognitive decision models to clinical assessment: Decomposing performance on the Bechara gambling task. *Psychological Assessment, 14,* 253-262.

Caspi, A., Moffit, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., & Craig, I.W. (2005). Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction. *Biological Psychiatry*, *57*, 1117 – 1127.

Christ, S.E., Huijbregts, S.C.J., De Sonneville, L.M.J., & White, D.A. (2010). Executive function in early-treated phenylketonuria: Profile and underlying mechanisms. *Molecular Genetics and Metabolism, 99*, S22-S32.

Coffey, C., Lynskey, M., Wolfe, R., & Patton, G.C. (2000). Initiation and progression of cannabis use in a population-based Australian adolescent longitudinal study. *Addiction, 95,* 1679–1690.

Cooper, Z.D., & Haney, M. (2009). Actions ode delta-9-tetrahydrocannabinol in cannabis: Relation to use, abuse, dependence. *International Review of Psychiatry, 21*, 104 – 112.

De Winter, A., Oldehinkel, A.J., Veenstra, R., Brunnekreef, J.A., Verhulst, F.C., & Ormel, J. (2005). Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. *European Journal of Epidemiology, 20,* 173–181.

Degenhardt, L., Hall, W., & Lynskey, M., (2001). The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. *Social Psychiatry and Psychiatric Epidemiology, 36,* 219–227.

Degenhardt, L., Hall, W., & Lynskey, M. (2003). Exploring the association between cannabis use and depression. *Addiction, 98,* 1493–1504.

D'Esposito, M., Postle, B.R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain and Cognition. 41*, 66-86.

Demenescu, L.R., Kortekaas, R., Den Boer, J.A., & Aleman, A. (2010). Impaired attribution of emotion to facial expressions in anxiety and major depression. *PLoS One, 5*, e15058.

Dodge, K., & Rabiner, D. (2004). Returning to roots: On social information processing and moral development. *Child Development, 75*, 1003-1008

Engels, R., & ter Bogt, T. (2001). Influences of risk behaviors on the quality of peer relations in adolescence. *Journal of Youth and Adolescence, 30,* 678–695.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2011). *Annual report 2011: the state of the drugs problem in Europe*. Publication office of the European Union, Luxembourg

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2006). Cannabis use and other drug use: testing the cannabis gateway hypothesis. *Addiction, 101*, 556-569.

Fergusson, D.M., & Horwood, L.J. (1997). Early onset cannabis use and psychosocial adjustment in young adults. *Addiction, (92)*, 279–296.

Fergusson, D.M., Horwood, L.J., & Swain-Campbell, N. (2002a). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction, 97,* 1123–1135.

Fergusson, D. M., Swain-Campbell, N. R., & Horwood, L. J. (2002b). Deviant peer affiliations, crime and substance use: a fixed effects regression analysis. *Journal of Abnormal Child Psychology, 30,* 419-430.

Fernández-Serrano, M.J., Pérez-Garcia, M., & Verdejo-García, A. (2011). What are the specific versus generalized effects of drugs of abuse on neuropsychological performance? *Neuroscience and Biobehavioral Reviews*, *35*, 377–406

Foltin, F.W., & Fischman, M.W. (1988). Effects of smoked marijuana on human social-behavior in small-groups. *Pharmacology Biochemistry and Behavior, 30,* 539-541

Foltin, R.W., Brady, J.V., Fischman, M.W., Emurian, C.S., & Dominitz, J. (1987). Effects of smoked marijuana on social-interaction in small-groups. *Drug and Alcohol Dependence, 20*, 87-93.

Gill, M., Donohoe, G., Corvin A. (2010) What have genomics ever done for the psychoses? *Psychological Medicine, 40*, 529-520.

Germine, L.T., & Hooker, C.I. (2011). Face emotion recognition is related to individual differences in psychosis-proneness. *Psychological Medicine, 41,* 937-947.

Hayatbakhsh, M.R., Najman, J.M., Jamrozik, K., Mamun, A.A., Alati, R., & Bor, W. (2007). Cannabis and anxiety and depression in young adults: a large prospective study. *Journal of the American Academy of Child and Adolescent Psychiatry, 46,* 408–417.

Hawkins, J.D., Catalano, R.F. & Miller, J.Y. (1992). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. *Psychological Bulletin, 112,* 64 – 105.

Henquet, C., Di Forti, M., Morrison, P., Kuepper, R., Murray, R.M. (2008). Gene-Environment interplay between cannabis and psychosis. *Schizophrenia Bulletin, 34,* 1111-21.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Lieb, H.U., & van Os., J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *British Medical Journal, 330*, 11 -14.

Huisman, M., Oldehinkel, A.J., de Winter, A., Minderaa, R.B., de Bildt, A., Huizink, A.C, Verhulst, F.C., & Ormel, J. (2008). Cohort profile: the Dutch 'tracking adolescents' individual lives survey; trails. *International Journal of Epidemiology. 37*, 1227–1235.

Kandel, D.B., Yamaguchi, K., & Chen, K. (1992). Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *Journal of Studies on Alcohol, 53*, 447–457.

Kerr, A, & Zelazo, P.D. (2004). Development of 'hot' executive function: the children's gambling task. *Brain and Cognition, 55*, 148–15.

Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders – focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142*, 1259–1264.

Kiehl, K.A., Smith, A.M., Hare, R.D., & Liddle, P.F. (2000). An event-related potential investigation of response inhibition in schizophrenia and psychopathy. *Biological Psychiatry*, *48,* 210-21

Klein, D. & Riso, L. (1994). *Psychiatric disorders: problems of boundaries and comorbidity.* In: Costello, G., (Ed.). Basic Issues in Psychopathology, New York: Guilford Press, pp. 19–66.

Kohler, C.G., Walker, J.B., Martin, E.A., Healey, K.M., & Moberg, P.J. (2010). Facial emotion perception in schizophrenia: a meta-analytic review. *Schizophrenia Bulletin, 36*, 1009-1019.

Lee, C.M., Neighbors, C., & Woods, B.A. (2007). Marijuana motives: Young adults' reasons for using marijuana. *Addictive behaviors, 32*, 1384-1394.

Lynskey, M.T., Heath, A.C., Nelson, E.C., Bucholz, K.K., Madden, P.A.F., Slustke, W.S., Statham, D.J., &Martin, N.G. (2002). Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychological Medicine, 32,* 195–207.

Lynskey, M., & Hall, W. (2000). The effects of adolescent cannabis use on educational attainment: a review. *Addiction, 95*, 1621-1630.

Lynskey, M.T., Vink, J.M., & Boomsma, D.I. (2006). Early Onset Cannabis Use and Progression to other Drug Use in a Sample of Dutch Twins. *Behavior Genetics, 36*, 195-200.

Malone, D.T., Hill, M.N., & Rubino, T. (2010). Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models, *British Journal of Pharmacology, 160*, 511-522.

Marsh, A.A., & Blair, R.J. (2008). Deficits in facial affect recognition among antisocial populations: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 32,* 454-465.

Miller, P., Lawrie, S. M., Hodges, A., Clafferty, R., Cosway, R., & Johnstone, E.C. (2001) Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*, 36, 338 -342.

Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet, 370,* 319–328.

Monshouwer, K., Van Dorsselaer, S., Verdurmen, J., Ter Bogt, T., De Graaf, R., & Vollebergh, W., (2006). Cannabis use and mental health in secondary school children. Findings from a Dutch survey. *British Journal of Psychiatry, 188,* 148–153.

Nederhof, E., Jorg, F., Raven, D., Veenstra, R., Verhulst, F.C., Ormel, J., & Oldehinkel, A.J. (2012). Benefits of extensive recruitment effort persist during follow-ups and are consistent across age group and survey method. The TRAILS study. *BMC Medical Research Methodology, 12*, doi:10.1186/1471-2288-12-93.

Nigg, J. (2000). On inhibition/disinhibition in developmental psychopathology: view from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin, 126*, 220-246.

Nigg, J. T., Quamma, J. P., Greenberg, M. T., & Kusche, C. A. (1998). A two-year longitudinal study of neuropsychological and cognitive performance in relation to behavioral problems and competencies in elementary school children. *Journal of Abnormal Psychology, 27,* 51–63.

Ochsner, K.N., & Feldman Barett, L. (2001). *A multiprocess perspective on the neuroscience of emotion*. In T.J. Mayne & G.A. Bonnano (Eds.), Emotions: Current issues and future directions. Guilford Press, New York, pp. 38-81.

Patton, G.C., Coffey, C., Carlin, J.B., Degenhardt, L., Lynskey, M., & Hall, W. (2002). Cannabis use and mental health in young people: cohort study. *British Medical Journal, 325,* 1195–1198.

Pettit G.S., & Mize J. (2007). *Social-cognitive processes in the development of antisocial and violent behavior*. In: Flannery D.J., Vazsonyi A.T., & Waldman I.D., (Eds.). The Cambridge handbook of violent behavior and aggression. Cambridge, MA: Cambridge University Press, pp. 322–343

Petraitis, J., Flay, B.R., & Miller, T.Q. (1995). Reviewing theories of adolescent substance use: organizing pieces in the puzzle. *Psychological Bulletin, 117*, 67 – 86.

Pijlman,F.T., Rigter,S.M., Hoek,J., Goldschmidt,H.M., & Niesink,R.J. (2005). Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. *Addiction Biology. 10*, 171-180.

Platt, B., Kamboj, S., Morgan, C.J., & Curran, H.V. (2010). Processing dynamic facial affect in frequent cannabis-users: evidence of deficits in the speed of identifying emotional expressions. *Drug and Alcohol Dependence, 112,* 27-32.

Pokhrel, P., Sussman, S., Rohrbach, L. A., & Sun, P. (2007). Prospective associations of social self-control with drug use among youth from regular and alternative high schools. *Substance Abuse and Treatment Prevention Policy, 2,* 22.

Pope, H.G., Gruber, A.J., Hudson, J.I., Huestis, M. A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry, 58*, 909-915.

Prencipe, A., Kesek, A., Cohen, J., Lamm, C., Lewis, M.D., & Zelazo, P.D. (2011). Development of hot and cool executive function during the transition to adolescence. *Journal of Experimental Child Psychology, 108,* 621-637.

Raaijmakers, M. A. J., Smidts, D. P., Sergeant, J. A., Maasen, G.H., Posthumus, J. A., van Engeland, H., & Matthys, W. (2008). Executive functions in preschool children with aggressive behavior: Impairments in inhibitory control. *Journal of Abnormal Child Psychology, 36*, 1097–1107.

Riggs, N.R., Greenberg, M.T., Kusché, C.A., & Pents, M. (2006). The Mediational Role of Neurocognition in the Behavioral Outcomes of a Social-Emotional Prevention Program in Elementary School Students: Effects of the PATHS Curriculum. *Prevention science, 7*, 91-102.

Rijsdijk F.V., Gottesman I.I., McGuffin, P., Cardno, A.G. (2011). Heritability estimates for psychotic symptom dimensions in twins with psychotic disorders. *American Journal of Medical Genetics part B: Neuropsychiatric Genetics, 156B*, 89-98.

Rössler, W., Vetter, S., Müller, M., Gallo, W.T., Haker, H., Kawohl, W., Lupi, G., & Ajdacic-Gross, V., 2011. Risk factors at the low end of the psychosis continuum: much the same as at the upper end? *Psychiatry Research, 189,* 77-81.

Shedler, J., & Block, J. (1990). Adolescent drug use and psychological health. A longitudinal inquiry. *American Psychologist, 45*, 612-630.

Simons, J., Correia, C.J., Carey, K., & Borsari, B.E. (1998). Validating a five-factor marijuana motives measure: Relations with use, problems, and alcohol motives. *Journal of Counseling Psychology, 45*, 265-273.

Schneider, M. (2008). Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addiction Biology, 13*, 253-263.

Solowij, N. (1998). *Cannabis and cognitive functioning*. Cambridge University Press, Cambridge, UK .

Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christansen, K., McRee, B., & Vendetti, J. (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA-Journal of The American Medical Association, 287*, 1123-1131.

Stacy, A.W., & Wiers, R.W. (2010). Implicit cognition and addiction: A tool for explaining paradoxical behavior. *Annual Review of Clinical Psychology, 6,* 551-575.

Sussman, S., McCuller, W. J., & Dent, C. W. (2003). The associations of social self-control, personality disorders, and demographics with drug use among high-risk youth. *Addictive Behaviors, 28,* 1159–1166.

Tarter, R. E. (1988). Are there inherited behavioral traits that predispose to substance abuse? *Journal of Consulting and Clinical Psychology, 56,* 189–196.

United Nations Office on Drugs and Crime (UNODC) (2012). *World Drug report 2012*. United Nations Publication, Sales No. E. 12.X1.1, New York.

Van Gastel, W.A., Wigman, J.T.W., Monshouwer, K., Kahn, R.S., van Os, J., Boks, M.P.M., & Vollebergh, W.A.M. (2011). Cannabis use and subclinical positive psychotic experiences in early adolescence: findings from a Dutch survey, *Addiction, 107,* 381-7.

van Laar, M., van Dorsselaer, S., Monshouwer, K., & de Graaf, R., (2007). Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction, 102,* 1251–1260.

van Os, J., Bak, M., Hanssen, M., Bijl, R.V., de Graaf, R., & Verdoux, H. (2002). Cannabis use and Psychosis: A Longitudinal Population-based Study. *American Journal of Epidemiology, 156,* 319-327.

Verdejo-Garcia, A., Lawrence, A.J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews, 32,* 777-810.

Verdoux, H., Gindre, C., Sorbara, F., Tournier, M., & Swendsen, J.D. (2003). *Psychological Medicine, 33*, 23-32.

Veselska, Z., Geckova, A. M., Orosova, O., Gajdosova, B., van Dijk, J. P., & Reijneveld, S. A. (2009). Self-esteem and resilience: the connection with risky behavior among adolescents. *Addictive Behaviors, 34*, 287-29.

Von Sydow, K, Lieb, R., Pfister, H., Höfler, M., Wittchen, H. (2002). What predicts insicent use of cannabis and progression to abuse and dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug and Alcohol Dependence, 68*, 49 – 64.

Warner, R., Taylor, D. & Wright, J. (1994). Substance use among the mentally ill: prevalence, reasons for use and effects on illness. *American Journal of Orthopsychiatry, 74*, 30–39.

Whitlow, C.T., Liguori, A., Livengood, L.B., Hart, S.L., Mussat-Whitlow, B.J., Lamborn, C.M., Laurienti, P.J., & Porrino, L.J. (2004). Long-term heavy marijuana users make costly decisions on a gambling task. *Drug And Alcohol Dependence, 76*, 107-111.

Zelazo, P.D., & Müller, U. (2002). Executive function in typical and atypical development. In U. Goswami (Ed.), *Handbook of Childhood Cognitive Development* (pp. 445-469). Oxford, Blackwell.

2.

Cannabis use and development of externalizing and internalizing behaviour problems in early adolescence
- a TRAILS study

Griffith-Lendering, M.F.H., Huijbregts, S.C.J., Mooijaart, A,, Vollebergh, W.A.M., & Swaab, H. (2011). Cannabis use and the development of internalizing and externalizing behaviour problems in early adolescence; A Trails study. *Drug and Alcohol Dependence*, *116*, 11-17.

Abstract

Aim: To examine the prospective relationship between externalizing and internalizing problems and cannabis use in early adolescence.

Materials and Methods: Data were used from the TRAILS study, a longitudinal cohort study of (pre) adolescents (n = 1,449), with measurements at age 11.1 (T1), age 13.6 (T2) and age 16.3 (T3). Internalizing (withdrawn behaviour, somatic complaints and depression) and externalizing (delinquent and aggressive behaviour) problems were assessed at all data waves, using the Youth Self Report. Participants reported on cannabis use at the second and third wave. Path analysis was used to identify the temporal order of internalizing and externalizing problems and cannabis use.

Results: Path analysis showed no associations between cannabis use (T2-T3) and internalizing problems (T1-2-3). However, cannabis use and externalizing problems were associated (r ranged from .19–.58); path analysis showed that externalizing problems at T1 and T2 preceded cannabis use at T2 and T3, respectively. In contrast, cannabis use (T2) did not precede externalizing problems (T3).

Conclusions: These results suggest that in early adolescence, there is no association between internalizing behaviour and cannabis use. There is an association between externalizing behaviour and cannabis use, and it appears that externalizing behaviour precedes cannabis use rather than the other way around during this age period.

Introduction

Regular cannabis use has been associated with a wide range of mental health problems including psychotic disorders (Arseneault et al., 2002; Moore et al., 2007), externalizing problems (aggressive and delinquent behaviour) (Fergusson et al., 2002; Monshouwer et al., 2006) and, to a lesser extent, internalizing problems, such as depression (Degenhardt et al., 2001; Degenhardt et al., 2003; Patton et al., 2002) and anxiety (Patton et al., 2002; van Laar et al., 2007; Hayatbakhsh et al., 2007a). Several hypotheses have been put forward to explain these associations, including the "damage hypothesis", which proposes that cannabis use precedes mental health problems (Brook et al., 1998; Kandel et al., 1992) and the "self medication hypothesis", which proposes that individuals with mental health problems tend to resort to drug use to sooth their problems (Khantzian, 1985). The "shared causes hypothesis" proposes that the linkage between cannabis use and mental health problems is the result of genetic and environmental factors associated with both problem behaviour and cannabis use (Fergusson and Horwood, 1997; Fergusson et al., 2002; Shelton et al., 2007).

Shared causes are often found for externalizing behaviour and cannabis use (Fergusson and Horwood, 1997; Fergusson et al., 2002). Several studies have shown substantially weaker associations between cannabis use and externalizing behaviour after statistical control for factors such as socialeconomic status and use of other substances (e.g. Korhonen et al., 2010). However, most studies do show some residual variance in associations between externalizing behaviour and cannabis use that cannot be explained by environmental factors (Fergusson et al., 2007; Fergusson et al., 2002; Pedersen et al., 2001). The temporal order of cannabis use and both externalizing and internalizing behaviour has not yet been disentangled (Fergusson et al., 2002; Monshouwer et al., 2006). Most longitudinal evidence supports the self-medication hypothesis, which states that externalizing problems precede the use of cannabis at this age (King et al., 2004; Fergusson et al., 2007; Pedersen et al., 2001). There is also evidence to suggest that externalizing behaviour during adolescence precedes cannabis use in early adulthood (Hayatbakhsh et al., 2007b). Although it is difficult to control for all potential confounders simultaneously, some of these studies did not control for important potential confounders, such as SES, use of other substances and parental psychopathology, and therefore may have left open the

possibility of shared causes more than necessary. For internalizing behaviour, the relationship is evenmorecomplex: firstly, compared to externalizing behaviour problems, there is less evidence for an association between cannabis use and internalizing behaviour problems (Monshouwer et al., 2006). In several studies that did initially find a significant association between cannabis use and internalizing behaviour, the association became non-significant after statistical control for confounding variables (Harder et al., 2008; McGee et al., 2000). Nonetheless, there are some studies that have found evidence for the self-medication hypothesis, with internalizing behaviour problems preceding cannabis use at later age (King et al., 2004; Wittchen et al., 2007). Again, shared causes cannot be ruled out, as the associations may be explained by residual confounding (Fergusson and Horwood, 1997; Fergusson et al., 2002; Hayatbakhsh et al., 2007a). There is also (contrasting) evidence suggesting that internalizing behaviour in young adolescence is not related to substance use at a later age, including the use of cannabis (Alati et al., 2008; Hayatbakhsh et al., 2008; Ferdinand et al., 2001). Thus, in general, evidence regarding (the direction of) associations between cannabis use and internalizing/ externalizing behaviour problems in adolescence is not yet convincing, which is mainly due to the fact that most studies did not analyze temporally bi-directional associations (i.e., where cannabis use can precede but also follow behaviour problems), and which might also partly be due to the fact many studies did not control comprehensively for potentially confounding variables.

It is important to study associations between externalizing and internalizing problems on the one hand and cannabis use on the other during early adolescence for several reasons. Firstly, early adolescence is a life phase characterized by rapid biological changes and consecutive maturation processes. These developmental processes might increase vulnerability for enduring effects of external influences like use of cannabis (Schneider, 2008). Secondly, cannabis use usually starts in early adolescence (Monshouwer et al., 2005), possibly because of increases in peer-influenced risk-taking behaviours (e.g. Fergusson and Horwood, 1997). So this appears to be the best possible time to collect behavioural data antedating initiation of cannabis use. The study of associations between internalizing and externalizing behaviours and cannabis use during early adolescence may thus help identifying individuals who are at an increased risk for multiple simultaneous problems (e.g. aggression and substance use), which have been associated with the poorest long-term outcomes. At this stage it

might still help targeting one of the problems (preferably the one that occurs first in time) in order to prevent other or combined problems.

In the present study, we investigated relations between both internalizing and externalizing behaviour problems and cannabis use in a large population sample of young adolescents enrolled in the Tracking Adolescents' Individual Lives Survey (TRAILS, Huisman et al., 2008). Using path analysis, we investigated the temporal order of the association between cannabis use and internalizing and externalizing behaviour, thereby controlling for confounding factors to eliminate, to some extent, the effect of shared causes. It was expected that the link between internalizing behaviour and cannabis use would be weaker than the association between externalizing behaviour and cannabis use. In addition, based on findings to date, it was expected that internalizing and externalizing behaviour problems would precede cannabis use and not the other way around.

Method

Sample

Data were gathered from participants in the Tracking Adolescents' Individual Lives Survey (TRAILS), a prospective cohort study among adolescents in the general Dutch population. TRAILS investigates the development of mental and physical health from preadolescence into adulthood (de Winter et al., 2005). The study covers biological, psychological and sociological topics and collects data from multiple informants. Participants come from five municipalities, including both urban and rural areas, in the North of the Netherlands. So far, three data collection waves have been completed: T1 (2001–2002), T2 (2003–2004) and T3 (2005–2007). Participants will be followed until (at least) the age of 24. Of all individuals asked to participate in TRAILS (N= 2935), 76,0% agreed to participate at T1 (N= 2230; mean age 11.09 years; SD 0.55; 50.8% girls). At T2, 96.4% of these participants (N= 2149) were re-assessed. T3 was completed with 81.4% of the original number of participants (N= 1816), mean age 16.27 years; SD 0.73 (52.3% girls). At T3, 42 subjects were unable to participate in the study, due to mental/ physical health problems, death, emigration, detention or by being untraceable. With these subjects left out, response rate increases to 83.0%. More detailed information on the selection procedures and non-response bias can be found elsewhere

(de Winter et al., 2005; Huisman et al., 2008). Analyses in the present study were based on 1.449 adolescents (53.3% girls, 46.7% boys) with non-missing data on all variables of interest (described below).

Measures

Cannabis use

Cannabis use was assessed at T2 and T3 by self-report questionnaires filled out at school, supervised by TRAILS assistants. Confidentiality of the study was emphasized so that adolescents were reassured that their parents or teachers would not have access to the information they provided. Among others, participants were asked about lifetime use and use in the last year with the following questions: 'How often have you used cannabis in your life/in the last year', with answer categories: 'I have never used', 'used it once', 'used it twice', 'three times',....., '10 times', '11–19 times', '20–39' times, '40 times or more'). Items were recoded into five categories; (1) those who had never used; (2) those who had used but not during the past year (discontinued use); (3) those who used once or twice during the past year (experimental use); (4) those who reported using cannabis between 3 and 39 times during the past year (regular use); and (5) thosewhoreported using it 40 times or more during the last year (heavy use). The construction of these categories was similar to that used in other studies investigating cannabis use and mental health in young adolescents (e.g. Monshouwer et al., 2006).

Behaviour problems

Internalizing and externalizing behaviour were assessed with the Youth Self Report (YSR), which is one of the most commonly used self report questionnaires in current child and adolescent psychiatric research (Achenbach, 1991; Verhulst and Achenbach, 1995). The YSR contains 112 items on behavioural and emotional problems in the past 6months. Participants can rate the items as being not true (0), somewhat or sometimes true (1), or very or often true (2). The YSR covers the following domains: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention (hyperactivity) problems, aggressive behaviour, and rule-breaking behaviour. For the present study, we used two broad-band dimensions of the YSR (Achenbach, 1991): (a) internalizing problems, consisting of items measuring anxious/depressed, withdrawn/ depressed, and somatic

complaints; and (b) externalizing problems, with items measuring aggressive and rule-breaking behaviour.

Control variables

Since SES, use of other substances and parental psychopathology have been shown to be among the most important correlates of cannabis use and both internalizing and externalizing behaviour (Fergusson and Boden (2008)), it was examined whether these should be included in the path analyses.

Socioeconomic Status (SES)

Socioeconomic Status (SES) was assessed at T1 using a 5 point scale consisting of five variables: educational level (father/mother), occupation (father/mother), and family income. The internal consistency of this measure is satisfactory (Cronbach's alpha 0.84; Veenstra et al., 2006).

Parental psychopathology

Parental psychopathology (i.e. depression, anxiety, substance abuse, antisocial behaviour, and psychosis) was measured by means of the Brief TRAILS Family History Interview (Ormel et al., 2005), administered at T1. Each syndrome was introduced by a vignette describing its main symptoms and followed by a series of questions to assess lifetime occurrence, professional treatment, and medication use. The scores for substance abuse and antisocial behaviour were used to construct a familial vulnerability index for externalizing disorder. The scores for depression and anxiety disorder were used to construct an index for internalizing disorder. The construction of a familial vulnerability index was based on Kendler et al. (2003), who performed multivariate twin modelling to investigate shared genetic risk factors for psychiatric and substance use disorders. More information on the construction of familial vulnerability within TRAILS is described elsewhere (Veenstra et al., 2005). For both internalizing and externalizing disorder, parents were assigned to one of the following categories: (0) = (probably) not; (1) = (probably) yes, (2) = yes and treatment/medication (substance abuse, depression, and anxiety) or picked up by police (antisocial behaviour).

Other substances

In order to assess alcohol and tobacco use, participants filled out a questionnaire at both T2 and T3 on the frequency of use in the past month. For tobacco use reported frequency was recoded into non-weekly (0) versus weekly (1), and for alcohol use, the reported frequency was recoded into non-monthly (0) versus monthly use (1). These categories were similar to those used in other studies investigating cannabis use and mental health in young adolescents (e.g. Monshouwer et al., 2006).

Data analysis

It was first examined whether non-responders differed from responders on SES (by means of t-test) and gender (by means of Pearson χ2-test). Next, it was examined whether, among the responders, there were differences between cannabis users and non-users with respect to SES, familial vulnerability for internalizing and externalizing behaviour, use of alcohol and tobacco and gender (using Pearson Chi-square analysis for alcohol, tobacco use and gender and t-tests or GLMunivariate analysis of variance for SES and familial vulnerability). These analyses were performed in order to determine which variables should be included in the main analyses as covariates. The temporal order of occurrence of cannabis use and internalizing and externalizing behaviour was investigated using path analyses. In path analysis, an extension of the regression model, the regression weights predicted by the model are compared with the observed correlation matrix for the variables, and a goodness of fit statistic is calculated. The path coefficient is a standardized regression coefficient (beta) indicating the effect of an independent variable on a dependent variable in the path model. Thus, when the model has two or more independent variables, path coefficients are partial regression coefficients, which measure the extent of effect of one variable on another in the path model controlling for other variables, using standardized data or a correlation matrix.

Following the two step approach recommended by Anderson and Gerbing (1988), confirmatory factor analysis (CFA) was used to investigate how well our hypothesized models fit the actual data. These models were based on previous research to assess temporal order of internalizing and externalizing behaviour (T1-T2-T3) and cannabis use (T2-T3) (e.g. Fergusson et al., 2002; McGee et al., 2000).

In the path analyses, both internalizing and externalizing behaviour were introduced as latent variables with multiple indicators. The latent variable ‘internalizing’

consisted of anxious/depressed, withdrawn/ depressed and somatic complaints. The latent variable 'externalizing' consisted of the indicators aggressive and delinquency. Cannabis use was represented by one indicator (i.e., the self-report measure consisting of the following categories: (1) those who had never used; (2) those who had used but not during the past year; (3) those who used once or twice during the past year; (4) those who reported using cannabis between 3 and 39 times during the past year; and (5) those who reported using it 40 times or more during the last year (see section 2.2.1). Next, we modelled prospectively cannabis use and internalizing/ externalizing identified in the CFA. Here, we included all possible associations between latent variables. To evaluate overall model fit, the root mean square error of approximation was used (RMSEA; Steiger, 1998); a RMSEAvalue less than .05 (Browne and Cudeck, 1993) indicates good model fit. Both $\chi 2$ statistics and RMSEA are dependent on the size of the sample: as we had a relatively large sample (n = 1,449), we also used the comparative fit index (CFI; Bentler, 1990) to evaluate overall model fit. A CFI value greater than .90 (Bentler, 1990) indicates good model fit. All analyses were performed using EQS 6.1 for Windows (Bentler, 1995).

Results

Non-responders analysis

Responders (n = 1,449) and non-responders (n = 739) differed in terms of SES ($t = -9.6$, $p < .001$); responders scored higher on SES than non-responders (M= .07, SD = .78 vs. M=−.28, SD = .79). Responders also differed from non-responders in terms of gender ($\chi 2$ (1) = 10.5, p = .001: responders were more likely to be female (53.3%) than non-responders (46.1%).

Descriptives

Descriptive information regarding the frequency of cannabis use is presented in Table 1 for participants with complete data on all variables of interest. The number of cannabis users increases with age as does the frequency of use. Cannabis users did not differ from non-users with respect to SES ($t(1447) = -.9$, p = .387), gender ($\chi 2$ (1) = 1.1, p = .289), familial vulnerability for internalizing ($t(1447) = -.4$, p = .705) and externalizing behaviour ($t(1447) = -1.8$, p = .071). Cannabis users and non-users differed significantly with respect to alcohol use at T2 ($\chi 2$ (1) = 90.3, $p < .001$),

alcohol use at T3 ($\chi 2$ (1) = 95.0, p < .001), tobacco use at T2 ($\chi 2$ (1) = 137.3, p < .001) and tobacco use at T3 $\chi 2$ (1) = 346.8, p < .001), with cannabis users using alcohol and tobacco more often than non-users (57.8% vs. 31.2% reported monthly alcohol use at T2; percentages for T3: 94.0% vs. 70.7%; 19.8% vs. 2.2% reported weekly tobacco use at T2; percentages for T3: 57.4% vs. 11.1%). Tobacco and alcohol use were also related to both internalizing and externalizing behaviour and therefore included as covariates in subsequent path analysis (for detailed information, see Table 2).

Table 1: Descriptive information on cannabis use at T2 and T3 (n=1,449)

	T2	T3
Never used	93.6 % (n=1359)	69.9 % (n=1013)
Discontinued use	1.4 % (n=20)	5.9 % (n=86)
Experimental use	3.7 % (n=54)	10.9 % (n=158)
Regular use	1.2 % (n=17)	9.6 % (n=139)
Heavy use	.1 % (n=2)	3.7 % (n=53)

Table 2: *t*-statistics of significant control variables (tobacco use and alcohol use) and internalizing and externalizing behaviour

	T2 tobacco use	T3 tobacco use	T2 alcohol use	T3 alcohol use
T1 Internalizing behaviour	-3.2*	-1.6	-.2	1.0
T2 Internalizing behaviour	-3.7*	-3.3*	–.7	2.7*
T3 Internalizing behaviour	-4.2*	-3.2*	-.1	2.0
T1 Externalizing behaviour	-6.1*	-5.4*	-4.2*	-3.1*
T2 Externalizing behaviour	-11.6*	-11.3*	-9.2*	-3.4*
T3 Externalizing behaviour	-10.3*	-19.2*	-7.8*	-8.4*

* p<.05

Path analyses: Preliminary analyses

Table 3 shows the correlations between all latent variables. Factor loadings of the indicators of the latent variables of internalizing behaviour and externalizing behaviour of all three measurement waves are presented in Table 4.

Table 3: Correlations of all latent variables of the CFA

	T2 Cannabis use	T3 Cannabis use
Model 1		
T1 Internalizing behaviour	.06*	-.04*
T2 Internalizing behaviour	.06*	-.02*
T3 Internalizing behaviour	.05*	.02*
Model 2		
T1 Externalizing behaviour	.19*	.23*
T2 Externalizing behaviour	.40*	.38*
T3 Externalizing behaviour	.24*	.58*

* p<.05

Model 1. Cannabis use and internalizing behaviour problems

The independence model testing the hypothesis that all cannabis scores and internalizing behaviour scores were uncorrelated was rejected: $\chi 2$ (30, N= 1,449) = 56.4, $p < .003$. The model provided an acceptable fit to the data (CFI = .99, RMSEA = .03). However, as shown in Table 3, correlations between internalizing behaviour problems (T1-2-3) and cannabis use (T2-T3) ranged from .02 to .06 and thus are very small. Although these correlations were significant (probably due to the large sample size), they were indicative of non-relationships between cannabis use and internalizing behaviour. This was confirmed by the Wald test. Dropping parameters indicative of associations between internalizing behaviour (T1, T2 and T3) and cannabis use (T2 and T3) resulted in a non-significant change of the model [$\chi 2$ (6, N= 1,449) = 11.2, p = .081]. Path-analysis revealed that although our model represented the data well [$\chi 2$ (66,N= 1,449) = 215.2, $p < .001$; RMSEA = .04, CFI = .97], all paths between internalizing (T1-2-3) and cannabis use (T2-T3) were non-significant.

Table 4: Factor loadings of the Indicators of the Latent variables of internalizing and externalizing behaviour and cannabis use.

Variable	Factor Loadings
Internalizing behaviour and cannabis	
T1 Internalizing behaviour	
Anxious/Depressed	.24
Withdrawn/Depressed	.21*
Somatic complaints	.17*
T2 Internalizing behaviour	
Anxious/Depressed	.27*
Withdrawn/Depressed	.21*
Somatic complaints	.15*
T2 Cannabis use	
Cannabis use	1.00
T3 Internalizing behaviour	
Anxious/Depressed	.26*
Withdrawn/Depressed	.23*
Somatic complaints	.16*
T3 Cannabis use	
Cannabis use	1.00
Externalizing behaviour and cannabis	
T1 Externalizing behaviour	
Aggressive behaviour	1.00
Rule-breaking behaviour	.90*
T2 Externalizing behaviour	
Aggressive behaviour	1.00*
Rule-breaking behaviour	1.38*
T2 Cannabis use	
Cannabis use	1.00
T3 Externalizing behaviour	
Aggressive behaviour	1.00
Rule-breaking behaviour	1.67*
T3 Cannabis use	
Cannabis use	1.00

* $p<.05$

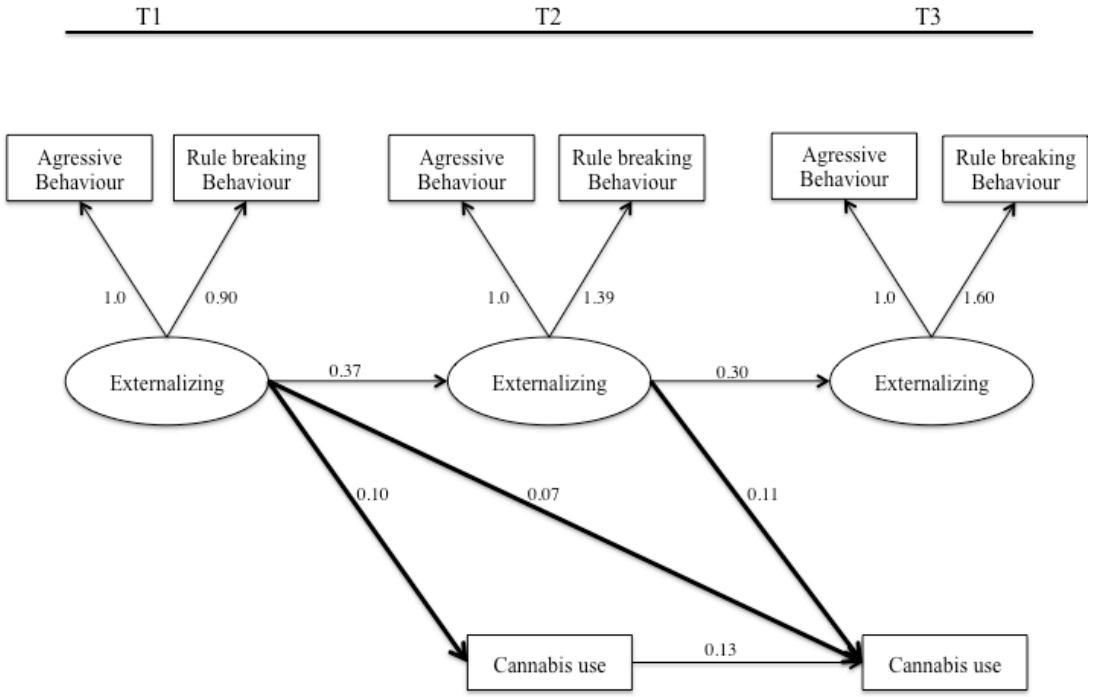
Model 2. Cannabis use and externalizing behaviour problems

The independence model that tested the hypothesis that all cannabis scores and externalizing behaviour scores were uncorrelated, was rejected: $\chi 2$ (9, N= 1,449) = 64.4, $p < .001$. Also, although RMSEA was relatively high (.07), the CFI was .99 and therefore our model provided an acceptable fit to the data. Correlations between externalizing behaviour (T1-2-3) and cannabis use (T2-T3) ranged from .19 to .58 and thus were indicative of a relationship between externalizing behaviour problems and cannabis use (see Table 4). Next, path analysis was performed to address the temporal order of cannabis use and externalizing behaviour problems (Fig. 1), hereby controlling for alcohol and tobacco use at T2 and T3.

Path analysis revealed that the model represented the data well [$\chi 2$ (34,N= 1,449) = 270.2, $p < .001$; RMSEA = .07, CFI = .96]. The paths between externalizing behaviour problems measured at T1, T2, and T3 were all significant (T1-T2; $z = 11.8$, $p < .05$; T1-T3; $z = 4.9$, $p < .05$; T2-T3; $z = 11.5$, $p < .05$). The path between cannabis use T2 and T3 was also significant ($z = 5.4$, $p < .05$). In addition, the paths between externalizing behaviour and tobacco use were all significant (T2; $z = 11.7$, $p < .05$; T3; $z = 16.9$, $p < .05$). Also, the paths between externalizing behaviour and alcohol use were all significant (T2; $z = 8.4$, $p < .05$; T3; $z = 6.6$, $p < .05$). The same occurred with cannabis use, where the paths between cannabis use and tobacco use were significant at T2 ($z = 17.8$, $p < .05$) and T3 ($z = 18.0$, $p < .05$) and also with alcohol use at T2 ($z = 2.9$, $p < .05$) and T3 ($z = 5.7$, $p < .05$). Moreover, externalizing behaviour and cannabis use significantly correlated at T2 ($r = 0.19$, $p < .05$) and T3 ($r = 0.34$, $p < .05$).

Externalizing behaviour at T1 significantly predicted cannabis use at T2 ($z = 3.8$, $p < .05$) and T3 ($z = 2.7$, $p < .05$). Externalizing behaviour at T2 also significantly predicted cannabis use at T3 ($z = 4.0$, $p < .05$). Cannabis use measured at T2 did not show significant association with externalizing behaviour problems at T3 ($z = -1.4$, $p > .05$) (Fig. 1).

Figure 1: Path analysis of externalizing behaviour, with indicators aggressive behaviour and rule breaking behaviour, and cannabis use in young adolescence after controlling for tobacco and alcohol use, measured at both T2 and T3. All non-significant paths have been removed from the full model. Latent variables are shown in ellipses, and observed variables are shown in rectangles.



Discussion

In the present longitudinal study, 1,449 respondents were followed from the age of 11 to 16 to assess the relationship between both internalizing and externalizing problems and cannabis use. Two different hypotheses, the damage hypothesis and the self-medication hypothesis, were tested using path analyses, thereby controlling for possible confounding factors.

First, our data showed that cannabis use is strongly related to externalizing behaviour problems in early adolescence, including aggressive and delinquent behaviour. This result is largely in agreement with previous studies (Fergusson et al., 2007; Fergusson et al., 2002; Khantzian, 1985; Monshouwer et al., 2006). As expected, our data supported the self-medication hypothesis, indicating that externalizing problems precede cannabis use during adolescence and not the other way around. Specifically, in our study, externalizing problems at age 11 were associated with cannabis use at age 13 and age 16. Also, externalizing behaviour at age 13 predicted cannabis use at age 16.

These results are in agreement with a number of other studies. King et al. (2004), for example, also showed that externalizing psychopathology at age 11 predicted cannabis use at age 14, although it did not take into account potential confounders, such as the use of other substances. Korhonen et al. (2010) recently showed that early onset of smoking predicts cannabis initiation, while controlling for co-occurring externalizing behaviour problems. Whereas Korhonen et al. (2010) focused specifically on whether time of smoking initiation was predictive of the onset of cannabis use, we focused on the temporal order of cannabis use and externalizing behaviour problems. Although this study therefore had a different focus compared to the present study, it does illustrate the importance of controlling for potentially confounding factors when investigating cannabis-behaviour associations (or of controlling for behaviour when studying associations between specific environmental factors and cannabis use). Another longitudinal study (spanning 25 years) that did control for confounding factors demonstrated that conduct disorders at even a younger age (7–9 years) were related to later substance use, including cannabis use (Fergusson et al., 2007). Also, Pedersen et al. (2001), confirmed that conduct disorder at a young age is strongly associated with cannabis use in young teenagers. All these studies supported results that externalizing problems precede cannabis use.

For the present study as well as earlier studies, it should be noted that externalizing behaviour explained only part of the variance of cannabis use, indicating that other factors are also important correlates of cannabis use during adolescence. Examples of such factors may be substance using peers and family functioning (e.g. Coffey et al., 2000; Fergusson and Horwood, 1997). In addition, considering the concurrent correlations of cannabis use and externalizing behaviour at different measurement points we cannot rule out reciprocal relations between the two, i.e. lagged associations remain possible (Fergusson et al., 2005). Nonetheless, some evidence is provided here that such lagged associations start with the presence of externalizing behaviour, as there was negligible cannabis use at T1, while there was externalizing behaviour at that time.

Although evidence of damaging effects of cannabis has been provided in other studies (Kandel et al., 1986; Kandel et al., 1992), our study did not support this hypothesis. This could be due to the fact that the sample was quite young and had not been using cannabis for a long period of time. Indeed, studies providing evidence for damaging effects of cannabis observed these effects in young adulthood (Fergusson et al., 2002; White et al., 1999). Possibly, such effects will also become evident in our sample at a later stage. For now, however, it should be concluded that externalizing problems at age of 11 and 13 predict cannabis use at later ages.

If the self-medication hypothesis is true, as the evidence suggests, it would be good to know in more detail which aspects of externalizing behaviour elicit the need for "medication". One explanation could be that those who show externalizing problems at age 11 use cannabis to get rid of feelings of hostility or anger. If the temporal order is not the consequence of some form of self-medication, a possible explanation is that cannabis use is a form of sensation seeking behaviour, which has regularly been identified as a characteristic of externalizing behaviour (Huizink et al., 2006; Marsman et al., 2008; Raine, 1996). There may be several mediating factors explaining the temporal order with externalizing problems preceding cannabis use as well. Examples include exclusion from peer groups that show less experimental behaviour and inclusion in peer groups showing increased levels of experimental behaviour among individuals characterized by externalizing behaviours (Coffey et al., 2000; Fergusson and Horwood, 1997).

With respect to internalizing behaviour problems, our study did not confirm the results of several earlier studies that did find associations with cannabis use

(Degenhardt et al., 2001; Degenhardt et al., 2003; Patton et al., 2002; Hayatbakhsh et al., 2007a). It should be noted that generally the relations between cannabis use and internalizing behaviour have been weaker than those with externalizing behaviour, and that existing associations could often be accounted for by co-occurring risk factors such as sociodemographic factors and use of other substances (Moore et al., 2007). Our results are in agreement with those studies not finding an association at all (Monshouwer et al., 2006; Harder et al., 2008; McGee et al., 2000).

A possible explanation for these mixed results might be that studies that did find significant associations focused mainly on older individuals (Brook et al., 1998; Hayatbakhsh et al., 2007a; Patton et al., 2002; van Laar et al., 2007; Wittchen et al., 2007), although there is evidence opposing this hypothesis as well (Hayatbakhsh et al., 2008). For example, Hayatbakhsh et al. (2007a) showed, using logistic regression analysis, that cannabis use at the age of 15 was associated with an increased risk for Anxiety and depression at the age of 21. One study providing compelling evidence in favor of the hypothesis was performed by Arseneault et al. (2002), who concluded that the association between cannabis use and depressive symptoms was age dependent, following findings showing that cannabis use at age 15 was not associated with depressive symptoms at age 26 while cannabis use at age 18 was. Hayatbakhsh et al. (2007a) suggested that the association is not only dependent on age, but also on duration and frequency; only those who already started cannabis use at age 15 and using it frequently until the age of 21 showed elevated levels of anxiety and depression in young adulthood. The fact that internalizing problems are more evident in late adolescence and young adulthood than in early adolescence may also play a significant role (Kessler et al., 2007).

The present study has a number of limitations. One limitation is that mental health and cannabis use data were obtained from self-reports. Use of multiple informants, particularly concerning mental health, would have been preferable (Offord et al., 1996). Despite the fact that previous studies have concluded that self-reporting on substance use is generally valid (Buchan et al., 2002) (and the fact that cannabis use in The Netherlands is not illegal, which possibly allows more honest answers), one could still argue that the nature of the questions might have led to socially-desirable answers (especially for young adolescents). Another limitation is the loss of respondents between measurement 1 and 3, especially since non-responders differed from responders in terms of SES and gender. However, it can be argued that if non-

responders would have been included in the present analysis, the present results would have strengthened, since it can be presumed that more cannabis users would be present among the non-responders. On the other hand, it can also be argued that the present results would have been weakened when non-responders (with lower SES) would have been included in the present analysis. SES could have explained a greater part of the variance of cannabis use, which in turn could have weakened the variance explained by externalizing behaviour. Lastly, despite the fact that we controlled for several important confounders, it cannot be ruled out that our results can be explained by non-observed confounding factors (thus supporting the shared causes hypothesis). For example, it has been shown that genetic factors are important determinants of both externalizing behaviour problems and cannabis use (Kendler et al., 2000; Lynskey et al., 2002; Rutter et al., 1999). Research using twin designs has also identified common genetic factors of externalizing problems and substance use behaviour during adolescence (Shelton et al., 2007; Young et al., 2000). For this study, we only had proxy variables of genetic confounding available (i.e. those constituting familial risk of internalizing and externalizing behaviour as well as substance use). There are also several environmental factors (e.g. family functioning, peer group influences) that could not be incorporated in this study.

Despite some clear limitations, it may be noted that this study is one of the few prospective studies focusing on cannabis use and both internalizing and externalizing problems that was able to incorporate data assessed before cannabis initiation, allowing testing of both the damage and the self-medication hypotheses. Whereas externalizing problems at age 11 and 13 preceded cannabis use at age 13 and 16, cannabis use did not precede externalizing problems at any age. Future research should focus on a broader age span and use longer follow-up periods to investigate relationships with mental health problems (both internalizing and externalizing) more thoroughly.

References

Achenbach, T.M. (1991). *Manual for the Youth Self-Report and 1991 Profile.* Burlington: University of Vermont

Alati, R., Kinner, S.A., Hayatbakhsh, M.R., Al Mamun, A., Najman, J.M., & Williams, G.M. (2008). Pathways to ecstacy in young adults; anxiety, depression of behavioural deviance? *Drug and Alcohol Dependence, 92,* 108–115.

Anderson, J.C., & Gerbing, D.W. (1988). Structural equation modeling in practice: A review and recommended two-step approach. *Psychological Bulletin 103,* 411–423.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal, 325,* 1212–1213.

Bentler, P.M. (1990). Comparative fit indexes in structural models. *Psychological Bulletin, 107,* 238–246.

Bentler, P.M. (1995). *EQS Structural Equations Program Manual.* Encino, CA: Multivariate Software.

Brook, J.S., Cohen, P., & Brook, D.W. (1998). Longitudinal study of co-occurring psychiatric disorders and substance use. *Journal of the American Academy of Child and Adolescent Psychiatry, 37,* 322–330.

Browne, M.W., & Cudeck, R. (1993). Alternative ways of assessing model fit. In: Bollen, K.A., & Long, J.S. (Eds.), *Testing Structural Equation Models* (pp. 136–162). Newbury Park, CA: Sage.

Buchan, B.J., Dennis, M.L., Tims, F.M., & Diamond, G.S. (2002). Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. *Addiction, 97,* 98–108.

Coffey, C., Lynskey, M., Wolfe, R., & Patton, G.C. (2000). Initiation and progression of cannabis use in a population-based Australian adolescent longitudinal study. *Addiction, 95,* 1679–1690.

de Winter, A., Oldehinkel, A.J., Veenstra, R., Brunnekreef, J.A., Verhulst, F.C., & Ormel, J. (2005). Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. *European Journal of Epidemiology, 20,* 173–181.

Degenhardt, L., Hall, W., & Lynskey, M. (2001). The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. *Social Psychiatry and Psychiatric Epidemiology, 36,* 219–227.

Degenhardt, L., Hall, W., & Lynskey, M. (2003). Exploring the association between cannabis use and depression. *Addiction, 98,* 1493–1504.

Ferdinand, R.F., Blum, M., & Verhulst, F.C. (2001). Psychopathology in adolescence predicts substance use in young adulthood. *Addiction, 96,* 861–870.

Fergusson, D.M., & Boden, J.M. (2008). Cannabis use and later life outcomes. *Addiction,*
103, 969–976.

Fergusson, D.M., & Horwood, L.J. (1997). Early onset cannabis use and psychosocial adjustment in young adults. *Addiction, 92,* 279–296.

Fergusson, D.M., Horwood, L.J., & Ridder, E.M. (2005). Test of causal linkages between cannabis use and psychotic symptoms. *Addiction, 100,* 354–366.

Fergusson, D.M., Horwood, L.J., & Ridder, E.M. (2007). Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. *Drug and Alcohol Dependence, 88,* 14–26.

Fergusson, D.M., Horwood, L.J., & Swain-Campbell, N. (2002). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction, 97,* 1123–1135.

Hayatbakhsh, M.R., Najman, J.M., Jamrozik, K., Mamun, A.A., Bor, W., & Alati, R. (2008). Adolescent problem behaviours predicting DSM-IV diagnoses of multiple substance use disorder. *Social Psychiatry and Psychiatric Epidemiology, 43,* 356–363.

Hayatbakhsh, M.R., McGee, T.R., Bor, W., Najman, J.M., Jamrozik, K., & Mamun, A.A. (2007b). Child and adolescent externalizing behaviour and cannabis use disorders in early adulthood: an Australian prospective birth cohort study. *Addictive Behaviors, 33,* 422–438.

Hayatbakhsh, M.R., Najman, J.M., Jamrozik, K., Mamun, A.A., Alati, R., & Bor, W., (2007a). Cannabis and anxiety and depression in young adults: a large prospective study. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*, 408–417.

Harder, V.S., Stuart, E.A., & Anthony, J.C. (2008). Adolescent cannabis problems and young adult depression: male-female stratified propensity score analyses. *American Journal of Epidemiology, 168,* 592–601.

Huisman, M., Oldehinkel, A.J., de Winter, A., Minderaa, R.B., de Bildt, A., Huizink, A.C, Verhulst, F.C., & Ormel, J. (2008). Cohort profile: the Dutch 'tracking adolescents' individual lives survey; trails. *International Journal of Epidemiology. 37*, 1227–1235.

Huizink, A.C., Ferdinand, R.F., Ormel, J., & Verhulst, F.C. (2006). Hypothalamicpituitaryadrenal axis activity and early onset of cannabis use. *Addiction, 101,* 1581–1588.

Kandel, D.B., Davies, M., Karus, D., & Yamaguchi, K. (1986). The consequences in young adulthood of adolescent drug involvement. An overview. *Archives of General Psychiatry, 43,* 746–754.

Kandel, D.B., Yamaguchi, K., & Chen, K. (1992). Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *Journal of Studies on Alcohol, 53*, 447–457.

Kendler, K.S., Karkowski, L.M., Neale, M.C., & Prescott, C.A. (2000). Illicit psychoactive substance use, heavy use, abuse and dependence in a US population-based sample of male twins. *Archives of General Psychiatry, 57*, 261–269.

Kendler, K.S., Prescott, C.A., Myers, J. & Neale, M.C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry, 60,* 929–937.

Kessler, R.C., Amminger, G.P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T.B. (2007). Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry, 20,* 359–364.

Khantzian, E.J. (1985). The self-medication hypothesis of addictive disorders – focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142,* 1259–1264.

Korhonen, T., Prince van Leeuwen, A., Reijneveld, S.A., Ormel, J., Verhulst, F.C., & Huizink, A.C. (2010). Externalizing behaviour problems and cigarette smoking as predictors of cannabis use: the TRAILS study *Journal of the American Academy of Child and Adolescent Psychiatry, 49*, 61–69.

King, S.M., Iacono, W.G., & Mcgue, M. (2004). Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction, 99,* 1548–1559.

Lynskey, M.T., Heath, A.C., Nelson, E.C., Bucholz, K.K., Madden, P.A.F., Slustke, W.S., Statham, D.J., & Martin, N.G. (2002). Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychological Medicine, 32,* 195–207.

Marsman, R., Swinkels, S.H.N., Rosmalen, J.G.M., Oldehinkel, A.J., Ormel, J., & Buitelaar, J.K. (2008). HPA-axis activity and externalizing behaviour problems in early adolescents from the general population: the role of comorbidity and gender – the TRAILS study. *Psychoneuroendocrinology, 33*, 789–798.

Mcgee, R., Williams, S., Poulton, R., & Moffitt, T. (2000). A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction, 95,* 491–503.

Monshouwer, K., Van Dorsselaer, S., Verdurmen, J., Ter Bogt, T., De Graaf, R., & Vollebergh, W. (2006). Cannabis use and mental health in secondary school children. Findings from a Dutch survey. *British Journal of Psychiatry, 188,* 148–153.

Monshouwer, K., Smit, F., de Graaf, R., van Os, J., & Vollebergh, W. (2005). First cannabis use: does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on Substance Use. *Addiction, 100,* 963–970.

Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet, 370,* 319–328.

Offord, D.R., Boyle, M.H., Racine, Y., Szatmari, P., Fleming, J.E., Sanford, M., Lipman, E.L., 1996. Integrating assessment data from multiple informants. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 1078–1085.

Ormel, J., Oldehinkel, A.J., Ferdinand, R.F., Hartman, C.A., De Winter, A.F., Veenstra, R., Vollebergh, W., Minderaa, R.B., Buitelaar, J.K., & Verhulst, F.C. (2005). Internalizing and externalizing problems in adolescence: general and dimension-specific effects of familial loadings and preadolescent temperament traits. *Psychological Medicine, 35*, 1825–1835.

Patton, G.C., Coffey, C., Carlin, J.B., Degenhardt, L., Lynskey, M., & Hall, W. (2002). Cannabis use and mental health in young people: cohort study. *British Medical Journal,* 325, 1195–1198.

Pedersen, W., Mastekaasa, A., & Wichstrom, L. (2001). Conduct problems and early cannabis initiation: a longitudinal study of gender differences. *Addiction, 96,* 415–431.

Raine, A., (1996). Autonomic nervous system factors underlying disinhibited, antisocial, and violent behaviour. Biosocial perspectives and treatment implications. *Annals of the New York Academic Sciences, 794*, 46–59.

Rutter, M., Silberg, J., O'Conner, T., & Simonoff, E. (1999). Genetics and child psychiatry: II empirical research findings. *Journal of Child Psychology and Psychiatry, 40,* 19–55.

Schneider, M. (2008). Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addiction Biology, 13,* 253–263.

Shelton, K.H., Liffor, K., Fowler, T., Rice, F., Neale, M., Gordon, H., Thapar, A., & van den Bree, M. (2007). The association between conduct problems and the initiation and progression of marijuana use during adolescence: a genetic analysis across time. *Behavior Genetics, 37,* 314–325.

Steiger, J.H. (1998). A note on multiple sample extensions of the RMSEA fit index. *Structural Equation Modeling, 5,* 411–419.

van Laar, M., van Dorsselaer, S., Monshouwer, K., de Graaf, R., 2007. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction 102,* 1251–1260.

Veenstra, R., Lindenberg, S., Oldehinkel, A.J., De Winter, A.F., & Ormel, J., (2006). Temperament, environment, and antisocial behaviour in a population sample of preadolescent boys and girls. *International Journal of Behavioral Development, 30,* 422–432.

Veenstra, R., Lindenberg, S., Oldehinkel, A.J., De Winter, A.F., Verhulst, F.C., & Ormel, J. (2005). Bullying and victimization in elementary schools: a comparison of bullies, victims, bully/victims, and uninvolved preadolescents. *Developmental Psychology, 41,* 672–682.

Verhulst, F.C., & Achenbach, T.M. (1995). Empirically based assessment and taxonomy of psychopathology – cross-cultural applications – a review. *European Child and Adolescent Psychiatry, 4,* 61–76.

White, H.R., Loeber, R., Stouthamer-Loeber, M., & Farrington, D.P. (1999). Developmental associations between substance use and violence. *Developmental Psychopathology, 11*, 785–803.

Wittchen, H.U., Frohlich, C., Behrendt, S., Gunther, A., Rehm, J., Zimmermann, P., Lieb, R., & Perknigg, A. (2007). Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. *Drug and Alcohol Dependence, 88,* S60–S70.

Young, S.E., Stallings, M.C., Corley, R.P., Krauter, K.S., & Hewitt, J.K. (2000). Genetic and environmental influences on behavioural disinhibition. *American Journal of Medical Genetics, 96,* 684–695.

3.

Cannabis Use and Vulnerability for Psychosis in Early Adolescence - a TRAILS Study

Griffith-Lendering, M.F.H., Wigman, J.T.W., Prince van Leeuwen, A., Huijbregts, S.C.J., Ormel, J., Verhulst, F.C., van Os, J., Swaab, H. & Vollebergh, W.A.M. Cannabis use and vulnerability for psychosis in early adolescence – a Trails study. *Addiction,* doi: 10.1111/add.12050

Abstract

Aims: To examine the direction of the longitudinal association between vulnerability for psychosis and cannabis use throughout adolescence.

Design: Cross-lagged path analysis was used to identify the temporal order of vulnerability for psychosis and cannabis use, while controlling for gender, family psychopathology, alcohol use and tobacco use.

Setting: A large prospective population study of Dutch adolescents [the TRacking Adolescents' Individual Lives Survey (TRAILS) study].

Participants: A total of 2,120 adolescents with assessments at (mean) age 13.6, age 16.3 and age 19.1.

Measurements: Vulnerability for psychosis at the three assessment points was represented by latent factors derived from scores on three scales of the Youth Self Report and the Adult Self Report, i.e. Thought Problems, Social Problems and Attention Problems. Participants self- reported on cannabis use during the past year at all three waves.

Findings: Significant associations (r=.12-.23) were observed between psychosis vulnerability and cannabis use at all assessments. Also, cannabis use at age 16 predicted psychosis vulnerability at age 19 (z=2.6, p<.05). Furthermore, psychosis vulnerability at ages 13 (z=2.0, p<.05) and 16 (z=3.0, p<.05) predicted cannabis use at, respectively, ages 16 and 19.

Conclusions: Cannabis use predicts psychosis vulnerability in adolescents, and vice versa which suggests that there is a bi-directional causal association between the two.

Introduction

Epidemiological research has provided extensive evidence of associations between cannabis use and psychosis (Arsenault et al., 2002; Compton et al., 2009; Fergusson et al., 2003, Henquet et al., 2005; Kuepper et al., 2011; Manrique-Garcia et al., 2012; Moore et al., 2007; Rössler et al., 2012; Van Gastel et al., 2011). Cannabis use has been associated with both subclinical psychotic experiences and clinical psychotic disorder. However, the direction of the (temporal) associations between cannabis use and psychotic symptoms has not yet been fully explained. Several hypotheses considering the direction of the effect have been proposed. There is evidence for a so-called 'self medication hypothesis', where individuals are hypothesized to use cannabis in order to alleviate their psychotic symptoms or to improve their mood (Khantzian, 1997; Kolliakou et al., 2011). There is more evidence, however, supporting an association in the opposite direction. This is referred to as the damage hypothesis, where cannabis use causes or exacerbates psychotic symptoms (Fergusson et al., 2003; Kuepper et al., 2011; Moore et al., 2006). Finally, there are some longitudinal studies suggesting a bidirectional relationship between cannabis use and psychotic experiences or symptoms (Moore et al., 2007; Ferdinand et al., 2005). Neurobiological studies have suggested that cannabis can indeed induce psychotic experiences when excessive Δ-9-tetrahydrocannabinol (Δ^9-THC-) stimulation of cannabinoid (CB_1-) receptors on GABAergic and glutaminergic terminals causes disruptions in dopaminergic projections from the brain stem to the striatum (Bhattacharyya et al., 2010; Morrison et al., 2009). It has also been proposed that the normally transient effects of Δ^9-THC on physiological control of the endogenous cannabinoid (CBD-) system over glutamate and GABA release may be more harmful during adolescence because of adverse effects on the ongoing rapid maturation of neural circuits (particularly prefrontal cortex) at that stage of life (Bossong & Niesink, 2010; Schneider, 2008).

Studies into longitudinal cannabis-psychosis associations have often linked cannabis use during adolescence to psychotic experiences or symptoms in adulthood. Considering the rapid maturation of brain regions and neurotransmitter systems associated with both psychosis and cannabis exposure, and subsequent increased vulnerability (Bossong & Niesink, 2010; Schneider, 2008), however, it is important to additionally focus on the adolescent life phase itself when studying possible

relationships. There are several other arguments for investigating the associations within adolescence itself. One is that psychosis proneness is often already evident during early adolescence, which may not be surprising considering its strong heritable component (Gill et al., 2010; Rijsdijk et al., 2011). Although there may not yet be very obvious manifestations at this stage, there are proxy measures including specific cognitive, social, and thought problems which appear to be good predictors of later subclinical or clinical psychosis (Bearden et al., 2000; Tarbox & Pogue-Geile., 2008; Welham et al., 2009; Wigman et al., 2009). Moreover, there is increasing evidence for stability or continuity (from adolescence onwards) of psychosis symptoms (Poulton et al., 2000; Wigman et al., 2011; Yung et al., 2009). This parallels the continuity (and sometimes transition into addiction and/or use of heavier drugs) observed for cannabis use Fergusson et al., 2006). Further evidence supporting a focus on (early) adolescence itself stems from studies showing that those who initiated cannabis use earlier and/or used cannabis for longer periods of time carried a greater risk for schizophrenia outcomes and psychotic experiences than those who initiated cannabis use later and/or used cannabis for shorter periods of time (Arsneault et al., 2002; Large et al., 2011; Schubart et al., 2010; Stefanis & van Os., 2004). Thus, in order to facilitate early recognition of psychosis (symptoms) and for a better understanding of the role of cannabis use in its development, research on their interrelations needs to incorporate important developmental stages including the entire period of adolescence.

The present study focused on the direction of temporal relationships between cannabis use and vulnerability for psychosis in a large population sample of adolescents (n=2,120) enrolled in the TRacking Adolescents' Individual Lives Survey (TRAILS) (Huisman et al., 2008), controlling for possible confounding variables such as SES, parental psychopathology and use of other substances. Assessment of both psychotic vulnerability and cannabis use at multiple time points allowed testing of both the self-medication hypothesis and the damage hypothesis.

Method

Participants

Data was gathered from participants in the TRacking Adolescents' Individual Lives Survey (TRAILS), an on-going prospective population study of Dutch adolescents investigated biennially until at least the age of 25 years.

The TRAILS target sample consisted of young adolescents from five municipalities in the north of the Netherlands, including both urban and rural areas. The sample selection involved two steps. First, the municipalities were requested to provide names and addresses of all inhabitants born between 10 January 1989 and 30 September 1990 (first two municipalities) or between 10 January 1990 and 30 September 1991 (last three municipalities), which yielded 3483 names. Simultaneously, primary schools (including schools for special education) within these municipalities were approached with a request to participate. School participation was a prerequisite for eligible adolescents and their parents to be approached by TRAILS, with the exception of adolescents who already attended secondary schools (<1%), who were contacted without involving their schools. Of the 135 primary schools within the municipalities, 122 (90.4%) schools agreed to participate, accommodating 90.3% of the adolescents.

Secondly, if schools agreed to participate, parents (or guardians) received two brochures, one for themselves and one for their adolescents, with information about the study. In addition, a TRAILS staff member visited the schools to inform eligible adolescents about the study. More details about the procedure have been published elsewhere (Huisman et al., 2008; de Winter et al., 2005).

The exclusion criteria were: (1) adolescent's inability of participating because of intellectual disability or a serious physical illness or handicap; (2) Dutch-speaking parent or parent surrogate not available, and not feasible to administer a part of the measurements in parent's own language. Of all subjects who were approached (n=3145), 6.7% were excluded.

Of the remaining 2935 young adolescents, 76.0% were included in the study (T1: n= 2,230, mean age: 11.1 years, SD: 0.6, 50.8% female). For the present study, data from the first assessment (T1, mean age: 11.09 years; SD: 0.55; 50.8% girls) only involved control variables. Main analyses were performed with data of T2 (mean age: 13.6; SD: 0.5, 51% girls), T3, (mean age: 16.3 years; SD: 0.7, 52.3% girls) and T4, (mean

age: 19.1; SD: 0.6, 52.3% girls), because there was no reporting on cannabis use at T1.

Measures

Cannabis use

Cannabis use by the participants was measured at the second, third and fourth assessments by self-report items on cannabis use in the last year with the following questions: 'How often have you used cannabis in your life/in the last year', with answer categories: 'I have never used', 'used it once', 'used it twice', 'three times',....., '10 times', '11–19 times', '20–39' times, '40 times or more'. Items were recoded into four categories; (1) no use; (2) 1-2 times during the past year, (3) 3-6 times during the past year; (4) 7 times or more during the past year.

Other studies focusing on cannabis use have recoded the above answer possibilities into the following categories: (1) those who had never used; (2) those who had used but not during the past year, (discontinued use); (3) those who used once or twice during the past year, (experimental use); (4) those who reported using cannabis between 3 and 39 times during the past year, (regular use); (5) those who reported using it 40 times or more during the last year (heavy use) (Griffith-Lendering et al., 2011; Monshouwer et al., 2006). Whereas it is more customary to use these categories, cross-lagged path analysis requires linear variables. The more traditional categorization did not result in a linear variable or a variable that could be used as such. In order to obtain a variable/categorization that best approached linearity, Tukey's transformation ladder was used (Tukey, 1977). According to Tukey, a variable can be interpreted as linear (with equal distances between categories) when a straight line results after plotting the logarithmic transformation of the variable against the raw data. Using categories no use (1), 1-2 times (2), 3-6 times (3), and 7 times or more (4) resulted in the best Tukey solutions for T2, T3, and T4.

Psychosis vulnerability

Psychosis vulnerability was conceptualized as a latent factor, indicated by three subscales of the Youth Self-Report (YSR) at measurement waves T2 and T3, and the Adult Self-Report (ASR) at T4; the Thought Problems, Attention Problems and Social Problems scales. The YSR is one of the most commonly used self-report questionnaires in current child and adolescent psychiatric research, and is appropriate

for ages 11-19 (Achenbach & Rescorla., 2001; Verhulst & Achenbach., 1995). The YSR contains 112 items on behavioural and emotional problems in the past 6 months that can be rated as being not true (0), somewhat or sometimes true (1), or very or often true (2). The ASR is the equivalent of the YSR for individuals aged 18-59, and includes many of the YSR items, including some extra items on transitions to adulthood (Achenbach & Rescorla., 2001). Attention Problems of both the YSR and the ASR include items such as 'having trouble concentrating'. The Thought Problems Scales of the YSR and the ASR include 12 items such as 'seeing things that other people do not see'. Following earlier work (Wigman et al., 2011), three items (on skin picking; storing up many things and sleeping less than other children) were excluded based on their low Spearman inter-item correlations with the other items, leaving nine items in this subscale. For consistency, these items were also excluded from the ASR. The Social Problems scale of the YSR includes 11 items such as 'feeling lonely' and 'not getting along with other boys and girls'. Since only 7 of the original 11 items of the Social Problems scale of the ASR were measured at T4, we have converted all measures of the YSR and ASR into z-scores in further analyses to account for potential biases. Internal consistency for all subscales of YSR and ASR, measured at T2-3-4, was acceptable (Cronbach's α ranged between 0.62 – 0.84).

Control variables

Use of other substances

Tobacco use was measured at T2, T3, and T4, where adolescents were asked about their use in the last month. Answers were recoded into non-weekly versus weekly tobacco use. Use of alcohol was also measured at T2, T3 and T4, where adolescents were asked about the frequency of alcohol use in the past month. Alcohol use was recoded into non-monthly versus monthly use. These categories (for both tobacco use and alcohol use) were similar to those used in other studies focusing on cannabis use and mental health (e.g. Monshouwer et al., 2006).

Socioeconomic status (SES)

SES was assessed at baseline (T1) using a 5-point scale consisting of five variables: educational level (father/mother), occupation (father/mother), and family income. The

internal consistency of this measure is good (Cronbach's alpha 0.84) (Ormel et al., 2005).

Parental psychopathology

Parental psychopathology, (i.e. depression, anxiety, substance abuse, antisocial behaviour, and psychosis) was measured by means of the Brief TRAILS Family History Interview (Ormel et al., 2005; Veenstra et al., 2005), administered at baseline (T1). The scores for substance abuse and antisocial behaviour were used to construct a familial vulnerability index for externalizing disorder. The scores for depression and anxiety disorder were used to construct an index for internalizing disorder. More information on the construction of familial vulnerability within TRAILS can be found elsewhere (Ormel et al., 2005; Veenstra et al., 2005).

Data-analysis

Around 50 % of the original sample (n=1123) had complete data on all variables of interest measured at various waves. Consequently, the results of 'complete-case' analyses could potentially be biased. Using the method of multiple imputation (Schafer., 1997; Schafer & Graham., 2002), where multiple versions of the dataset are produced, each containing its own set of imputed values, and parameter estimates for all imputed datasets are pooled for further statistical analyses, missing data at T2, T3 and T4 were imputed. First, participants missing data on either 'cannabis use' or 'psychosis vulnerability' at all three waves were deleted from the sample (n=110), before imputation was carried out. Fully Conditional Specification (FCS), an iterative Markov chain Monte Carlo (MCMC) method, which for each variable in the order specified in the variable list fits a univariate model using all other available variables in the model as predictors, was chosen for multiple imputation. Data from T1 were entered only as 'predictor variables' of missing data of T2, T3 and T4. These included SES, gender, parental psychopathology and YSR scales of Social Problems, Attentional Problems and Thought Problems. All abovementioned variables plus cannabis use from T2, T3, and T4 were included in the model as both predictors and imputed data.

In order to determine which variables should be included in the main analyses as covariates, it was examined whether there were differences between cannabis users (those indicating having used cannabis at least once) and non-users with respect to SES, parental psychopathology, use of alcohol and tobacco and gender.

The temporal order of occurrence of cannabis use and psychosis vulnerability was investigated using path analyses. Following the two-step approach recommended by Anderson and Gerbin (1988), confirmatory factor analysis (CFA) was first used to investigate how well our hypothesized models fit the actual data. The models were based on the notion that either vulnerability for psychosis predicted cannabis use or the other way around.

Next, cannabis use and vulnerability for psychosis, identified in the CFA, were modelled prospectively. Here, we included all possible associations between latent variables and all significant control variables. To evaluate the overall model fit, the Root Mean Square error of approximation was used (RMSEA) (Steiger, 1988); a RMSEA value less than .05 indicates good model fit (Browne & Cudeck., 1993). Both χ^2 statistics and RMSEA are dependent on the size of the sample: as we had a relatively large sample (n=2,120), we also used the Comparative Fit Index (CFI) (Bentler., 1990) to evaluate overall model fit. A CFI value greater than .90 indicates good model fit [43]. All analyses were performed using EQS 6.1 for Windows (Bentler., 1995).

Results

Preliminary analysis

Cannabis users (n=940) did not differ from non-users (n = 1180) with respect to familial vulnerability for internalizing disorders (t(2,118)=-.1.8, p=.066). Cannabis users were more often boys than girls (54.9% vs. 43.6%; χ^2(1)=26.9, p<.001), monthly alcohol users (54.0% vs. 29.2%; χ^2(1)=133.9, p<.001 at T2; 89.5% vs. 68.2%; χ^2(1)=136.1, p<.001 at T3; 94.3% vs. 77.8%; χ^2(1)=110.9, p< .001 at T4) and weekly tobacco users (16.2% vs. 3.1%; χ^2(1)=109.5, p<.001 at T2; 57.9% vs. 18.0%; χ^2(1)=363.2, p<.001 at T3; 54.0% vs. 29.2%; χ^2(1)=133.9, p<.001 at T4). Furthermore, cannabis users and non-users differed significantly with respect to SES (t (2,118)=-3.0 p=.002) and familial vulnerability for externalizing disorders (t (2,118) = -2.3, p=.022), where cannabis users scored higher on familial vulnerability for externalizing disorders and SES than non users. Of these variables, SES was not related to indicators of psychosis vulnerability and therefore not introduced as a covariate. Gender, familial vulnerability for externalizing disorders, alcohol use and

tobacco use were related to psychosis vulnerability and therefore included as covariates in subsequent path analyses.

Descriptives

Descriptive information regarding the frequency of cannabis use is presented in Table 1.

Table 1; Descriptive information on cannabis use during the past year T2, T3 and T4 (*n*=2,120).

	T2	T3	T4
No use	94.2 % (n=1,997)	74.2 % (n=1,574)	65.3 % (n=1,385)
1-2 times	3.0 % (n=63)	7.6 % (n=162)	10.7 % (n=227)
3-6 times	1.5 % (n=32)	7.4 % (n=157)	8.1 % (n=171)
7 times or more	1.3 % (n=28)	10.7 % (n=227)	15.8 % (n=336)

Path analysis; Preliminary analysis (CFA)

The independent model which tested the hypothesis that all cannabis scores and psychosis vulnerability were uncorrelated was rejected: $\chi^2(33,N=2,120)=207.1$, $p=<.001$; *RMSEA*=.05; *CFI*=.98. The model provided an acceptable fit to the data. Table 2 shows the correlations between all latent variables. All correlations between psychosis vulnerability and cannabis use were significant ($p=<.05$). Also, correlations became stronger over time.

Table 2. Correlations between cannabis use and the latent variables for psychosis vulnerability from the Confirmatory Factor Analysis (*n*=2,120)

	T2 Cannabis use	T3 Cannabis use	T4 Cannabis use
T2 Vulnerability for psychosis	.12*	.15*	.12*
T3 Vulnerability for psychosis	.08*	.17*	.15*
T4 Vulnerability for psychosis	.07*	.17*	.23*

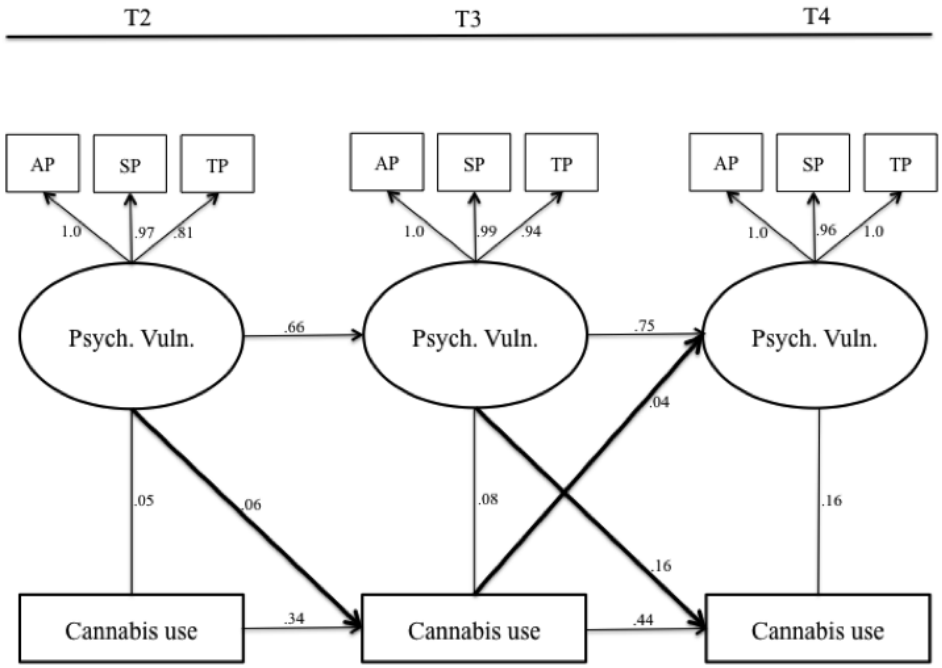
* p < .05

Cannabis use and psychosis vulnerability

Next, we performed a path analysis to address the temporal order of cannabis use and psychosis vulnerability, after including the following covariates: gender, familial vulnerability for externalizing disorders, alcohol (T2-3-4) and tobacco use (T2-3-4). Figure 1 presents details on the path analysis of psychosis vulnerability and cannabis use, including factor loadings and correlations.

The model represented the data well $\chi^2(146,N=2,120)=1214,5$, $p<.001$; *RMSEA*=.06, *CFI* =.92. As expected, the stability paths between vulnerability for psychosis measured at T2, T3, and T4 were all significant (T2-T3; $z=22.6$, $p<.05$ and T3-T4; $z=23.8$, $p<.05$) and so were the stability paths for cannabis use at the three different assessment points (T2-T3; $z=8.1$, $p<.05$ and T3-T4; $z=20.6$, $p<.05$).Vulnerability for psychosis at T2 predicted cannabis use at T3 ($z=2.0$, $p<.05$). Similarly, vulnerability for psychosis at T3 predicted cannabis use at T4 ($z=3.0$, $p<.05$). Also, cannabis use measured at T3 significantly predicted psychosis vulnerability measured at T4 ($z=2.6$, $p<.05$). Lastly, cannabis use measured at T2 did not predict psychosis vulnerability measured at T3 ($z=.3$, $p>.05$).

Figure 1. Path analysis of psychosis vulnerability (Psych. Vuln.), with indicators: Thought Problems (TP), Social Problems (SP) and Attention Problems (AP) and cannabis use during adolescence after controlling for gender, parental psychopathology, tobacco (T2-3-4) and alcohol use (T2-3-4) (*n*=2,120). All non-significant paths have been removed from the full model. Latent variables are shown in ellipses, and observed variables are shown in rectangles.



Discussion

This study investigated the longitudinal and bidirectional relationship between cannabis use and vulnerability for psychosis, as indicated by thought problems, social problems and attention problems, in a sample of 2,120 adolescents from the Dutch general population. The directionality of the longitudinal association between cannabis use and vulnerability for psychosis was examined by testing two contrasting hypotheses, the damage hypothesis and the self-medication hypothesis, using path analyses and controlling for possible confounding factors.

The results showed that throughout adolescence, vulnerability for psychosis was associated with cannabis use. When investigating the temporal order of this relationship, bidirectional associations became apparent. More specifically, cannabis use at age 16 predicted vulnerability for psychosis at age 19, but psychosis vulnerability at age 16 also predicted cannabis use at age 19. Moreover, psychosis vulnerability at age 13 predicted cannabis use at age 16. Cannabis use at age 13 did not predict vulnerability for psychosis at age 16, but this could be due to a lack of statistical power, since the number of adolescents that had actually used cannabis at T2 was quite small (n=123).

It may be concluded that the results provide empirical support for both the damage and the self-medication hypothesis. Whereas evidence has been provided for apparent unidirectional associations in many earlier studies (Arsenault et al., 2002; Compton et al., 2009; Ferdinand et al., 2005; Fergusson et al., 2003, Henquet et al., 2005; Khantzian., 1997; Kolliakou et al., 2011; Kuepper et al., 2011; Manrique-Garcia et al., 2012; Moore et al., 2007; Rössler et al., 2012; Van Gastel et al., 2011), not many studies have been able to include multiple measurement points and thus test bidirectional associations. Moreover, some very plausible explanations have been offered for why the temporal association would head one way or the other. With respect to self-medication, it has been specifically hypothesized that individuals with psychosis symptoms use cannabis to improve their mood or to control one's feelings, boredom, social motives, improving sleep, anxiety and agitation, although some studies indicate that individuals with psychosis symptoms use cannabis for similar reasons as the general population as well, i.e. 'to get high', relax and have fun (Caspi et al., 2005; Khantzian., 1997; Kolliakou et al., 2011). With respect to the damage hypothesis, there is support from neurobiological studies, which also indicate

adolescence as a particularly vulnerable period for the effects of cannabis. Still, when studies have been able to include multiple measurement points, the existence of bidirectional associations generally becomes evident (Ferdinand et al., 2005). The results of the present study give rise to the thought that a cascading model would fit the temporal associations between cannabis use and psychosis vulnerability best, particularly because associations between cannabis use and psychosis vulnerability became stronger at later assessments. In order to be able to study this in more detail, different statistical approaches might have to be chosen and possible moderation effects should also be taken into account. There are several studies showing interactions between particular gene variants as well as environmental factors and cannabis use in the prediction of psychosis Caspi et al., 2005; Cougnard et al., 2007; Decoster et al., 2012; Henquet et al., 2008).

Some limitations of the present study should be kept in mind when interpreting the results. Firstly, data of the present study are all based on self-report. Although clinical interviews for assessment of psychosis vulnerability and multiple informants would have been preferable, previous studies have concluded that both substance use behaviour and mild psychotic symptoms can be reliably investigated by self-report (Buchan et al., 2002). Another limitation is that, despite the fact that several important potential confounders have been taken into account, we cannot claim to have been all-inclusive in this respect. Whereas this would be the case for most, if not all large cohort studies, it may be argued that the choice of potential confounders could have been more refined. For example, the genetic variation associated with psychosis vulnerability and substance use could manifest itself in (impairments in) certain (dopamine or serotonin-dependent) cognitive abilities that could have been assessed as well. A third possible limitation is that three scales of the Youth Self Report and Adult Self-Report were used as indicators of psychosis vulnerability. Although these scales were shown to be associated with psychosis (Bearden et al., 2000; Tarbox & Pogue-Geile., 2008; Welham et al., 2009; Wigman et al., 2009), and may be good indicators of early manifestations of psychosis that could develop into the clinical disorder, future studies may want to include instruments measuring psychosis symptoms more directly as well (Rössler et al., 2011).

Strengths of the current study include its longitudinal design, which allowed for investigation of the bi-directional relationship between cannabis use and vulnerability

for psychosis. Second, the starting point of the TRAILS-study is early adolescence, which allowed investigation of (factors associated with) cannabis use and development of psychosis from an earlier and possibly more crucial age compared to most other studies. This is particularly important considering recent hypotheses stating that cannabis-induced psychosis may be a distortion of normal adolescent brain maturation (Bossong & Niesink., 2010). Thirdly, a number of important control variables were included in the analyses, including the use of other substances and parental psychopathology.

In conclusion, the present study showed that cannabis use at age 16 predicted psychosis vulnerability at age 19, and psychosis vulnerability at age 13 and 16 predicted cannabis use at, respectively, age 16 and 19, thereby providing evidence for both the damage-hypothesis and self-medication hypotheses. Prevention programs aimed at delaying and preventing transition from subclinical psychotic symptoms to clinical disorder should target the entire adolescent life phase and pay attention to cannabis use at this period in time.

References

Achenbach, T.M., & Rescorla, L.A. (2001). *Manual for the Aseba School-age Forms & Profiles.* Burlington, VT: University of Vermont, Research Center for Children Youth and Families.

Anderson, J. C., & Gerbing, D.W. (1988). Structural equation modelling in practice: A review and recommended two-step approach. *Psychological Bulletin, 103,* 411 – 23.

Arsenault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *British Medical Journal, 325,* 1212-3.

Bearden, C.E., Rosso, I.M., Hollister, J.M., Sanchez, L.E., Hadley, T., & Cannon, T.D. (2006). A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia. *Schizophrenia Bulletin, 26,* 395-410.

Bentler, P.M. (1990). Comparative fit indexes in structural models. *Psychological Bulletin, 107,* 238–246.

Bentler, P.M. (1995). *EQS Structural Equations Program Manual.* Encino, CA: Multivariate Software.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'carroll, C.M., Seal, M., Allen, P., Mehta, M.A., Stone, J.M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R.M., Zuardi, A.W.,

Crippa, J.A., Atakan, Z., & McGuire, P.K. (2010). Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology, 35,* 764-774.

Bossong, M.G., & Niesink, R.J.M. (2010) Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Progress in Neurobiology, 92,* 370-385.

Browne, M.W., & Cudeck, R. (1993). Alternative ways of assessing model fit. In: Bollen, K.A., & Long, J.S. (Eds.), *Testing Structural Equation Models* (pp. 136–162). Newbury Park, CA: Sage.

Buchan, B.J., Dennis, M.L., Tims, F.M., & Diamond, G.S. (2002). Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. *Addiction, 97,* 98–108.

Caspi, A., Moffit, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., & Craig, I.W. (2005). Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction. *Biological Psychiatry*, *57*, 1117 – 1127.

Compton, M.T., Kelley, M.E., Ramsay, C.E., Pringle, M., Goulding, S.M., Esterberg, M.L., Stewart, T., & Walker, E.F. (2009). Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *American Journal of Psychiatry, 166*, 1251–7.

Cougnard, A., Mercelis, M., Myin-Germeys, I., de Graaf, R., Vollebergh, W., Krabbendam, L., Lieb, R., Wittchen, H.U., Henquet, C., Spauwen, J., van Os, J. (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychological Medicine, 37,* 513-527.

Decoster J., Van Os J., Myin-Germeys I., De Hert M., Van Winkel R. (2012). Genetic variation underlying psychosis-inducing effects of cannabis: critical review and future directions. *Current Pharmaceutical Design, 18,* 5015-23.

Ferdinand, R.F., Sondeijker, F., van der Ende, j., Selten, J., Huizink, A., & Verhulst, F.C. (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction, 100,* 612– 618.

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2006). Cannabis use and other drug use: testing the cannabis gateway hypothesis. *Addiction, 101*, 556-569.

Fergusson, D.M., Horwood, L.J., & Swain-Campbell, N.R. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine, 33,* 15-21.

Gill, M., Donohoe, G., Corvin A. (2010) What have genomics ever done for the psychoses? *Psychological Medicine, 40*, 529-520.

Griffith-Lendering, M.F.H., Huijbregts, S.C.J., Mooijaart, A., Vollebergh, W.A.M., & Swaab, H. (2011). Cannabis use and development of externalizing and internalizing behaviour problems in early adolescence; a TRAILS study. *Drug and Alcohol Dependence, 116,* 11-17.

Henquet, C., Di Forti, M., Morrison, P., Kuepper, R., Murray, R.M. (2008). Gene-Environment interplay between cannabis and psychosis. *Schizophrenia Bulletin, 34,* 1111-1121.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Lieb, H.U., Wittchen, H., & van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *British Medical Journal, 330:* d11.

Huisman, M., Oldehinkel, A.J., de Winter, A., Minderaa, R.B., de Bildt, A., Huizink, A.C., Verhulst, F.C., Ormel, J., 2008. Cohort profile: the Dutch 'tracking adolescents' individual lives survey; trails. International Journal of Epidemiology, 37, 1227–1235.

Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders – focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142*, 1259–1264.

Kolliakou, A., Joseph, C., Ismall, K., Atakan, Z., & Murray, R.M. (2011). Why do patients with psychosis use cannabis and are they ready to change their use? *International Journal of Developmental Neuroscience, 29*, 335-346.

Kuepper, R., van Os, J., Lieb, R., Wittchen, H., Höfler, M., & Henquet, C. (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *British Medical Journal, 342:* d738.

Large, M., Sharma, S., Compton, M.T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry, 68,* 555-61.

Morrison, P.D., & Murray, R.M. (2009). From real-world events to psychosis: the emerging neuropharmacology of delusions. *Schizophrenia Bulletin, 35,* 668-764.

Ormel, J., Oldehinkel, A.J., Ferdinand, R.F., Hartman, C.A., De Winter, A.F., Veenstra, R., Vollebergh, W., Minderaa, R.B., Buitelaar, J.K., & Verhulst, F.C. (2005). Internalizing and externalizing problems in adolescence: general and dimension-specific effects of familial loadings and preadolescent temperament traits. *Psychological Medicine, 35*, 1825–1835.

Poulton, R., Caspi, A., Moffit, T.E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: A 15-year longitudinal study. *Archives of General Psychiatry, 57*, 1053-1058.

Manrique-Garcia, E., Zammit, S., Hemmingsson, T., Andreasson, S., & Allebeck, P. (2012). Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort, *Psychological Medicine, 42,* 1321-1328.

Monshouwer, K., Smit, F., de Graaf, R., van Os, J., & Vollebergh, W. (2005). First cannabis use: does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on Substance Use. *Addiction, 100,* 963–970.

Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet, 370,* 319–328.

Rössler, W., Hengartner, M.P., Ajdacic-Gross, V., Haker, H., Gamma, A., & Angst, J. (2011). Sub-clinical psychosis symptoms in young adults are risk factors for subsequent mental disorders. *Schizophrenia Research, 13,* 18-23.

Rössler, W., Hengartner, M.P., Angst, J., & Ajdacic-Gross, V. (2012). Linking substance use with symptoms of subclinical psychosis in a community cohort over 30 years. *Addiction, 107,* 1174-1184.

Rijsdijk F.V., Gottesman I.I., McGuffin, P., Cardno, A.G. (2011). Heritability estimates for psychotic symptom dimensions in twins with psychotic disorders. *American Journal of Medical Genetics part B: Neuropsychiatric Genetics, 156B*, 89-98.

Schafer, J.L. (1997). *Analysis of Incomplete Multivariate Data*. London, Chapman and Hall.

Schafer, J.L., & Graham, J.W. (2002). Missing data: Our view of the state of the art. *Psychological Methods, 7*, 147-77.

Schneider, M. (2008). Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addiction Biology, 13*, 253-263.

Schofield, D., Tennant, C., Mash, L., Degenhardt, L., Cornish, A., Hobbs, C., Brennan, G. (2006). Reasons for cannabis use in psychosis. *Australian and New Sealand Journal of Psychiatry, 40,* 570-574.

Schubart, C.D., Van Gastel, V.A., Breetvelt, E.J., Beetz, S.L., Ophoff, R.A., Sommer, I.E.C., Kahn, R.S., & Boks, M.P. (2010). Cannabis use at a young age is associated with psychotic experiences. *Psychological Medicine, 41,* 1–10.

Steiger, J. H. A note on multiple sample extensions of the RMSEA fit index. *Structural Equation Modeling, 5,* 411–9.

Stefanis, C.N., & Van Os, J. (2004). Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction, 99,* 1333–41.

Tarbox, S.I., & Pogue- Geile, M.F. (2008). Development of social functioning in preschizophrenia children and adolescents: A systematic review. *Psychological Bulletin, 134,* 561 – 583.

Tukey, J. W. (1977). *Exploratory Data Analysis*. Reading (MA): Addison-Wesley.

Van Gastel, W.A., Wigman, J.T.W., Monshouwer, K., Kahn, R.S., van Os, J., Boks, M.P.M., & Vollebergh, W.A.M. (2011). Cannabis use and subclinical positive psychotic experiences in early adolescence: findings from a Dutch survey, *Addiction, 107,* 381-387.

Veenstra, R., Lindenberg, S., Oldehinkel, A.J., De Winter, A.F., Verhulst, F.C., & Ormel, J. (2005). Bullying and victimization in elementary schools: a comparison of bullies, victims, bully/victims, and uninvolved preadolescents. *Developmental Psychology, 41,* 672–682.

Verhulst, F.C., & Achenbach, T.M. (1995). Empirically based assessment and taxonomy of psychopathology – cross-cultural applications – a review. *European Child and Adolescent Psychiatry, 4,* 61–76.

Welham, J., Scott, J., Williams, G.M., Najman, J., Bor, W., O'Callaghan, M., McGrath, J. (2009). Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: A 21-year birth cohort study. *Psychological Medicine, 39*, 625–634.

Wigman, J.T.W., Vollebergh, W.A.M., Raaijmakers, Q.A.W., Iedema, J., van Dorsselaer, S., Ormel, J., Verhulst, F.C., Van Ops, J. (2009). The structure of the

extended psychosis phenotype in early adolescence - A cross-sample replication. *Schizophrenia Bulletin, 37,* 850-860.

Wigman, J.T.W.,Van Winkel, R., Raaijmakers, Q.A.W., Ormel, J., Verhulst, F.C., & Reijneveld, S. (2011). Evidence for a persistent, deteriorating subtype of subclinical psychotic experiences: A six-year longitudinal general population study. *Psychological Medicine, 41,* 2317-2329.

de Winter, A., Oldehinkel, A.J., Veenstra, R., Brunnekreef, J.A., Verhulst, F.C., Ormel, J., 2005. Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. *European Journal of Epidemiology, 20,* 173–181.

Yung, A.R., Nelson, B., Baker, K., Buckby, J.A. Baksheev, G.N. & Cosgrave, E.M. (2009). Psychotic-like experiences in a community sample of adolescents: Implications for the continuum model of psychosis and prediction of schizophrenia. *Australian and New Zealand Journal of Psychiatry, 43,* 118–28.

4.

Social Skills as Precursors of Cannabis Use in Young Adolescents - a TRAILS Study

Griffith- Lendering, M.F.H., Huijbregts, S.C.J., Huizink, A.C., Ormel, J., Verhulst, F.C., Vollebergh, W.A.M., & Swaab, H. (2011). Social skills as precursors of cannabis use in young adolescents; A Trails study. *Journal of Child & Adolescent Psychology, 40*, 706 – 714.

Abstract

Social skills (cooperation, assertion, and self-control) were assessed by teachers for a longitudinal cohort of (pre)adolescents, with measurements at average ages 11.1 (baseline) and 16.3 years (follow-up). Prospective associations with participants' self-reported use of cannabis, (age of) onset of cannabis use, and frequency of use at follow-up were examined using multinomial logistic regression analyses. Teacher-reported social skills predicted different aspects of cannabis use independent of better known factors such as presence of externalizing behaviour and use of other substances. The direction of associations depended on the type of social skill. Good cooperation skills during early adolescence were associated with a reduced risk of lifetime cannabis use and a reduced risk of using cannabis on a regular basis. On the other hand, assertion at age 11 increased the risk of lifetime cannabis use and of using cannabis on an experimental basis.

Introduction

Cannabis is the most widely used substance after tobacco and alcohol, with a particularly high prevalence among adolescents and young adults (European Monitoring Centre for Drugs and Drug Addiction, 2009; Substance Abuse and Mental Health Services Administration, 2009). Most cannabis users start consuming cannabis in early adolescence (Monshouwer, Smit, de Graff, van Os, & Vollebergh, 2005). Cannabis use during this life phase is associated with several problematic outcomes, such as use of other (illicit) drugs (Fergusson, Boden, & Horwood, 2006; Lynskey et al., 2003), educational problems (Lynskey & Hall, 2000), and deviant peer affiliations (Fergusson, Swain- Campbell, & Horwood, 2002). Because of these adverse outcomes, it seems crucial to identify risk factors associated with cannabis use during adolescence.

Many correlates or risk factors of cannabis use during adolescence have already been identified, including demographic factors (e.g., low socioeconomic status [SES]), poor academic performance, early onset of tobacco and alcohol use, drug using peers, family problems, and externalizing behaviour (e.g., Fergusson, Horwood, & Ridder, 2007; Griffith-Lendering, Huijbregts, Mooijaart, Vollebergh, & Swaab, 2011; Korhonen et al., 2010; von Sydow, Lieb, Pfister, Hofler, & Wittchen, 2002). Associations between social functioning and social skills, on one hand, and cannabis use, on the other, have not yet been extensively studied, despite the fact that cannabis use during adolescence generally takes place in social contexts such as at parties, in dancing clubs, or on the street.

Some studies did investigate cannabis use in relation to specific social skills or aspects of social functioning, such as social self-control and self-esteem (Pokhrel, Sussman, Rohrbach, & Sun, 2007; Sussman, McCuller, & Dent, 2003). Lack of social self-control refers to one's tendency to act without thinking (Tarter, 1988), especially in a social context. Here, the use of cannabis was associated with lack of social self-control. Negative self-esteem has also been associated with cannabis use in adolescence (Veselska et al., 2009), although self-esteem is not necessarily a social skill but rather a personality factor. Relations between social skills and cannabis use have not always been straightforward. For example, some findings suggest that those who experiment with cannabis during adolescence are socially better adjusted and have better social skills than both abstainers and heavy users (Shedler & Block,

1990). In addition, Engels and Ter Bogt (2001) showed that adolescents who experiment with cannabis had stronger peer relationships and were more socially competent in their relationships with peers than abstainers. Veselska et al. (2009) also focused on social competence and showed that adolescents with higher levels of assertive behaviour were more likely to use cannabis. They hypothesized that more socially competent adolescents may find themselves in social contexts where exposure to cannabis is high. These social contexts make adolescents more prone to experiment with cannabis. These findings illustrate that adolescence is a developmental phase where social interactions with peers become more important and more complex (Spear, 2000). To unravel the complex relations between cannabis use and social skills in adolescence, it therefore appears especially relevant to discriminate between different types of social skills. From a preventive perspective, one might assume that further discrimination is required with respect to outcome variables as well. Whether or not someone has (ever) used cannabis should be distinguished from onset and frequency of cannabis use. Both age of onset and frequency of use constitute risk factors for the use of other, possibly more dangerous or more addictive drugs, including alcohol and hard drugs (Fergusson et al., 2006; Lynskey et al., 2003).

It is important to focus on early adolescence when examining social risk factors of cannabis use for several reasons. First, (neurobiological) developmental processes at this age could constitute increased vulnerability for enduring effects of external influences such as cannabis use (Arsenault et al., 2002; Schneider, 2008). Furthermore, associations between cannabis use and poor outcomes (e.g., crime, suicidal behaviour, depression, other illicit drug use, deviant peer affiliations) appear to be age related, with (much) stronger associations in the youngest adolescents (14–15; Fergusson et al., 2002).

The purpose of this study was to investigate the possible relationship between multiple social skills (cooperation, assertion, and self-control) and different cannabis-use-related outcomes (i.e., whether cannabis was (ever) used, age of cannabis use onset, and frequency of cannabis use) during adolescence. It was hypothesized that cooperation and self-control would be negatively related to cannabis use. Cooperative behaviour is inversely related to aggressive-disruptive behaviour (Tinoco, Lagares, Moreno, Tessier, & Schneider, 2009). Because cannabis use is positively related to externalizing behaviour (Griffith-Lendering et al., in press; Monshouwer et al., 2006),

including aggressive and rule-breaking behaviour, it was hypothesized that good cooperative skills would be associated with less aggressive and rule-breaking behaviour as well as less cannabis use. The hypothesis regarding self-control and cannabis use was based on the findings by Pokhrel et al. (2007) and Sussman et al. (2003). Based on findings and arguments by Veselska et al. (2009), it was further expected that higher levels of assertive behaviour would be associated with higher risks of using cannabis. It was further hypothesized that poor social skills would predict early onset and high frequency of cannabis use. The predictive value of social skills on different aspects of cannabis use was examined while controlling for a number of well-established correlates of cannabis use, including SES, use of other substances (alcohol and tobacco), parental psychopathology, and externalizing behaviour. Moreover, based on differences in prevalence of cannabis use and presence of correlates of cannabis use for boys and girls (Nationale Drug Monitor, 2009; Substance Abuse and Mental Health Services Administration, 2009), moderating effects of gender on social skills in predicting cannabis outcomes were studied.

Method

Sample

The present study is part of the TRacking Adolescents' Individual Lives Survey (TRAILS) study and uses data from the first (T1) and third (T3) assessments of TRAILS, which ran from 2001 to 2002, and from 2005 to 2007, respectively. A detailed description of the sampling procedure and methods is provided in De Winter et al. (2005) and Huisman et al. (2008). The study was approved by the (Dutch) Central Committee on Research Involving Human Subjects. Briefly, the TRAILS target sample involved all 10- to 11-year-old children living in five municipalities, including both urban and rural areas, in the northern part of the
Netherlands. Of all individuals asked to participate in TRAILS (N=2,935), 76.0% agreed to participate at T1 (N=2,230; M age=11.09 years, SD=0.55; 50.8% girls). Responders and non-responders did not differ with respect to the prevalence of teacher-rated problem behaviour, sociodemographic variables, and health indicators (de Winter et al., 2005). T3 was completed with 81.4% of the original number of participants (N=1,816; M age=16.27 years old, SD=0.73; 52.3% girls). Analyses in

the present study were based on 1,363 adolescents (54.2% girls, 45.8% boys) with nonmissing data on all variables of interest (described next). This sample consisted of the following nationalities: 88.8% Dutch, .3% Turkish, .5% Moroccan, 1.5% Surinam, 1.2% Antillean, 1.5% Indonesian or Mollucan. The remaining 6.2% had other non-Western nationalities.

Measures

Cannabis use

Cannabis use by the participants was measured at T3 by four self-report items. The first question concerned the age of first cannabis use, with the following answer categories: never used, 9 years or younger, 10, 11, 12, 13 or 14, 15 or 16 years. In addition, participants were asked about lifetime use, use in the last year, and use in the last month with the following questions: 'How often have you used cannabis in your life in the last year/ in the last month?' with answer categories 'I have never used,' 'used it once,' 'used it twice,' 'three times,' . . . '10 times,'' '11–19 times,' '20–39 times,' '40 times or more'). Those who reported using cannabis at least once during their lifetime were classified as cannabis users in the dichotomous variable used for the first set of analyses. For age of onset, items were recoded into three categories: (a) those who had never used, (b) those who used before the age of 15, and (c) those who used at age 15 or older. For frequency of use, items were recoded into five categories: (a) those who had never used, (b) those who had used but not during the past year (discontinued use), (c) those who used once or twice during the past year (experimental use), (d) those who reported using cannabis between 3 and 39 times during the past year (regular use), and (e) those who reported using it 40 times or more during the last year (heavy use). The construction of these categories was similar to that used in other studies focusing on cannabis use in the Netherlands (Griffith-Lendering et al., 2010; Monshouwer et al., 2006).

Social skills

Social skills of the participants were evaluated by teachers at T1. The Social Skills Rating System (SSRS; Gresham & Elliott, 1990) is a standardized questionnaire that evaluates children's social skills and is appropriate for the age range of 3 to 18 years. In the Teacher version of the SSRS, 30 items assess ''Social Skills.'' The Social

Skills domain contains the subscales of Cooperation (10 items, α =.90), Assertion (10 items, α =.88), and Self-Control (10 items, α =.91). The Cooperation subscale includes behaviours such as helping others and complying with rules and directions. The Assertion subscale includes initiating behaviours, such as asking others for information and introducing oneself. The Self-Control subscale includes behaviours that emerge in conflict situations such as appropriate management of teasing, and in non-conflict situations such as 'taking turns' and compromising. Teachers rated items on a 3-point scale: 1 (never), 2 (sometimes), and 3 (very often). For the SSRS–Teacher form, Gresham and Elliot (1990) reported evidence for acceptable internal consistency, test–retest and interrater reliability, content validity, and criterion-related validity. In addition, van Oord et al. (2005) evaluated psychometric properties of the Dutch translation of the SSRS and concluded that all SSRS scales had adequate internal consistency (all above .76).

Socialeconomic Status (SES)

The TRAILS database contains several variables contributing to an overall score for Socialeconomic Status (all measured at T1): income level, educational level of both the father and the mother, and occupational level of each parent, using the International Standard Classification for Occupations (Ganzeboom & Treiman, 1996). SES was operationalized as the standardized average of these five items (standardized). The internal consistency of this measure is satisfactory (Cronbach's alpha=.84; Veenstra, Lindenberg, Oldehinkel, De Winter, & Ormel, 2006).

Parental psychopathology

Parental psychopathology (i.e., for depression, anxiety, substance abuse, and antisocial behaviour) was measured by means of the Brief TRAILS Family History Interview (Ormel et al., 2005), administered at T1. Each syndrome was introduced by a vignette describing its main symptoms and followed by a series of questions to assess lifetime occurrence, professional treatment, and medication use. The scores for substance abuse and antisocial behaviour were used to construct a familial vulnerability index for externalizing disorder. The scores for depression and anxiety disorder were used to construct an index for internalizing disorder.

The construction of familial vulnerability indices was based on Kendler, Prescott,

Myers, and Neale (2003), who performed multivariate twin modelling to investigate shared genetic risk factors for psychiatric and substance use disorders, and performed for TRAILS by Veenstra and colleagues (Veenstra et al., 2005). For both internalizing and externalizing disorder, parents were assigned to one of the following categories: (probably) not (0); (probably) yes (1); yes plus either the use of treatment=medication (for substance abuse, depression, and anxiety) or having been picked up by police (antisocial behaviour) (2).

Externalizing behaviour problems

Externalizing behaviour at T1 was assessed using the Youth Self Report (YSR), which is one of the most commonly used self-report questionnaires in current child and adolescent psychiatric research (Achenbach, 1991; Verhulst & Achenbach, 1995). The YSR contains 112 items on behavioural and emotional problems in the past 6 months. Participants can rate the items as being not true (0), somewhat or sometimes true (1), or very or often true (2). For the present study, we used the Externalizing Behaviour Problems scale, which consists of items measuring aggressive and rule-breaking behaviour (Achenbach, 1991). Reliability and validity of the Dutch version of the YSR have been shown to be satisfactory (de Groot, Koot, & Verhulst, 1996; Verhulst, van der Ende, & Koot, 1997).

Use of other substances

Alcohol use and tobacco use by the participants were measured at the third assessment. Participants self-reported on the frequency of use in the past month. For tobacco use reported frequency was recoded into nonweekly (0) versus weekly (1), and for alcohol use, the reported frequency was recoded into nonmonthly (0) versus monthly use (1). These categories were similar to those used in other studies focusing on cannabis use in the Netherlands
(Monshouwer et al., 2006).

Data Analyses

It was first examined whether those with missing values on one or more variables of interest (n=453) differed from those without missing values (n=1,363) on SES (by means of t test) and gender (by means of Pearson chi-square test). Next, it was

investigated whether control variables should be included in the main statistical analyses as covariates (i.e., whether cannabis users differed from nonusers on these variables) using t tests or GLM univariate analysis of variance for SES, parental psychopathology, externalizing behaviour problems, and using Pearson chi-square analysis for gender, alcohol, and tobacco use. It was then tested whether these variables were related to social skills using Pearson correlation for SES, parental psychopathology, externalizing behaviour, and using t-tests or GLM univariate analysis of variance for gender, alcohol, and tobacco use.

Logistic regression analysis was performed to examine the impact of social skills on whether or not cannabis was used during adolescence. Using multinomial regression analysis, onset of cannabis use was predicted by social skills using the three-category variable (a) no use (reference group), (b) early onset, and (c) late onset. Next, multinomial regression analyses were used to predict frequency of cannabis use at T3 from social skills, using a five-category cannabis variable as the dependent variable: (a) those who had never used (reference group), (b) discontinued use, (c) experimental use, (d) regular use, and (e) heavy use.

Results

Preliminary Analyses

Participants with and without missing values did not differ in terms of SES. Participants without missing values were more likely to be girls (54.2%) compared to those with missing values (46.6%): $\chi 2$ (1) =8.0, p=.005. In the sample used for further statistical analyses (n=1,363), cannabis users (n=400) did not differ from nonusers with respect to gender ($\chi 2$=.34, p=.561), SES (t=.97, p=.332), and familial vulnerability for internalizing behaviour (t=_-84, p=.404). Cannabis users and nonusers did, however, differ significantly on familial vulnerability for externalizing behaviour (t=-2.1, p=.037), externalizing behaviour (t=-6.4, p<.001), alcohol use ($\chi 2$=83.6, p<.001) and tobacco use ($\chi 2$=367.1, p<.001). Cannabis users scored higher on both familial vulnerability for externalizing behaviour (M=.2, SD=.4) and internalizing behaviour (M=.3, SD=.2) than nonusers (M=.1, SD=.4 and M=.2, SD=.2, respectively). In addition, cannabis users were more often monthly alcohol users (92.8% vs. 69.7%) and also more often weekly tobacco users than nonusers (60.8% vs. 11.0%). Familial vulnerability for externalizing behaviour, externalizing

behaviour, tobacco use, and alcohol use were also related to social skills and therefore introduced as covariates in further statistical analyses (Table 1).

Table 1: Correlation among variables

	Control variables				Teacher-Reported Social Skills			Cannabis use variables		
	1. Fam. Vuln. Ext	2. Ext Beh.	3. Tob-acco use	4. Alco-hol use	5. Coope ration	6. Assert ion	7. Self-Contr ol	8. Life-time use	9. Age of onset	10. Freq. Of use
1.	–									
2.	.1*	–								
3.	.1**	.28*	–							
4.	.0	.1**	.2**	–						
5.	-.1**	-.2**	-.288	.0	–					
6.	-.1**	-.1**	-.1**	.1**	.5**	–				
7.	-.1**	-.2**	-.1**	.1	.7**	.7**	–			
8.	.1*	.2**	.5**	.3**	-.2**	.0	-.1**	–		
9.	.0	.1**	.4**	.2**	-.2**	.0	-.1**	.9*8	–	
10.	.1*	.2**	.5**	.2**	-.2**	.0	-.1**	.9**	.8**	–

Note: *n*= 1,363.

Fam Vuln Ext.=familial vulnerability externalizing behaviour;

Ext. Beh = Externalizing Behaviour.

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

Descriptives

At follow-up (i.e., when participants had a mean age of 16.3 years), 71.1% had never used cannabis, 6.1% had used cannabis but not during the past year (discontinued use), 10.6% had used it once or twice during the past year (experimental use), 8.8% had used cannabis between 3 and 39 times during the past year (regular use), and 3.4% had used it more than 39 times in the past year (heavy use). Forty-six percent (n=184) of users were 'early starters,' indicating onset of cannabis use before the age of 15; 54% (n=216) were 'late starters,' indicating onset of cannabis use at age 15 or older.

Predicting Cannabis Use

The impact of social skills (cooperation, assertion, and self-control) on cannabis use during adolescence (yes/no) was investigated using logistic regression analyses.

Tobacco use, alcohol use, and externalizing behaviour problems all increased the chance of cannabis use (Table 2). After adjusting for these control variables, logistic regression analyses revealed that at baseline, high levels of SSRS–Cooperation were associated with reduced chances of cannabis use during adolescence (odds ratio [OR]=.4; 95% confidence interval [CI] [.3, .6]; p<.001). High levels of SSRS–Assertion were associated with increased chances of cannabis use (OR=1.8; 95% CI [1.1, 2.8]; p=.014; Table 2). No moderating effect of gender was found.

Table 2. *Summary of Logistic Regression Analysis Predicting Cannabis Use (n=1369).*

	B	SE	OR
Covariates			
Familial vulnerability for externalizing behaviour	0.1	0.2	1.1
Externalizing behaviour	1.0**	0.4	2.8
Tobacco use	2.3***	0.2	10.0
Alcohol use	1.3***	0.2	3.7
Social Skills			
Cooperation	-0.9	0.2	0.4
Assertion	0.6	0.2	1.8
Self control	-0.2	0.2	0.8
Constant	-3.9		
$\chi 2$	24.9***		
df	7		

B = Unstandardized coefficient; SE = standard errors; OR = Odds Ratio.

* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Predicting Age of Onset

Multinomial regression analyses revealed that of the control variables, tobacco use and alcohol use were related to both early and late onset of cannabis use (Table 3), indicating a heightened risk for both early and late onset of cannabis use compared to nonuse. Externalizing behaviour problems, however, were associated only with early onset of cannabis use. After adjusting for externalizing behaviour problems, alcohol use, and tobacco use, cooperation predicted both early (OR=.4; 95% CI [.2, .7]; p=.001) and late (OR=.4; 95% CI [.3, .7], p=.002) onset compared to nonuse. Assertion also predicted both early (OR=1.9; 95% CI [1.0, 3.4], p=.041) and late (OR=1.7; 95% CI [1.0, 2.9]; p=.046) onset of cannabis use compared to nonuse (Table 3). Cooperation and assertion did not significantly discriminate between the early onset and late onset. Again, there were no significant Gender x Social Skill

interactions.

Table 3. Summary of Multinomial Logistic Regression Analysis Predicting Early (9–14 Years) and Late Onset (15–16 Years) of Cannabis Use.

	Early Starters			*Late Starters*		
	B	*SE*	*OR*	*B*	*SE*	*OR*
Familial Vulnerability						
Ext.Beh.	0.3	0.2	1.4	-0.1	0.2	0.9
Externalizing Behaviour	1.7***	0.5	5.7	0.5	0.5	1.7
Tobacco Use	2.8***	0.2	16.3	1.9***	0.2	7.0
Alcohol Use	1.4***	0.3	4.0	1.3***	0.3	3.6
Cooperation	-1.0***	0.3	0.4	-0.8**	0.3	0.4
Assertion	0.6*	0.3	1.9	0.5*	0.3	1.7
Self control	0.0	0.3	1.0	-0.3	0.3	0.7
Constant	-6.1			-3.5		
$\chi 2$	457.5***					
df	14					

Note: n = 1,363. Reference category consists of subjects who did not report any cannabis use at T3. OR = odds ratio; Ext. Beh. = externalizing behaviour.

*$p < .05$. **$p < .01$. ***$p < .001$.

Predicting Frequency of Cannabis Use

As the separate categories for discontinued and heavy use were considered to contain too few participants, these were merged with the 'never used' and 'regular use' categories, respectively. This resulted in the following categories for statistical analysis: (a) those who had never used and discontinued users, (b) experimental users, and (c) regular and heavy users. When predicting frequency of cannabis use by cooperation, assertion, and self-control, multinomial regression analyses showed that, of the control variables, tobacco use and alcohol use were related to both experimental use and regular use of cannabis, whereas externalizing behaviour problems was only related to regular/ heavy use of cannabis (Table 4).

After controlling for family vulnerability for externalizing behaviour, externalizing behaviour problems, alcohol use, and tobacco use, high scores on cooperation predicted lower regular/heavy use (OR=.4; 95% CI [.2, .6], p=.001). Good cooperation skills reduced the relative chance of being a regular or heavy cannabis

user compared to being a nonuser. Chances of being an experimental user as opposed to a nonuser also reduced as a function of cooperative skills, although this effect just failed to reach significance. Assertion predicted higher experimental use (OR=2.1; 95% CI [1.1, 3.7]; p=.021) as opposed to non-use. Thus, although cooperation did not predict regular use compared to experimental use, there are indications that good cooperative skills particularly prevent adolescents from becoming a regular or heavy user. Also, assertive skills only predicted experimental use, not regular or heavy use, which may also be important when social skills are considered intervention or prevention targets. Social skills and gender did not significantly interact.

Table 4 Summary of Multinomial Logistic Regression Analysis Predicting Experimental and Regular/ Heavy Cannabis Use.

	Experimental users			*Regular / Heavy users*		
	B	*SE*	*OR*	*B*	*SE*	*OR*
Familial Vulnerability Ext. Beh.	-0.1	0.2	0.9	0.2	0.2	1.3
Externalizing Behaviour	0.7	0.2	1.9	1.5**	0.5	4.3
Tobacco Use	1.6***	0.2	4.9	2.5**	0.2	11.8
Alcohol Use	1.3***	0.3	3.8	1.5**	0.4	4.6
Cooperation	-0.5***	0.3	0.6	-1.0**	0.3	0.4
Assertion	-0.7*	0.3	2.0	0.5	0.3	1.1
Self control	-0.4	0.3	2.7	-0.1	0.3	1.1
Constant	4.8					
χ^2	359.8***					
df	14					

Note: n=1,363. Reference category consists of subjects who did not report any cannabis use at T3. OR = odds ratio; Ext. Beh.= externalizing behaviour.

*p<.05. **p<.01. ***p<.001.

Discussion

The present study examined multiple social skills as possible risk factors for cannabis use during adolescence. Those who had used cannabis by the age of 16 had lower levels of cooperation at age 11, compared to nonusers. Assertion was differently related to cannabis use; specifically, cannabis users were more assertive than nonusers. Cooperation includes behaviours such as helping others, complying with rules and directions, and sharing materials. Assertion involves behaviours such as asking others for information, introducing oneself, and responding to the actions of

others. Self-control was not related to cannabis use during adolescence. It is important to note that cooperation and assertion were predictive of cannabis use independent of other, better-known factors associated with cannabis use, such as use of other substances or externalizing behaviour.

Social skills did not predict early versus late onset of cannabis use. Chances of both early and late onset decreased with higher levels of cooperation and increased with higher levels of assertion. Social skills did not predict regular/heavy use versus experimental use either, although high levels of cooperative behaviour particularly appeared to reduce the chances of being a regular/heavy user rather than a nonuser. Assertion particularly increased the chance of being an experimental user rather than a nonuser. This result could indicate that, although assertion increases the chance of cannabis use during adolescence, it does not do so for heavy cannabis use, which may be considered a risk factor for using other more addictive drugs (Fergusson et al., 2006). Still, despite the fact that both cooperation and assertion are considered positive social skills, our results show that they are differentially predictive of what may be considered risky behaviour (i.e., becoming a cannabis user). Cooperative behaviour, as expressed in, for example, complying with rules and directions, reduces chances of risky behaviour, whereas the type of engagement represented by the assertion items appears to increase chances of risky behaviour.

Our results are in line with expectations. Previous studies have shown negative associations between cooperative behaviour and aggressive/ disruptive behaviour during adolescence (Tinoco et al., 2009). Because cannabis use has been positively associated with aggressive and rule-breaking behaviour repeatedly (Fergusson et al., 2002; Griffith-Lendering et al., 2010 Monshouwer et al., 2006), it was expected that cooperative behaviour would also be related to a reduction in chances of cannabis use. This is what our findings indicated. When focusing on assertive behaviour, Veselska et al., (2009) also showed that higher levels of assertion (or social competence) were associated with cannabis use among adolescents (M age=14.3 years). Veselska et al. argued that those adolescents with high levels of social competence (i.e., those who were more assertive) are more likely to find themselves in places where exposure to drug (cannabis) use is high, thereby providing a social context for cannabis use. One can also argue that assertive adolescents are inclined to enter new social situations more frequently; in other words, they are less inhibited and therefore show more risk-taking behaviour, such as the use of cannabis.

Our data did not confirm the social skill of self-control to be related to cannabis use, age of onset, or frequency of use. This appears to be inconsistent with previous studies focusing on self-control and cannabis use (Pokhrel et al., 2007; Sussman et al., 2003). This discrepancy in findings may be explained by different operationalizations of the construct self-control or by assessment through different informants. Although self-control refers to one's tendency to act without thinking (Tarter, 1988), social self-control is a self-control measure related to interpersonal relations. In addition, in this study, self-control, defined by the SSRS as 'behaviours that emerge in conflict and non-conflict situations' was rated by the participants' teachers. Whereas assertion and cooperative behaviour may be behaviours that occur frequently in (generally well-structured) classroom settings, self-control items may be more difficult to observe and rate in this context.

Strengths of this study are its prospective design and its large population. Also, this is one in a few studies that focused on different social skills rather than general social ability, which could have masked the differential effects of different social skills. Furthermore, this study focused on different cannabis use variables (i.e., cannabis use, age of onset, and frequency of use). A possible limitation of the study is that participants self-reported on cannabis use. Although previous studies have concluded that self-reporting on substance use is generally valid (Buchan, Dennis, Tims, & Diamond, 2002), one can still argue that the nature of the questions could have led to socially desirable answers (especially for young adolescents). Another limitation is the loss of respondents between baseline and follow-up. Furthermore, the reliability of the measurement of social skills could have benefited from the use of multiple informants (i.e., parents=caretakers as well as teachers). This could have covered social skills in different contexts. Also, because of the liberal laws regarding cannabis use in the Netherlands, it is unclear whether the results of the present study are applicable across countries. Despite these differences in laws, the percentage of young adults using cannabis in the Netherlands is similar to that in other European countries (European Monitoring Centre for Drugs and Drug Addiction, 2009) and the United States (Substance abuse and mental health services administration, 2008).

The general conclusion of this study is that different teacher-reported social skills are differentially predictive of cannabis use during early adolescence and that these associations are not explained by important other correlates of both cannabis use and

social behaviour. Good cooperative skills decreased the chance of cannabis use, whereas high levels of assertion increased the probability of (experimental) cannabis use.

The results of this study show that social functioning might deserve more attention in studies investigating precursors of substance use and abuse. In the present study, we focused on social skills, but other aspects of social functioning may also be of importance. Examples include functioning and roles within peer groups and quality of other interpersonal relations. The presence of psychopathology or, for example, externalizing behaviour in high but subclinical gradations may be stronger predictors of substance use and, possibly, the transition into addiction. However, there appears to be a role for social functioning in general as well. The extent to which different aspects of social functioning contribute to substance use and addiction should be clarified further, both their unique contribution and their contribution in combination with other risk factors, such as psychopathology, but also poor sociodemographic circumstances.

In social skills interventions, it should be taken into account that specific social skills are not by definition, or under all circumstances, ‘‘good’’ or ‘‘bad.’’ A more subtle approach appears to be required. For example, it seems unlikely that suppressing assertive behaviour would be beneficial. Still, the positive associations between assertive behaviour and cannabis use suggest something could be done with this type of behaviour. Possibly, the focus regarding this behaviour should lie on stimulating assertive refusal behaviour (Botvin, 2000; Botvin & Griffin, 2007). Whereas the findings regarding cooperative behaviour appear to be relatively straightforward, it might be important here as well to not stimulate every form of cooperative behaviour. Moreover, it may be important to take into account individual goals. That is, if someone is cooperative to fit within certain peer groups (which could or could not be a group involved in substance use), it may be beneficial to target contextual factors, emphasizing situations during which cooperative behaviour should or should not be shown. One can also imagine that certain forms of assertive behaviour can actually help decision making in such situations. Thus, the important point is that positive results regarding the prevention of cannabis use or the transition into addiction could be obtained not by suppressing or stimulating particular types of social behaviour, but by considering the different forms of certain social behaviours in different contexts and by considering different social behaviours in combination with each other.

References

Achenbach, T. M. (1991). *Manual for the Youth Self-Report and 1991 profile.* Burlington: University of Vermont.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *British Medical Journal, 325,* 1212–1213.

Botvin, G. J. (2000). Preventing drug abuse in schools: Social and competence enhancement approaches targeting individual-level etiological factors. *Addictive Behaviors, 25*, 887–897.

Botvin, G. J., & Griffin, K. W. (2007). School-based programmes to prevent alcohol, tobacco and other drug use. *International Review of Psychiatry, 19,* 607–615.

Buchan, B. J., Dennis, M. L., Tims, F. M., & Diamond, G. J. (2002). Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. *Addiction, 97,* 98–108.

de Groot, A., Koot, H. M., & Verhulst, F. C. (1996). Cross-cultural generalizability of the Youth Self-Report and Teacher's Report Form cross-informant syndromes. *Journal of Abnormal Child Psychology, 24,* 651–664.

de Winter, A., Oldehinkel, A. J., Veenstra, R., Brunnekreef, J. A., Verhulst, F. C., & Ormel, J. (2005). Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. *European Journal of Epidemiology, 20,* 173–181.

Engels, R., & ter Bogt, T. (2001). Influences of risk behaviors on the quality of peer relations in adolescence. *Journal of Youth and Adolescence, 30,* 678–695.

European Monitoring Centre for Drugs and Drug Addiction. (2009). *Annual report 2009: The state of the drugs problem in Europe.* Luxembourg: Publication Office of the European Union.

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2006). Cannabis use and other drug use: testing the cannabis gateway hypothesis. *Addiction, 101*, 556–569.

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2007). Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: Results of a 25-year longitudinal study. *Drug and Alcohol Dependence, 88*, 14–26.

Fergusson, D. M., Swain-Campbell, N. R., & Horwood, L. J. (2002). Deviant peer affiliations, crime and substance use: A fixed effects regression analysis. *Journal of Abnormal Child Psychology, 30,* 419–430.

Ganzeboom, H. B. G., & Treiman, D. J. (1996). Internationally comparable measures of occupational status for the 1988. *International Standard Classification of Occupations. Social Science Research, 25,* 201–239.

Gresham, F. M., & Elliott, S. N. (1990). *Social Skills Rating System.* Circle Pines, MN: American Guidance Service.

Griffith-Lendering, M. F. H., Huijbregts, S. C. J., Mooijaart, A., Vollebergh, W. A. M., & Swaab, H. (2010). Cannabis use and development of internalizing and externalizing behavior problems in early adolescence: A TRAILS study. *Drug and Alcohol Dependence, 116,* 11–17.

Huisman, M., Oldehinkel, A. J., de Winter, A., Minderaa, R. B., de Bildt, A., Huizink, A. C., et al. (2008). Cohort profile: The Dutch 'Tracking Adolescents' Individual Lives' Survey: TRAILS. *International Journal of Epidemiology, 37,* 1227–1235.

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry, 60,* 929–937.

Korhonen, T., Prince van Leeuwen, A., Reijneveld, S. A., Ormel, J., Verhulst, F. C., & Huizink, A. C. (2010). Externalizing behavior problems and cigarette smoking as predictors of cannabis use: The TRAILS study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49,* 61–69.

Lynskey, M., & Hall, W. (2000). The effects of adolescent cannabis use on educational attainment: A review. *Addiction, 95,* 1621–1630.

Lynskey, M. T., Heath, A. C., Bucholz, K. K., Slutske, W. S., Madden, P. A., Nelson, E. C., et al. (2003). Escalation of drug use in early-onset cannabis users vs. co-twin controls. *Journal of American Medical Assocation, 289,* 427–433.

Monshouwer, K., Smit, F., de Graaf, R., van Os, J., & Vollebergh, W. (2005). First cannabis use: Does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on Substance Use. *Addiction, 100,* 963–970.

Monshouwer, K., Van Dorsselaer, S., Verdurmen, J., Ter Bogt, T., De Graaf, R., & Vollebergh, W. (2006). Cannabis use and mental health in secondary school children. Findings from a Dutch survey. *British Journal of Psychiatry, 188,* 148–153.

Nationale Drug Monitor. (2009). *Jaarbericht 2009.* Utrecht, the Netherlands: Trimbos Instituut.

Ormel, J., Oldehinkel, A. J., Ferdinand, R. F., Hartman, C. A., De Winter, A. F., Veenstra, R., et al (2005). Internalizing and externalizing problems in adolescence: General and dimension-specific effects of familial loadings and preadolescent temperament traits. *Psychological Medicine, 35,* 1825–1835.

Pokhrel, P., Sussman, S., Rohrbach, L. A., & Sun, P. (2007). Prospective associations of social self-control with drug use among youth from regular and alternative high schools. *Substance Abuse and Treatment Prevention Policy, 2,* 22.

Schneider, M. (2008). Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addiction Biology, 13,* 253–263.

Shedler, J., & Block, J. (1990). Adolescent drug use and psychological health. A longitudinal inquiry. *American Psychologist, 45,* 612–630.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews, 24,* 417–463.

Substance Abuse, & Mental Health Services Administration. (2009). *Results from the 2008 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09–4434)*. Rockville, MD: Author.

Sussman, S., McCuller, W. J., & Dent, C. W. (2003). The associations of social self-control, personality disorders, and demographics with drug use among high-risk youth. *Addictive Behaviors, 28,* 1159–1166.

Tarter, R. E. (1988). Are there inherited behavioral traits that predispose to substance abuse? *Journal of Consulting and Clinical Psychology, 56,* 189–196.

Tinoco, V. M., Lagares, I. J., Moreno, C., Tessier, N. G., & Schneider, B. H. (2009). The nature and basis of teachers' concerns about Spanish Secondary-School students. *School Psychology International, 30,* 585–602.

van Oord, S., van der Meulen, E. M., Prins, P. J. M., Oosterlaan, J., Buitelaar, J. K., & Emmelkamp, P. M. G. (2005). A psychometric evaluation of the social skills rating system in children with attention deficit hyperactivity disorder. *Behaviour Research and Therapy, 43,* 733–746.

Veenstra, R., Lindenberg, S., Oldehinkel, A. J., De Winter, A. F., & Ormel, J. (2006). Temperament, environment, and antisocial behavior in a population sample of preadolescent boys and girls. *International Journal of Behavioral Development, 30,* 422–432.

Veenstra, R., Lindenberg, S., Oldehinkel, A. J., De Winter, A. F., Verhulst, F. C., & Ormel, J. (2005). Bullying and victimization in elementary schools: A comparison of bullies, victims, bully/victims, and uninvolved preadolescents. *Developmental Psychology, 41,* 672–682.

Verhulst, F. C., & Achenbach, T. M. (1995). Empirically based assessment and taxonomy of psychopathology–cross-cultural applications—A review. *European Child & Adolescent Psychiatry, 4,* 61–76.

Verhulst, F. C., van der Ende, J., & Koot, H. M. (1997). *Manual for the Youth Self Report (YSR) [Dutch]*. Rotterdam, the Netherlands: Erasmus University/ Department of Child and Adolescent Psychiatry, Sophia Children's Hospital.

Veselska, Z., Geckova, A. M., Orosova, O., Gajdosova, B., van Dijk, J. P., & Reijneveld, S. A. (2009). Self-esteem and resilience: The connection with risky behavior among adolescents. *Addictive Behaviors, 34,* 287–291.

von Sydow, K., Lieb, R., Pfister, H., Hofler, M., & Wittchen, H. U. (2002). What predicts incident use of cannabis and progression to abuse and dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug and Alcohol Dependence, 68,* 49–64.

5.

Motivational and cognitive inhibitory control in recreational cannabis users.

Griffith- Lendering, M.F.H., Huijbregts, S.C.J., Vollebergh, W.A.M., & Swaab, H. (2012). Motivational and cognitive inhibitory control in recreational cannabis users. *Journal of Clinical and Experimental Neuropsychology, 34,* 688-697.

Abstract

Substance use disorders have been associated with impaired decision-making and increased impulsive behaviour. Lack of inhibitory control may underlie such higher-order cognitive difficulties and behaviour problems. This study examined inhibitory control in 53 recreational cannabis users and 48 controls. Inhibitory control was tested with two computer tasks, one with a motivational component and one without such a component. Impulsive behaviour was assessed using the Barratt Impulsiveness Scale. Results showed that the recreational cannabis users had poorer motivational inhibition (i.e. were more inclined to 'gamble') than controls. There were no group differences in the cognitive inhibition task. Cannabis users also reported more impulsive behaviour in daily life. This behaviour was related to response style in the motivational inhibition task, but not to performance in the cognitive inhibition task. It is concluded that, among recreational cannabis users, lack of inhibitory control depends on contextual or situational factors, i.e. it becomes evident only when situations or tasks involve a motivational component.

Introduction

Cannabis abusers share a considerable number of neuropsychological weaknesses with abusers of other drugs such as psychostimulants, opoids and alcohol (and with polysubstance abusers) (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011). These include impairments in episodic memory, emotional processing, implicit cognition and executive function (EF). Although there is evidence suggesting some more specific deficits as well, including those regarding prospective memory, processing speed, and complex planning, there are generally abusers of other substances showing these deficits as well (Fernández-Serrano et al., 2011; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Piechatzek et al., 2009). Many studies have employed tasks or investigated psychological constructs that appear to be built up of multiple, more basic components. One such component is inhibitory control. Next to deficits in memory and processing speed, the most consistently reported basic impairment among cannabis users is a lack of inhibitory control, particularly when required together with other cognitive abilities (Lamers, Bechara, Rizzo, & Ramaekers, 2006; Piechatzek et al., 2009; Solowij et al., 2002; Verdejo-García, Lawrence, & Clark, 2008). Less consistent results were obtained when investigating other executive functions (Piechatzek et al., 2009). When other EF-impairments were reported the tasks that were used often also involved an inhibitory component (Verdejo-Garcia et al., 2007; Whitlow et al., 2004). Whereas deficits in memory and processing speed both appear to be likely consequences of acute and chronic cannabis use, deficient inhibitory control has been considered both a potential consequence of (chronic) cannabis (and other substance) use and as a vulnerability marker predisposing towards substance use. Several studies have suggested a gradual attrition of inhibitory control that could be mediated by structural changes in the prefrontal cortex (e.g. cell death and tissue shrinkage, decreases in neurogenesis and synaptogenesis) (Chanraud et al., 2007; Cowan et al., 2003; Goldstein & Volkow, 2002; Robinson & Kolb, 2004). Alternatively, deficient inhibitory control may be present prior to drug initiation, and represent a vulnerability marker predisposing individuals towards recreational use (and mediate the transition to drug dependence) (Chambers, Taylor, & Potenza, 2003; Dalley et al., 2007; Kreek, Nielsen, Butelman, & LaForge, 2005).

Further indirect evidence for associations between a lack of inhibitory control and cannabis use stems from studies into cannabis and behaviour, which have frequently shown associations with impulsive behaviour in daily life (Clark, Rosier, Robbins & Sahakian, 2009; Malmberg et al., 2010) or with externalizing (e.g. aggressive and delinquent) behaviour characterized by impulsivity deficits (e.g. Fergusson, Horwood & Ridder, 2007; Griffith-Lendering et al., 2011; Nelson & Trainor, 2007). Some of these studies show that the behaviour problems (and subsequently the possible lack of inhibitory control) precede the drug use, providing (indirect) evidence for the vulnerability hypothesis (e.g. Griffith-Lendering et al., 2011).

Despite all the evidence, even inhibitory control deficits among cannabis users have not always been replicated (Clark et al., 2009; Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001). Although it is generally very difficult to rule out whether sample and methodological differences (e.g. which instruments were used to measure inhibitory control?) accounted for mixed results, it is important to consider differences in the definition of inhibitory control as well. Inhibition is not a unitary construct. Several empirically and statistically-validated taxonomies have been proposed. One of these distinguishes inhibition of prepotent responding, resistance to distractor interference, and resistance to proactive interference (Friedman & Miyake, 2004). For cannabis and other substance (ab-) use, inhibition of prepotent responding may be most relevant, e.g. the ability to resist automatic response tendencies when presented with specific (substance- or non-substance related) cues (Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011; Gruber & Yurgelun-Todd, 2005; Tapert et al., 2007). Another taxonomy differentiates cognitive and motivational inhibitory control. Cognitive inhibitory control is required for solving abstract, decontextualized problems, and motivational inhibitory control is required when problems involve regulation of affect and motivation (Huijbregts, Warren, De Sonneville & Swaab, 2008; Sonuga-Barke, 2002; Zelazo & Müller, 2002). There is neuro-anatomical evidence to support this distinction, with relatively more activity in the orbitofrontal cortex (OFC) during tasks involving motivational inhibition and relatively more activity in the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) during tasks involving cognitive inhibition (Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006). The two types of inhibition have also been associated with different dopaminergic pathways: the mesocortical pathway has been associated with cognitive inhibitory control and the mesolimbic pathway with motivational

inhibitory control (Pierce & Kumaresan, 2006; Sonuga-Barke, 2002). Both originate in the ventral tegmental area, but the mesocortical pathway particularly innervates DLPFC, whereas the mesolimbic dopaminergic pathway passes the nucleus accumbens, amygdala, and hippocampus and innervates ventromedial areas/OFC.

The main question of the present study is whether, among recreational cannabis users, cognitive and motivational inhibitory control can be distinguished, i.e. whether they show specific problems with either cognitive or motivational control. Although based on the existing knowledge cognitive inhibitory control deficits cannot be ruled out, there are several reasons to hypothesize that cannabis users will particularly show problems with motivational inhibitory control. First of all, several different studies have shown motivational deficits in (heavy) cannabis users, both when they were not under the influence of THC, the main active component of cannabis, and when they were (e.g. Cherek, Lane, & Dougherty, 2002; Lane et al., 2005; 2007). Second, many studies provide support for the hypothesis that dysfunctional reward processing, which, by definition, involves motivational inhibition, is central to the phenomenon of substance abuse (Blum et al., 2000; Nestor, Hester, & Garavan, 2010). Examples are studies into implicit cognition which generally involve the memory of the rewarding qualities of certain behaviours (Stacy & Wiers, 2010) and (emotional) decision-making (Bechara, 2003; Busemeyer & Stout, 2002), but also studies showing abnormal activation patterns and dopamine dysregulation for substance abusers specifically in the brain regions that are part of the reward circuitry (Kamarajan et al., 2010; Nestor et al., 2010).

In addition to examining user - non-user differences in laboratory measures of inhibitory control, we investigated whether these groups also differ regarding impulsive behaviour in daily life. This has been shown before and we expect to replicate this finding (Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010; Gruber et al., 2011). Based on the fact that the questionnaire used to assess impulsivity in daily life contains items with and without motivational components, we expected associations between both laboratory tasks and outcomes of the questionnaire.

Method

Participants

Participants were classified as cannabis users if they reported using cannabis every month during the past year and as non-users if they reported the use of cannabis zero times during the past year. Based on these criteria (Monshouwer et al., 2006), 53 cannabis users (mean age of 22.6, SD=2.4, with an abstinence period of at least 24 hours) and 48 non-users (mean age 22.3, SD=2.3) were recruited among University of Leiden undergraduate students. Written informed consent was obtained from all participants before the start of the study. Ethical approval for this study was granted by Leiden University's Education and Child Studies Ethics Committee.

Measures

Questionnaires

Cannabis use was assessed by asking participants about their use during the past year and month. Participants also reported on the use of alcohol (weekly yes/no), tobacco (daily yes/no) and other drugs including stimulants (cocaine, (met)amphetamine), opioids (heroin, methadone), and 3,4-methylenedioxymethamphetamine (MDMA: Ecstacy) (past year and past month: yes/no, plus frequency of use during past year/month). Impulsive behaviour in daily life was assessed with the Barratt Impulsiveness Scale (BIS-11; Barrat, 1985), which contains 30 items measuring behavioural impulsivity. Respondents rate statements on a four-point scale: rarely/never (1), occasionally (2), often (3), or almost always (4). The BIS-11 has 3 subscales (Barratt, 1985, Miller, Joseph & Tudway, 2004): cognitive impulsivity (8 items, $\alpha = 0.74$), motor impulsivity (11 items, $\alpha = 0.59$) and non-planning impulsivity (11 items, $\alpha = 0.72$). The cognitive impulsivity subscale includes items such as 'I don't pay attention' and 'I have racing thoughts'; the motor impulsivity subscale includes items such as 'I do things without thinking' and 'I act on impulse'; and examples of items from the non-planning impulsivity subscale are 'I say things without thinking' and 'I get easily bored when solving thought problems' (Stanford et al., 2009).

Neuropsychological tasks

Two computer tasks were performed individually in a quiet room at Leiden University. Participants were seated at a table at a distance of 80 cm from a computer screen.

Cognitive inhibitory control: Response Organization Arrows

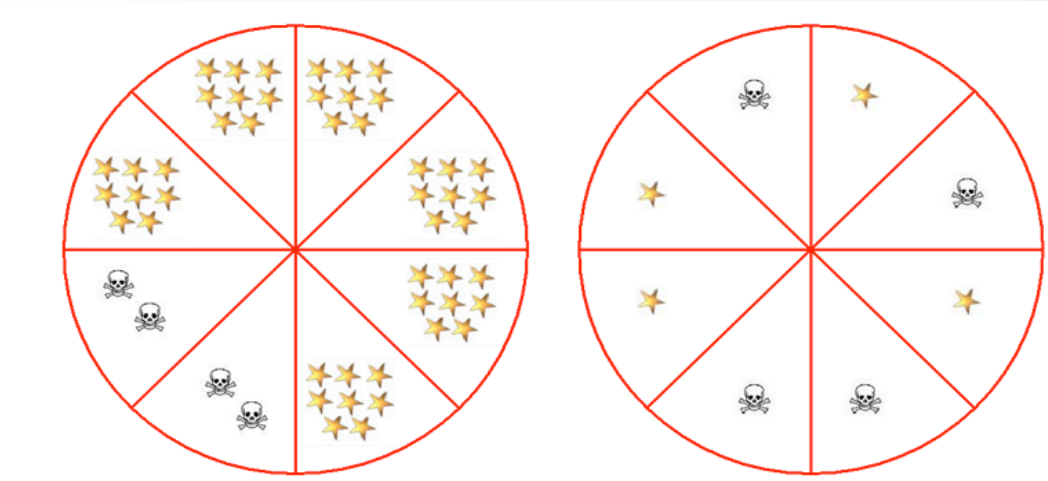
In the Response Organization Arrows task (ROA) from the Amsterdam Neuropsychological Tasks (ANT, De Sonneville, 1999), participants had to provide compatible responses in Part 1 of the task and incompatible responses in Part 2 of the task (For an illustration of this task, please see Rowbotham, Pit-ten Cate, Sonuga-Barke & Huijbregts, 2009). An arrow pointing either to the right or the left appeared centrally on the computer screen. In Part 1 (40 trials), a green arrow appeared. When the arrow pointed to the left, participants had to press the left-hand mouse button; when it pointed to the right, participants had to press the right-hand mouse button. In Part 2 (40 trials), the stimulus was a red arrow. When it pointed to the left, participants had to press the right-hand mouse button, and when it pointed to the right, participants had to press the left-hand mouse button. A response had to be generated between 200 and 6,000 ms. The fixed post-response interval was 1,200 ms. Error rates were recorded for compatible and incompatible responses.

Motivational inhibitory control: Risky Choice Task

A version of the Risky Choice Task (RCT) (Fairchild et al., 2009; Rogers et al., 2003) was used to measure motivational inhibitory control. Two wheels were presented on screen, each containing eight compartments (Figure 1). These compartments showed either possible gains or possible losses. The relative number of compartments showing gains provided the relative probability of gain for this particular wheel. On eight types of trials, one wheel served as a "control" wheel, providing a 50% chance of winning and a 50% chance of losing. The alternative, "experimental" wheel varied systematically in terms of the probability of a gain (.75 or .25), the magnitude of the possible gain (2 or 8 points), and the magnitude of the possible loss (2 or 8 points). Different combinations of these variables yielded eight trial types varying in the relative expected value (EV) of the experimental wheel (see Figure 1). There were also two trial types with an EV of 0 (the so-called framing trials): one presenting a wheel with 50% chance of winning 8 points, and a 50% chance of winning 0 points, and another wheel with a 100% chance of winning 4 points (positive framing, denoted as EV: 0+). The second presenting a wheel with a 50% chance of losing 8 points and a 50% chance of losing 0 points, and another wheel with a 100% chance of losing 4 points (negative framing; denoted as EV: 0-). All ten trial types were presented twice per block (there were 4 blocks) in a pseudorandom order, and participants played four blocks per session. The control and experimental wheels appeared randomly on the left or right of the display, and participants indicated their choice using a computer mouse. Participants were given ten points at the start

of each block and were instructed to try to win as many points as possible. Auditory feedback on wins or losses was provided and the revised points total was presented for two seconds before the next trial (Fairchild et al, 2009).

Figure 1. Example of a trial of the Risky Choice Task. The left wheel represents an experimental wheel (expected value = 5.5 (.75*8 - .25*2)), with a high probability of winning. The right wheel represents a control wheel (expected value = 0 (0.5*1 – 0.5*1)).



Data analyses

First, it was investigated whether control variables should be included in the main statistical analyses as covariates, i.e. whether cannabis users differed from non-users with respect to gender, alcohol-, tobacco-, and other drug use, using Pearson Chi-square analyses, and whether the potential control variables were related to impulsivity as measured by the BIS-11 and performance on the two inhibition tasks. Next, group differences between cannabis users and non-users regarding impulsivity and inhibitory control were investigated. General Linear model (GLM) repeated measures analyses of variance were performed to examine inhibition of prepotent responding in the ROA-task, with group (cannabis users vs. non-users) as between-subjects factor, response type (compatible versus incompatible) as within-subjects factor and error rate as dependent variable. With respect to the RCT, it was first examined whether risky or safe choices increased over time, and whether this depended on the number of points gained. GLM repeated measures analysis was used to investigate points gained during the task, with group (cannabis users vs. non-users) as between-subjects factor and block (block 1 to 4) as within-subjects factor. Next, GLM multivariate analysis of variance was performed to investigate whether cannabis users and non users differed on proportions of

experimental gambles or risky choices (as opposed to control gambles) in general and for each trial type (i.e., for each expected value when the gambling choice was made). Multivariate analysis of variance was also performed to investigate whether cannabis users and non-users differed on the three scales of impulsive behaviour.

In case there were significant differences between controls and cannabis users, we further investigated whether these differences could be attributed to differences between controls and heavy users (defined here as cannabis use 11 times or more in the last month), controls and moderate users (defined here as 1-10 times in the last month) or both, and whether there were significant differences between moderate and heavy users. Because of unequal group sizes and unequal variance distributions for relevant dependent variables between the groups, we used non-parametric statistics, i.e. Kruskal-Wallis tests for analyses involving all three groups simultaneously, and Mann-Whitney tests for comparisons between two groups.

Finally, Pearson correlations were used to investigate possible relationships between impulsive behaviour, cognitive and motivational inhibition.

Results

Cannabis users and non-users differed with respect to gender distribution, tobacco use, and MDMA-use (see Table 1), indicating that, compared to controls, there were relatively more men among the cannabis users and cannabis users were more often daily smokers and monthly MDMA-users. There were no differences regarding alcohol use, and there were no reports of other drug use (e.g. cocaine, amphetamines). Of the factors associated with cannabis use, gender was related to all BIS-11 scales of impulsivity: cognitive impulsivity [t =3.6, p = .001], motor impulsivity [t =2.9, p = .005] and non-planning impulsivity [t =2.8, p = .007]. Men scored higher on all impulsivity measures. Therefore, gender was introduced as a covariate in the group analyses comparing impulsivity in daily life between cannabis users and non-users. Also, smoking was related to experimental gambling when the EV was -1 [t= -2.2, p = .033), to performance in the first part of the ROA-task (t= -2.1, p= .040) and to one BIS-11 scale, i.e. the motor impulsivity scale [t =3.7, p < .001]. Therefore, smoking was introduced as a covariate to the analyses measuring cognitive inhibitory control, motivational inhibitory control and impulsivity. MDMA-use was unrelated to task outcomes and impulsivity, and therefore omitted from further analyses.

Table 1. χ^2-statistics of cannabis users and non users on control variables (gender, tobacco use and alcohol use).

	Cannabis users	Non users	χ^2
Male	86.8 %	31.2 %	χ^2 (1) = 32.5**
Daily Smokers	65.3 %	6.1 %	χ^2 (1) = 37.4**
Weekly alcohol users	88.7 %	75.0 %	χ^2 (1) = 3.2
Monthly MDMA-users	22.6%	4.2%	χ^2 (1) = 7.2**

* p <.05; ** p <.01

Cognitive inhibitory control: Response Organization Arrows (ROA)

The repeated measures ANOVA comparing cannabis users and non-users showed no effect for group [F(1,99) = .1, p = .794] regarding error rate. There was no significant interaction between group and condition (task part) on error rate either (F(1,99) = .5, p = .493]. These results indicate that cannabis users and non-users did not differ with respect to cognitive inhibitory control.

Motivational decision-making: Risky Choice Task (RCT)

Performance data

Firstly, it was investigated whether there were effects for group and group x block (1-4) on points gained during the task. The repeated measures ANOVA comparing cannabis users and non-users showed no effect for group [F(1,97) = .3, p = .567]. There was no significant interaction between group and block regarding points gained during the task either [F(1,97) = 2.8, p = .096]. These results indicate that both groups gained/lost equal amounts of points throughout the task. They also indicate that, as the task progressed, groups did not start to differ in the amount of points won/lost.

Group comparisons on choice of experimental gamble by trial type.

Multivariate analysis of variance showed a significant main group effect of choice of experimental gambles [$F(10, 90) = 3.5$, $p = .001$, partial $\eta^2 = .28$]. Overall, cannabis users chose the experimental wheel more often than non-users. Univariate effects per trial type are presented in Table 2. As shown in Table 2, cannabis users chose the experimental wheel more often than non-users especially when a choice for the experimental wheel was more risky (i.e. when EVs based on relative probabilities were ambiguous or negative).

After controlling for smoking, there was still a significant main group effect for experimental choice of gambling [$F(10, 89) = 2.5$, $p = .011$, partial $\eta^2 = .22$]. As shown in Table 2, all

univeriate effects that had been significant initially remained significant after controlling for smoking, with the exception of the effect when the EV was .5.

Table 2. Mean proportions of time the experimental gamble was chosen in preference to the control gamble for each risky choice task trial type by group (n=101). The difference in expected value between the experimental and control gambles for each trial type is shown.

Expected value	Cannabis users (Mean %, SD)	Non users (Mean %, SD)	F- value	F-value after controlling for smoking
5.5	98.1 % (5.2)	98.2 % (7.7)	F(1, 99) = .0	F(1, 98) = .1
4.0	93.8 %(12.6)	90.2 % (20.7)	F(1, 99) = 1.1	F(1, 98) = .2
1.0	94.5 %(12.4)	95.3 % (12.9)	F(1, 99) = .1	F(1, 98) = .5
0.5	56.9 % (29.3)	44.0 % (25.1)	F(1, 99) = 5.6*	F(1, 98) = 3.4*
-0.5	62.6 % (30.8)	61.0 % (34.3)	F(1, 99) = .1	F(1, 98) = .1
-1.0	18.1 % (19.8)	3.9 % (8.9)	F(1, 99) = 20.9 **	F(1, 98) = 15.7**
-4.0	23.2% (26.5)	13.5 % (19.3)	F(1, 99) = 4.4 *	F(1, 98) = 4.5*
-5.5	8.7 % (14.3)	1.0 % (4.6)	F(1, 99) = 12.8**	F(1, 98) = 11.2**
0 + frame	87.8 % (19.6)	80.0 % (27.2)	F(1, 99) = 2.8	F(1, 98) = .3
0 - frame	46.2 % (32.7)	30.2 %(26.6)	F(1, 99) = 7.1 **	F(1, 98) = 5.0**

* p <.05; ** p <.01

Impulsive behaviour: the Barratt Impulsiveness Scale

Multivariate analysis of variance showed a significant main group effect [$F(3,96) = 10.0$, $p = .005$, partial $\eta^2 = .24$], indicating more impulsive behaviour in daily life among cannabis users. Univariate effects were found for cognitive impulsivity [$F(1,98) = 19.3$, $p < .001$, partial $\eta^2 = .17$]; motor impulsivity [$F(1,98) = 18.5$, $p < .001$, partial $\eta^2 = .16$], and non-planning impulsivity [$F(1,98) = 14.4$, $p < .001$, partial $\eta^2 = .13$], with cannabis users scoring higher on each of the three impulsivity types measured: cognitive impulsivity (M=17.1, SD=2.6 vs. M=14.7, SD = 2.7), motor impulsivity (M=23.4, SD=3.7 vs. M=20.2, SD=3.9) and non-planning impulsivity (M=26.5, SD = 4.4 vs. M=23.2, SD=4.2).

After controlling for gender and smoking, the multivariate main group effect remained significant [$F(3,94) = 4.6$, $p = .005$, partial $\eta^2 = .13$], as well as univariate effects for cognitive impulsivity [$F(1,96) = 10.2$, $p = .002$, partial $\eta^2 = .10$] and non-planning impulsivity [$F(1,96) = 8.7$, $p = .004$, partial $\eta^2 = .08$]. The group difference for motor impulsivity was no longer significant, although a non-significant trend was still present [$F(1,96) = 3.8$, $p = .055$, partial $\eta^2 = .04$].

Influence of frequency of cannabis use.

Of the cannabis users, 21 had used cannabis up to 10 times in the past month (moderate use: 39.6%), and 32 had used it 11 times or more (heavy use). First of all, Kruskal-Wallis tests with controls, moderate and heavy users confirmed overall group differences (DV: mean percentage of choosing the experimental wheel: χ^2 (2) = 12.0, p = .002). Controls and moderate users differed when the EV was 0.5 (Mann-Whitney U = 309.5, z = -2.5, p = .011) or -1 (U = 306, z = -3.2, p = .001), and in both the positive and negative framing trials (when the EV was 0): U = 345.5, z = -2.3, p = .022, and U = 284.5, z = -2.9, p = .004, respectively. In all instances the cannabis users were more inclined than the non-users to choose the experimental wheel. Controls and heavy users differed when the EV was -5.5 (U = 458.0, z = -4.1, p < .001), -4 (U = 541.0, z = -2.3, p = .019), or -1 (U = 390.0, z = -4.4, p < .001), again in every instance indicating a greater tendency to 'gamble' among cannabis users. Comparisons between the two groups of users did not reveal a consistent pattern: heavy users were more inclined to pick the experimental wheel when the EV was -5.5 (U = 292.0, z = -2.0, p = .049), whereas moderate users were more inclined to gamble than heavy users when the EV was 0 (positive framing: U = 235.0, z = -2.1, p = .037).

With respect to impulsivity in daily life as measured by the BIS-11, Kruskal-Wallis analyses showed group differences for attentional impulsivity (χ^2 (2) = 15.6, p < .001), motor impulsivity (χ^2 (2) = 12.9, p = .002), and non-planning impulsivity (χ^2 (2) = 14.4, p < .001), with both groups of users reporting to be more impulsive than non-users. This was confirmed by significant differences between controls and moderate users on all three dimensions: Attentional: U = 284.0, z = -2.9, p = .004; Motor: U = 262.5, z = -3.2, p = .002; Non-planning: U = 277.0, z = -2.9, p = .004, and between controls and heavy users: Attentional: U = 410.5, z = -3.5, p < .001; Motor: U = 507.0, z = -2.6, p = .010; Non-planning: U = 421.0, z = -3.3, p = .001. There were no significant differences between moderate and heavy users.

Cognitive inhibition, motivational inhibition & impulsive behaviour.

Pearson correlations were used to investigate relationships between inhibition as measured by the two computer tasks and self-reported impulsive behaviour. Performance on the ROA-task was not significantly related to any of the three scales of impulsivity. In contrast, mean percentage of trials the experimental gamble which was chosen in preference to the control gamble in the RCT was associated with the impulsivity scales 'cognitive impulsivity' (r = .24, p=.014) and 'non-planning impulsivity' (r = .21, p=.038), with a trend for 'motor impulsivity' (r = .16, p = .050). All correlations indicated that the higher the percentage of trials the experimental gamble was chosen, the more impulsivity the participant showed in daily life. With respect to specific expected values, attentional impulsivity was significantly correlated with choice for the experimental wheel when the EV was -0.5 (r = .28, p = .003), -4 (r = .25, p = .005, or 0- (r = .22, p = .015), and non-planning impulsivity was significantly correlated with a choice for the experimental wheel when the EV was -1 (r = .20, p = .023), with further trends for five other EVs (0.5, -4, 1, 0+, and 0-).

Discussion

The results of the present study showed that recreational cannabis users differed from non-users with respect to motivational inhibition. This was particularly evident when the chances of reward were small or relatively difficult to estimate. Contrasting results were observed for the inhibitory control task without reward (or motivational) component: there were no differences whatsoever between cannabis users and non-users. Furthermore, recreational cannabis users reported higher levels of impulsive behaviour in daily life, which, in turn, were related to motivational but not cognitive inhibitory control as measured by the laboratory tasks. It had been expected that both laboratory measures of inhibitory control would be related to impulsivity in daily life, as many questions of the BIS-11 do not appear to involve motivational or affective components. It may be speculated that, when self-reporting on impulsivity, informants generally activate the memory of social contexts where such behaviour had to be suppressed in order to reach a certain goal, i.e. when motivational processes were involved. This could explain the lack of associations between daily life impulsivity reports and cognitive inhibitory control measured in the absence of a socially meaningful context.

Frequency of use did not have a clear influence on the results: there were no differences between moderate and heavy cannabis users regarding daily life impulsivity, and only two

differences regarding measures of motivational inhibitory control, one showing greater gambling tendencies for the heavy users, when chances of a reward were quite small, and one showing greater gambling tendencies for the moderate users, when chances of a reward were difficult to estimate. Together with the type of differences observed between controls and moderate users and between controls and heavy users, respectively, this might indicate that heavy users are the bigger risk-takers, whereas the moderate users are the greater 'doubters', but a more consistent pattern of results would be required to substantiate such inferences. .

The finding that cannabis users only experienced deficits in inhibitory control when a motivational component was present might be indicative of relatively strong reward sensitivity that cannot be countered by normal or even good cognitive control skills. For the interpretation of this result it may be relevant to consider group characteristics in more detail. Cannabis users in the present study were considered recreational users (although a number of them reported rather heavy use). Impairments in cognitive inhibitory control have quite clearly been established in addicted individuals, and have been suggested to underlie the transition into addiction (Everitt et al., 2008; Goldstein & Volkow, 2002; Stacy & Wiers, 2010; Wiers et al., 2007). Thus, what may distinguish recreational cannabis users from both non-users and addicted users is a unique involvement of poor motivational inhibition. Non-users could have good motivational inhibition, whereas addicted individuals could have both poor motivational inhibition and weak cognitive control (see also: Kalivas & Volkow, 2005).

Regarding specificity of results, this study does appear to provide evidence for some specific relations between cannabis use and motivational inhibitory control. Concurrent smoking weakened associations to some extent but they remained significant. Alcohol intake did not differ between cannabis users and non-users, whilst MDMA-use was not related to any of the dependent variables. Although the instruments used to measure substance use were similar to those used in other studies into correlates of cannabis use (e.g. Monshouwer et al., 2006), these could be further refined (e.g. establish in more detail the intake amounts), and it would have been preferable to have multiple informants. Moreover, it may be expected that more variation in substance use will be observed in a broader sample of the population. Another consideration here is that cannabis users did show different motivational inhibition compared to non-users, but that the rewards were unrelated to the substance of interest, which is in line with results from other studies (e.g. Kamarajan et al., 2010; Nestor et al., 2010). This appears to contrast with implicit cognition approaches, which generally assume spontaneously activated memory associations and courses of action involving a specific substance (Stacy and Wiers, 2010). Although there is not necessarily a contrast, as implicit cognition was not

examined here (and could therefore just as well produce even stronger evidence for motivational inhibition problems in this sample), this result may be indicative of non-specificity of associations between substance use and motivational inhibitory control (see also Fernández-Serrano et al., 2011).

As mentioned, the instruments used to assess drug use could be further refined. A similar argument could be made about the instruments that were used to assess cognitive outcomes. It should be noted, however, that the choice for these instruments was based on earlier studies investigating the cognitive constructs that are of interest here (Fairchild et al., 2009; Rogers et al., 2003; Rowbotham et al., 2009). The cognitive inhibition task used in the present study, which is a variant of the well-established Eriksen flanker-paradigm, is a standardized task with good reliability and validity scores (De Sonneville, 1999; Rowbotham et al., 2009). In order to measure inhibitory control in a motivational context, the most widely used task is the Iowa Gambling Task (IGT; Bechara et al., 1994), which indeed has shown differences between substance (ab-)using individuals and controls (Bolla, Eldreth, Matochik, & Cadet, 2005; Verdejo-Garcia et al., 2008; Whitlow et al., 2004). It has however been argued that IGT performance deficits particularly reflects decision-making impairments, which, in turn involves multiple neuropsychological processes, including working memory, reversal learning, and sensitivity to reward/punishment (Busemeyer & Stout, 2002; Dunn, Dalgleish, & Lawrence, 2006). Since we wanted to clearly contrast cognitive and motivational inhibition, we used a version of the Risky Choice Task (Rogers et al., 2003). In this task it is more difficult to use a strategy based on cognitive assertions, i.e. built-up knowledge of rewards and punishments (Fairchild et al., 2009). It should however be acknowledged that it might have been preferable to have multiple tasks or questionnaires for each construct we tested, or perhaps, regarding the outcome measures, to have had two laboratory tasks differing purely with respect the requirement of motivational inhibitory control (cf. Daniel & Pollmann, 2010; Vadhan et al., 2009).

Despite the obvious opportunities to expand this research, it may be concluded from the present study that motivational inhibitory control in recreational cannabis users differs from that of non-users, and that the relatively poor impulse control cannabis users show in their daily lives is associated with this specific type of inhibitory control deficit.

References

Barratt, E. S (1985). Impulsiveness subtraits: arousal and information procesing. In J. T. Spence, & C. E. Itard, (Eds.), *Motivation, Emotion and Personality* (pp. 43-68). North Holland: Elsevier.

Bechara, A. (2003). Risky business: Emotion, decision-making, and addiction. *Journal of Gambling Studies, 19,* 23-51.

Bechara, A., Damásio, A. R., Damásio, H.,& Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*, 7–15.

Blum, K., Braverman, E.R., Holder, J.M., Lubar, J.F., Monastra, V.J., Miller, D., Lubar, J.O., Chen, T.J., & Comings, D.E. (2000). Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *Journal of Psychoactive Drugs, 32, Suppl: i-iv,* 1-112.

Bolla, K.I., Eldreth, D.A., Matochik, J.A., & Cadet, J.L. (2005). Neural substrates of faulty decision-making in abstinent marijuana users. *Neuroimage, 26,* 480-492.

Busemeyer, J.R., & Stout, J.C. (2002). A contribution of cognitive decision models to clinical assessment: Decomposing performance on the Bechara gambling task. *Psychological Assessment, 14,* 253-262.

Chambers, R.A., Taylor, J.R., & Potenza, 2003. Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. *American journal of psychiatry, 160,* 1041-1052.

Chanraud, S., Martelli, C., Delain, F., Kostogianni, N., Douaud, G., Aubin, H.J., Reynaud, M., & Martinot, J.J. (2007). Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology, 32,* 429-438.

Cherek, D.R., Lane, S.D., & Dougherty, D.M. (2002). Possible amotivational effects following marijuana smoking under laboratory conditions. *Experimental and Clinical Psychopharmacology, 10,* 26-38.

Churchwell, J.W., Lopez-Larson, M., & Yurgelun-Todd, D.A. (2010). Altered frontal cortical volume and decision making in adolescent cannabis users. *Frontiers in Psychology, 1,* 225.

Clark, L., Rosier, J.P., Robbins, T.W., & Sahakian, B.J. (2009). Disrupted 'reflection' impulsivity in cannabis users but not current or former ecstacy users. *Journal of Psychopharmacology, 23,* 14-22.

Cowan, R.L., Lyoo, I.K., Sung, S.M., Ahn, K.H., kim, M.J., Hwang, J., Haga, E., Vimal, R.L., Lukas, S.E., & Renshaw, P.F. (2003). Reduced cortical gray matter density in human MDMA (ecstacy) users: A voxel-based morphometry study. *Drug and Alcohol Dependence, 72,* 225-235.

Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D.E., Laane, K., Pena, Y., Murphy, E.R., Shah, Y., Probst, K., Abakumova, I., Aigbirhio, F.I., Richards, H.K., Hong, Y., Baron, J.C., Everitt, B.J., & Robbins, T.W. (2007). Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science, 315,* 1267-1270.

Daniel, R., & Pollmann, S. (2010). Comparing the neural basis of monetary reward and cognitive feedback during information-integration category learning. *Journal of Neuroscience, 30,* 47-55.

De Sonneville, L.M.J. (1999). Amsterdam Neuropsychological Tasks: a computer-aided assessment program. In Den Brinker, B.P.L.M., Beek, P.J., Brand, A.N., Maarse, S.J., & Mulder, L.J.M. (Eds.), *Computers in Psychology; Cognitive Ergonomics, Clinical Assessment and Computer-assisted Learning* (pp. 187-203). Swets and Zeitlinger, Lisse.

Dunn, B.D., Dalgleish, T., & Lawrence, A.D. (2006). The somatic marker hypothesis: A critical evaluation. *Neuroscience and Biobehavioral Reviews, 30,* 239-271.

Everitt, B.J., Belin, D., Economidou, D., Pelloux, Y., Dalley, J.W., & Robbins, T.W. (2008). Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical transactions of the Royal Society of London, 363,* 3125-3135.

Fairchild, G., Van Goozen, S.H.M., Stollery, S.J., Aitken, M.R.F., Savage, J., Moore, S.C., & Goodyer, I.M. (2009). Decision making and executive function in male adolescents with early-onset or adolescence-onset conduct disorder and control subjects. *Biological Psychiatry, 66,* 162-168.

Fergusson, D. M., Horwood, L. J., & Ridder, E. M., (2007). Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: Results of a 25-year longitudinal study. *Drug and Alcohol Dependence, 88*, 14-26.

Fernández-Serrano, M.J., Pérez-García, M., Verdejo-García, A. (2011). What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? *Neuroscience and Biobehavioral Reviews, 35,* 377-406.

Friedman, N., & Miyake, A. (2004). The relations among inhibition and interference control functions: A latent-variable analysis. *J. Exp. Psychol. Gen., 133,* 101-135.

Goldstein, R.Z, & Volkow, N.D. (2002). Drug Addiction and its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex. *American Journal of Psychiatry*, *159*, 1642-1652.

Grant, I., Gonzalez, R., Carey, C.L., Natarajan, L., & Wolfson, T. (2003). Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society, 9*, 679-689.

Griffith-Lendering, M.F.H., Huijbregts, S.C.J., Mooijaart, A., Vollebergh, W.A.M., & Swaab, H. (2011). Cannabis use and development of externalizing and internalizing behavior problems in early adolescence: A TRAILS-study. *Drug and Alcohol Dependence, in press*

Gruber, S.A., Silveri, M.M., Dahlgren, M.K., & Yurgelun-Todd, D. (2011). Why so impulsive? White matter alterations are associated with impulsivity in chronic marijuana smokers. *Experimental and Clinical Psychopharmacology, 19,* 231-242.

Gruber, S.A., Yurgelun-Todd, D.A. (2005). Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Brain Research. Cognitive Brain Research, 23*, 107–118.

Huijbregts, S.C.J., Warren, A.J., De Sonneville, L.M.J., & Swaab-Barneveld, H. (2008). Hot and cool forms of inhibitory control and externalizing behavior in children of mothers who smoked during pregnancy: An exploratory study. *Journal of Abnormal Child Psychology, 36,* 323-333.

Kalivas, P.W., & Volkow, N.D. (2005). The neural basis of addiction: A pathology of motivation and choice. *American Journal of Psychiatry, 162,* 1403-1413.

Kamarajan, C., Rangaswamy, M., Tang, Y., Chorlian, D.B., Pandey, A.K., Roopesh, B.N., Manz, N., Saunders, R., Stimus, A.T., & Porjesz, B. (2010). Dysfunctional reward processing in male alcoholics: An ERP study during a gambling task. *Journal of Psychiatric Research, 44,* 576-590.

Krain, A.L., Wilson, A.M., Arbuckle, R., Castellanos, F.X., & Milham, M.P. (2006). Distinct neural mechanisms of risk and ambiguity: A meta-analysis of decision-making. *NeuroImage, 32,* 477-484.

Kreek, M.J., Nielsen, D.A., Butelman, E.R., & LaForge, K.S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscience, 8,* 1450-1457.

Lamers, C.T.J., Bechara, A., Rizzo, M., & Ramaekers, J.G. (2006). Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. *Journal of Psychopharmacology, 20,* 302-311.

Lane, S.D., Cherek, D.R., Tcheremissine, O.V., Steinberg, J.L., & Sharon, J.L. (2007). Response perseveration and adaptation in heavy marijuana-smoking adolescents. *Addictive Behaviors, 32,* 977-90.

Lane, S.D., Cherek, D.R., Peitras, C.J., & Steinberg, J.L. (2005). Performance of heavy marijuana-smoking adolescents on a laboratory measure of motivation. *Addictive Behaviors, 30,* 815-828.

Malmberg, M., Overbeek, G., Monshouwer, K., Lammers, J., Vollebergh, W.A., & Engels, R.C. (2010). Substance use risk profiles and associations with early substance use in adolescence. *Journal of Behavioral Medicine, 33,* 474-485.

Miller, E., Joseph, S., & Tudway, J. (2004). Assessing the component structure of four self-report measures of impulsivity. *Personality and Individual Differences, 37*, 349–358.

Monshouwer, K., Van Dorsselaer, S., Verdurmen, J., Ter Bogt, T., De Graaf, R., & Vollebergh, W. (2006). Cannabis use and mental health in secondary school children. Findings from a Dutch survey. *British Journal of Psychiatry, 188*, 148-153.

Nelson, R.J., & Trainor, B.C. (2007). Neural mechanisms of aggression. *Nature Reviews Neuroscience, 8,* 536-546.

Nestor, L., Hester, R., & Garavan, H. (2010). Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *Neuroimage, 49,* 1133-1143.

Piechatzek, M., Indlekofer, F., Daamen, M., Glasmacher, C., Lieb, R., Pfister, H., Tucha, O., Lange, K.W., Wittchen, H-U., & Schütz, C.G. (2009). Is moderate substance use associated with altered executive functioning in a population-based sample of young adults? *Human. Psychocopharmacology, 24,* 650-665.

Pierce, R.C., & Kumaresan, V. (2006). The mesolimbic dopaminergic system: The final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience and Biobehavioral Reviews, 30,* 215-238.

Pope, H.G., Gruber, A.J., Hudson, J.L., Huestis, M.A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry, 58,* 909-915.

Robinson, T.E., & Kolb, B. (2004). Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology, 42 (Suppl. 1),* 33-46.

Rogers, R.D., Turnbridge, E.M., Bhagwagar, Z., Drevets, W.C., Sahakian, B.J., & Carter, C.S. (2003). Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. *Neuropsychopharmacology, 28,* 153-162.

Rowbotham, I., Pit-ten Cate, I.M., Sonuga-Barke, E.J.S., & Huijbregts, S.C.J. (2009). Cognitive control in adolescents with neurofibromatosis type 1. *Neuropsychology, 23*, 50–60.

Solowij, N., Stephens, R.S., Roffman, R.A. et al (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *Journal of the American Medical Association, 287,* 1123-1131.

Sonuga-Barke, E.J. (2002). Psychological heterogeneity in AD/HD: A dual pathway model of and cognition. *Behavioural Brain Research, 130*, 29-36.

Stacy, A.W., & Wiers, R.W. (2010). Implicit cognition and addiction: A tool for explaining paradoxical behavior. *Annual Review of Clinical Psychology, 6,* 551-575.

Stanford M.S., Mathias C.W., Dougherty D.M., Lake S.L., Anderson N.E., & Patton, J.H. (2009). Fifty years of the Barratt Impulsiveness Scale: An update and review. *Personality and Individual Differences*, *47*, 385–395.

Tapert, S.F. Schweinsburg, A.D., Drummond, S.P., Paulus, M.P., Brown, S.A., Yang, T.T. & Frank, L.R. (2007). Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology, 194,* 173-83.

Vadhan, N.P., Hart, C.L., Haney, M., Van Gorp, W.G., & Foltin, R.W. (2009). Decision-making in long-term cocaine users: Efects of a cash monetary contingency on gambling task performance. *Drug and Alcohol Dependence, 102,* 95-101.

Verdejo-Garcia, A., Benbrook, A., Funderburk, F., David, P., Cadet, J.L., & Bolla, K.I. (2007). The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug and Alcohol Dependence, 90,* 2-11.

Verdejo-Garcia, A., Lawrence, A.J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews, 32,* 777-810.

Whitlow, C.T., Liguori, A., Livengood, L.B., Hart, S.L., Mussat-Whitlow, B.J., Lamborn, C.M., Laurienti, P.J., & Porrino, L.J. (2004). Long-term heavy marijuana users make costly decisions on a gambling task. *Drug and Alcohol Dependence, 76*, 107-111.

Wiers, R.W., Bartholow, B.D., Van den Wildenberg, E., Thush, C., Engels, R.C.M.E., Sher, K.J., Grenard, J., Ames, S.L., & Stacy, A.W. (2007). Automatic and controlled processes and the development of addictive behaviors in adolescents: A review and a model. *Pharmacology, Biochemistry and Behavior, 86,* 263-283.

Zelazo, P.D., & Müller, U. (2002). Executive function in typical and atypical development. In U. Goswami (Ed.), *Handbook of Childhood Cognitive Development* (pp. 445-469). Oxford, Blackwell.

6.

Quality of social perception moderates associations between cannabis use and psychological problems

Huijbregts, S.C.J., Griffith- Lendering, M.F.H., Vollebergh, W.A.M., & Swaab, H. Quality of social perception moderates associations between cannabis use and psychological problems. *Manuscript submitted for publication.*

Abstract

Objective: Genetically and/or environmentally determined risk dispositions might increase vulnerability of cannabis users to experience psychological problems. Such risk dispositions may be expressed as (specific) cognitive weaknesses. The present study examined whether relatively poor social perception skills in combination with cannabis use would result in higher levels of psychological problems.

Method: Cannabis users (N = 75, mean age 24.6 years) were compared to non-users (N = 75, mean age 24.7 years) with respect to performance on two social perception tasks (Face Recognition (FR) and Matching Facial Emotions (MFE), which can be distinguished from FR because it requires emotion recognition and greater working memory capacity) and the extent of self-reported psychological problems. Analyses of (co-) variance were used to determine whether quality of social perception mediated or moderated possible associations between cannabis use and psychological problems.

Results: Cannabis users performed significantly more poorly than controls on the two social perception tasks, and reported more psychological problems than non-users. Quality of social perception moderated associations between cannabis use and psychological problems in that only users with relatively poor performance on the MFE reported elevated levels of psychological problems (i.e. insufficiency of thoughts and actions, distrust, depression, and psychoneuroticism). Further specification of the user group showed that the moderation effect could be attributed to heavy cannabis users versus moderate- and non-users. No interactions were found between cannabis use and FR-performance.

Conclusion: Heavy cannabis use and relatively poor (complex) social perception skills exacerbate each other's effects on psychological well-being.

Introduction

Cannabis is the most widely used substance after tobacco and alcohol in Western countries, with a particularly high prevalence among adolescents and young adults (European Monitoring Centre for Drugs and Drug Addiction, 2009; Substance Abuse and Mental Health Services Administration, 2008). Cannabis use has been associated with poor psychosocial adjustment (Fergusson & Boden, 2008; Fergusson et al., 2002; Griffith-Lendering et al., 2011a) and different (sometimes subclinical) forms of psychopathology, such as psychosis (Arseneault et al., 2002; Degenhardt et al., 2003a; Griffith-Lendering et al., in press; Moore et al., 2007), antisocial behaviour (Fergusson et al., 2007; Griffith-Lendering et al., 2011b; Monshouwer et al., 2006; Rey et al., 2002) and depression (Degenhardt et al., 2003b; Fergusson & Boden, 2008; Patton et al., 2002; Rey et al., 2002). In addition, reduced educational achievement (Lynskey & Hall, 2000) and cognitive difficulties have been reported. Domains of cognitive impairment include executive function (EF), implicit cognition, episodic memory, and emotional processing (Pope et al., 2001; Solowij, 1998; Solowij et al., 2002; Stacy & Wiers, 2010; Verdejo-Garcia et al., 2008). Many of these difficulties have been observed among users of other drugs as well (Fernández-Serrano et al., 2011). Moreover, there are quite some discrepancies among reported findings (see, for example, Fisk & Montgomery, 2008; Pope et al., 2001), which can, in part, be attributed to methodological differences between studies. One of these methodological issues concerns the definition or operationalization of broad cognitive concepts such as executive function and emotional processing. Core EF-abilities include inhibitory control and working memory, which are multi-faceted concepts themselves (cf. Christ et al., 2010; D'Esposito et al., 1999; Nigg, 2000). Core aspects of emotional processing include social perception (e.g. emotion recognition), Theory of Mind (i.e. the ability to "mentalize"), empathy, and reward/punishment sensitivity (Adolphs, 2002; Beer et al., 2004; Dodge & Rabiner, 2004; Ochsner, 2008; Pettit and Mize, 2007). Studies have often used task paradigms addressing combinations of different (social-) cognitive skills. Examples include decision-making and implicit cognition tasks, which require working memory, and cognitive and motivational inhibitory control (Busemeyer & Stout, 2002; Stacy & Wiers, 2010; Whitlow et al., 2004). Aspects of cognition for which it is more difficult to consider them as constellations of other cognitive constructs and that appear to be impaired in cannabis users are prospective memory and motivational inhibitory control (Griffith-Lendering et al., 2012; Solowij et al., 2002). A

further consistent finding is a slower processing and/or motor speed among cannabis users (Kelleher et al., 2004).

In the present study we focused on social perception, which constitutes a basic element of social information processing (Dodge & Rabiner, 2004) and has not yet been extensively investigated among cannabis users. Social perception tasks may or may not involve emotion recognition. The amygdalae play an important role in emotion recognition (Adolphs, 2002; Ochsner, 2008). Among long-term cannabis users reduced amygdala volumes have been observed (Yucel et al., 2008). Also, Phan et al. (2008) reported reduced amygdala reactivity during social information processing after administration of delta-9-tetra-hydrocannabinol (Δ^9-THC), the principle constituent of cannabis inducing positive emotional states as well as anxiety and psychosis-like symptoms (D'Souza et al., 2004). Gruber et al. (2009) showed reduced amygdala activity during emotion perception in chronic cannabis users. Although these studies yielded relatively consistent results, thereby using stimuli that required the ability to recognize emotions from facial expressions, they did not focus on the quality of emotion recognition. Only one recent study, by Platt and colleagues (2010), did focus on performance during an emotion recognition task. Cannabis users were significantly slower than controls at identifying emotional expressions in a paradigm where facial expressions gradually changed from neutral to more intense expressions of sadness, anger or happiness. Although the authors discussed the possible implications of their findings for vulnerability to psychological problems in cannabis users, they did not investigate this further. We sought to extend the research by Platt and colleagues by examining social perception in relation to psychological problems among cannabis users. With respect to type of psychological problems, we focused on subclinical levels of psychosis/schizophrenia, and internalizing and externalizing behaviour problems, all of which have been related both to cannabis use (Arseneault et al., 2002; Degenhardt et al., 2003a; Fergusson et al., 2002; Moore et al., 2007) and to social perception impairments (Demenescu et al., 2010; Germine & Hooker, 2011, Kohler et al., 2010; Marsh & Blair, 2008; Rössler et al., 2011). Interrelations between psychological problems and cognitive weaknesses in cannabis users have not yet been clearly established. Moreover, it is unclear whether cannabis users with cognitive difficulties are more prone to (experiencing) psychological problems than cannabis users without such difficulties. We hypothesized that cannabis users would perform more poorly than non-users on face recognition- and matching emotions from facial expressions-tasks, and would report more psychological problems. It was also hypothesized that relatively poor social perception

skills and cannabis use would disproportionately increase the chances of experiencing psychological problems.

Method

Participants

Participants were classified as cannabis users if they reported using cannabis every month during the past year and as non-users if they reported the use of cannabis zero times during the past year. Based on these criteria, 75 cannabis users (mean age: 24.6, SD=3.7, with an abstinence period of at least 24 hours) and 75 non-users (mean age: 24.7, SD=3.7) were recruited among University of Leiden undergraduate students and through advertisements on internet forums concerning cannabis topics. Written informed consent was obtained from all participants before the start of the study. Ethical approval for this study was granted by Leiden University's Education and Child Studies Ethics Committee.

Measures

Cannabis use

Cannabis use was assessed by asking participants about their lifetime use, their use during the past year and month (yes/no, plus frequency of use). Participants also reported on the use of alcohol (weekly yes/no), tobacco (daily yes/no) and other drugs including stimulants (cocaine, (met)amphetamine), opioids (heroin, methadone), and 3,4-methylenedioxymethamphetamine (MDMA: Ecstacy) (monthly: yes/no) (cf. Griffiths-Lendering et al., 2012; Huizink et al., 2006; Monshouwer et al., 2006) (Table 1).

Psychological problems

The Symptom Checklist-90 (SCL-90) (Derogatis, 1973; Elliot et al., 2006), a 90-item self-report symptom inventory developed to measure psychological symptoms and distress, was used to measure psychological problems. It was designed to be appropriate for use not only in clinical populations but also for use within community samples. The SCL-90, for which items are rated on five-point scales reflecting the extent to which problems were experienced in the past 7 days, generates the following scales: Somatic complaints (12 items), Insufficiency of thoughts and actions (9 items), Distrust (18 items), Depression (16 items), Anxiety (10 items), Hostility (6 items), Agoraphobia (6 items) and Sleeping problems (3 items). In addition, a global score is obtained, called Psychoneuroticism, using the overall

score of the 90 items. Internal reliability of the different scales ranges from .77-.97 (Cronbach's alpha).

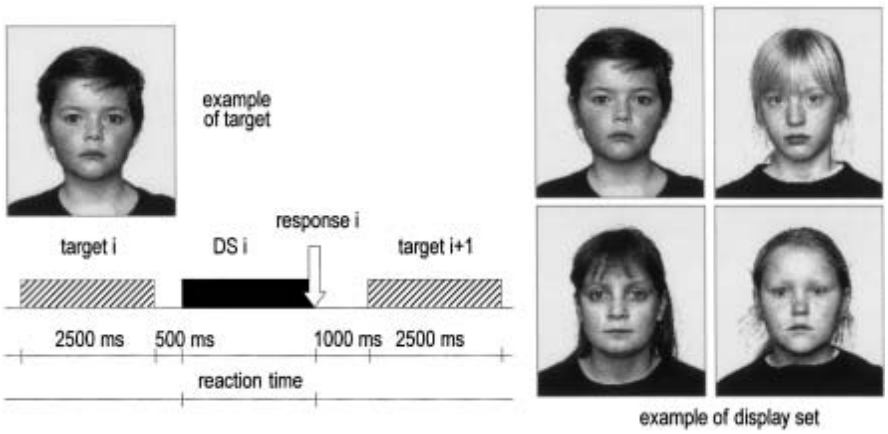
Social perception

Two tasks from the Amsterdam Neuropsychological Tasks (ANT, De Sonneville, 1999), a battery of computerized tests, were used to assess social perception. Test-retest reliability, construct-, criterion-, and discriminant validity of the ANT-tasks are satisfactory and have extensively been described elsewhere (e.g. De Sonneville et al., 2002; Serra et al., 2003; Huijbregts et al., 2010). Before each part of a task the participants were given a standard verbal instruction and were given the opportunity to ask questions and to practice.

Face Recognition (FR)

This task (duration: 5 minutes) examined the ability to recognize neutral faces. A target-face was presented on the monitor for 2.5s. Following the presentation of the target face, a set of four photographs of individuals was presented and participants had to indicate whether or not the target individual appeared in the set of four (Figure 1). The gender and age category of the target (i.e. boys, girls, men or women) match those of the subsequently shown set of four faces. A yes-response was given by pressing the mouse button below the index finger of the preferred hand; a no-response required a press of the mouse button below the index finger of the non-preferred hand. There were 40 trials, in half of which the display set contained the target face.

Figure 1. Stimulus example (target face + display set) and timing of the trials for the Face Recognition task



Matching of Facial Emotions (MFE)

This task (duration: 10 minutes) measured the ability to match emotions using facial expressions. The expressed emotions are happiness, sadness, anger and fear. In each of the 160 trials, two (digitized photographs of) faces expressing a particular emotion were presented simultaneously on the computer screen. The participants had to press the yes-button when the two faces expressed the same emotion and the no-button when the facial emotions did not match (Figure 2). MFE may be considered a more demanding task than FR. The tasks can also be distinguished based on the fact that MFE specifically involves emotion recognition, whereas FR does not.

Figure 2. Stimulus examples for the Matching Facial Emotions task

Data analysis

First, Pearson correlations were calculated to get an impression of which psychological problems were associated with cannabis use (lifetime, past year and month).

Next, group differences between cannabis users and non-users regarding psychological problems and performance on the social perception tasks were investigated using General Linear Model (GLM) univariate and multivariate analyses of variance. Accuracy and speed of task performance were first analyzed separately. In order to account for potentially slower processing speed among cannabis users and to account for possible speed-accuracy trade-offs, ratio variables (i.e. number correct/mean RT for correct responses) were calculated and used as dependent variables in further analyses of task performance. In order to investigate the role of social perception in potential differences between cannabis users and non-users regarding psychological problems, participants were assigned to groups with either relatively poor or relatively good social perception (based on mean RT-corrected accuracy scores during the tasks). Next, two-way (multivariate) analyses were performed with cannabis use and social perception as between-subjects factors and the scales of the SCL-90 as dependent variables. Separate analyses were performed for social perception operationalized as Face Recognition and Matching Facial Emotions. Control variables (gender and other substance use) were included in the analyses as covariates when they were related to both dependent and independent variables.

In order to get an impression of possible dose-dependency, the two-way multivariate analyses of variance were repeated comparing non-users to relatively moderate users (<40 times in the past year) and relatively heavy users (≥ 40 times in the past year).

Results

Lifetime cannabis use correlated significantly with SCL-90 dimensions insufficiency of thoughts and actions ($r = .19$, $p = .012$), depression ($r = .17$, $p = .025$), anxiety ($r = .21$, $p = .006$), hostility ($r = .24$, $p = .002$), and the overall psychoneuroticism score ($r = .21$, $p = .007$), with a trend for the correlation with distrust ($r = .13$, $p = .067$). Cannabis use in the last 12 months was significantly correlated with insufficiency of thoughts and actions ($r = .18$, $p = .014$), distrust ($r = .17$, .023), and hostility ($r = .21$, $p = .006$), with trends for the correlations with psychoneuroticism ($r = .14$, $p = .051$) and

anxiety (r = .13, p = .060). Similar correlations were observed for cannabis use in the last four weeks and SCL-90 dimensions (insufficiency of thoughts and actions: r = .14, p = .047; distrust: r = .18, p = .019; hostility r = .20, p = .007; and psychoneuroticism r = .12, p = .078). For the other dimensions of the SCL-90, somatic complaints, agoraphobia, and sleep problems, no significant correlations with any of the cannabis measures were observed. Therefore, these were dropped from further analyses.

Group comparisons

Error rates on both the FR- and the MFE tasks were significantly higher for cannabis users compared to non-users [FR: $F(1,148) = 18.0$, $p < .001$, partial $\eta^2 = .11$; MFE: $F(1,148) = 10.8$, $p = .001$, partial $\eta^2 = .07$]. Cannabis users were also significantly slower than non-users in the MFE-task [$F(1,148) = 5.9$, $p = .017$, partial $\eta^2 = .04$], but there was no significant difference in response speed for the FR-task [$F(1,148) = 1.2$, $p = .28$, partial $\eta^2 = .01$]. Significant group differences regarding both speed and accuracy in the MFE-task were present for pairings involving matches of all four different emotions, i.e. happiness, sadness, anger and fear (see Table 2 for descriptive statistics on task performance and psychological problem ratings). In order to incorporate in further analyses the fact that cannabis users performed less accurately and more slowly than non-users in the MFE-task, and in order to take into account the possibility of speed-accuracy trade-off in the FR-task, ratio-variables (number correct/mean RT for correct responses) were used. A MANOVA comparing users and non-users on the FR- and MFE ratio-scores showed a significant multivariate group effect [$F(2,147) = 5.4$, $p = .006$, partial $\eta^2 = .07$], with significant univariate effects for both tasks: FR: $F(1,148) = 4.0$, $p = .047$, partial $\eta^2 = .03$; MFE: $F(1,148) = 10.7$, $p = .001$, partial $\eta^2 = .07$, indicating poorer performance of cannabis users. Cannabis users differed from non-users with respect to gender distribution (relatively more men among cannabis users) (Table 1), and women performed better on the social perception tasks (FR: $t(146) = -1.9$, $p = .06$; MFE: $t(146) = -2.7$, $p = .008$). However, entering gender as a covariate in the above analyses did not affect the group differences on social perception between cannabis users and non-users

With respect to behavior problems significant differences between users and non-users were observed for insufficiency of thoughts and actions [$F(1,132) = 4.1$, $p = .044$, partial $\eta^2 = .03$] and hostility [$F(1,132) = 6.0$, $p = .016$, partial $\eta^2 = .04$], with

further trends for anxiety [F(1,132) = 3.3, p = .070, partial η^2 = .03] and psychoneuroticism [F(1,132) = 3.5, p = .065, partial η^2 = .03]. All results indicated higher scores for cannabis users; these were also observed for distrust and depression, although here the group differences were not significant (Table 2).

When FR- or MFE-scores were introduced to these analyses as covariates in order to examine possible mediation effects, the only difference between cannabis users and non-users that was significantly reduced was that for insufficiency of thoughts and actions when the MFE-score was controlled for [F(1, 131) = 2.5, p = .12, partial η^2 = .02).

Table 1. Descriptive information on cannabis users (*n*=75) and non-users (*n*=75)

	Users	Non-users	*t* / $\div^2$
Age (Mean, SD)	24.7 (3.7)	24.6 (3.7)	t(148) = 0.0
Male	66.7 %	30.7 %	$\div^2$ (1) = 21.2**
Daily smokers	41.3 %	9.3 %	$\div^2$ (1) = 20.3**
Weekly alcohol	92.0 %	76.0 %	$\div^2$ (1) = 7.1*
Monthly MDMA	14.7%	5.3%	$\div^2$ (1) = 3.6^+
Monthly cocaine	4.0%	1.3%	$\div^2$ (1) = 1.0

** p<.01; * p<.05; $^+$ p <.10

Table 2. Means error rates and RTs (SD's) of cannabis user and non-user groups on the social perception tasks and mean scores on the Sympom Checklist-90

		Non-users (n = 75)	*Moderate users (n = 41)*	*Heavy users (n = 34)*
Face Recognition	ER	1.6 (1.2)	2.9 (2.2)	2.7 (2.0)
	RT	1281 (259)	1310 (303)	1341 (237)
MFE Happiness	ER	0.9 (0.7)	1.2 (1.6)	1.7 (1.9)
	RT	1194 (240)	1310 (334)	1278 (266)
MFE Sadness	ER	6.4 (3.9)	8.7 (5.1)	9.1 (4.0)
	RT	1819 (383)	1986 (490)	1971 (373)
MFE Anger	ER	5.5 (4.0)	6.4 (5.3)	7.8 (4.4)
	RT	1778 (382)	1904 (422)	1908 (350)
MFE Fear	ER	4.9 (3.5)	5.9 (4.3)	8.1 (4.5)
	RT	1797 (398)	1959 (494)	1944 (338)
Somatic complaints		15.7 (3.6)	16.5 (5.5)	15.2 (3.0)
Insuff. thoughts and actions		12.3 (3.5)	13.1 (4.3)	14.5 (4.5)
Distrust		22.3 (5.0)	22.1 (4.3)	25.7 (8.0)
Depression		20.6 (5.3)	22.4 (7.6)	22.4 (7.3)
Anxiety		11.9 (3.0)	13.1 (5.3)	13.2 (3.1)
Hostility		7.0 (1.3)	7.6 (3.0)	8.6 (3.8)
Agoraphobia		7.4 (1.2)	7.4 (1.7)	7.6 (1.1)
Sleep problems		4.6 (2.4)	4.6 (2.1)	4.2 (1.3)
Psychoneuroticism		112.1 (21.6)	118.1 (29.0)	122.8 (27.8)

Moderate users: reported use of cannabis < 40 times/past year; Heavy users: reported use of cannabis ≥ 40 times/past year. MFE: Matching Facial Emotions. ER: Error Rate. RT: Reaction Time (msec).

Moderation effects

When groups with relatively poor and relatively good social perception were formed (split at mean for FR- and MFE-ratio scores) and introduced to the analyses as a second independent variable (next to cannabis use) some clear moderation effects emerged for performance of the MFE-task. Significant interactions between cannabis use and MFE-performance were observed for insufficiency of thoughts and actions [$F(1,130) = 5.6$, $p = .019$, partial $\eta^2 = .04$], distrust [$F(1,130) = 4.0$, $p = .048$, partial $\eta^2 = .03$], depression [$F(1,130) = 4.5$, $p = .036$, partial $\eta^2 = .03$], and psychoneuroticism [$F(1,130) = 5.0$, $p = .027$, partial $\eta^2 = .04$]. These moderation effects indicated that psychological problems of cannabis users were evident among those who also performed relatively poorly on the MFE-task (see Figure 3a-d). Cannabis users did not differ from non-users when they performed relatively well on this task (see Table 3 for results of contrast analysis). Similar, but non-significant patterns were observed for anxiety and hostility.

In analyses where cannabis use was further subdivided into relatively moderate (<40 times in the past year) and relatively heavy use (≥ 40 times in the past year), significant interactions were again observed for insufficiency of thoughts and actions [$F(2,128) = 4.2$, $p = .017$, partial $\eta^2 = .06$], distrust [$F(2,128) = 3.4$, $p = .018$, partial $\eta^2 = .06$], and psychoneuroticism [$F(2,128) = 3,4$, $p = .037$, partial $\eta^2 = .05$], with a trend for depression [$F(2,131) = 2.7$, $p = .07$, partial $\eta^2 = .04$] (see Figure 4a-d). These interactions indicated that psychological problems were particularly observed for heavy cannabis users with relatively poor social perception as measured by the MFE.

Cannabis users and non users differed with respect to gender distribution, and they also used tobacco, alcohol, and MDMA more often than non-users (Table 1). None of these factors were significantly associated with psychological problems. Adding them as covariates did not affect the interactions between cannabis use and MFE-performance predicting psychological problems. No significant interactions were observed between cannabis use and FR-performance when predicting psychological problems.

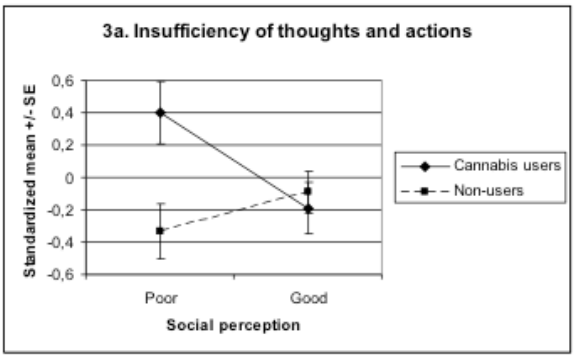
Table 3. Helmert contrasts for psychological problems

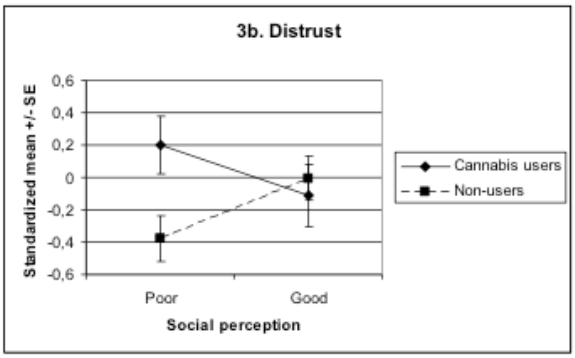
	Contrast Estimate (SE), Sig.			
	Insufficiency of thoughts and actions	*Distrust*	*Depression*	*Psychoneuroticism*
Level 1 vs. later	.553 (.18), .002**	.424 (.18), .019*	.484 (.18), .008**	.501 (.19), .008**
Level 2 vs. later	-.007 (.22), .976	.071 (.22), .750	-.001 (.22), .995	.072 (.23), .751
Level 3 vs. Level 4	-.261 (.23), .260	-.418 (.24), .078	-.214 (.23), .356	-.316 (.24), .189

* p <.05; ** p <.01

Level 1: Cannabis use + poor social perception; Level 2: Cannabis use + good social perception; Level 3: No use + poor social perception; Level 4: No use + good social perception

Figure 3. Moderating effects of social perception quality (MFE-performance) on associations between cannabis use and psychological problems





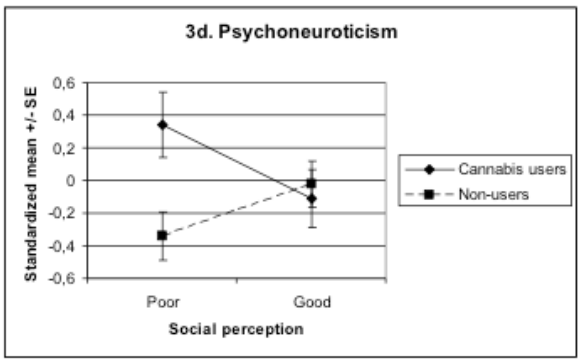
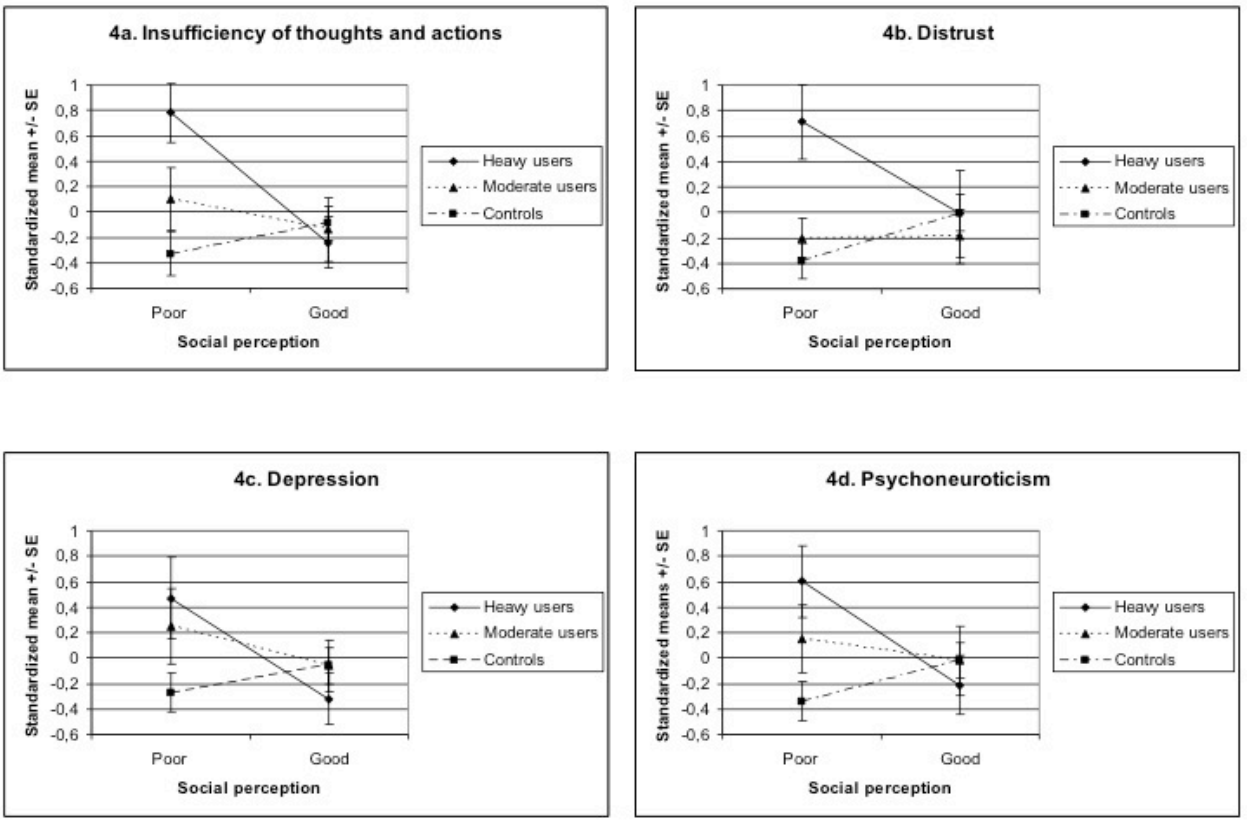


Figure 4. Exposure-dependent moderating effects of social perception quality on associations between cannabis use and psychological problems



Discussion

The results of this study show that compared to non-users, cannabis users reported more insufficiency of thoughts and actions, hostility, anxiety and psychoneuroticism. Furthermore, cannabis users performed more poorly than non-users on the social perception tasks, with the greatest differences observed for the matching emotions task. Another important question was whether quality of social perception would mediate or moderate associations between cannabis use and psychological problems. Whereas there was little evidence supporting mediation effects (except for insufficiency of thoughts and actions), the moderation hypothesis was confirmed by the finding of interactions between cannabis use and performance on the Matching Facial Emotions-task in predicting insufficiency of thoughts and actions, distrust, depression, and psychoneuroticism. Cannabis users who performed relatively poorly on that task had the most pronounced psychological problems. Cannabis users with relatively good performance on the task did not report elevated levels of psychological problems compared to non-using controls. It is important to note that no such interactions were observed when the Face Recognition-task was

used to measure social perception. Thus, the moderating effects are only apparent when the social perception task is either more demanding (for example, because of the requirement of additional cognitive skills in order to perform the task) or when it specifically involves the perception of emotional expressions. It should also be noted that it is not entirely clear yet whether these results are specific to cannabis use. Group differences and interactions were not affected by introducing other substance use or gender as covariates to the analyses. However, in order to measure other substance use dichotomous measures were used and, even though cannabis users more often reported the use of other substances as well, other substance use did not predict the type of psychological problems measured here. More continuous variables incorporating dosage or frequency of use, as selected to measure cannabis use, may be preferable for other substances as well (cf. Fernandez-Serrano et al., 2010). The associations between cannabis use and psychosis/schizophrenia-type (subclinical) psychological problems appears to concur with results from earlier studies (Arseneault et al., 2002; Degenhardt et al., 2003a; Moore et al., 2007; Rössler et al., 2011), although one should be careful in categorizing hostility and anxiety/depression as part of the spectrum of psychosis-/schizophrenia-type problems. They could represent independent psychological problems as well.

Whereas this study does not cover directionality of effects, relatively strong evidence exists indicating that cannabis use precedes or increases the risk of psychosis/schizophrenia-type problems (possibly on top of the so-called self-medication effects where increased vulnerability to develop psychosis is "soothed" with substance use) (Casadio et al., 2011). It is however clear that only a minority of cannabis users develop actual psychosis, and there is an intensive search under way for factors that might compound the effects of psycho-active cannabis ingredients in this respect. Most attention has been given to genetic factors enforcing susceptibility towards development of psychosis (Caspi et al., 2008; Henquet et al., 2008). Although inevitably influenced by genetic and environmental factors as well, specific cognitive weaknesses may, in combination with cannabis exposure, also increase chances of developing psychosis. This is what the present study suggests for social perception (as measured by the MFE), although it may be argued that better instruments could be available for detecting psychosis, also at a subclinical level in generally healthy populations (e.g., the Community Assessment of Psychic Experiences – CAPE, Stefanis et al., 2002; or the Symptom Checklist-90-R, Olsen et al., 2004; Rössler et al., 2011) and that a wider range of instruments should be used to cover (and clearly distinguish) all possible (combinations of) (social-)cognitive abilities where relative weakness could increase mental health effects of cannabis use. This view is supported by neurophysiological data: whereas a relatively singular pathway from cannabis to psychosis has been proposed, in which excessive Δ^9-THC- stimulation of cannabinoid (CB_1-) receptors on GABAergic and

glutaminergic terminals causes disruptions in dopaminergic projections from the brain stem to the striatum (Morrison & Murray, 2009), there are relatively high concentrations of CB_1-receptors throughout the prefrontal and anterior cingulate cortices (Casadio et al., 2011; Yacubian and Büchel, 2009). This, in turn, would suggest more widespread (social-)cognitive abnormalities that might increase the risk of experiencing psychological problems following heavy and prolonged cannabis use.

When these issues are further resolved, a clinical implication of our findings could be that social perception will be targeted in programs aimed at reducing the risk of psychopathology following cannabis use and possibly even in programs aimed at the prevention or treatment of addiction. Whereas more evidence is required to confirm a role for social perception in addiction progression, our findings do indicate more serious social perception deficits among heavier, and thus more likely to be addicted users. Recreational cannabis users and addicted substance users appear to have different cognitive outcomes (Everitt et al., 2008; Kalivas & Volkow, 2005; Stacy & Wiers, 2010). Whereas this has particularly been investigated with respect to inhibitory control (indicating more comprehensive inhibitory control deficits for addicted substance users), similar distinctions may be present for other aspects of cognition as well.

In conclusion, it may be stated that this study has provided evidence showing that cannabis users have problems with social perception in comparison to non-using controls, particularly when these social perception skills involve emotion recognition and need to be used in combination with other (e.g. working memory) skills. Moreover, heavy cannabis users experience significantly more psychological problems when they have relatively poor social perception skills.

References

Adolphs, R. (2002). Recognizing emotion from facial expressions: psychological and neurological mechanisms. *Behavioral and Cognitive Neuroscience Reviews, 1,* 21-62.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *British Medical Journal, 325,* 1212-1213.

Beer J.S., Shimamura A.P., & Knight R.T. (2004). Frontal lobe contributions to executive control of cognitive and social behavior. In: M.S. Gazzaniga (Ed.) *The Cognitive Neurosciences III. 3rd Ed.* (pp. 1091-1104). Cambridge, MA: MIT Press.

Busemeyer, J.R., & Stout, J.C. (2002). A contribution of cognitive decision models to clinical assessment: Decomposing performance on the Bechara gambling task. *Psychological Assessment, 14,* 253-262.

Casadio, P., Fernandes, C., Murray, R.M., & Di Forti, M. (2011). Cannabis use in young people: The risk for schizophrenia. *Neuroscience and Biobehavioral Reviews, 35,* 1779-1787.

Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., & Craig I.W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological Psychiatry, 57,* 1117-27.

Christ, S.E., Huijbregts, S.C.J., De Sonneville, L.M.J., & White, D.A. (2010). Executive function in early-treated phenylketonuria: Profile and underlying mechanisms. *Molecular Genetics and Metabolism, 99,* S22-S32.

De Sonneville, L.M.J., Verschoor, C.A., Njiokiktjien, C., Op het Veld, V., Toorenaar, N., & Vranken, M. (2002). Facial identity and facial emotions: Speed, accuracy, and processing strategies in children and adults. *Journal of Clinical and Experimental Neuropsychology, 24,* 200-213.

Degenhardt, L., Hall, W., & Lynskey, M. (2003a). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence*, *71,* 37-48.

Degenhardt, L., Hall, W., & Lynskey, M. (2003b). Exploring the association between cannabis use and depression. *Addiction, 98,* 1493-1504.

Demenescu, L.R., Kortekaas, R., Den Boer, J.A., & Aleman, A. (2010). Impaired attribution of emotion to facial expressions in anxiety and major depression. *PLoS One, 5,* e15058.

Derogatis, L.R., Lipman, R.S., & Covi, L. (1973). SCL-90: An outpatient psychiatric rating scale--preliminary report. *Psychopharmacological Bulletin, 9,* 13-28.

De Sonneville, L. M. J., 1999. Amsterdam neuropsychological tasks: A computer-aided assessment program. In: B.P.L.M. den Brinker, A.N. Brand, F.J. Maarse, & L.J.M. Mulder (Eds.) *Cognitive ergonomics, clinical assessment and computer-assisted learning: Computers in psychology* (pp. 87-203). Lisse, The Netherlands: Swets and Zeitlinger.

D'Esposito, M., Postle, B.R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain and Cognition, 41,* 66-86.

Dodge, K.A., & Rabiner, D.L. (2004). Returning to roots: on social information processing and moral development. *Child Development, 75,* 1003-1008.

D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y.T., Braley, G., Gueorguieva, R., & Krystal, J.H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology, 29,* 1558-1572.

Elliott, R., Fox, C.M., Beltyukova, S.A., Stone, G.E., Gunderson, J., & Zhang, X. (2006). Deconstructing therapy outcome measurement with Rasch analysis of a measure of general clinical distress: the Symptom Checklist-90-Revised. *Psychological Assessment, 18,* 359-372.

European Monitoring Centre for Drugs and Drug Addiction (2009). *The state of the drugs problem in Europe: Annual report*. http://www.emcdda.europa.eu/publications/annual-report/2009

Everitt, B.J., Belin, D., Economidou, D., Pelloux, Y., Dalley, J.W., & Robbins, T.W. (2008). Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 363,* 3125-3135.

Fergusson, D.M., & Boden, J.M. (2008). Cannabis use and later life outcomes. *Addiction, 103,* 969-976.

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2007). Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: Results of a 25-year longitudinal study. *Drug and Alcohol Dependence, 88,* 14-26.

Fergusson, D.M., Horwood, L.J., & Swain-Campbell, N. (2002). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction, 97,* 1123-1135.

Fernández-Serrano, M.J., Lozano, O., Pérez-Garcia, M., & Verdejo-Garcia, A. (2010). Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. *Drug and Alcohol Dependence, 109,* 57-64.

Fisk, J.E., & Montgomery, C. (2008). Real-world memory and executive processes in cannabis users and non-users. *Journal of Psychopharmacology, 22,* 727-736.

Germine, L.T., & Hooker, C.I. (2011). Face emotion recognition is related to individual differences in psychosis-proneness. *Psychological Medicine, 41,* 937-947.

Griffith-Lendering, M.F.H., Huijbregts, S.C.J., Huizink, A.C., Ormel, J., Verhulst, F.C., Vollebergh, W.A.M., & Swaab, H. (2011a). Social skills as precursors of cannabis use in young adolescents: A TRAILS-study. *Journal of Clinical Child and Adolescent Psychology, 40,* 706-714.

Griffith-Lendering, M.F.H., Huijbregts, S.C.J., Mooijaart, A., Vollebergh, W.A.M., & Swaab, H. (2011b). Cannabis use and development of externalizing and internalizing behavior problems in early adolescence: A TRAILS-study. *Drug and Alcohol Dependence, 116,* 11-17.

Griffith-Lendering, M.F.H., Huijbregts, S.C.J., Vollebergh, W.A.M., & Swaab, H. (2012). Motivational and cognitive inhibitory control in recreational cannabis users. *Journal of Clinical and Experimental Neuropsychology, 34,* 688-697.

Griffith-Lendering, M.F.H., Wigman, J.T.W., Prince van Leeuwen, A., Huijbregts, S.C.J., Huizink, A.C., Ormel, J., Verhulst, F.C., van Os, J., Swaab, H., & Vollebergh, W.A.M. Cannabis use and vulnerability for psychosis in early adolescence: a TRAILS Study. *Addiction, in press*.

Gruber, S.A., Rogowska, J., & Yurgelun-Todd, D.A. (2009). Altered affective response in marijuana smokers: an fMRI study. *Drug and Alcohol Dependence, 105,* 139-153.

Henquet, C., Di Forti, M., Morrison, P., Kuepper, R., & Murray, R.M. (2008). Gene-environment interplay between cannabis and psychosis. *Schizophrenia Bulletin, 34,* 1111-1121.

Huijbregts, S., Jahja, R., De Sonnneville, L., De Breij, S., & Swaab-Barneveld, H. (2010). Social information processing in children and adolescents with Neurofibromatosis Type 1. *Developmental Medicine and Child Neurology, 52,* 620-625.

Huizink, A.C., Ferdinand, R.F., Ormel, J., & Verhulst, F.C. (2006). Hypothalamic-pituitary-adrenal axis activity and early onset of cannabis use. *Addiction, 101,* 1581-1588.

Kalivas, P.W., & Volkow, N.D. (2005). The neural basis of addiction: A pathology of motivation and choice. *American Journal of Psychiatry, 162,* 1403-1413.

Kelleher, L.M., Stough, C., Sergejew, A.A., & Rolfe, T. (2004). The effects of cannabis on information-processing speed. *Addictive Behaviors, 29,* 1213-1219.

Kohler, C.G., Walker, J.B., Martin, E.A., Healey, K.M., & Moberg, P.J. (2010). Facial emotion perception in schizophrenia: a meta-analytic review. *Schizophrenia Bulletin, 36,* 1009-1019.

Lynskey, M., & Hall, W. (2000). The effects of adolescent cannabis use on educational attainment: A review. *Addiction, 95,* 1621-1630.

Marsh, A.A., & Blair, R.J. (2008). Deficits in facial affect recognition among antisocial populations: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 32,* 454-465.

Monshouwer, K., Van Dorsselaer, S., Verdurmen, J., Ter Bogt, T., De Graaf, R., & Vollebergh, W. (2006). Cannabis use and mental health in secondary school children. Findings from a Dutch survey. *British Journal of Psychiatry, 188,* 148-153.

Moore, T.H.M., Zammit, S., Ligford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet, 370,* 319-328.

Morrison, P.D., & Murray, R.M. (2009). From real-world events to psychosis: the emerging neuropharmacology of delusions. *Schizophrenia Bulletin, 35,* 668-674.

Nigg, J. (2000). On inhibition/disinhibition in developmental psychopathology: view from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin, 126,* 220-246.

Ochsner, K.M. (2008). The social-emotional processing stream: five core constructs and their translational potential for schizophrenia and beyond. *Biological Psychiatry, 64,* 48-61.

Olsen, L.R., Mortensen, E.L., & Bech, P. (2004). The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample. *Acta Psychiatrica Scandinavica, 110,* 330-350.

Patton, G.C., Coffey, C., Carlin, J. B., Degenhardt, L., Lynskey, M., & Hall, W. (2002). Cannabis use and mental health in young people: Cohort study. *British Medical Journal, 325,* 1195-1198.

Pettit G.S., & Mize J. (2007). Social-cognitive processes in the development of antisocial and violent behavior. In: D.J. Flannery, A.T. Vazsonyi, & I.D. Waldman (Eds.) *The Cambridge Handbook of Violent Behavior and Aggression* (pp. 322-343). Cambridge, MA: Cambridge University Press.

Phan, K.L., Angstadt, M., Golden, J., Onyewuenyi, I., Popovska, A., & De Wit, H. (2008). Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. *Journal of Neuroscience, 28,* 2313-2319.

Platt, B., Kamboj, S., Morgan, C.J., & Curran, H.V. (2010). Processing dynamic facial affect in frequent cannabis-users: evidence of deficits in the speed of identifying emotional expressions. *Drug and Alcohol Dependence, 112,* 27-32.

Pope, H.G., Gruber, A.J., Hudson, J.I., Huestis, M. A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry, 58,* 909-915.

Rey, J.M., Sawyer, M.G., Raphael, B., Patton, G.C., & Lynskey, M. (2002). Mental health of teenagers who use cannabis - results of an Australian survey. *British Journal of Psychiatry, 180,* 216-221.

Rössler, W., Vetter, S., Müller, M., Gallo, W.T., Haker, H., Kawohl, W., Lupi, G., & Ajdacic-Gross, V. (2011). Risk factors at the low end of the psychosis continuum: much the same as at the upper end? *Psychiatry Research, 189,* 77-81.

Serra, M., Althaus, M., de Sonneville, L.M., Stant, A.D., Jackson, A.E., & Minderaa, R.B. (2003). Face recognition in children with a pervasive developmental disorder not otherwise specified. *Journal of Autism and Developmental Disorders, 33,* 303-317.

Solowij, N. (1998). *Cannabis and cognitive functioning.* Cambridge, UK: Cambridge University Press,.

Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., Vendetti, , & Marijuana Treatment Project Research Group (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *Journal of the American Medical Association, 287,* 1123-1131.

Stacy, A.W., & Wiers, R.W. (2010). Implicit cognition and addiction: A tool for explaining paradoxical behavior. *Annual Review of Clinical Psychology, 6,* 551-575.

Stefanis, N.C., Hanssen, M., Smirnis, N.K., Avramopoulos, D.A., Evdokimidis, I.K., Stefanis, C.N., Verdoux, H., & Van Os, J. (2002). Evidence that the three dimensions of psychosis have a distribution in the general population. *Psychological Medicine, 32,* 347-358.

Substance Abuse and Mental Health Services Administration (2008). *Results from the 2007 National Survey on Drug Use and Health: National Findings.* Rockville, MD.

Verdejo-Garcia, A., Lawrence, A.J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews, 32,* 777-810.

Whitlow, C.T., Liguori, A., Livengood, L.B., Hart, S.L., Mussat-Whitlow, B.J., Lamborn, C.M., Laurienti, P.J., & Porrino, L.J. (2004). Long-term heavy marijuana users make costly decisions on a gambling task. *Drug and Alcohol Dependence, 76,* 107-111.

Yacubian, J., & Büchel, C. (2009). The genetic basis of individual differences in reward processing and the link to addictive behavior and social cognition. *Neuroscience, 164,* 55-71.

Yucel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., & Lubman, D.I. (2008). Regional brain abnormalities associated with long-term heavy cannabis use. *Archives of General Psychiatry, 65,* 694-701.

7. General discussion

Discussion

Summary and Integration of main results

Cannabis use and mental health

In general, our studies confirm that cannabis use is related to different mental health problems. Firstly, we focused on the prospective relationship between cannabis and both internalizing and externalizing behaviour problems. Results showed that cannabis use during adolescence was associated with the risk for externalizing behaviour. More specifically, after controlling for potentially confounding factors, including the use of other substances, path analyses showed that level of externalizing problems (measured at age 11 and 13) predicted the risk for cannabis use a few years later (measured at age 13 and 16, respectively). Cannabis use did not predict later externalizing behaviour. These findings supported the so called 'self-medication' hypothesis, where mental health problems precede the use of cannabis (Khantzian , 1985). We also studied cannabis use and its relation to internalizing behaviour problems. Results showed however that internalizing problems were unrelated to cannabis use.

The next focus was on the prospective relationship of vulnerability for psychosis and cannabis use during adolescence. After controlling for potentially confounding factors, symptoms indicative of the risk for psychosis at age 13 and 16 predicted cannabis use at age 16 and 19, respectively. Although our earlier study indicated that externalizing behaviour did precede cannabis use, but did not increase following use of cannabis, vulnerability for psychosis followed use of cannabis (at age 16), therefore allowing the conclusion that cannabis also predicted mental health problems (i.e. psychosis vulnerability at age 19). Hereby, evidence was provided not only for the self-medication hypothesis (as for externalizing behaviour), but also for the damage hypothesis, which suggests that cannabis use induces neurobiological changes leading to different forms of psychopathology (Brook, Cohen & Brook, 1998; Kandel, Yamaguchi & Chen, 1992; Moore et al., 2007).

Both studies described above provided evidence for the self-medication hypothesis, where behaviour problems (externalizing behaviour problems and psychosis

vulnerability) preceded cannabis use during adolescence. Previous evidence supporting the self-medication hypothesis stems from clinical observations of patients suffering from psychiatric disorders (e.g. Klein et al., 1994; Warner et al., 1994). Here, those suffering from psychiatric disorders tend to self-medicate (or sooth) the associated psychiatric distress by using cannabis. Indeed, it has been hypothesized that those suffering from psychosis symptoms use cannabis to improve their mood or control their feelings, to improve sleep, and reduce anxiety and agitation (Schofield et al., 2006). However, there are also studies that indicate that individuals with symptoms of psychosis use cannabis for reasons similar to those of the general population, i.e. 'to get high', relax and have fun (Kolliakou et al., 2001). This may be particularly plausible in the present study sample, as it consists of a group of adolescents drawn from the general population. In the case of externalizing behaviour problems, previous studies have also shown that problem behaviour precedes cannabis use (Fergusson et al., 2007; King et al., 2004; Pederson et al., 2001). Possibly here, those suffering from externalizing behaviour problems use cannabis to get rid of anger and hostile feelings. Alternatively, adolescents with externalizing behaviour problems are likely to show sensation seeking behaviour, which may be expressed in a greater tendency to use substances (Huizink et al., 2006; Marsman et al., 2008; Raine, 1996).

In addition to evidence for the self-medication hypothesis, the present study also provided evidence for the damage hypothesis, where the use of cannabis leads to the development of various mental health problems, although this was only observed for vulnerability to psychosis. This result corroborated findings from earlier studies, which also showed cannabis use to precede psychosis (Ferdinand, 2005; Fergusson et al., 2003; Kuepper et al., 2011; Moore et al., 2007), and also appears to be in line with neurobiological findings indicating relatively specific effects of delta-9-tetra-hydrocannabinol (Δ^9-THC), the main psycho-active ingredient of cannabis, on systems/brain networks involved in psychosis/schizophrenia. Thus, a bidirectional relationship was observed between cannabis use and vulnerability for psychosis during adolescence. Interestingly, when cannabis use preceded psychosis vulnerability, this became apparent during late adolescence, which might indicate stronger damaging effects of cannabis when it has been used over a longer period of time. It can however not be ruled out that the developmental trajectory of psychosis

plays an important role in this context. Psychosis usually becomes evident during young adulthood, which would mean that predictors of psychosis, including cannabis use, have a greater amount of phenotypic variability to predict at later ages. Although this could also be true for the proxy variables used here to represent psychosis vulnerability, i.e. social, attention, and thought problems, it seems likely that these have a greater amount of phenotypic variability at earlier ages. Future research should address the "cascading" effect for cannabis use and psychosis vulnerability in more detail, also taking into consideration differential susceptibility to cannabis exposure based on genetic and/or environmental vulnerability.

This relates to the vulnerability hypothesis, which states that the cause and effect relationship of cannabis use and mental health problems might be moderated by particular forms of vulnerability, i.e. biological, personal or familial factors that increase chances of both substance use and mental health problems (Caspi et al., 2005; Henquet et al., 2005; Miller et al., 2001; Verdoux et al., 2003). Such factors could also render individuals more vulnerable to the effects of cannabis, which, subsequently, might increase chances to develop not only the types of mental health problems discussed above, but also substance abuse and substance dependence (Hicks et al., 2011; Kendler et al., 2003). Preliminary evidence from one of the smaller samples supported the vulnerability hypothesis (see section "Cannabis Use and Cognitive Functioning").

In the studies on temporal order of cannabis use and different mental health problems, we have controlled for several well-known confounding factors (e.g. use of other substances, parental psychopathology), when analysing associations between cannabis use and mental health problems, thereby largely ruling out the so called 'shared causes hypothesis'. This hypothesis argues that the linkage between cannabis use and mental health problems is largely non-causal and may be the result of several factors associated with the use of cannabis and mental health problems, such as disadvantaged background and difficult childhood circumstances (Fergusson & Horwood, 1997; Fergusson, Horwood & Swain-Cambell, 2002a). However, according to Hawkins, Catalano & Miller's 1992 and Petraitis, Flay & Miller's 1995 risk factor taxonomies, confounders can be categorized into (1) socio-environmental variables, including gender and SES; (2) substance-related variables, including the use of alcohol and tobacco; (3) intrapersonal variables, including mental health problems and (4) interpersonal variables, including family functioning, and not having been

brought up by both parents (Von Sydow et al., 2002). As we could not incorporate all possible confounders (from the different categories) of cannabis – mental health associations (e.g. family functioning, relationship with mother, drug-using peers/ family), we cannot completely rule out "shared causes". Future research could address this issue by providing a more comprehensive study of potential confounders, although it should be noted that it appears impossible to include all possible factors related to both substance use and mental health problems.

Cannabis use and Social Functioning

The second aim of this dissertation was to determine the influence of difficulties in social skills as possible risk factors for cannabis use, early initiation age of cannabis use and high frequency of use during adolescence. Mental health problems are often characterized or aggravated by problems in social skills (Fergusson et al., 2002; Tarbox & Pogue-Geile, 2008). Transitions into addiction or problematic substance use do not only occur amongst those with (obvious) mental health problems. To learn more about the relation between social skills and the risk for cannabis use, we studied cannabis correlates in a non-clinical cohort of adolescents, providing a particularly suitable context for investigating social skills in relation to cannabis use. There may be much more variation in social skills in this population than in a population characterized by mental health problems. We hypothesized that associations between cannabis use and social skills may not always be straightforward in that poor social skills would be associated with higher chances of (early initiation of) substance use (which would correspond with the self-medication hypothesis for mental health problems). After all, many adolescents consider cannabis a 'social drug', which is used mainly with friends, to 'bond' and to 'hang out' (Lee et al., 2007). Therefore, we tested whether different social skills differentially predicted cannabis use. Results showed associations between social parameters and cannabis use, where both cooperation and assertive behaviours at age 11 were related to cannabis use at age 16. More specifically, higher levels of assertive behaviour were associated with higher levels of cannabis use, whereas lower levels of cooperative behaviour at age 11 predicted higher levels of cannabis use at age 16. In other words, cannabis users were less cooperative, as expressed in, for example, complying with rules and directions, than non-users but, on the other hand, they were more assertive than non-users, which

might indicate that young adolescents who more readily engage in relations with peers and others, are also more likely to use cannabis. There were no associations with the social skill "self-control", and specific predictions of early versus late onset of use or frequency of use could not be made either. Previous studies however have found associations between cannabis use and self-control (Pokhrel et al., 2007; Sussman et al., 2003). Possibly, different operationalizations of self-control could explain differences in study results. Whereas in the present study, self-control was defined as 'behaviours that emerge in conflict and non-conflict situations', and was rated by the participant's teachers (Gresham, 1990), others have defined this type of behaviour as 'one's tendency to act without thinking' and the behaviour was often judged or scored by, for example, experimenters or parents (Tarter, 1988). A lack of (involvement in) conflict situations in the classroom may have resulted in less variability in self-control scores, and subsequently a lack of associations with cannabis use. Indirect support for this suggestive explanation stems from our finding of significant associations between cannabis use and impulsive behaviour in daily life (chapter 5).

The concept of social skills or functioning in relation to substance use appears very interesting, but social functioning should be operationalized in different ways, and, as our results show, no unidirectional effects may be expected. The finding that cooperative behaviour reduced the chances of adolescents using cannabis, whereas assertive behaviour (also usually considered a social strength) increased the chances, emphasized that different aspects of social functioning may have differential relations with substance use.

Cannabis use and Cognitive Functioning

In previous sections we disucssed our findings indicating that when specific mental health problems (also at subclinical levels) were present, or when specific social skills had not developed optimally, chances of (initiating) drug use were higher. Evidence was also provided to suggest interrelations between cannabis use and poor social skills and mental health problems on the one hand, and cognitive difficulties on the other. Pre-existing mental health problems and social skills may, like particular cognitive weaknesses (e.g. in areas necessary for behaviour regulation) either predispose towards tendencies to take drugs, or serve as moderating factors in

associations between cannabis use and (further) mental health or behaviour problems. Mental health problems (including addiction and substance abuse) and poor social skills are often found to be associated to particular cognitive dysfunctions, suggesting specific underlying neurocognitive mechanisms that can help explain associations between substance use and behaviour. Consequently, development of cognitive abilities is frequently targeted in treatment of mental health problems or training of social skills. They are often found to be required in order for treatment or training programs to be effective. Therefore, investigating possible cognitive difficulties among cannabis users is highly relevant.

Cannabis use (like use of many other substances) has been associated with many different cognitive weaknesses. Previous studies did not always opt for administration of neuropsychological tasks that addressed singular cognitive domains, which we consider necessary to disentangle different contributing elements. Therefore we attempted to select cognitive tasks with clearcut measurement potentials. We compared performance of cannabis users and non-users on tasks distinguishing the following functions: inhibition (with and without an motivational aspect) and social perception (with and without the element of recognizing emotions). 53 Cannabis-users (mean age of 22.6) and 48 non-users (mean age of 22.3) were compared on inhibitory control and impulsive behaviour. Results showed that cannabis users differed from non-users on motivational inhibition. Interestingly, cannabis users did not differ from non-users on inhibitory control without a motivational component. In addition, cannabis users reported higher levels of impulsive behaviour in daily life. This behaviour was related to motivational inhibitory control, but not to inhibitory control without the motivational component.

In our other study on cognitive abilities and cannabis use, 75 cannabis users (mean age 24.6 years) and 75 non-users (mean age 24.7 years) were compared with respect to performance on two different social perception tasks, one addressing the ability to recognize faces and the other addressing the ability to match facial emotions. The second task can be distinguished from the first as it requires emotion recognition and more working memory capacity. Also, cannabis users and non-users were compared on specific psychological problems. Results show that cannabis users experience more problems on the two social perception tasks and reported more psychological problems, i.e. more insufficiency of thoughts and actions, hostility, anxiety and psychoneuroticism. In addition, quality of social perception moderated associations

between cannabis use and psychological problems. Only cannabis users with relatively poor performance in the matching emotions-task showed significantly elevated levels of psychological problems. Non-users and cannabis-users with good social perception as measured by the matching emotions task did not. Moreover, the interactions were only observed when the matching emotions task was used as a measure for social perception, not when the face recognition task was used. Thus, specific weaknesses in emotion recognition (and possibly working memory) seem to play an important role (cf. Solowij & Battisti, 2008). Moreover, the effect was dose-dependent: psychological problems were particularly experienced by heavy cannabis users with relatively poor social perception as measured by the matching emotions task.

It may be concluded from the previous TRAILS studies into social and behavioural correlates of cannabis use that the presence of symptoms of (subclinical) psychopathology, including vulnerability for psychosis and externalizing behaviour problems, may increase the risk of cannabis use. Cannabis use, in turn, may increase the risk of developing or deteriorating further (specific) mental health problems. Social functioning (regardless of the presence or absence of (subclinical) levels of psychopathology) also influences the chances that people will be inclined to use cannabis, although it should be taken into account that some aspects of social functioning increase chances of cannabis use, whereas others reduce these chances.

Whereas the previous studies on the TRAILS-sample described in this thesis focused on the temporal order of cannabis use and mental health problems, the last two studies investigated possible underlying mechanisms explaining behavioural difficulties. The study on social perception (chapter 6) could be regarded as supportive of the vulnerability hypothesis. Studies have shown that different biological or environmental factors moderate associations between cannabis use and mental health outcomes. However, rather than focusing on genetics, as a number of earlier studies have done (Caspi et al., 2005; Henquet et al., 2008, Gill et al., 2010; Rijsdijk et al., 2011), we focused on aspects of cognition (which are of course themselves influenced by genetic make-up and environmental factors) in order to examine the vulnerability hypothesis for cannabis use and psychological problems. Evidence was provided showing that (complex) social perception deficits significantly increased the chances

of psychological problems among heavy cannabis users. Future research on this issue would benefit from prospective designs, in order to find out whether (specific) cognitive weaknesses early in life predispose towards cannabis use and mental health problems later on, and to find out whether the combination of cognitive vulnerability and cannabis use disproportionately increase the risk for developing mental health problems.

Critical reflections and directions for future research

Some critical notes should be made when interpreting results of the present thesis. Throughout all studies (chapter 2-6) we made use of self-reported data to determine cannabis use (tobacco and alcohol use were also self-reported). Questions concerning initiation age and frequency of use might have led to socially desirable answers, especially for young adolescents. Although this may have been the case, there are several studies that have concluded that self-reporting of substance use is generally a valid method (e.g. Bushan et al., 2002). Also, cannabis use is generally condoned in the Netherlands, which possibly allows for more honest self-reports of cannabis use compared to studies in other countries with stricter cannabis policies. Data on mental health and behaviour (externalizing symptoms, internalizing behaviour, vulnerability for psychosis, social behaviour, impulsive behaviours) were also obtained from self-reports. Use of multiple informants would have been preferable (Offord et al., 1996).

One particular strength is the focus on temporal order of behavioural and social correlates of cannabis use within a large population based sample (n=2,230). Also, the starting point of TRAILS is early adolescence (Mean age T1: 11.1), hereby providing the opportunity to collect prospective data antedating initiation to cannabis in very early starters and to investigate multiple hypotheses on cannabis use and behaviour difficulties.

The focus on early adolescence is relevant for several different reasons. During adolescence, rapidly developing biological changes (puberty) and maturation processes take place. These developmental processes might make the human organism vulnerable for enduring effects of external influences such as exposure to cannabis (Court, 1998; Schneider 2008). Indeed, different studies have shown that cannabis use during early adolescence constitutes a risk factor for enduring negative

effects of cannabis use, including impaired reaction times (Ehrenreich et al. 1999), mental health problems and behaviour difficulties (Arsenault et al., 2002; Fergusson et al., 2002a, 2002b). Early onset delinquents, for example, not only show earlier onset of cannabis use, but also a much faster rate of increase in cannabis dependence symptoms (Lynskey et al., 2002). Thus, early adolescence seems to be characterized by a heightened risk for irreversible effects, and a heightened risk for more significant adverse outcomes as well.

A limitation of the series of studies presented in this thesis is that we were only able to select a limited amount of potential confounders to introduce to our analyses. Therefore, we may have missed a number of other factors that could also be important correlates of cannabis use and mental health problems during adolescence. For example, we have not investigated the issue of a possible heightened sensitivity for the effects of cannabis in individuals with a particular genetic make-up, or have done so only indirectly, based on the assumption that the genes of interest partly determine certain cognitive outcomes. Experimentation with cannabis use might be harmless for some, but quite harmful for other children, and patterns of cause and effect might differ accordingly. Children enter adolescence with different levels of inherited and acquired psychobiological vulnerability (or conversely, resilience) to mental disorder due to differences in a person's genetic make-up (Loehlin, 1992, Rutter et al., 1999). Although parental psychopathology may be seen as a clear marker for vulnerability in children, which we have controlled for in the present study, this does not directly investigate genetic make-up of their children.

A further recommendation for future research is to focus on a broader age span and longer follow-ups to investigate the relationships with mental health problems (including internalizing problems, externalizing behaviour and vulnerability for psychosis). There are several reasons for this. First of all, at the second measurement wave, the number of adolescents who used cannabis, but also the frequency of use, was relatively low. It is assumed that more adolescents will start using cannabis during later adolescence, around the age of 15 (Monshouwer et al., 2005). Also, the sample was quite young and had not been using cannabis for a long period of time, thereby possibly reducing the chances of finding support for the so called ‘damage hypothesis’ in relation to internalizing and externalizing behaviour problems. Studies providing evidence for damaging effects of cannabis observed these effects in young

adulthood (Fergusson et al., 2002; White et al., 1999). Possibly, such effects will also become evident in our sample at a later stage. Lastly, it can be assumed that some of those who started using at a young age, may start using it more frequently in late adolescence, which in turn forms an extra risk factor for the development of behaviour and cognitive deficits as well as addiction (Substance Use Disorders).

Another recommendation for future research is to include instruments measuring other aspects of social functioning as well, now that we have provided additional evidence for differential relations between different social skills and cannabis use. For example, in order to measure social functioning, we focused on three specific skills in relation to cannabis use. Examples of instruments which could be used in the future include the Scale for Interpersonal Behavior (Arrindell & van der Ende, 1985), to assess frequency and associated distress during social interaction, the Novotni Social Skills Checklist to assess a wider range of social skills, and the Youth Self Report (Achenbach, 1991; Verhulst and Achenbach, 1995) and the Strengths and Difficulties Questionnaire (Goodman, 1997) to assess social and peer problems next to social skills.

Clinical implications

The results of our studies may have implications for clinical and preventive practices. First and foremost, the present study has shown that prevention programs should take into consideration presenting information on associations between cannabis use and mental health problems, especially during adolescence. As described earlier, adolescence is a life phase characterized by brain maturation and growth, which might increase the risk of possible damaging effects of cannabis (Schneider et al., 2008). Prevention programs should also focus on certain vulnerable groups, such as adolescents suffering from psychosis symptoms or exhibiting externalizing behaviour problems. These individuals may tend to self-medicate by using cannabis, already during adolescence. Since these behavioural difficulties could further develop into clinical disorders with poor long-term outcomes, prevention programs should focus on these at-risk adolescents.

Considering social functioning in relation to cannabis in prevention programs, it should be considered to fine-tune the approach to different social skills, and not simply stimulate all positive social skills. Previous studies have shown different 'life skills' to be effective in prevention of cannabis use, including self-esteem (Tobler et al., 2000), focus on norms, commitment not to use and intention not to use (Cuijpers et al., 2002). Also, a 'social influence approach' seems effective in prevention, where the focus is, among others, on assertiveness (Donaldson et al., 1996; Cuijpers, 2002; Tobler et al., 2000). However, these assertive skills were mainly defined in the context of 'resistant skill training'; in other words, it seems effective to be 'assertive to say no to drugs'. Here, being assertive seems an effective preventive approach. The present study however, showed that being assertive in somewhat different contexts or situations may also serve as a risk factor of using cannabis. It may be concluded that adolescents need to show specific assertive behaviour, so it can operate as a protective factor in drug using behaviour. Also, the present study showed that prevention programs should stimulate cooperation, since higher levels of cooperation served as a protective factor in the prediction of cannabis use.

Lastly, substance use disorders have been associated with impaired decision-making and increased impulsive behaviour, which may be due to lack of motivational inhibitory control. This study showed that cannabis users also experience difficulties with social perception. Therefore, it may be considered to include training of social perception and motivational inhibitory skills in prevention and intervention programs. These aspects of cognition have not yet featured prominently in existing programs, which have focused on, for instance, management of negative thinking, problem solving skills and relaxation training. Further research is required to identify more comprehensively the range of (social) cognitive abilities that are impaired in cannabis users and may thus be targeted in prevention and intervention programs.

Conclusions

Given the five research questions of this study, we can conclude the following:

During early adolescence, there is no association between internalizing behaviour and cannabis use. There is an association between externalizing behaviour and cannabis use, where externalizing behaviour precedes cannabis use rather than the other way around. Secondly, during adolescence, there is an association between psychosis vulnerability and cannabis use, where cannabis use predicts psychosis vulnerability and vice versa, suggesting a bi-directional cascading association.

Thirdly, during early adolescence, the social skill "self-control" was (unexpectedly) unrelated to cannabis use. Cooperation and assertiveness are associated with cannabis use during this life phase, where higher levels of cooperation decrease the chance of using cannabis and higher levels of assertiveness increase the chance of using cannabis during early adolescence. Cooperation and assertiveness did not differentiate between early and late onset of cannabis use or predict frequency of use.

In addition, compared to non-users, cannabis users experience problems only in motivational inhibitory control, not in cognitive inhibitory control. Also, cannabis users experience problems in behavioural impulsivity, which is related to motivational inhibitory control.

Lastly, cannabis users have problems with social perception in comparison to non-using controls, particularly when these social perception skills involve emotion recognition. Also, heavy cannabis users experience significantly more psychological problems when they have relatively poor social perception skills.

Future research must determine whether the behavioural and cognitive concepts and constructs examined in this thesis in relation to cannabis use should be incorporated in prevention and intervention programs.

References

Achenbach, T.M., 1991. *Manual for the Youth Self-Report and 1991 Profile.* University of Vermont, Burlington.

Arrindell, W.A., & Van der Ende, J. (1985). Cross-sample invariance of the structure of self-reported distress and difficulty in assertiveness: Experience with the scale for interpersonal behaviour. *Advances in Behavior Research and Therapy, 7*, 205-243.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T.E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal, 325,* 1212–1213.

Brook, J.S., Cohen, P., & Brook, D.W. (1998). Longitudinal study of co-occurring psychiatric disorders and substance use. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*, 322–330.

Buchan, B.J., Dennis, M.L., Tims, F.M., Diamond, G.S., (2002). Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. *Addiction, 97*, 98–108.

Caspi, A., Moffit, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., & Craig, I.W. (2005). Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction. *Biological Psychiatry*, *57*, 1117 – 1127.

Court, J.M. et al. (1998). Cannabis and brain function. *Journal of Paediatric Child Health, 34,* 1-5.

Cuijpers, P. (2002). Effective ingredients of school-based drug prevention programs; A systematic review. *Addictive Behaviors, 27,* 1009-1023. ,

Donaldson, S. I., Sussman, S., MacKinnon, D. P., Severson, H. H., Glynn, T., Murray, D. M., & Stone, E. J. (1996). Drug abuse prevention programming; do we know what contents works? *American Behavioral Scientist, 39*, 868–883.

Ehrenreich, H., Rinn, T., Kunert, H. J., Moeller, M.R., Poser, W., Schilling, L., Gigerenzer, G., & Hoehe, M.R. (1999) Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology*, 142, 295 -301.

Ferdinand, R.F., Sondeijker, F., van der Ende, j., Selten, J., Huizink, A., & Verhulst, F.C. (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction, 100,* 612– 8.

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2006). Cannabis use and other drug use: testing the cannabis gateway hypothesis. *Addiction, 101*, 556-569.

Fergusson, D.M., & Horwood, L.J. (1997). Early onset cannabis use and psychosocial adjustment in young adults. *Addiction, (92)*, 279–296.

Fergusson, D.M., Horwood, L.J., & Swain-Campbell, N. (2002a). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction, 97,* 1123–1135.

Fergusson, D. M., Swain-Campbell, N. R., & Horwood, L. J. (2002b). Deviant peer affiliations, crime and substance use: a fixed effects regression analysis. *Journal of Abnormal Child Psychology, 30,* 419-430.

Fergusson, D.M., Horwood, L.J., & Swain-Campbell, N.R. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine,, 33,* 15-21.

Fergusson, D.M., Horwood, L.J., & Ridder, E.M. (2007). Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. *Drug and Alcohol Dependence, 88,* 14–26.

Gill, M., Donohoe, G., Corvin A. (2010) What have genomics ever done for the psychoses? *Psychological Medicine, 40*, 529-520.

Goodman, R. (1997). The Strengths and Difficulties Questionnaire: A Research Note. *Journal of Child Psychology and Psychiatry, 38,* 581-586.

Gresham, F. M., & Elliott, S. N. (1990). *Social Skills Rating System.* Circle Pines, MN: American Guidance Service.

Hawkins, J.D., Catalano, R.F. & Miller, J.Y. (1992). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. *Psychological Bulletin, 112,* 64 – 105.

Hicks, B.M., Schalet, B.D., Malone, S.M., Iacono, W.G., & McGue, M. (2011). Psychometric and Genetic Architecture of Substance Use Disorder. and Behavioral Disinhibition Measures for Gene Association Studies. *Behavior Genetics, 41,* 459-475.

Henquet, C., Di Forti, M., Morrison, P., Kuepper, R., Murray, R.M. (2008). Gene-Environment interplay between cannabis and psychosis. *Schizophrenia Bulletin, 34,* 1111-21.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Lieb, H.U., & van Os., J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *British Medical Journal, 330*, 11 -14.

Huisman, M., Oldehinkel, A.J., de Winter, A., Minderaa, R.B., de Bildt, A., Huizink, A.C., Verhulst, F.C., Ormel, J., 2008. Cohort profile: the Dutch 'tracking adolescents' individual lives survey; trails. Int. J. Epidemiol. 37, 1227–1235.

Huizink, A.C., Ferdinand, R.F., Ormel, J., & Verhulst, F.C. (2006). Hypothalamicpituitaryadrenal axis activity and early onset of cannabis use. *Addiction, 101,* 1581–1588.

Kandel, D.B., Yamaguchi, K., & Chen, K. (1992). Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *Journal of Studies on Alcohol, 53*, 447–457.

Kendler, K.S., Prescott, C.A., Myers, J. & Neale, M.C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry, 60,* 929–937.

Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders – focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142*, 1259–1264.

King, S.M., Iacono, W.G., & Mcgue, M. (2004). Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction, 99,* 1548–1559.

Klein, D. & Riso, L. (1994). *Psychiatric disorders: problems of boundaries and comorbidity.* In: Costello, G., (Ed.). Basic Issues in Psychopathology, New York: Guilford Press, pp. 19–66.

Kolliakou, A., Joseph, C., Ismall, K., Atakan, Z., & Murray, R.M. (2011). Why do patients with psychosis use cannabis and are they ready to change their use? *International Journal of Developmental Neuroscience, 29*, 335-346.

Kuepper, R., van Os, J., Lieb, R., Wittchen, H., & Höfler, M., (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *British Medical Journal, 342*, d738.

Lee, C.M., Neighbors, C., & Woods, B.A. (2007). Marijuana motives: Young adults' reasons for using marijuana. *Addictive behaviors, 32*, 1384-1394.

Loehlin J.C. (1992). *Genes and Environment in Personality Development*. Newbury Park, CA: Sage.

Lynskey, M.T., Heath, A.C., Nelson, E.C., Bucholz, K.K., Madden, P.A.F., Slustke, W.S., Statham, D.J., &Martin, N.G. (2002). Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychological Medicine, 32,* 195–207.

Marsman, R., Swinkels, S.H.N., Rosmalen, J.G.M., Oldehinkel, A.J., Ormel, J., & Buitelaar, J.K. (2008). HPA-axis activity and externalizing behaviour problems in early adolescents from the general population: the role of comorbidity and gender – the TRAILS study. *Psychoneuroendocrinology, 33*, 789–798.

Miller, P., Lawrie, S. M., Hodges, A., Clafferty, R., Cosway, R., & Johnstone, E.C. (2001) Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*, 36, 338 -342.

Monshouwer, K., Smit, F., Graaf, R., Van Os, J., Volleberg, W. (2005). First cannabis use: does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on Substance Use. *Addiction, 100,* 963-970.

Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet, 370,* 319–328.

Offord, D.R., Boyle, M.H., Racine, Y., Szatmari, P., Fleming, J.E., Sanford, M., Lipman, E.L., 1996. Integrating assessment data from multiple informants. J. Am. Acad. Child Adolesc. Psychiatry 35, 1078–1085.

Pedersen, W., Mastekaasa, A., & Wichstrom, L. (2001). Conduct problems and early cannabis initiation: a longitudinal study of gender differences. *Addiction, 96,* 415–431.

Petraitis, J., Flay, B.R., & Miller, T.Q. (1995). Reviewing theories of adolescent substance use: organizing pieces in the puzzle. *Psychological Bulletin, 117*, 67 – 86.

Pokhrel, P., Sussman, S., Rohrbach, L. A., & Sun, P. (2007). Prospective associations of social self-control with drug use among youth from regular and alternative high schools. *Substance Abuse and Treatment Prevention Policy, 2,* 22.

Raine, A., (1996). Autonomic nervous system factors underlying disinhibited, antisocial, and violent behaviour. Biosocial perspectives and treatment implications. *Annals of the New York Academic Sciences, 794*, 46–59.

Rijsdijk F.V., Gottesman I.I., McGuffin, P., Cardno, A.G. (2011). Heritability estimates for psychotic symptom dimensions in twins with psychotic disorders. *American Journal of Medical Genetics part B: Neuropsychiatric Genetics, 156B*, 89-98.

Rutter, M., Silberg, J., O'Conner, T., & Simonoff, E. (1999). Genetics and child psychiatry: II empirical research findings. *Journal of Child Psychology and Psychiatry, 40,* 19–55.

Schneider, M. (2008). Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addiction Biology, 13*, 253-263.

Solowij, N., & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: a review. *Current drug abuse reviews, 1,* 81-98.

Sussman, S., McCuller, W. J., & Dent, C. W. (2003). The associations of social self-control, personality disorders, and demographics with drug use among high-risk youth. *Addictive Behaviors, 28,* 1159–1166.

Tarbox, S.I., & Pogue- Geile, M.F. (2008). Development of social functioning in preschizophrenia children and adolescents: A systematic review. *Psychological Bulletin, 134,* 561 – 583.

Tarter, R. E. (1988). Are there inherited behavioral traits that predispose to substance abuse? *Journal of Consulting and Clinical Psychology, 56,* 189–196.

Tobler, N. S., Roona, M. R., Ochshorn, P., Marshall, D. G., Streke, A. V., & Stackpole, K. M. (2000). Schoolbased adolescent drug prevention programs: 1998 meta-analysis. Journal of Primary Prevention, 20, 275–336.

Verdoux, H., Gindre, C., Sorbara, F., Tournier, M., & Swendsen, J.D. (2003). *Psychological Medicine, 33*, 23-32.

Verhulst, F.C., & Achenbach, T.M. (1995). Empirically based assessment and taxonomy of psychopathology – cross-cultural applications – a review. *European Child and Adolescent Psychiatry, 4,* 61–76.

Von Sydow, K, Lieb, R., Pfister, H., Höfler, M., Wittchen, H. (2002). What predicts insicent use of cannabis and progression to abuse and dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug and Alcohol Dependence, 68*, 49 – 64.

Warner, R., Taylor, D. & Wright, J. (1994) Substance use among the mentally ill: prevalence, reasons for use and effects on illness. *American Journal of Orthopsychiatry, 74*, 30–39.

White, H.R., Loeber, R., Stouthamer-Loeber, M., & Farrington, D.P. (1999). Developmental associations between substance use and violence. *Developmental Psychopathology, 11*, 785–803.

de Winter, A., Oldehinkel, A.J., Veenstra, R., Brunnekreef, J.A., Verhulst, F.C., Ormel, J., 2005. Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. *Eur. J. Epidemiol. 20,* 173–181.

Acknowledgements

Studies described in chapter 2, 3 and 4 are part of the TRacking Adolescents' Individual Lives Survey (TRAILS). Participating centers of TRAILS include various departments of the University Medical Center and University of Groningen; the Erasmus University Medical Center, Rotterdam; the University of Utrecht; the Radboud Medical Center, Nijmegen; and the Parnassia Bavo group, all in the Netherlands. TRAILS has been financially supported by various grants from the Dutch Organization for Scientific Research NWO (Medical Research Council program grant GB-MW 940-38-011; ZonMW Brainpower grant 100-001-004; ZonMW Risk Behaviour and Dependence grants 60-60600-98-018 and 60-60600-97-118; ZonMW Culture and Health grant 261-98-710; Social Sciences Council medium-sized investment grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project grants GB-MaGW 457-03-018, GB-MaGW 452-04-314, and GB-MaGW 452-06-004; NWO large-sized investment grant 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013); the Sophia Foundation for Medical Research (projects 301 and 393), the Dutch Ministry of Justice (WODC), the European Science Foundation (EuroSTRESS project FP-006), and the participating universities. We are grateful to all adolescents, their parents and teachers who participated in this research and to everyone who worked on this project and made it possible.

We would like to thank Prof. Dr. Pieter Kroonenberg for his valuable advice concerning statistical analyses in Chapter 3.

Summary

Cannabis use has been associated with a wide range of mental health problems, including psychotic disorder, aggressive and delinquent behaviour (externalizing behaviour problems), depression and anxiety (internalizing behaviour problems). To a lesser extent, cannabis use has been associated with specific social skills deficits, including low social self-control, self-esteem problems and lower social competence. Also, there are reports of cannabis users experiencing cognitive difficulties, including memory problems, slower processing speed, specific deficits in complex planning and other executive dysfunctions.

For the present thesis, the temporal order of associations between cannabis use and internalizing and externalzing behaviour as well as psychosis vulnerability was investigated. Furthermore, interrelations between possible cognitive dysfunctions and behavioural and mental health problems among cannabis users were examined. Also, the cognitive and social profiles of cannabis users were examined in more detail. Different hypotheses have been proposed in order to explain associations between cannabis use and mental health problems or behaviour difficulties. The damage hypothesis proposes that cannabis use precedes behavioural difficulties. Conversely, the self-medication hypothesis proposes that behavioural difficulties precede cannabis use. The shared causes hypothesis argues that the linkage between cannabis use and mental health problems is largely non-causal and may be explained by other factors associated with the use of cannabis and mental health problems. Finally, the vulnerability hypothesis states that the linkage between cannabis use and mental health problems might be particularly evident in individuals who are, due to their biological, personal or familial make-up, particularly sensitive to the damaging effects of cannabis or more likely to use drugs for their soothing effects.

The first aim was to determine the temporal order of cannabis use and mental health problems during (early) adolescence. Secondly, we focused on social parameters in association with cannabis use. The third aim was to investigate several cognitive correlates of cannabis use, namely social perception and inhibitory control, thereby specifically focusing on their contribution to in cannabis-behaviour associations.

The five main research questions of this thesis were outlined in the general introduction (**chapter 1**):

1. Is there a relationship between cannabis use and both internalizing and externalizing behaviour problems in early adolescence? And if so, what is the temporal order of these relationships?
2. Is there a relationship between cannabis use and vulnerability for psychosis, as measured by social problems, thought problems and attentional problems, in adolescence? And if so, what is the temporal order of this relationship?
3. Are the social skills cooperation, assertiveness and self-control precursors of cannabis use during early adolescence? Specifically, are these social skills precursors of (early) cannabis initiation and the frequency of use?
4. Do cannabis users experience problems with motivational inhibitory control, cognitive inhibitory control or both? Also, do cannabis users experience problems in behavioural impulsivity, and is this related to motivational and/or cognitive inhibitory control?
5. Do cannabis users experience problems with respect to social perception? Also, are cannabis users with problems in social perception more likely to experience psychological problems?

Research questions 1-3 were investigated using data from a large prospective cohort study of Dutch adolescents named TRAILS; Tracking Adolescents Individual Lives Survey. With respect to temporal associations the following results were obtained (described in **chapter 2** and **chapter 3**). Cannabis use was not related to internalizing behaviour problems. In contrast, externalizing behaviour problems were related to cannabis use, where externalizing problems (measured at age 11 and 13) predicted cannabis use (measured at age 13 and 16, respectively). Cannabis use did not predict externalizing behaviour. These findings supported the self-medication hypothesis, where mental health issues precede cannabis use. Vulnerability for psychosis at age 13 and 16 predicted cannabis use at age 16 and 19, respectively. An important difference with the results of the analyses of cannabis-externalizing behaviour associations was that cannabis use (at age 16) also predicted mental health problems (i.e. vulnerability for psychosis at age 19). Hereby, evidence was provided for both the self-medication hypothesis and the damage hypothesis, which suggests that

cannabis use induces neurobiological changes leading to different forms of psychopathology.

With respect to research question #3, on whether social skills could predict (different aspects of) cannabis use, results showed that both cooperation and assertiveness could predict cannabis use, although in different ways. Low levels of cooperative behaviour at age 11 were associated with cannabis use at age 16, whereas higher assertiveness at age 11 predicted cannabis use at age 16 (**chapter 4**). Cooperative and assertive behaviour did not discriminate between early and late onset of cannabis use or predict frequency of cannabis use, and, unexpectedly, self-control was unrelated to cannabis use.

Research questions 4 and 5 were addressed using data from two samples of (mostly) undergraduate students. Cannabis users differed from non-users with respect to motivational inhibition, but not with respect to inhibitory control without a motivational component. Also, cannabis users reported higher levels of impulsive behaviour in daily life. This behaviour was related to motivational control, but not to inhibitory control without the motivational component (see **chapter 5)**. Cannabis users also performed relatively poorly when social perception was required (**chapter 6**). This was observed in two tasks, one involving the ability to recognize faces and the other involving the ability to recognize and match facial emotions. Differences compared with non-using controls were particularly evident for the task involving emotion recognition. Also, cannabis users reported more psychological problems, namely more insufficiency of thoughts and actions, hostility, anxiety and psychoneuroticism. Quality of social perception as measured by the task involving emotion recognition, moderated associations between cannabis use and psychological problems, in that only relatively heavy users with relatively poor social perception reported significantly elevated levels of psychological problems.

Whereas findings reported in chapters 2 and 3 provided (partial) evidence for the self-medication hypothesis and the damage hypothesis, the findings regarding social perception provide some evidence supporting the vulnerability hypothesis. No evidence was found for the shared-causes hypothesis, although it should be noted that we were necessarily limited to a relevant but selective number of potentially confounding variables. These and other limitations as well as possible implications for prevention and intervention programs are discussed in **chapter 7**.

Samenvatting

Het gebruik van cannabis is gerelateerd aan een breed scala van psychische problemen, waaronder psychotische stoornissen, agressief en delinquent gedrag, depressie en angst. Ook zijn er verbanden aangetoond tussen cannabisgebruik en problemen met specifieke sociale vaardigheden, zoals sociale zelfbeheersing en gevoel van eigenwaarde. Daarnaast is er bewijs dat cannabisgebruikers vaker problemen ervaren met bepaalde cognitieve vaardigheden zoals verschillende geheugenprocessen, informatieverwerkingssnelheid en executieve functies.

Voor het huidige onderzoek zijn deze verbanden opnieuw onderzocht, maar zijn er accenten geplaatst op tot nog toe onderbelichte kanten van die relaties. Zo is geprobeerd verbanden te leggen tussen mogelijke cognitieve problemen enerzijds en (mogelijke) gedrags- en psychische problematiek anderzijds. Ook werden aspecten van het cognitief en sociaal functioneren belicht die tot nog toe weinig zijn onderzocht, met een nadruk op mogelijk differentiële verbanden met cannabisgebruik. Een verder belangrijk onderzoeksdoel was het vaststellen van de "volgorde" van de associatie tussen cannabisgebruik en psychische- en gedragsproblemen. Er zijn verschillende hypothesen geformuleerd ten aanzien van de temporele volgorde van cannabisgebruik en psychische – en gedragsproblematiek. Zo stelt de '*damage hypothese'* dat cannabisgebruik voorafgaat aan psychische problemen. Omgekeerd stelt de '*self-medication hypothese'* dat psychische problemen voorafgaan aan cannabisgebruik. De '*shared causes hypothese'* stelt dat het verband tussen cannabisgebruik en psychische problemen grotendeels kan worden verklaard door factoren die zowel aan cannabisgebruik als aan psychische problemen zijn gerelateerd. Als laatste stelt de '*vulnerability hypothese'* dat de relatie tussen cannabisgebruik en psychische problemen met name aanwezig is bij personen die, vanwege hun biologische, persoonlijke of familiare achtergrond of omgeving, gevoelig zijn voor de schadelijke effecten van cannabis (als bij de *damage hypothese*) of mogelijk een hogere kans hebben om cannabis te gaan gebruiken voor de kalmerende of geruststellende effecten (als bij de *self-medication hypothese*).

De vijf belangrijkste onderzoeksvragen zijn beschreven in de algemene introductie (**Hoofdstuk 1**):

1. Is er een relatie tussen cannabisgebruik en zowel internaliserende als externaliserende gedragsproblemen tijdens de vroege adolescentie? En zo ja, wat is de temporele volgorde van deze relatie?
2. Is er een relatie tussen cannabisgebruik en kwetsbaarheid voor psychose, gemeten aan de hand van sociale problemen, denkproblemen en aandachtsproblemen, tijdens de adolescentie? En zo ja, wat is de temporele volgorde van deze relatie?
3. Voorspellen de sociale vaardigheden coöperatief gedrag, assertiviteit en zelfbeheersing cannabisgebruik tijdens de vroege adolescentie? En zijn deze sociale vaardigheden ook voorspellers van (vroege) initiatie van cannabis en frequentie van cannabisgebruik?
4. Ondervinden cannabisgebruikers problemen met motivationele inhibitie, cognitieve inhibitie of beide? En zijn deze inhibitievormen gerelateerd aan impulsiviteitsproblemen in het dagelijks leven?
5. Ondervinden cannabisgebruikers problemen met sociale perceptie? En, ervaren cannabisgebruikers met sociale perceptie-problemen vaker psychische problematiek?

Onderzoeksvragen 1-2-3 werden beantwoord met behulp van gegevens uit een groot, prospectief, algemeen bevolkingsonderzoek onder Nederlandse jongeren, genaamd TRAILS; *Tracking Adolescents Individual Lives Survey.* In **hoofdstuk 2** en **hoofdstuk 3** werd bepaald of internaliserende- en externaliserende gedragsproblemen en kwetsbaarheid voor psychose vooraf gingen aan cannabisgebruik of daar juist op volgden. Internaliserende gedragsproblemen hadden geen verband met cannabisgebruik. Externaliserende gedragsproblemen daarentegen hadden wel een verband met cannabisgebruik, waarbij externaliserende gedragsproblemen (gemeten of de leeftijd van 11 en 13) het gebruik van cannabis voorspelden (gemeten op de leeftijd van, respectievelijk, 13 en 16 jaar). Cannabisgebruik voorspelde externaliserende gedragsproblemen niet. Deze bevindingen zijn in overeenstemming met de self-medication hypothese, waarbij psychische problemen voorafgaan aan cannabisgebruik. Kwetsbaarheid voor psychose, gemeten op de leeftijd van 13 en 16 jaar, voorspelde cannabisgebruik op de leeftijd van 16 en 19 jaar. Een belangrijk

verschil met het verband tussen cannabis-externaliserende gedragsproblemen was dat het gebruik van cannabis (op de leeftijd van 16 jaar) ook kwetsbaarheid voor psychose (op de leeftijd van 19 jaar) voorspelde. Met andere woorden, in de relatie tussen psychotische kwetsbaarheid en cannabisgebruik is er bewijs gevonden voor zowel de self-medication hypothese als de damage hypothese, die suggereert dat het gebruik van cannabis neurobiologische veranderingen met zich mee brengt die kunnen leiden tot verschillende vormen van psychische problematiek.

Wat betreft de relaties tussen sociale vaardigheden en (verschillende aspecten van) cannabisgebruik (onderzoeksvraag 3) werd gevonden dat zowel coöperatie als assertiviteit cannabisgebruik voorspelden, maar op verschillende manieren. Coöperatief gedrag verlaagde de kans op het gebruik van cannabis, terwijl assertiviteit juist de kans verhoogde (**hoofdstuk 4**). Coöperatief en assertief gedrag konden niet vroege versus late initiatie van cannabisgebruik voorspellen, en waren ook niet voorspellend voor de frequentie van cannabisgebruik. Tegen onze verwachtingen in was de vaardigheid zelfbeheersing niet gerelateerd aan cannabisgebruik.

Onderzoeksvragen 4 en 5 werden beantwoord met behulp van gegevens uit twee steekproeven bestaande uit (voornamelijk) studenten. Cannabisgebruikers verschilden van niet-gebruikers op motivationele inhibitie, maar niet op cognitieve inhibitie. Ook scoorden cannabisgebruikers hoger op impulsief gedrag in het dagelijkse leven. Dit gedrag was gerelateerd aan motivationele inhibitie, maar niet aan cognitieve inhibitie (**hoofdstuk 5**). Cannabisgebruikers presteerden ook relatief slechter op sociale perceptie-taken in vergelijking met niet- gebruikers (**hoofdstuk 6**). De slechtere prestaties werden waargenomen bij een gezichts- en een emotieherkenningstaak (waarbij de emotieherkenningstaak ook een groter beroep deed op het werkgeheugen) De verschillen ten opzichte van niet-gebruikers waren het grootst op de emotieherkenningstaak. Cannabisgebruikers rapporteerden ook meer psychologische problemen, namelijk meer insufficiëntie van denken en handelen, vijandigheid, angst en psychoneuroticisme. Opvallend was dat relatief zware cannabisgebruikers met relatief slechte sociale perceptie (als gemeten met de emotieherkenningstaak) significant meer psychische problemen hadden dan niet-gebruikers en gebruikers met relatief goede sociale perceptie, hetgeen impliceert dat cognitieve kwetsbaarheid een rol speelt in hoeveel psychologische schade het gebruik van cannabis kan aanrichten.

Waar de bevindingen uit hoofdstuk 2 en 3 (gedeeltelijke) ondersteuning opleverden voor zowel de self-medication hypothese als de damage-hypothese, ondersteunen de bevindingen uit hoofdstuk 6 de vulnerability-hypothese. Ook deze laatste hypothese zou echter het beste verder kunnen worden onderzocht in longitudinale studies. In dit proefschrift is er geen bewijs gevonden voor de shared causes hypothese, al moet opgemerkt worden dat we slechts een beperkt aantal potentieel betrokken factoren konden onderzoeken. Deze en andere beperkingen, samen met implicaties voor preventie en interventieprogramma's worden besproken in **hoofdstuk 7**.

Curriculum Vitae

Merel Griffith – Lendering was born on September 3 1983 in Curacao. She finished secondary school at Peter Stuyvesant College in Curacao. After graduating, she moved to the Netherlands in 2001, where she started studying Psychology at the University of Leiden. She obtained her Propedeuse in 2002. In 2004, she got the opportunity to study 6 months abroad, at the University of Stellenbosch, South Africa, where she followed an undergraduate program at the faculty of Arts and Social Sciences. She obtained her Master's degree in Health Psychology at the University of Leiden in 2007.

After graduating she started her PhD project on cannabis use and mental health issues at the Department of Clinical Child and Adolescence Studies, Leiden University. During her work as a PhD student she moved back to Curacao in September 2011, where she commenced working as trainer of SiRene, providing educational guidance to students and schools. She is also a guest lecturer for different institutions in Curacao and Aruba. In January 2013, she founded MGL Research and Consultancy, focusing on conducting scientific research in Curacao and other islands of the former Dutch Antilles.

Merel Griffith – Lendering is geboren op 3 September 1983 op Curaçao.

Na het behalen van haar VWO diploma aan het Peter Stuyvesant College, verhuisde ze in 2001 naar Nederland om te gaan studeren. Aan de Universiteit Leiden begon ze met de opleiding Psychologie. Ze behaalde haar Propedeuse in 2002. In 2004 kreeg Merel de mogelijkheid om 6 maanden te studeren aan faculteit van 'Arts en Social Sciences' aan de Universiteit van Stellenbosch, Zuid Afrika. In 2007 behaalde Merel haar Masterdiploma in Gezondheidspsychologie te Universiteit Leiden.

Na haar studie begon Merel aan haar promotietraject over cannabisgebruik en gezondheidsproblematiek aan de afdeling Orthopedagogiek, Universiteit Leiden. Tijdens haar promotie onderzoek verhuisde ze naar Curaçao, waar ze als trainer en docent startte bij het onderwijskundig bureau SiRene. Momenteel is ze gastdocente van verschillende instituten op Curaçao en Aruba.

In Januari 2013 richtte ze het onderzoeksbureau MGL Research and Consultancy op, gericht op onderzoek, uitvoering en rapportage van wetenschappelijk onderzoek op Curaçao en overige eilanden van de voormalige Nederlandse Antillen.

Dankwoord

Graag wil ik de volgende mensen bedanken voor hun bijdrage aan mijn proefschrift.

Als eerste mijn promotoren Hanna Swaab en Wilma Vollebergh. Hanna, dank voor je begeleiding en daarbij het creëren van een plek voor mij in Leiden. En bovenal het vertrouwen in het afmaken van mijn promotie vanuit mijn geliefde eiland Curaçao. Wilma, bedankt voor je kritische blik op mijn artikelen en tevens je specifieke kennis op het gebied van marihuanagebruik bij jongeren. Mijn co-promotor Stephan Huijbregts, dank voor je realistische en kritische houding ten aanzien van mijn gehele project. Daarnaast, vooral dank voor je intensieve begeleiding, zowel inhoudelijk als statistisch gezien.
Dank aan de vele collega's bij TRAILS, maar ook in Leiden. Mijn paranimfen: Selene, mijn trouwe kamergenoot; wat was het een fijn traject samen. We hebben veel gelachen en gepraat over het AIO-proces. Naast het AIO-schap hebben we nog veel meer gemeen met elkaar; je bent een topper. Lieve Elles, dank voor je enorme interesse in mijn project en als mede onderzoeker ben ik vereerd dat ook jij mijn paranimf bent.

Mijn schoonouders, broers en schoonzussen, dank voor jullie interesse en enthousiasme in het verloop van mijn traject. Ook Robby, die nog een aantal artikelen heeft gelezen en mij van (positieve en kritische) feedback voorzag.
Mam en pap, jullie interesse en steun vanaf het begin van mijn studietijd in Nederland is iets wat ik enorm waardeer. Alleen met jullie als 'rots' op de achtergrond, heb ik dit allemaal kunnen realiseren.

Lieve Ramiro: jij was degene die mij pushte om aan dit promotietraject te beginnen, ook al waren we eigenlijk al van plan om terug te gaan naar ons geliefde eiland Curaçao. Masha danki mi amor.
En Robintje (samen met spruitje nummer 2 straks): jij maakt ons leven meer dan compleet!

Merel Griffith - Lendering