Blunt Vulnerabilities

Identifying Risks for Initiation and Continued Use of Cannabis in a Dutch Adolescent Population

Andrea Prince van Leeuwen

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Identifying risks for initiation and continued use of cannabis in a Dutch adolescent population

Cool en kwetsbaar

Risicobepaling voor beginnend en gecontinueerd cannabisgebruik in een Nederlandse adolescenten populatie

THESIS

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
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by

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born in Princeton West Virginia USA

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DEDICATION

I dedicate this thesis to Osnat and Philip Teitelbaum. Thank you for teaching me how to see the world in *movement* and for showing me how to "*Give Luck a Break*".

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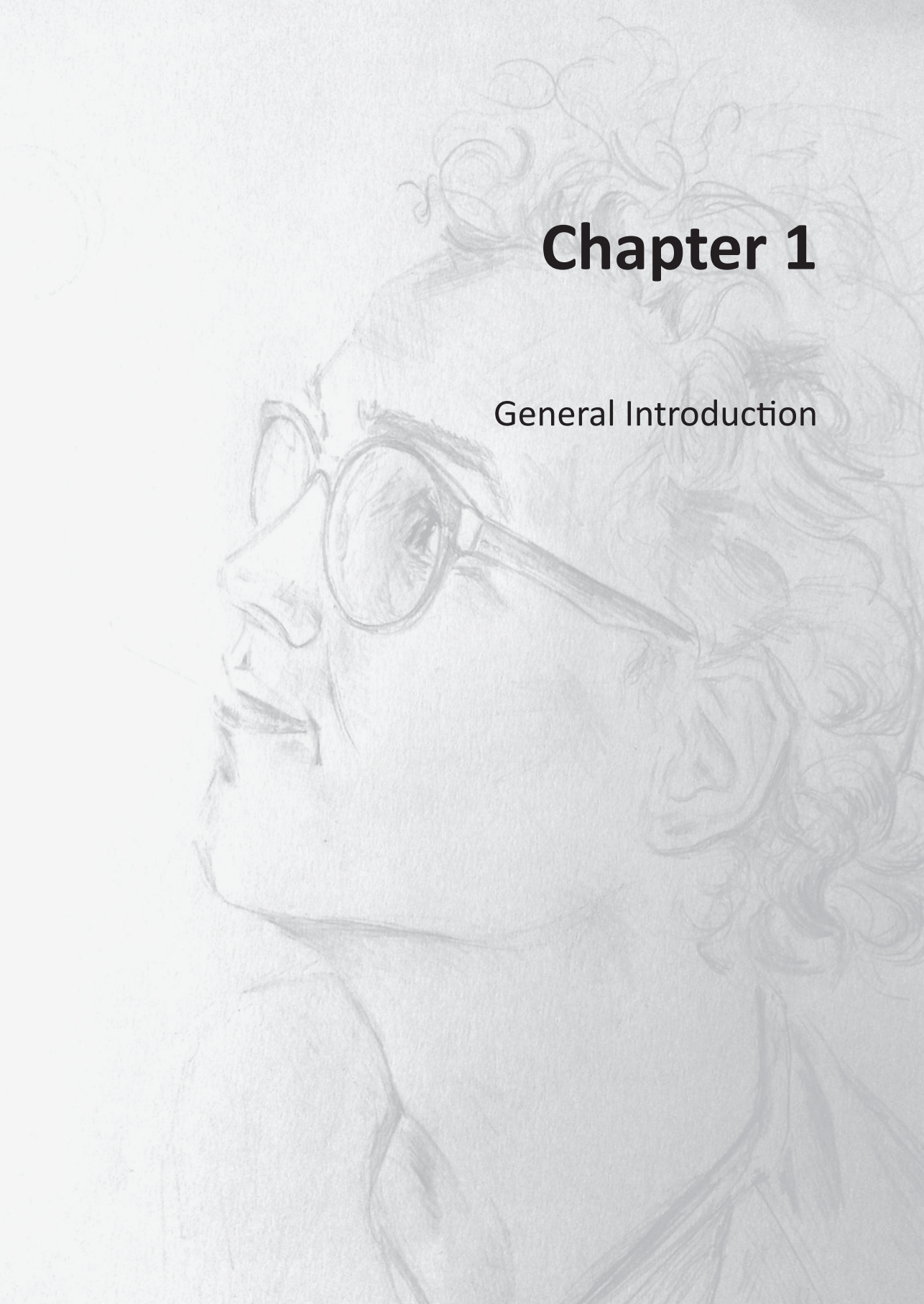

Chapter 1

General Introduction

General Background

Cannabis is the most commonly used and abused illicit drug in Western countries (1, 2). Onset of its use often follows that of tobacco or alcohol use, which are commonly regarded as licit drugs in research literature, although any use of substances before the age of 18 is legally regarded as illicit in many countries. Initiation of cannabis use typically occurs in adolescence (3-6). With a lifetime prevalence rate of 28% for cannabis use in Dutch youth, compared to 29% in British, 20% in German, and 30% in American youth (7-9), the position of the Dutch youth with regard to the prevalence of lifetime cannabis use is somewhat above the center of the distribution (10, 11).

For some lifetime users, initial use may progress to more regular patterns of use. Regular use may further lead to cannabis abuse or cannabis dependence. A recent survey in the Netherlands showed that an increasing number of Dutch adolescents and young adults requested help for cannabis use related problems (12). This may be partly related to high levels of the active compound in cannabis related products from the Netherlands (13). For instance, the average amount of concentrated THC in Dutch cannabis is 16.4% whereas in weed from other western countries the average is 8.5%. Similarly, the concentrated amount of THC in Dutch hash is 27.6% compared to 16.2% in other western countries (13).

While the majority of ever users may be regarded as recreational users or experimenters, still 10-20% of them develops symptoms of a cannabis use disorder (14, 15). Already in adolescence, some cannabis users develop symptoms of cannabis use disorders (16-22). Moreover, particularly early onset of cannabis use is related to an elevated risk for negative psychosocial outcomes, such as poor school performance, early school-dropout, unemployment, and affiliation with deviant peers, as well as to negative health-related outcomes including cardiovascular and respiratory problems, symptoms of depression or psychosis and progression to substance abuse or dependence (18, 20, 23-30). Therefore, more insight in risk factors and mechanisms that may lead to initiation and continuation of cannabis use in adolescence is needed. This insight may aid the development of targeted and effective prevention and treatment programs and will help identify adolescents at risk for early onset and progression of cannabis use.

Cannabis Use in Relation to Tobacco Use

In the Netherlands, cannabis is often used mixed with tobacco, and rolled into 'joints', and the combined product is inhaled by smoking. Many cannabis users also smoke tobacco on a regular basis. It may therefore be expected that cannabis and tobacco users share several risk factors. To be able to identify and target individuals that run the risk of using cannabis, or progress from smoking cigarettes to smoking joints, it is of importance to be able to differentiate between tobacco users and cannabis users. Thus, in this thesis, several analyses have been conducted in which tobacco users and cannabis users are directly compared.

Gateway Drug, Common Vulnerability or Shared Method of Intake?

Besides the often observed combined cannabis and tobacco use in Dutch adolescents and young adults, which may be due to the specific method of smoking *joints*, there are other

ways to approach the association between tobacco smoking and cannabis use. Several studies have focused on the pathway from first experimentation of use with easily available substances, such as tobacco or alcohol, to other *illicit* drugs, such as cannabis. Indeed, in adolescence, tobacco is often the first drug used (31), and for some individuals, smoking is followed by cannabis use. Because this sequence in substance use is found frequently, several studies have focused on tobacco use, but also alcohol use, as a first "gateway" for cannabis use (e.g., Kandel et al., 2006). Subsequently, cannabis use is regarded as a second "gateway": to the subsequent use of other illicit drugs (32-34). These gateway theories for tobacco and alcohol use, and particularly for cannabis use, are also referred to as "stepping stone theory" and have been a source of a lively debate (34-38).

Some of these authors suggested that a common vulnerability model may be an alternative, and perhaps better fitting, model to describe the co-occurrence of tobacco and cannabis use, even if a temporal pattern is observed. This model could reflect an individual's propensity to associate with others who use drugs (39), or a common genetic vulnerability underlying any substance use (40). A common genetic vulnerability could first be expressed by (early onset) tobacco use, and at later ages, by cannabis use.

As evidence contradicting the gateway drug model, or *gateway theory* of Kandel et al. (2006), a reverse gateway, in which cannabis use precedes cigarette smoking, has been found in certain populations (41-43). Such findings would suggest that a common liability or common vulnerability model, representing a common underlying factor, may explain the often observed co-occurrence of tobacco use and cannabis use, irrespective of the sequence of use of these substances.

Notwithstanding these findings, our research group recently showed that especially in a younger population of adolescents from Finland, initiation of illicit drug use, including cannabis, does not precede smoking initiation. Rather, early-onset smoking appears to be a strong predictor of illicit drug use by age 17.5 years (44). This finding was supported by genetic modeling of the associations between early onset smoking, progression of smoking, early onset illicit drug use, and progression of illicit drug use. A causal model, in which early onset smoking led to early onset illicit drug use, explained the data best (45). In this model, it was further shown that some shared genetic influences explained both early onset smoking and onset of cannabis use, but specific genetic influences for cannabis use were also found as part of the best fitting model. Thus, as some of our own results in a European adolescent population suggest that smoking initiation may indeed have a direct impact on the propensity to initiate illicit drug use, a common genetic vulnerability shared with tobacco users does not fully explain the progression to cannabis use in some smokers.

These findings perhaps fit partly with the gateway drug model, but this model postulates that the use of either tobacco or alcohol, both more easily available than cannabis, would predict onset of cannabis use. Most recent findings, however, point to a strong and specific association between tobacco use and cannabis use. Agrawal and Lynskey (2009) recently suggested, based on a longitudinal study of a large-scale U.S. adult sample, that a so-called *shared inhalation route of administration (ROA)* may additionally explain the specific association between use of tobacco and cannabis. For example, individuals who have experimented with or regularly inhaled tobacco smoke would be more willing to experiment

with other substances for which the predominant route of administration is via inhalation, including cannabis. Aero-respiratory adaptations and changes in implicit cognitive processes following tobacco smoking might facilitate the use of cannabis (46). Another possibility may be that the *ROA* helps to sustain cannabis use in tobacco smokers through persistent exposure to smoking cues and continued positive cannabis use experiences, thus resulting in more cannabis use by tobacco smokers (46).
In sum, there is substantial research linking tobacco and alcohol use to subsequent cannabis use, yet the specificity of this relationship is still under debate. In this thesis, we examined which substance use model—the gateway hypothesis, the common liability model and/or the route of administration model—best explains the relationship between early onset of tobacco and alcohol use and subsequent cannabis use initiation.

To this end, we compared the incidence of cannabis use among early onset tobacco users (initiating tobacco use before the age of 13), early onset alcohol users (initiating alcohol use before the age of 13) and adolescents who reported never using alcohol and/or tobacco before the age of 13 years.

The Interplay of Early Onset Smoking and Externalizing Behavior Problems

Early onset smoking seems to be a risk factor for progression to cannabis use (44, 45). In addition, externalizing behavior problems have been linked to cannabis use by numerous studies (47, 48), but also to smoking (47, 49). Although research has established that externalizing behavior problems and early onset smoking are quite often comorbidly found in cannabis users, most of this research has been conducted in a clinical setting. As a result, knowledge about the links between adolescent tobacco and cannabis use and subclinical levels of externalizing behavior is limited. Furthermore, many of the previous studies only focused on males, leaving a large piece of the "cannabis use picture" in dire need of being investigated. We therefore set out to examine the relative importance of externalizing behavior and early smoking onset as predictors of cannabis use among adolescent boys and girls. More specifically, we investigated the interplay between externalizing behavior and cigarette smoking using mediation and moderation models.

Individual Factors Related to Cannabis Use

Numerous studies have reported how various individual risk factors may predict substance use. These factors have been related to different forms of substance use, such as smoking, drinking, and using other drugs including cannabis, and may not be very specific predictors. For instance, temperament and personality factors such as novelty seeking and extraversion have been associated with alcohol (ab)use (50), smoking (51) and cannabis use (52, 53). However, different levels of these individual characteristics may perhaps predict why some individuals only experiment with smoking a cigarette, and others progress to daily smoking. Along the same line of reasoning, these individual variations in levels of a certain type of trait may predict why some adolescents stick to smoking, whereas others progress to using other drugs, including cannabis. We now shift our attention to levels of two individual factors that may be able to differentiate between experimental and repeated users, and

between smokers of tobacco only and smokers of cannabis (often combined with tobacco in the Netherlands): impulsivity and stress sensitivity.

Impulsivity

As a common liability to any substance use, impulsive behavior, also described as behavioral disinhibition, or lack of self-control, has been examined in relation to alcohol use (54), smoking (55, 56), and cannabis use (20, 57-59). Especially during adolescence, when maturation is still ongoing in areas in the prefrontal cortex of the brain, in particular of the orbitofrontal cortex (60-62), less than optimal self-controlling behavior can be observed. Individual differences in the level of this behavior could contribute to the likelihood of substance use.

One way of assessing individual variation in the level of impulsivity is using the Behavioral Activation System (BAS) and the Behavioral Inhibition System (BIS) approach, developed by Gray and colleagues (63-66). The manifestation of impulsive or disinhibited behavior has been related to the functioning of the BAS and the BIS, which are proposed to be the two neurological and motivational systems that underlie much of our behaviors and personality (64, 66). The BAS is thought to be sensitive to signals of reward and non-punishment, and relates to approach-oriented behavior, while the BIS is sensitive to signals of punishment and non-reward, and relates to avoidance or withdrawal behavior. Research has found that an overactive BAS is associated with impulsivity whereas a hypoactive BIS is associated with a reduced capacity to inhibit behavior that leads to negative or painful outcomes, resulting in reward-seeking behavior (64, 67). Individuals with high levels of BAS (67, 68) and low levels of BIS (69, 70) are more likely to engage in problematic behaviors such as gambling, criminal behavior and substance use (71-73). Given these findings, it may be expected that adolescent cannabis users differ from adolescents who only smoke tobacco in their level of both BAS and BIS.

While the BIS/BAS instrument is a self-reported measure, observing impulsive behavior of adolescents in a controlled setting may also give important insight into differences in impulsivity levels of adolescent cannabis users and adolescent tobacco users. Researchers such as Dahl and colleagues (2004) suggest that there are two different types of “impulsive behavior reasoning skills”: a) what adolescents think that they would use in a real world situation (e.g. The answer they would fill out in a questionnaire when asked if they would accept a cigarette when a friend would offer it to them), and b) the impulsive behavior that they would actually exhibit when they are caught off guard and have to react (e.g. Would they actually be able to decline their friends who offer them a cigarette?) (61). The latter type of impulsive behavior can be examined using observed measures of impulsivity assessed in experimental settings, for instance risky decision making in simulated driving experiments and gambling tasks.

In this thesis, we examined the predictive value of both observed (the Bangor Gambling Task) and self-reported (questionnaire BIS/BAS) impulsive behavior on adolescent lifetime and repeated cannabis use. Since we are unsure if adolescents who start using tobacco and transition to cannabis use are different from adolescents who smoke tobacco but not cannabis, or from adolescents who chose to abstain from tobacco and cannabis use, we

examined if these groups of adolescents can be differentiated based upon self-reported and observed measures of impulsivity.

Stress Sensitivity

Only a few studies have examined how individual variation in vulnerability to stress may be related to substance use in adolescence. Yet, findings from the adult population suggest that stress and substance use are associated. For instance, adults dependent upon alcohol, nicotine and other drugs show chronic activation of the hypothalamic-pituitary-adrenal axis (HPA axis) (74), which is a central component of the body's neuroendocrine response to stress. Individual differences in activation of the HPA axis can be assessed by measuring cortisol, the end-product of the HPA axis. Cortisol can be measured during basal functioning (i.e. daily rhythm) or during (lab-induced) stressful situations, with the latter reflecting the stress-reactivity of the HPA-axis. The link between stress and substance use is found in studies reporting that both increased perceived levels of stress and augmented stress reactivity are associated with more frequent or intense smoking and drinking (75, 76).

It is unclear, however, whether the difference in HPA reactivity which has been established in substance users is a consequence of prolonged intake of drugs, which seems plausible, or whether these alterations were already present in individuals prone to develop substance use disorders. Studies of Moss et al. (1995;1999) showed that stress responses to a lab stressor were blunted in adolescent and young adult males whose father had a history of alcoholism (77, 78). To gain further insight into how individual variation in HPA axis functioning is related to substance (ab)use from adolescence onwards, it is necessary to conduct a prospective longitudinal study in which HPA axis activity is assessed prior to the onset of substance use. Using such a design, our research group showed previously that lower basal cortisol levels 30 minutes after awakening predated early onset of cannabis use (initiating cannabis use before the age of 13) (79). Interestingly, when examining basal cortisol levels in *tobacco* users, our research team found that higher HPA axis basal functioning increases the risk of initiating tobacco use during adolescence (80). This might suggest that HPA axis functioning has differential associations with various types of substances, i.e. hypoarousal is related to (early onset) cannabis use, whereas hyperarousal is related to smoking onset.

In this thesis we extended this line of research by addressing the link between HPA axis stress reactivity, as indicated by an increase in cortisol level following a social stress task, and lifetime and repeated cannabis use in a population based cohort of adolescents. Because of our interest in cannabis use, rather than in the often-accompanied use of tobacco, we additionally focused on the differentiation between cannabis users and tobacco smokers.

Aims and Outline of this Thesis

The main objective of this thesis is to provide a better understanding of which factors predict cannabis use among adolescents, and to examine which of these factors are able to differentiate cannabis users from tobacco users. To that end, the following aims are addressed:

1. To examine how early onset smoking and drinking is associated with cannabis use onset, and which theoretical model best explains these associations: the gateway model, the common liability model or the route of administration model (***chapter 2***).
2. To investigate whether early onset smoking and/or drinking and continued smoking and/or drinking is related to an increased likelihood of developing a cannabis use disorder during adolescence (***chapter 3***).
3. To examine the interplay between externalizing behavior and early onset smoking as predictors of cannabis use in adolescence (***chapter 4***).
4. To examine the predictive value of observed versus reported measures of impulsivity on the onset of cannabis use and repeated cannabis use, and to test whether cannabis users can be differentiated from tobacco users on these measures (***chapter 5***).
5. To investigate whether any and repeated cannabis use is related to HPA axis reactivity to social stress, and to test whether cannabis users can be differentiated from tobacco users on patterns of HPA axis reactivity (***chapter 6***).

Finally, a summary of findings, general discussion, strengths and limitations, implications for practice and recommendations for future research are presented (***chapters 7-8***).

Study Sample

The studies described in this thesis were all embedded within the TRacking Adolescents' Individual Lives Survey (TRAILS), a large prospective population study of Dutch adolescents with bi- or triennial assessments from age 11 to at least age 25. The main objective of TRAILS is to chart and explain the development of physical and mental health problems at the level of underlying vulnerability and environmental risk factors. The four assessment waves completed so far ran from March 2001 to July 2002 (T1) (mean age 11.09 years, SD 0.55, 50.8% girls), September 2003 to December 2004 (T2) (mean age 13.56 years, SD 0.53, with 51.0% girls), September 2005 to December 2007 (T3) (mean age 16.27 years, SD 0.73, with 52.3% girls) and November 2009 to October 2010 (T4) (mean age 19.05 years, SD 0.58, with 54.7% girls). The TRAILS target sample consisted of young adolescents from five municipalities in the North of the Netherlands, including both urban and rural areas. Of all individuals approached for participation in the study (n=3,145), 6.7% were excluded. The exclusion criteria were 1) an incapability to participate because of mental retardation or serious physical illness or handicap, and 2) no availability of a Dutch-speaking parent or parent surrogate, and no feasibility to administer a part of the measurements in the parent's own language. Of the remaining individuals (n=2,935), 76.0% participated in the study (T1, n=2,230). Participants did not differ from those who refused to participate with respect to the proportion of single parent families, the prevalence of teacher rated problem behavior, several socio-demographic variables, and mental health outcomes (80). Of the 2230 children who were enrolled in the study at baseline, 1714 (77.0%) participated at T4. During all four assessments, adolescents were assessed at school or other test locations, where they completed questionnaires, in groups, under the supervision of one or more TRAILS assistants. Before each assessment wave, informed consent was obtained from all

adolescents and their guardian(s) after the nature of the study had been fully explained. Furthermore, the International Ethical Committee in the Netherlands (Central Committee on Research Involving Human Subjects (CCMO)) approved of all study procedures (81).

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Chapter 2

Can the Gateway Hypothesis, the Common Liability Model and/or the Route of Administration Model Predict Initiation of Cannabis Use During Adolescence? A Survival Analysis. The TRAILS Study

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ABSTRACT

Purpose: There is substantial research linking tobacco use and alcohol use to subsequent cannabis use, yet the specificity of this relationship is still under debate. The aim of this study is to examine which substance use model, i.e. the gateway hypothesis, the common liability model and/or the route of administration model, best explains the relationship between early onset tobacco/alcohol use and subsequent cannabis use initiation.

Methods: We used data from 2113 (51% female) Dutch adolescents who participated in three consecutive assessment waves (mean age: 11.09 years, 13.56 years, and 16.27 years, respectively) of the TRacking Adolescents' Individual Lives Survey (TRAILS) study. (Pre)adolescent cannabis, tobacco and alcohol use was assessed using the Youth Self-Report and a TRAILS developed questionnaire.

Results: We found that, during adolescence, early onset tobacco use does not pose a significantly higher risk of initiating cannabis use than early onset alcohol use. Therefore, we can rule out the route of administration model. Moreover, we found that adolescents who reported early onset comorbid use of both tobacco and alcohol have a higher likelihood to initiate cannabis use than adolescents who have tried either tobacco or alcohol. The gateway hypothesis is not broad enough to explain this finding. Therefore, the common liability model best predicts our findings.

Conclusion: Future research on adolescent cannabis initiation should focus on testing the robustness of the common liability model. Furthermore, identifying adolescents who use both tobacco and alcohol, before the age of 13, may help to curtail the onset of cannabis use.

Introduction

Adolescence is a critical phase for many forms of development, resulting in a unique 'window' of vulnerability, especially with regard to substance use. The majority of cannabis use initiation occurs during adolescence. Early onset of cannabis use in adolescence has been associated with a higher risk of experimenting with other substances (1, 2) developing a substance use disorder or dependence (3), substance related problems (2, 4, 5), juvenile delinquency, (6), higher rates of cannabis use and other illicit substance use in (young)adulthood (7) and, mental health problems (8-10). To better understand as well as curb cannabis use, several researchers have examined which factors may be predictive of cannabis use onset in adolescence. Among those factors, particularly tobacco (11, 12), and alcohol (13) initiation have been linked to a higher propensity to initiate and maintain cannabis use (2, 14). For example, in two previous studies among Dutch and Finnish adolescents, Korhonen and colleagues found that smoking onset before the age of 13 is a powerful predictor for subsequent use of cannabis (11, 12). Given these findings, one would expect early onset tobacco use to increase the likelihood of cannabis use during adolescence.

The gateway hypothesis (GW) and the common liability model (CL) aim to identify vulnerable individuals, which have a higher likelihood of transitioning to other illicit types of substance use such as cannabis. The GW proposes that drug consumption progresses in a stage-like sequence. According to this hypothesis, cannabis use would typically follow licit drug use such as tobacco and/or alcohol use, whereas illicit hard drug use (e.g. cocaine or heroine) would follow illicit soft drug use such as regular cannabis use (15, 16). The CL proposes that using both licit and illicit drugs may be due to the influence of a common liability. This liability may include a genetic and individual vulnerability, such as proneness to deviancy and familial liability to addiction. Unlike the GW, which proposed the sequential progression of drug use, the CL proposes that (a) the "choice" of which substance is used first can be the result of factors described above, and (b) no a priori order is expected in the sequence of drug use. Unfortunately, neither of these theories can account for the specific causal nature of the association between tobacco use and cannabis use that was recently reported (11, 12, 17).

Alternatively, the recently postulated route of administration model (ROA) (17) suggests that the shared route in which substances are administered (e.g. inhalation) may account for the future initiation of other types of substance use, thus explaining why tobacco and cannabis use commonly coexist. For example, an adolescent who inhales tobacco may be more likely to progress to using other types of inhaled substances such as cannabis. Agrawal and colleagues tested this theory in an adult population that participated in the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Although use of any type of tobacco product (smoked or chewed forms) placed participants at a higher risk for cannabis use, once the exclusive route of administration was taken into account, adults who smoked/inhaled tobacco had an increased risk (3.3-4.5 times more) to use cannabis when compared to the other forms of tobacco users or never users (17). Given these findings, one may anticipate that individuals who have experimented with inhaled tobacco smoke would be more willing to experiment with other substances, such as cannabis, which is also

commonly inhaled (17,18). Based on the ROA (92), we expect early onset tobacco use (EOTU), before the age of 13, to be an independent predictor of cannabis use.

The aim of this study is to examine which of the three substance use models discussed in this paper can best explain the relationship between early onset tobacco/alcohol use and subsequent initiation of cannabis use in an adolescent population. To test the GW and the CL, which both hold that EOTU and EOAU increase the likelihood to initiate cannabis use, we conducted two Cox regression analyses to first examine, 1) whether early onset tobacco users have a higher likelihood of initiating cannabis use**,** before the age of 18 years, than adolescents who have not tried tobacco by the age of 13 years, and 2) whether early onset alcohol users have a higher likelihood of initiating cannabis use**,** before the age of 18 years**,** than adolescents who have not tried alcohol by the age of 13 years. Second, given the expectations from both the GW and CL, one would expect that EOTU and EOAU equally predict initiation of cannabis use. Alternatively, the ROA would predict that adolescents who reported EOTU are more likely to initiate cannabis use because they have prior experience inhaling tobacco smoke. To be able to discriminate between the conflicting predictions of these theories we conducted another Cox regression analysis to examine 3) whether adolescents who reported EOTU are more likely to initiate cannabis use, before the age of 18 years, than adolescents who reported EOAU. Finally, to test the robustness of the GW we conducted two Cox regression analyses to examine 4) whether adolescents who reported both EOTU and EOAU have a higher likelihood to initiate cannabis use, before the age of 18 years, than adolescents who did not use either tobacco or alcohol at an early age and 5) whether adolescents who reported both EOTU and EOAU have a higher likelihood to initiate cannabis use, before the age of 18 years, than adolescents who reported only early onset use of either tobacco or alcohol. We will use data from the TRacking Adolescents' Individual Lives Survey (TRAILS) study, which allows us the unique opportunity to analyze data from a non-clinical, longitudinal Dutch study among adolescents that assesses substance use before regular use or addiction has occurred. Furthermore, the prospective design of the TRAILS study makes it possible to follow the age of onset and order of substance use onset during (pre)adolescence.

Methods

Sample characteristics

TRAILS: The TRacking Adolescents' Individual Lives Survey is a large prospective population study of Dutch adolescents. The present study involves data from the first (T1), second (T2) and third (T3) assessment waves of TRAILS, which ran from, respectively, March 2001 to July 2002, September 2003 to December 2004 and September 2005 to August 2008. At T1, 2230 subjects were enrolled in the study (mean age 11.09 years, SD 0.55, 50.8% girls). At T2, 2,149 subjects participated (mean age 13.56 years, SD 0.53, with 51.0% girls). Finally, at T3, 1816 subjects participated (mean age 16.27 years, SD 0.73, with 52.3% girls). For more details, see (19,20). Before each assessment wave, informed consent was obtained from all adolescents and their guardian(s) after the nature of the study had been fully explained. Furthermore, the Central Committee on Research Involving Human subjects (CCMO) approved all of the TRAILS study protocols

Procedure

During the first and third assessments, well-trained data collectors visited one of the parents or guardians at their homes to administer an interview. In addition to the interview, the parent was asked to fill out a self-report questionnaire. Adolescents were assessed at school or other testing locations, where they completed questionnaires, under the supervision of one or more TRAILS assistants, during all three assessments (T1, T2 and T3). In addition, information processing capacities, intelligence, and a number of biological and physiological parameters were assessed individually. The second assessment involved only self-report questionnaires, to be completed by the adolescent, their parents, and teachers (19, 20). All forms of (pre)adolescent substance use (i.e. tobacco use, alcohol use, and cannabis use) were assessed using the Youth Self-Report (YSR) (21, 22) and a TRAILS developed questionnaire (23). Lifetime use and frequency of use were assessed at T1, T2 and T3, and age of onset was assessed at T2 and T3, for tobacco use, alcohol use and cannabis use. Confidentiality of the study was emphasized.

Measures

Assessment of Onset of Cannabis Use, Tobacco Use and Alcohol Use

Age at which the adolescent used cannabis for the first time was used as the outcome variable in the present analyses. Adolescents were asked, in separate questions, about the age in which they first tried cannabis, tobacco and alcohol using the following question: "*How old were you when you first (smoked tobacco/ drank alcohol/ smoked weed or hash)?*" The options were: *0= never tried, 1= 9 years or younger, 2=10 years, 3=11 years, 4= 12 years, 5= 13 years, 6= 14 years, 7= 15 years, and 8= 16 years*. Self-reported age of first use was asked at waves T2 and T3. If there was a discrepancy between the age of onset reported at T2 and T3, then the age reported at T2 was preferred because less time had elapsed between the onset of substance use and assessment time, thereby decreasing the likelihood of errors in recall. This decision is supported by our findings that the adolescents in our study were more likely to report an older age of substance use onset at T3 than at T2 (Table 2.1).

Furthermore, all substance use questions at T3 allowed the adolescents to choose an onset age of up to only 16 years, yet some adolescents were 17-18 years old at the T3 assessment. Thus, onset of use could have taken place later than 16 years of age. To correct for this problem we did the following: if the adolescents did not report using cannabis at T1 or T2, but did report cannabis use at T3, then the adolescent was considered to be a new onset cannabis user. We then referred to the questions: *"Have you (smoked tobacco/ drunk alcohol/ smoked weed or hash) within the past 12 months?"* and "*Have you (smoked tobacco / drunk alcohol/ smoked weed or hash) within the past 4 weeks?"* If the adolescents answered yes to using cannabis within the past 12 months or past 4 weeks, we chose to use the assessment age at T3. If the adolescents answered no to (smoking tobacco/ drinking alcohol/ smoking weed or hash) within the past 12 months, we subtracted one year from the T3 assessment age.

To determine whether an individual smoked tobacco at an early age, adolescents were asked the following questions from a TRAILS developed questionnaire at T1: "Have you ever

smoked a cigarette?" "If yes, how many cigarettes (or hand rolled cigarettes) have you had in the last four weeks?". The options were: *0= I have never smoked tobacco, 1= once, 2= twice or three times, 3= four through six times, 4= seven or more times*. We dichotomized cigarette smoking at T1 as: 0= never use of tobacco and 1= ever use of tobacco.

A similar procedure was followed to determine early onset alcohol use. The following question was asked at T1: "Have you ever drunk alcohol (for example a bottle of beer or a glass of wine)?" *"If yes, how many times have you drunk alcohol?"*. The options were: *0= I have never drunk alcohol, 1= once, 2= twice or three times, 3= four through six times, 4= seven or more times*. Responses were dichotomized into: 0= never use of alcohol and 1= ever use of alcohol.

Table 2.1 Percent of adolescents who reported the same or different onset of substance use ages during T2 and T3.

	Alcohol	Tobacco	Cannabis
T2 reported age of onset is the *same as* T3 reported age of onset	20%	49%	71%
T2 reported age of onset is *older* than T3 reported age of onset	8%	9%	1%
T2 reported age of onset is *younger* than T3 reported age of onset	72%	42%	28%
Total	100%	100%	100%

Assessment of Externalizing/Internalizing Problems (T1)

Externalizing behavior problems were assessed using both the CBCL and the YSR which are two of the most frequently used questionnaires in current child and adolescent psychiatry research (21, 22, 24). Both the CBCL and the YSR provide researchers with DSM-IV based externalizing behavior scales (DSM-IV Ext(b)), which is a compilation of Attention Deficit Hyperactivity Problems (7 items, α=0.72), Oppositional Problems (5 items, α=0.62), and Conduct Problems (15 items, α=0.72) and DSM-IV based internalizing behavior scales (DSM-IV Inter(b)), which is a compilation of Affective Problems (13 items, α=0.77), Anxiety Problems (6 items, α=0.63), and Somatic Problems (7 items, α=0.69). Reliability and validity of the Dutch translated American version of the CBCL and YSR have been confirmed (24, 25).

Assessment of Exact Age

Date of birth was assessed via the self-report questionnaires administered during T1, T2 and T3, respectively.

Assessment of Socioeconomic Status (SES)

SES was calculated as the average of income level, educational level, and occupational level of each parent using the International Standard Classification for Occupations at T1 and was categorized into low, average and high SES (26).

Assessment of Paternal and Maternal vulnerability of Addiction and psychopathology
Familial loading information of psychopathology was collected during the TRAILS Family History Interview (T1) by interviewing a parent (usually the mother). Five dimensions of psychopathology were assessed: depression, anxiety, substance dependence, persistent antisocial behavior, and psychosis. Each dimension was introduced by a vignette, which described the main DSM-IV characteristics, followed by a series of questions assessing lifetime occurrence, professional treatment and medication use (27).

Statistical Analyses
The analyses were conducted using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL), version 15. Correlations of the variables used in our study were calculated using bivariate correlation analyses.

Survival Analyses
We used Cox regression survival analyses (28) to examine which model, i.e. the GW, the CL or the ROA, best explains the relationship between EOTU and/or EOAU and subsequent initiation of cannabis use. The Cox regression survival analysis method allowed us to examine cannabis use onset by age in years. Furthermore, the survival analysis also includes censored data, which allowed us to retain a large amount of subjects in our study that would not be possible with other types of statistical testing methods. All analyses were adjusted for child-reported externalizing behavior problems, paternal vulnerability of addiction, maternal vulnerability of addiction and SES. We defined survival time in years of age at onset of cannabis use. Given that age was calculated as a whole number of years, we used the exact method in SPSS for treatment of ties.

First, we examined if adolescents who reported EOTU (1= EOTU occurred) were more likely to initiate cannabis use than adolescents who had never tried tobacco by the age of 13 years (0= EOTU did not occur). Furthermore, we examined whether adolescents who reported EOAU (1= EOAU occurred) were more likely to initiate cannabis use than adolescents who had never tried alcohol by the age of 13 years (0= EOAU did not occur). The existence of differences between users and nonusers would confirm the predictions of the GW and the CL. For example, both the GW and the CL suggest that individuals who have used either tobacco or alcohol should be equally likely to use cannabis than abstainers. Second, we examined whether adolescents who reported EOTU (1= EOTU occurred) were more likely to initiate cannabis use than adolescents who reported EOAU (0= EOAU occurred). If EOTU resulted in a higher likelihood to initiate cannabis use, as compared to EOAU, this finding would confirm the predictions of the ROA, but not of the GW or the CL.

Finally, to explore our last two aims, we examined the influence of early onset of comorbid tobacco and alcohol use (EOTAU) upon subsequent cannabis use. First, we examined if adolescents who reported EOTAU (1= EOTAU occurred) were more likely to initiate cannabis use than adolescents who reported that they had never used either tobacco or alcohol by the age of 13 years (0= EOTAU did not occur). Second, we examined whether adolescents who reported EOTAU (1= EOTAU occurred) were more likely to initiate cannabis use than adolescents who reported ever use of either tobacco or alcohol (0= ever

use of *either* tobacco or alcohol by the age of 13 years). The existence of differences between comorbid users and users of either substance would confirm the predictions of the CL, but not of the GW given that the GW does not differentiate between comorbid use and single substance use (i.e. The GW does not take into account the additive effects of using more than one substance.). In contrast, the CL does suggest that adolescents who are comorbid users of substances such as tobacco and alcohol may be likely to use cannabis. The proportional hazard assumption was not violated in any of the conducted analyses. We assumed statistical significance at the p<0.01 level.

Results

Descriptive Results

Analyses were based on 2113 adolescents (51% female) who participated in the TRAILS study. The mean age at the outcome assessment (T3) was 16.3 years (SD 0.73, range 14.5 – 18.5). By the end of T3, 587 (34.4%) adolescents had used cannabis at least once during their lifetime. The difference in prevalence between boys and girls for cannabis use was not significant. The percentage of adolescents who reported ever using tobacco, cannabis or alcohol is listed by age in Table 2.2. At T1, 302 (13.7%) adolescents reported ever use of tobacco and 681 (31.0%) adolescents reported ever use of alcohol at T1.

The association between EOTU and subsequent cannabis use

We carried out a Cox regression analysis for EOTU as a predictor of lifetime cannabis use by age. Adolescents who initiated tobacco use early are at an increased risk for cannabis use (hazard ratio 1.80, p<0.001, 95% CI 1.73 to 2.59) compared to adolescents who had never tried cigarettes by the age of 13 years. We controlled for child-reported externalizing behavior problems, EOAU, paternal vulnerability of addiction, maternal vulnerability of addiction, and SES.

Table 2.2 Percentage of adolescents who initiated cannabis use by age group. [a] Age of self-reported cannabis ever use: T2 age taken over T3 age.

Age[a]	% Cannabis Use	%Tobacco Smoking	% Alcohol Use
9 years old or younger[a]	0.5	12.1	5.2
10 years old[a]	0.7	10.4	11.3
11 years old[a]	1.5	15.0	18.3
12 years old[a]	9.4	23.0	26.7
13 years old[a]	21.0	16.7	20.2
14 years old[a]	22.3	10.9	8.6
15 years old[a]	29.8	9.4	8.0
16 years old[a]	7.3	0.1	0 .9
17 years old[a]	5.6	1.8	0 .5
18 years old[a]	1.9	0.6	0 .20
Total Ever Use by the end of T3	34.4	54.9	87.5

The association between EOAU and subsequent cannabis use

Our next Cox regression analysis model showed that adolescents who initiated alcohol use early are at an increased risk to initiate cannabis use (hazard ratio 1.43, p<0.001, 95% CI 1.19 to 1.72). In this model, we controlled for child-reported externalizing behavior problems, EOTU, paternal vulnerability of addiction, maternal vulnerability of addiction, and SES.

EOTU versus EOAU as predictors of subsequent cannabis use

Adolescents who reported EOTU did not have a significantly higher likelihood of initiating cannabis use than adolescents who reported EOAU (hazard ratio of 1.13, p>0.05, 95% CI 0.89 to 1.91).

EOTAU versus no use of either tobacco or alcohol as predictors of cannabis use

When comparing EOTAU to abstainers (no tobacco or alcohol use before the age of 13), we found that adolescents who reported EOTAU were more likely to initiate cannabis use than abstainers (hazard ratio 2.52, p<0.001, 95% CI 1.94 to 3.26) (Figure 2.1).

In the subsequent analysis we compared EOTAU versus ever use of either tobacco or alcohol as predictors of cannabis use. Our findings showed that adolescents who reported EOTAU run a higher risk to initiate cannabis use than ever users of either tobacco or alcohol (hazard ratio 1.72, p<0.001, 95% CI 1.33 to 2.22) (Figure 2.1).

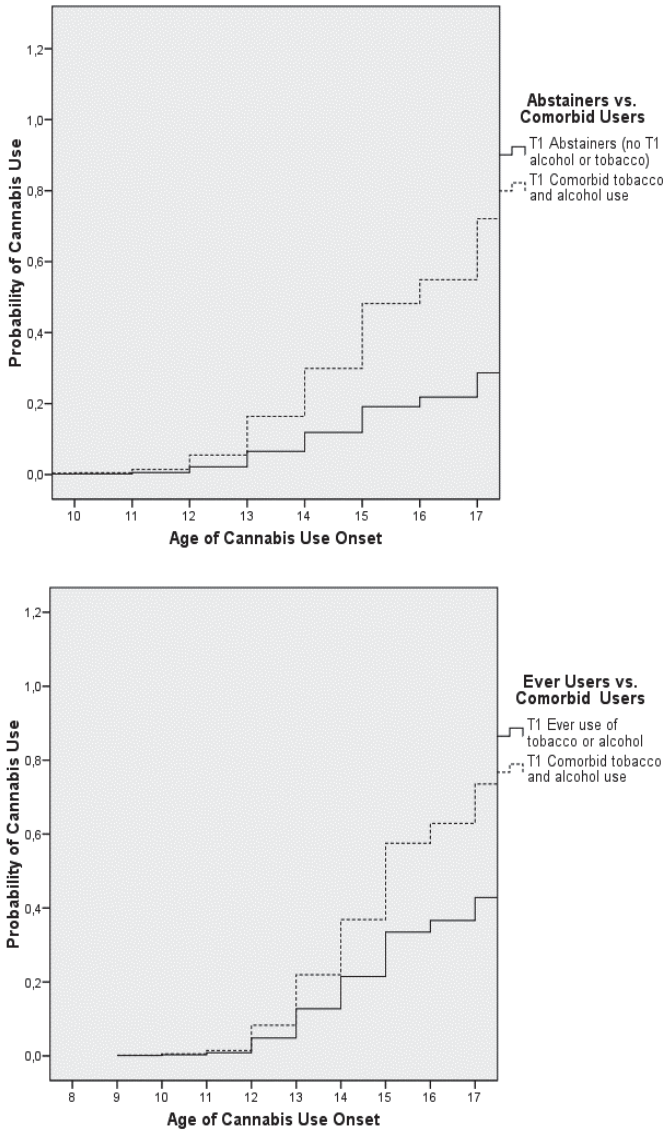

Figure 2.1 *Top*: Cumulative probability to initiate cannabis use in adolescents who reported comorbid early onset tobacco and early onset alcohol use vs. abstainers (no T1 tobacco or alcohol use) *Bottom:* Cumulative probability to initiate cannabis use in adolescents who reported comorbid early onset tobacco and early onset alcohol use vs. T1 ever users of alcohol or tobacco.

Discussion

As predicted by the gateway hypothesis (GW) and the common liability model (CL) (12, 15, 16, 18, 29), the current study shows that both early onset tobacco use (EOTU) and early onset alcohol use (EOAU) increase the risk of initiating cannabis use. In addition, when comparing early onset of comorbid tobacco and alcohol use (EOTAU) to both abstainers (no tobacco or alcohol use before the age of 13) and to early ever users of either tobacco or alcohol, we found that adolescents who reported EOTAU had a higher likelihood to initiate cannabis use.

When examining if EOTU is more likely than EOAU to increase the likelihood of cannabis use initiation, we found that these adolescent user groups did not significantly differ from each other. This finding does not support the route of administration model (ROA) presented by Agrawal and colleagues (17), given that the adolescents who reported EOTU (e.g. the "experienced inhalers") were equally likely to initiate cannabis use as adolescents who reported EOAU . It is important to mention that our population measured an adolescent population, whereas the Agrawal study (17) measured an adult population. Perhaps as substance use progresses, the ROA becomes more important and therefore reinforces the type of substance used (30). For instance, in a recently published study, Huizink and colleagues (31) found that cannabis use might increase the risk (path coefficient of .32) of continued smoking behavior in an adolescent population. Therefore, the route of administration may play a larger role in maintenance of substance use than it does in initiation of substance use. Perhaps, when taking tobacco and cannabis users into account, the experience of inhaling has to be more developed than what one usually finds in early onset tobacco users (e.g. as the amount of tobacco use increases the likelihood of initiating/using cannabis use also increases and vice versa).

Furthermore, findings from our EOTAU analyses indicate that comorbid users are more likely to use cannabis than ever users of either tobacco or alcohol. The GW is not broad enough to explain this increased likelihood. On the contrary, comorbid users and ever users should have an equally increased likelihood of initiating cannabis use according to the GW.

Given our findings, and the mentioned limitations resulting in the lack of support for the other predictive models, we conclude that the CL is the most robust model to predict the onset of cannabis use during adolescence.

Implications

Curbing early onset tobacco and alcohol use with a specific focus on comorbid tobacco and alcohol use, before the age of 13, may help to diminish the amount of adolescents who initiate early onset cannabis use.

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Chapter 3

Legal Substance Use and the Development of a DSM-IV Cannabis Use Disorder during Adolescence. The TRAILS Study

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ABSTRACT

Aim: To examine whether early onset of tobacco or alcohol use, and continued use of tobacco or alcohol at several assessments throughout adolescence, are related to a higher likelihood of developing a CUD during adolescence.

Methods: We used data from 1108 (56% female) Dutch adolescents who participated in four consecutive assessment waves (mean ages: 11.09 years, 13.56 years, 16.27 years, and 19.20 years, respectively) of the TRacking Adolescents' Individual Lives Survey (TRAILS). Cannabis use disorders were assessed using the Composite International Diagnostic Interview 3.0 (CIDI). Adolescent tobacco and alcohol use were assessed using self-report questionnaires.

Results: Early onset tobacco use (OR = 1.80, CI = 1.04-3.11, $p<0.05$), but not early onset alcohol use (OR = 1.38, CI = 0.87-2.19, $p>0.05$), increased the likelihood of developing a cannabis use disorder (CUD). Similarly, adolescents who reported continued use of tobacco (OR = 1.66, CI = 1.30-2.11, $p<0.01$), but not continued use of alcohol (OR = 2.28, CI = 0.99-2.11, $p>0.05$), were more likely to develop a CUD.

Conclusion: Early onset and continued smoking predicted the development of CUD in adolescence, while early onset and continued drinking alcohol were not related to CUD.

INTRODUCTION

Adolescence is a period in which many youth engage in cannabis use. At the same time, early onset of cannabis use and at least weekly cannabis use during adolescence have been identified as risk factors for problems later in life. For instance, cannabis use in this age period may impair educational performance, may cause respiratory disease in the long run, and increases the probability to develop psychotic symptoms (1-6). Besides these adverse outcomes, it has been estimated that one in seven adolescents who have ever tried cannabis will experience dependency problems during their lifetime (7). The risk of developing a cannabis use disorder is also illustrated by the growing number of cannabis clients in addiction care. For instance, according to the Substance Abuse and Mental Health Services Administration (SAMHA) in the United States of America, the number of individuals who are seeking treatment for cannabis abuse/dependence has increased from 81 per 100,000 individuals in 1995, to 118 per 100,000 in 2005 (8). The increase in cannabis using clients is also observed in the Netherlands, where the number of individuals presenting with cannabis use disorders has tripled between 1995 and 2009 to 56 per 100,000 (9). Since adolescents with heavy cannabis use are less likely to attain some of the important young adult milestones such as graduating high school and maintaining or getting a job (10), which may hamper their future roles in society, it is important to investigate which adolescents are vulnerable for developing a cannabis use disorder.

We previously reported that early onset use of tobacco and alcohol, i.e. initiation at or before the age of 12 years, increased the likelihood to progress to cannabis use during adolescence (11, 12). Thus, early onset of smoking or drinking may be regarded as first steps on a risky pathway towards use of other substances in adolescence. As yet, it is unknown whether such early onset use of these substances is also predictive of further progression of cannabis use later in adolescence, eventually leading to cannabis use disorders. Based on previous research, suggesting that substance use that starts in adolescence increases the risk of developing a substance use disorder (13) in adulthood, we expect to find that onset of smoking and/or drinking at or before the age of 12 years will indeed predict cannabis use disorders by the age of 20 in our cohort study. Furthermore, it can be expected that continued use of substances such as tobacco and alcohol in adolescence may also increase the risk to progress to use of other substances, such as cannabis, which eventually may cause cannabis use disorders. This latter pathway may result from an increased sensitivity to substance use - particularly the adolescent brain reward circuitry - fastening the addiction process (14).

Recent research further found a strong and specific association between tobacco use and cannabis use. Agrawal and Lynskey (15) suggested, based on a longitudinal study of a large-scale U.S. adult sample, that a so-called *shared inhalation route of administration (ROA)* may explain the specific association between use of tobacco and cannabis. According to this theory, individuals who have experimented with inhaled tobacco smoke are expected to be more willing to experiment with other substances for which the predominant route of administration is via inhalation, including cannabis. Tobacco smoking may lead to aero-respiratory adaptations and changes in implicit cognitive processes, which might facilitate the use of cannabis (15). We therefore specifically tested the unique contribution of smoking

and alcohol consumption at early age and continued smoking and alcohol consumption throughout adolescence on the likelihood of developing a CUD.

Using data from the TRacking Adolescents' Individual Lives Survey (TRAILS) study, which is a non-clinical, ongoing longitudinal study among Dutch adolescents that assesses substance use from initiation onwards, the aim of this study is to further examine whether a) initiation of tobacco and alcohol use at an early age increases the likelihood of developing a cannabis use disorder (CUD), and b) continued use of tobacco and alcohol increases the risk of developing a CUD. Given that previous research has shown that peer cannabis use (16), familial vulnerability to addiction(17, 18), externalizing behavior problems (19, 20), and gender (21) influence cannabis use (20), we take these risk factors into account.

METHODS

Participants and Procedure

Data of the Tracking Adolescents' Individual Lives Survey (TRAILS), a large prospective population study of Dutch adolescents with bi- or triennial assessments from age 11 to at least age 25, were used for the present study. A detailed description of the sampling procedure and methods is provided in De Winter et al. (22) and Huisman et al. (23). Briefly, the TRAILS target sample involved all 10- to 11-year-old children living in five municipalities in the North of the Netherlands, including both urban and rural areas. Seventy-six per cent of the target population (T1: n=2230, mean age = 11.09, SD = 0.55, 50.8% girls) was enrolled in the study (i.e., both child and parent agreed to participate). Responders and non-responders did not differ with respect to the prevalence of teacher-rated problem behavior and the associations between sociodemographic variables and mental health indicators (22). The four assessments waves completed so far ran from March 2001 to July 2002 (T1), September 2003 to December 2004 (T2) (mean age 13.56 years, SD 0.53, with 51.0% girls), September 2005 to December 2007 (T3) (mean age 16.27 years, SD 0.73, with 52.3% girls) and November 2009 to October 2010 (T4) (mean age 19.05 years, SD 0.58, with 54.7% girls). At T4, data was collected from 1714 of the 2230 participants (77.0%). During all four assessments, adolescents were assessed at school or other test locations, where they completed questionnaires, in groups, under the supervision of one or more TRAILS assistants. Before each assessment wave, informed consent was obtained from all adolescents and their guardian(s) after the nature of the study had been fully explained. Furthermore, the International ethical committee in the Netherlands (Central Committee on Research Involving Human Subjects (CCMO) approved of all study procedures (22, 23).

For this study, adolescents who completed the CIDI interview at T4 and had complete data for all relevant variables were selected (N=1328, 55,3% female). Next, adolescents who reported onset of cannabis use before the onset of tobacco or alcohol use (N=56 for tobacco and N=9 for alcohol), or at the same age (N=112 for tobacco and N=39 for alcohol), were excluded from the sample. This resulted in the inclusion of 1108 adolescents (58% female). The prevalence of early onset tobacco (χ^2 (1, n=2201) = 3.02, p = 0.08) and alcohol use (χ^2 (1, n=2192) = 1.47, p = 0.23) was not significantly different for included as compared to non-included participants.

Measures

Cannabis Use Disorder DSM-IV (CUD)

In the present analyses, cannabis abuse or dependence according to the DSM-IV criteria was used as the outcome variable. To obtain this information, computer-assisted personal interviews were carried out face-to-face at the fourth measurement wave, using the World Mental Health Surveys Composite International Diagnostic Interview (CIDI 3.0) (24). Adolescents who answered yes to ever use of cannabis were directed to a substance use section in which DSM-IV defined criteria for cannabis abuse/dependence were assessed for their lifetime occurrence. Criteria for cannabis abuse include: 1) failure to fulfill major role obligations; 2) continued use despite trouble with friends or family; 3) use in hazardous situations; and 4) legal problems/getting arrested. Criteria for cannabis dependence include: 1) more than once trying to stop or cut down use of drug; 2) spent time getting or using drug; 3) tolerance; 4) use of drug despite health/psychological problems; 5) give up or cut down on important activities; and 6) using larger amounts/for longer than intended. We dichotomized CUD as: 0= no cannabis use disorder and 1= cannabis abuse (endorsement of one or more criteria of cannabis abuse) or cannabis dependence (endorsement of three or more criteria of cannabis dependence within a period of 12 months).

Early Onset of Tobacco or Alcohol

To determine whether an individual smoked tobacco at an early age, adolescents were asked the following question from a TRAILS developed questionnaire at T1 (mean age 11.09 years): ‘‘Have you ever smoked a cigarette?’’ Response options were: 0= I have never smoked tobacco, 1=once, 2=twice or three times, 3=four through six times and 4=seven or more times. Early onset tobacco use (EOTU) was defined as any cigarette use at T1 (0=no early onset tobacco use, 1=early onset tobacco use).

A similar procedure was followed to determine early onset of alcohol use. Participants were asked at T1: ‘‘Have you ever drunk alcohol (for example a bottle of beer or a glass of wine), and if yes, how many times have you drunk alcohol?’’. Response options were: 0=I have never drunk alcohol, 1=once, 2=twice or three times, 3=four through six times and 4=seven or more times. Early onset alcohol use (EOAU) was defined as any alcohol use at T1 (0=no early onset alcohol use, 1=early onset alcohol use).

Continued use of Tobacco or Alcohol

Continued use of tobacco or alcohol was defined according to information provided at T1, T2 and T3. At T1, adolescents were asked if they had ever smoked tobacco or drank alcohol. At T2 and T3, adolescents were asked to report the frequency of cigarette smoking and alcohol consumption in the past four weeks. Responses at T2 and T3 were dichotomized into monthly smoking and monthly drinking (25). Continued tobacco and alcohol use were defined as tobacco or alcohol use on at least two measurement waves (T1, T2, T3), respectively.

Covariates

Externalizing Behavior Problems

Externalizing behavior problems at T1 were assessed using the YSR which is one of the most frequently used questionnaires in current child and adolescent psychiatry research (26-28). Reliability and validity of the Dutch translated American version of the YSR have been confirmed (28, 29). The YSR provides researchers with a DSM-IV based externalizing behavior scale (DSM-IV ExB), which is a compilation of the DSM-oriented problem scales Attention Deficit Hyperactivity Problems, Oppositional Problems, and Conduct Problems. The externalizing behavior scale was derived by combining the means of three continuous DSM-oriented problem scales.

Peer cannabis use

Peer cannabis use was assessed at T3 from a self-report questionnaire in which participants were asked how many of their friends use cannabis, with response options ranging from no one, a few, half, most, to all of them.

Socioecomic status (SES)

Socioeconomic status was measured at T4 with five indicators: educational level of father and mother (five levels ranging from 'Elementary education' to 'University'), occupation level of father and mother (nine levels of the International Standard Classification of Occupationsranging from 'Elementary Occupations' to Legislators, Senior Officials and Managers'), andfamily income (< €600/month to > €3,500/month in 9 steps). Each of the variables was standardized (z-scores), and the mean of the five standardized variables was used as the score of socio-economic status (30, 31).

Familial Vulnerability for Externalizing Disorder (FV)

Parental psychopathology was measured using the Brief TRAILS Family History Interview, administered at the parent interview at T1. Each syndrome was introduced using 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 behavior were used to construct a familial vulnerability index for externalizing disorder. Parents were assigned to any of the following categories: 0 = (probably) *not*, 1 = (probably) *yes*, and 2 = *yes* and *treatment/medication* (substance abuse) or *picked* up by *police* (antisocial behavior).

Gender

Gender was assessed using the self-report questions administered during the first measurement wave (female =0, male =1).

Statistical Analyses

The analyses were conducted using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL), version 20. Percentages of CUD, early onset tobacco and alcohol use and continued tobacco and alcohol use were calculated, and gender differences in percentages were analyzed by χ^2-tests. Correlations between the variables used in our study were calculated using bivariate (Pearson and Spearman) correlation analyses.

We performed logistic regression analyses to examine whether early onset of tobacco use and early onset of alcohol use, or continued use of tobacco and continued use of alcohol, were related to a higher likelihood of developing a CUD during adolescence. To this end, we first performed two logistic regression analyses to test the interaction effects of 1) early onset tobacco *X* early onset alcohol use and, 2) continued tobacco use *X* continued alcohol use, adjusting for externalizing behavior problems, peer cannabis use, socioeconomic status, gender, and familial vulnerability for externalizing disorders.

Based upon the findings from these analyses we conducted further logistic regression analyses, also adjusting for the aforementioned covariates. In case of non-significant interactions, we continued with testing the main effects of tobacco and alcohol use in two regression models, one focusing on early onset of use and one focusing on continued use. In case of significant interactions between tobacco and alcohol use, we continued with testing the association between tobacco smoking (early onset and/or continued, depending on interaction effect) and CUD within each of the alcohol groups (no early onset/continued alcohol use versus early onset/continued alcohol use).

RESULTS

Descriptive Results

Of the 1108 adolescents who were included in this study, 473 (43.0% of 1108; 56.0% Female) reported ever using cannabis. Of those 473 ever users, 23.7% (N=110, 61.0% Male) met the DSM-IV definition of a cannabis use disorder (Table 3.1). Correlation analyses indicated that fulfilling the criteria of a cannabis use disorder was positively associated with early onset and continued use of tobacco and alcohol, being male, peer cannabis use and externalizing behavior problems.

Table 3.1 Descriptive statistics

	Total %	Female %	Male %	χ	df
Cannabis Use Disorder	10.70	7.60	15.0	15.39**	1
Early Onset Tobacco Use	12.50	11.70	13.5	0.84	1
Early Onset Alcohol Use	29.80	23.80	38.0	25.86**	1
Continued Tobacco Use	38.70	40.30	36.5	1.70	1
Continued Alcohol Use	76.40	76.20	76.6	0.03	1

** = $p<0.01$

The association between early onset tobacco and alcohol use and a DSM-IV cannabis use disorder

Our first analyses testing the interaction between early onset tobacco use and alcohol use yielded a non-significant interaction effect. Therefore, we continued with testing the main effects of early onset tobacco and alcohol use keeping all covariates in the model. As presented in Table 3.2, early onset tobacco use (OR = 1.80, CI = 1.04-3.11, $p<0.05$) increased the likelihood of CUD, whereas early onset of alcohol use (OR = 1.38, CI = 0.87-2.19, $p>0.05$) did not.

The association between continued tobacco and alcohol use and a DSM-IV cannabis use disorder

The analysis testing the interaction between continued tobacco use and alcohol use also yielded a non-significant interaction effect. Therefore, we continued with testing the main effects of continued tobacco and alcohol use, keeping all covariates in the model. Results indicated that continued tobacco use (OR = 1.66, CI = 1.30-2.11, $p<0.01$) increased the likelihood of CUD, whereas continued alcohol use (OR = 2.28, CI = 0.99-2.11, $p>0.05$) did not (See Table 3.2). To make sure that continued tobacco use increased the risk of CUD above and beyond ever use of tobacco, we repeated the analyses while excluding the never users from the model (thus comparing continued use of tobacco and alcohol with non-continued use of tobacco and alcohol). These analyses yielded the same results. The interaction between continued tobacco use and alcohol use was non-significant (OR = 2.28, CI = 0.55-9.35, $p>0.05$). Similarly, continued tobacco use increased the risk of CUD (OR = 1.59, CI = 1.08-2.35, $p<0.05$), whereas continued alcohol use did not.

Table 3.2 Final Logistic Regression Models for Early Onset and Continued Tobacco and Alcohol Use.

	OR	95% CI Upper	Lower
EARLY ONSET USE			
Early Onset Tobacco Use	1.80*	1.04	3.11
Early Onset Alcohol Use	1.38	0.87	2.19
Socioeconomic Status	1.06	0.79	1.42
Familial Vulnerability for Externalizing Disorder	0.87	0.52	1.46
Gender	1.76*	1.15	2.70
Peer Cannabis Use	2.50**	2.06	3.05
Externalizing Behavior Problems	1.39*	1.04	1.86
CONTINUED USE			
Continued Tobacco Use	1.66**	1.30	2.11
Continued Alcohol Use	2.28	0.99	5.27
Socioeconomic Status	1.08	0.80	1.46
Familial Vulnerability for Externalizing Disorder	0.92	0.55	1.53
Gender	2.08**	1.35	3.22
Peer Cannabis Use	2.26**	1.84	2.76
Externalizing Behavior Problems	1.34*	1.01	1.78

* = $p<0.05$, ** = $p<0.01$

DISCUSSION

This is one of the first studies that prospectively tracks the progression of early initiation and/or continuation of alcohol and tobacco use in adolescence, and determines the association between each of these substance use patterns and the development of a cannabis use disorder. In this study, 10.7 per cent of all included adolescents met the DSM-IV criteria of cannabis abuse or dependence (mean age at assessment was 19.05, SD=0.58). Among lifetime cannabis users, 23.7 per cent transitioned to a cannabis use disorder. The latter percentage is somewhat higher than earlier estimations of 18 to 20 per cent among adolescent cannabis users (32, 33). The prevalence of early tobacco use in our study is comparable to national estimates of the proportion of youngsters who have tried tobacco use at or before age 11, whereas the prevalence of early alcohol use is higher in our study (34). Compared to European estimates of early onset of tobacco and alcohol use, the proportion of Dutch adolescents who experiment with tobacco and alcohol use at an early age is somewhat below the center of the distribution (35).

Taking the influence of externalizing behavior problems, peer cannabis use, socioeconomic status, gender, and familial vulnerability for externalizing disorder into account, we identified an increased risk

for developing a cannabis use disorder in adolescents with an early onset of tobacco use. Early onset of drinking alcohol did not contribute to the risk of developing a cannabis use disorder. Similarly, we found that continued tobacco users were more likely to develop a CUD than non-continued tobacco users. Continued alcohol use did not significantly increase the likelihood to develop a CUD. We therefore conclude that early onset and continued use of tobacco seem to be more important as risk factors of CUD than early onset and continued use of alcohol.

Several reasons could account for these findings. First, early onset use of tobacco and alcohol are regarded as risk-taking behaviors that could easily progress in further risk-taking with other substances. This has previously been reported and explained with the gateway theory, the stepping stone theory, or the common vulnerability theory (25, 36). Yet, the insignificant finding for early onset of alcohol use in this study suggests that early alcohol use may be regarded as less deviant in terms of risk-taking behavior than early tobacco use. Along the same line of reasoning, continued smoking during adolescence may be regarded as more deviant or risk-taking behavior nowadays than continued drinking, which is more commonly found in youth. Indeed, our descriptive data showed that continued alcohol use occurred in 76.4% of our adolescent population, whereas continued smoking was reported by 38.7%. Therefore, adolescents who continue smoking may indicate a particular group of adolescents more prone to risk-taking. They could therefore more readily progress to other deviant behaviors, eventually developing a CUD. Another explanation may be found in the shared method of intake through inhalation (Route of Administration) for both tobacco and cannabis (12, 37). According to this theory, tobacco use may sensitize the physiological and neurological system to other inhaled substances, such as cannabis, increasing the risk of developing a CUD (38). That may explain why the early onset and continued use of tobacco seem to be better predictors of developing a CUD than similar patterns of alcohol use.

Strengths and Limitations

The strength of the current study is that we based our findings on data from an ongoing longitudinal general population study, which allowed us to assess substance use as it progressed from its earliest stages onwards. Furthermore, we were able to derive DSM variables to define CUD from the CIDI interview, which is an internationally accepted and often used measure. However, our study is not without limitations. Our sample is of rather homogeneous Dutch ethnic background, and may not generalize to youth of non-Western backgrounds directly, given that drug use patterns are not the same. For instance, alcohol use is less common in youth of non-western backgrounds and if used continuously, may perhaps be regarded as more deviant than smoking in certain ethnic groups of youth (39).

Implications and conclusion

A high percentage of adolescents who reported ever using cannabis in our study qualified for a cannabis use disorder. Early onset tobacco use as well as continued tobacco use increase the risk of developing a CUD, whereas early and continued alcohol use do not significantly contribute to the risk of developing a CUD. We suggest that future research should focus on

elucidating vulnerability for early onset and continued tobacco use and on the underlying mechanism that explains the pathway from smoking to CUD. For prevention programs, targeting early onset users of tobacco and continued smokers in adolescence may be effective in reducing the number of CUD cases in adolescence as well.

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Chapter 4

Externalizing Behavior Problems and Cigarette Smoking as Predictors of Cannabis Use: The TRAILS Study

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ABSTRACT

Objective: To examine externalizing behavior problems and cigarette smoking as predictors of subsequent cannabis use.

Method: Dutch adolescents (N=1,606; 854 girls, 752 boys) from the TRacking Adolescents' Individual Lives Survey (TRAILS) ongoing longitudinal study were examined at baseline [age 10-12 (T1)] and at two follow-up assessments [ages 12-15 (T2) and 15-18 (T3)]. The analysis focused on DSM-IV externalizing behavior – conduct, attention deficit hyperactivity, and oppositional – problems at T1 assessed by the Youth Self Report and the Child Behavior Check List, on self-reported ever smoking at T2 and on cannabis use at T3.

Results: All associations of parent-rated externalizing behavior problems with cannabis were mediated by earlier smoking. Considering self-reported problems, none of these associations with cannabis were mediated by smoking, except the influence of self-reported conduct problems in girls. Interestingly, even after adjusting for externalizing problems, earlier smoking independently and consistently predicted cannabis use. The adjusted Odds Ratios for smoking varied in boys from 4.8-5.2 (ever) to 10-12 (daily) and 22-23 (early onset) and in girls 4.9-5.0, 5.6-6.1 and 27-28, respectively (all p-values <.001).

Conclusions: Our findings challenge the view that externalizing behavior problems directly predict cannabis initiation. Such associations were inconsistent across informants and sexes and were often mediated by earlier smoking. Early smoking onset is a powerful predictor of later cannabis initiation independent of preceding externalizing behavior problems. Although externalizing behavior problems are important as a starting point for substance use trajectories, early onset smoking should be identified as an important marker of cannabis use risk.

Introduction

The harmful consequences of cannabis use have fueled researchers to elucidate vulnerabilities in adolescents, who initiate and subsequently maintain cannabis use. Given that cannabis is one of the most commonly used drugs in western civilization (1), detecting vulnerabilities is important to prevent cannabis initiation. Several studies have examined genetic and environmental predictors of cannabis use (2). Genetic factors have a modest effect, while the influence of environmental factors predominates among adolescents (3, 4). Among environmental influences, several individual, family, and peer factors have been studied (5-10).

Many researchers have focused on the influences of externalizing behaviors (ExtB), such as attention deficit hyperactivity, conduct, and oppositional problems, on the onset of substance use, including cannabis use. Literature has established that externalizing disorders are commonly comorbid with substance use disorders among adolescents (11-13). It should be noted, however, that many studies used all-male or unbalanced-gender designs based on clinical populations (14-16). These samples are not representative of the general population, but biased towards extreme problematic cases of ExtB. Nonetheless, several general population studies have also shown that ExtB problems are associated with tobacco (17, 18) and cannabis use (18, 19). In particular, conduct disorders predict later cannabis use (20). Further, cigarette smoking, particularly early onset, is related to an increased risk of cannabis use (8, 21-23) For example, in a Finnish study, cigarette smoking by age of 12 showed over 20-fold odds for later cannabis use, while the ExtB-to-cannabis associations were weaker and less consistent (8).

This study addresses the following questions: How important are ExtB problems and early smoking onset in predicting cannabis use? Do ExtB problems play an independent role after early cigarette smoking is taken into account? Comprehensive data within the TRacking Adolescents' Individual Lives Survey (TRAILS) allowed us to include DSM-IV based ExtB problem measures, instead of the personality scales used in previous studies. This study provides further understanding of the interplay between externalizing problem behaviors and cigarette smoking as predictors of cannabis use among both genders.

Methods

Subjects and Procedures

TRAILS is a prospective population study of Dutch adolescents investigated biennially until at least the age of 25. This study involves data from the first, second and third assessment waves, conducted from March 2001 to July 2002, September 2003 to December 2004, and September 2005 to August 2008, respectively. During the baseline measurement (T1) 2,230 subjects were enrolled (mean age 11.1 years, SD 0.55, 50.8% girls). During the first follow-up (T2) 2,149 subjects (13.6, 0.53, 51.0% girls) participated, while during the second follow-up (T3) 1,816 subjects (16.3, 0.73, 52.3% girls) participated. Previous TRAILS studies have reported more detailed descriptives (24, 25).

At T1 and T3, well-trained interviewers visited one of the parents at their homes for an interview covering a wide range of topics, including the child's developmental history and

somatic health, parental psychopathology and care utilization. Parents also filled out a questionnaire. Adolescents were assessed at school or other test locations, where they completed questionnaires in groups, supervised by one or more TRAILS assistants during all measurements (T1-T3). The second assessment involved only questionnaires completed by the adolescent, parents and teachers (24, 25).

These analyses were based on 1,606 adolescents (854 girls, 752 boys) with non-missing data on child-rated externalizing problems at T1, smoking at T2, and cannabis use at T3. The mean age at T3 was 16.3 years (SD 0.67, range 14.7 – 18.4). Due to missing values in parental ratings those analyses included 1,537 adolescents (813 girls, 724 boys).

Measures

Substance use was assessed using the Youth Self-Report (YSR) and a TRAILS-developed survey (26). Cannabis use was measured at T1, T2 and T3. The outcome variable for these analyses was self-reported ever use of cannabis at T3, while age of onset and frequency of use was also assessed.

The ExtB problems were assessed using the Child Behavior Checklist (CBCL) and the YSR (27-29) The CBCL is a 120 items parent questionnaire designed to assess problems in 4- to 18-year-olds. The YSR, similar to the CBCL, is a self-report questionnaire for adolescents (28, 30). All items in both questionnaires ask about behavioral or emotional problems that occurred within the past six months before the questionnaire fill-in date. Reliability and validity of the Dutch translation of the CBCL and YSR (American version) have been confirmed (31). The YSR and CBCL can be scored on DSM-IV scales, as constructed by Achenbach et al. (2003), for conduct (CD), oppositional (OD), and Attention Deficit Hyperactivity (ADH) problems (32). For this study, we used a sum score of these scales, reflecting ExtB problems in general. It is important to notice that the ExtB problems (OD, CD and ADH) used in our study are not diagnoses but CBCL/YSR subscales which are based on questions that correspond to DSM IV criteria.

Smoking was assessed in three ways. First, ever smoking at T2 as a dichotomous variable, where the first category included those who had never smoked, while the second category included the smokers, i.e. who had smoked at least 1 or 2 times. Second, ever daily smoking at T2 analyzed as a dichotomy (no/yes). Third, using data on age of onset reported retrospectively at T3, we created a variable: *0= I have never smoked, 1= I had my first cigarette after age of 12, 2= I had my first cigarette at age of 12 or earlier.* This variable allowed us to replicate the findings from a population-based longitudinal study among Finnish adolescent twins with three assessments at similar ages, wherein smoking onset by the age of 12 was found to be a powerful predictor of cannabis use (8).

For covariates, information about gender and age were collected via the Parent and Adolescent questionnaires. Familial loading information of psychopathology, including substance dependence at T1, was collected via the TRAILS Family History Interview, by interviewing a parent (usually the mother). Five dimensions of psychopathology were assessed: depression, anxiety, substance dependence, persistent antisocial behavior, and psychosis. Each dimension was introduced by a vignette, which described the main DSM-IV

characteristics, followed by a series of questions assessing lifetime occurrence, professional treatment, and medication use (33).

Statistical Methods

In accordance with previous research suggesting gender differences (7, 31, 34), and based on the means of the DSM-IV scale sum scores showing significant sex differences in behavioral problems (Table 4.1), we conducted all analyses by gender. To test specifically for sex differences, we also examined gender interactions. Because the sum scores tended to be skewed, we used the weighted means. Due to modest correlation between the child- and parent-reported ExtB problems sum scores (r=0.39) we analyzed these ratings as separate variables. The main analyses conducted were logistic regression models using the STATA statistical package, version 9 (35).

We conducted logistic regressions to investigate ExtB problems and cigarette smoking as cannabis use predictors. We tested whether the associations of ExtB problems and cigarette smoking on cannabis use were independent of each other - or whether they were mediated or moderated by each other. Considering mediation, MacKinnon et al (2007), suggest that complete mediation occurs if the direct association becomes zero (36). However, in psychological research it is unrealistic to show complete mediation by a single variable. Thus, in our study, mediation was met if the direct association became non-significant, even if there was some effect left. Regarding moderation, we tested how ExtB and smoking influence the associations of each other on cannabis. If smoking is a moderator, the association between ExtB and cannabis depends on smoking status and a significant ExtB × smoking interaction exists (37).

We focused on cannabis use predictors. In order to investigate mediation, we first analyzed whether ExtB problems predict smoking. Second, we analyzed whether that smoking predicts cannabis use. Third, we analyzed whether ExtB predict cannabis use. For each ExtB measure, we examined if the Odds Ratio (OR) was attenuated and if the p-value became non-significant (>0.05) when smoking was added to the model. In order to investigate moderation, we added ExtB × smoking interactions into the model. We also tested gender × ExtB × smoking interactions. We repeated all analyses regarding new onsets of cigarette smoking at T2 and cannabis use at T3 by excluding those reporting ever smoking or cannabis use at a previous measurement. All analyses were adjusted for exact assessment age at the outcome: T2 when smoking was the outcome, whereas T3 when cannabis use was the outcome. Models including ExtB problems were analyzed using the compiled externalizing score (OD+CD+ADH), as well as the individual scales (OD, CD and ADH). However, the models analyzing the influence of smoking on cannabis use were adjusted for the compiled externalizing scores. Further adjustment included familial loading to substance use and antisocial behaviors (33).

Table 4.1 The Means of the DSM-IV Scores (SD) among Boys and Girls [a]: Parental Ratings (CBCL) and Child Ratings (YSR) at T1 (age 10-12): The TRAILS Study

	CBCL Parental Ratings			YSR Child Ratings		
DSM-IV Externalizing	Boys (n=724)	Girls (n=813)		Boys (n=752)	Girls (n=854)	
Behavior Problems Score	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Conduct Problems	2.75 (2.84)	1.65 (2.02)	<0.001	4.19 (3.25)	2.72 (2.26)	<0.001
Attention Deficit Hyperactivity Problems	4.37 (3.32)	3.28 (2.92)	<0.001	4.21 (2.53)	4.08 (2.39)	0.296
Oppositional Problems	3.07 (2.09)	2.64 (1.95)	<0.001	2.36 (1.79)	2.07 (1.64)	0.001
Externalizing Problems [b]	10.2 (7.08)	7.57 (5.92)	0.001	10.8 (6.31)	8.86 (5.17)	0.001

Note: SD = standard deviation; CBCL= Child Behavior Check List; YSR= Youth Self Report

[a] Among participants with non-missing data on smoking at T2 and cannabis use at T3; [b] Sum of conduct, attention deficit hyperactivity and oppositional problems scores

Results

By the T3 survey 30.5% of adolescents (29.7% girls, 31.6% boys, p=0.41) had used cannabis at least once; 10.0% used 1-3 times (11.2% girls, 8.5% boys), 6.6% 4-9 times (7.5%, 5.6%) 4.7% 10-19 times (4.7%, 4.8%), and 9.2% 20 times or more (6.0%, 12.8%). Out of the T3 respondents 0.4% reported they had their first cannabis experiment before age of 12 - the lowest age of the T2 survey participants - while 14.1% by age of 15 - the highest age within that survey. Concerning cigarette smoking at T2, 34.8% (37.5% girls, 31.8% boys, p<0.05) had ever smoked at least one cigarette, whereas 11.0% (13.6%, 8.0%) reported having ever been daily smokers. At the T3 survey 58.7% of girls and 53.3% of boys had ever smoked a cigarette. Out of the T3 respondents, 25.2% of girls and 24.1% of boys reported they had their first cigarettes by the age of 12. Among most participants smoking was initiated first and cannabis use was initiated after smoking. There were few deviations so that 0.7% (n=6) of girls and 1% (n=9) of boys started to use cannabis first and then started to smoke cigarettes. Among those who had never smoked, 4.0 % of girls and 5.2% of boys had used cannabis.

The first models examined whether ExtB problems predicted cigarette smoking. When adjusted for age at T2, baseline ExtB problems predicted ever smoking at T2 independent of informant and gender. Some of the DSM-IV-scales, such as parent-reported CD, showed a strong association (Table 4.2). However, the 95% confidence intervals were very wide; probably due to relatively high standard deviations in the mean scores (Table 4.1).We additionally adjusted the ExtB-to-smoking associations for familial liability to substance dependence. Familial loading was associated with increased risk of smoking among girls (OR=2.54; p<0.001), yet not among boys (OR=0.97; p>0.05), but most of the ExtB-to-smoking associations were not attenuated if adjusted for familial liability (data not shown). Finally, we analyzed smoking initiation among 647 boys and 756 girls without cigarette smoking at baseline. The influence of child-rated ADH problems on new smoking onset did not remain significant among boys (OR=1.41; 95%CI 0.86, 2.31) nor among girls (OR=1.45; 95%CI 0.92, 2.29).

Table 4.2. Odds Ratios (OR) (95%CI) of the Age Adjusted Logistic Regressions on Externalizing Problems (T1) Predicting Ever Cigarette Smoking (T2): The TRAILS Study

	Boys			Girls		
Predictor at T1	n	OR	95%CI	n	OR	95%CI
DSM-IV Conduct Problems						
Parent	724	13.6	5.22, 35.4	813	30.9	8.67, 109
Child	752	7.70	3.73, 15.9	852	15.3	5.81, 40.2
DSM-IV Attention Deficit Hyperactivity Problems						
Parent	724	1.82	1.31, 2.53	812	2.42	1.71, 3.43
Child	752	1.70	1.11, 2.60	854	1.60	1.06, 2.42
DSM-IV Oppositional Problems						
Parent	724	1.89	1.30, 2.76	812	1.92	1.32, 2.78
Child	752	2.54	1.65, 3.90	851	2.34	1.53, 3.60
DSM-IV Externalizing Problems [a]						
Parent	724	1.46	1.23, 1.74	813	1.60	1.33, 1.92
Child	752	1.60	1.31, 1.95	854	1.57	1.27, 1.93

Note: OR = odds ratio; 95%CI = 95% confidence interval ; [a] Sum of conduct, attention deficit hyperactivity and oppositional problems scores

The second models considered cigarette smoking as a cannabis use predictor. Ever and daily smoking by T2 strongly predicted cannabis use at T3 for both sexes. Early onset smoking (first cigarette by the age of 12) was a powerful predictor of cannabis use (boys OR=25.0; girls OR=29.1). When adjusting for ExtB problems at T1, these estimates of smoking were only slightly attenuated. Daily smoking at T2 had a strong influence on cannabis use particularly among boys (age adjusted OR=11.3) and this association became stronger when adjusted for parent rated ExtB (Table 4.3). We also adjusted the smoking influences for familial liability, but those associations were slightly attenuated among girls only (data not shown). Further, we analyzed new cannabis initiations among 797 girls and 691 boys who had no cannabis use at baseline or T2. We found a strong risk among those who had their first cigarette by the age of 12 (boys OR=24.2; 95%CI 14.0, 42.1; girls OR=28.6; 95%CI 15.7, 52.1). The risk for those who had their first cigarette after the age of 12 was also high (boys OR=15.4; 95%CI 9.10, 26.1; girls OR=18.2; 95%CI 10.1, 32.6), when compared to never smokers. Adjustment for familial loading did not attenuate these associations (data not shown).

The third models considered ExtB predicting cannabis use. In the age adjusted logistic regressions, the baseline ExtB problem scores significantly increased the risk for cannabis use independent of the informant (parent or child him/herself), with the exception of the association of self-rated conduct problems among girls, which approached significance. However, when we added smoking at T2 into the model, the associations of parent-rated

problem behaviors were clearly attenuated, resulting in non-significant values for all behaviors. The associations of child-rated behaviors were less dramatically attenuated through cigarette smoking. Among girls the associations of CD and OD became non-significant, while the association of ADH problems remained significant. Among boys the associations of all child-rated ExtB remained significant independent of the smoking association (Table 4.4).

Similar results were observed when adjusting the problem behavior influences for age of smoking onset instead of ever smoking (data not shown). Further, familial loading to substance use as such increased the risk of cannabis use significantly among girls (OR=2.02; 95%CI 1.36, 3.01), but not among boys (OR=0.73; 95%CI 0.48, 1.30). However, the influences of the ExtB were not significantly attenuated if adjusted for familial liability (data not shown).

Further, we analyzed new cannabis use onset among those with no use at baseline or at T2. Within the parental-ratings, oppositional problems among those 660 boys (OR=1.35; 95%CI 0.90, 2.04) and 758 girls (OR=1.38; 95%CI 0.91, 2.09), as well as ADH problems among girls (OR=1.41; 95%CI 0.96, 2.07) did not remain significant predictors of new onset of cannabis use. All child-rated problem behaviors remained significant, except for CD (OR=1.44; 95%CI 0.49, 4.22) and OD (OR=1.57; 95%CI 0.97, 2.53) among girls.

Finally, interactions were tested. When considering ever smoking moderating the influence of ExtB, we found one interaction for girls (p=0.02): among those 513 girls who never smoked cigarettes, parent-rated oppositional problem score did not significantly influence cannabis use (OR=0.71; 95%CI 0.37, 1.36). In contrast, among those 299 girls who ever smoked at least one cigarette that score significantly increased the likelihood of trying cannabis (OR=1.86; 95%CI 1.06, 3.25). No significant daily smoking x ExtB interactions existed. Concerning gender interactions, sex × conduct problem interaction approached significance (p=.07), suggesting that self-report scores predicted cannabis use more strongly among boys than girls. Also, daily smoking × sex interaction approached significance (p=.08), suggesting that daily smoking predicted cannabis more strongly among boys than among girls (data not shown).

Table 4.3 Odds Ratios (OR) (95%CI) of the Logistic Regressions on Cigarette Smoking at T2 Predicting Cannabis Use at T3:The TRAILS Study

	Boys						Girls					
Predictor at T2	Adjusted for T3 Age		Adjusted for T3 Age and Parent Rated T1 Externalizing Problems [a]		Adjusted for T3 Age and Child Rated T1 Externalizing Problems [a]		Adjusted for T3 Age		Adjusted for T3 Age and Parent Rated T1 Externalizing Problems [a]		Adjusted for T3 Age Child Rated T1 Externalizing Problems [a]	
	n=752		n=724		n=752		n=854		n=813		n=854	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Ever smoking at T2												
Never	1.00		1.00		1.00		1.00		1.00		1.00	
Ever	5.28	3.76, 7.43	5.19	3.65, 7.37	4.84	3.43, 6.84	5.11	3.71, 7.04	5.02	3.60, 6.99	4.92	3.56, 6.79
	n=748		n=721		n=748		n=846		n=807		n=844	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Daily smoking at T2												
Never	1.00		1.00		1.00		1.00		1.00		1.00	
Ever	11.3	5.69, 22.3	11.6	5.64, 23.7	10.1	5.03, 20.2	5.67	3.70, 8.68	6.07	3.87, 9.53	5.58	3.63, 8.59
	n=761		n=732		n=761		n=864		n=822		n=864	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age of smoking onset												
Never	1.00		1.00		1.00		1.00		1.00		1.00	
Late (>12 years)	15.9	9.43, 27.0	15.3	9.01, 26.0	16.0	9.43, 27.2	18.2	10.1, 32.6	17.2	9.58, 31.0	18.1	10.1, 32.6
Early (≤12 years)	25.0	14.5, 43.2	22.7	13.0, 39.5	22.0	12.7, 38.2	29.1	16.0, 53.0	27.5	15.0, 50.4	27.9	15.3, 50.8

Note: OR = odds ratio; 95%CI = 95% confidence interval; [a] Sum of conduct, attention deficit hyperactivity and oppositional problems scores

Table 4.4 Odds Ratios (OR) (95%CI) of the Logistic Regressions on DSM-IV Externalizing Problems (T1) Predicting Cannabis Use (T3): The TRAILS Study

Predictor at T1	Boys						Girls					
	Adjusted for T3 Age			Adjusted for T3 Age and T2 ever smoking			Adjusted for T3 Age			Adjusted for T3 Age and T2 ever smoking		
DSM-IV Conduct Problems	n=724 (parental) n=752 (child)						n=813(parental) n=852 (child)					
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Parent	4.37	1.72, 11.1	0.002	1.93	0.69, 5.38	0.208	8.59	2.49, 29.6	0.001	3.12	0.83, 11.7	0.091
Child	7.87	3.77, 16.4	<0.001	4.64	2.11, 10.2	<0.001	2.59	0.99, 6.78	0.053	0.97	0.34, 2.74	0.951
DSM-IV ADH Problems	n=724(parental) n=752 (child)						n=812(parental) n=854(child)					
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Parent	1.66	1.19, 2.31	0.003	1.41	0.98, 2.02	0.065	1.50	1.05, 2.13	0.025	1.11	0.75, 1.63	0.594
Child	2.18	1.42, 3.37	<0.001	1.96	1.23, 3.12	0.004	1.96	1.27, 3.04	0.003	1.77	1.11, 2.82	0.017
DSM-IV Oppositional Problems	n=724(parental) n=752 (child)						n=812(parental) n=851 (child)					
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Parent	1.54	1.06, 2.26	0.025	1.26	0.84, 1.91	0.266	1.49	1.02, 2.19	0.040	1.23	0.81, 1.85	0.323
Child	2.93	1.89, 4.55	0.009	2.36	1.47, 3.78	<0.001	1.81	1.16, 2.82	0.009	1.41	0.87, 2.28	0.166
DSM-IV Externalizing Problems [a]	n=724(parental) n=752 (child)						n=813(parental) n=854 (child)					
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Parent	1.32	1.11, 1.57	0.002	1.18	0.97, 1.42	0.089	1.29	1.07, 1.55	0.007	1.11	0.91, 1.35	0.307
Child	1.75	1.42, 2.14	<0.001	1.56	1.26, 1.95	<0.001	1.42	1.15, 1.77	0.001	1.25	0.99, 1.57	0.061

Note: OR = odds ratio; 95%CI = 95% confidence interval ; [a] Sum of conduct, attention deficit hyperactivity and oppositional problems scores

Discussion

Our findings suggest that when early onset smoking is taken into account, ExtB problems have inconsistent associations on subsequent cannabis use initiation. A striking feature is that particularly early onset smoking mediates the associations of parent-rated behavior problems with cannabis use, although the role of self-reported ExtB problems is relatively independent from smoking among boys.

These results somewhat differ from previous findings, mostly based on US studies. A population-based twin sample (20) showed higher odds for cannabis use/abuse for individuals with CD assessed at age 17. Tarter et al. (2006) reported, among 224 male adolescents, that delinquency in childhood was more strongly related to marijuana than licit drug use (6). McGue and Iacono reported that adolescent problem behavior predicted later psychopathology, including substance use disorders (38). In our study, smoking onset before age of 12 was a strong independent predictor of later cannabis use. The associations of smoking on cannabis use were mostly not mediated through ExtB problems or familial liability to substance use. Such strong association of cigarette smoking may partly be explained by changing attitudes towards smoking, i.e. smoking is becoming more deviant for adolescents. This could partly explain why some of our findings differ from earlier studies where more independent associations for ExtB problems existed. Further, differences in results between US and Dutch studies may also reflect differences in environmental and cultural conditions between countries in relation to cannabis. Our findings do not invalidate earlier studies showing a robust relationship of ExtB to drug use, but indicate that smoking may be an essential mediating variable of this relationship.

Moreover, this study on Dutch adolescents replicates the powerful association of early onset cigarette smoking on subsequent drug use, reported earlier in Finnish adolescents of similar age (8). Strikingly, both studies show risk estimates exceeding 20 for adolescents who had their first cigarette by the age of 12. In both studies, this association remained significant even when adjusted for familial liability and ExtB problems. To adjust for familial influences, the Finnish twin study applied a discordant twin pair design, while the Dutch study adjusted for familial drug abuse risk data collected within TRAILS. The Finnish study additionally adjusted for peer substance use and socioeconomic status of the family. Although the findings of these two studies establish a link between early-onset smoking and subsequent cannabis use, neither of them provides exhaustive evidence for causality. Thus, it remains a challenge to show whether this is a causal link reflecting the 'gateway' hypothesis (39) or whether there are common genetic or environmental risk factors for both early smoking onset and cannabis use initiation (40). Despite the replicated association between early smoking onset and subsequent cannabis use initiation, independent of ExtB problems, we should note that different scales detecting ExtB were applied in the Dutch and the Finnish studies. Although both studies utilized continuous measurement scales, the Finnish scale consisted of the Multidimensional Peer Nomination Inventory Teacher and Parental ratings, where the scales for hyperactivity-impulsivity, aggression, and inattention, formed a factor for ExtB problems (41). The Dutch analyses were based on separate CBCL and YSR DSM-IV scales which clearly differentiate between ADH, CD and OD, but can also be used as sum score of these scales reflecting ExtB problems in general (27, 28, 30).

Based on statistics in 2003, 28% of adolescents in the Netherlands and 11% in Finland reported using cannabis (42). Part of the differences between the two countries may be related to different legislations of cannabis use. In the Netherlands cannabis is 'semi-legal', i.e. officially tolerated for both possession and sales in restricted locations and quantities (43). Strikingly, in both studies early onset smoking overshadowed the predictive power of ExtB with regard to cannabis initiation.

Considering sex differences and interactions, boys scored higher in ExtB while cigarette smoking was more common in girls. However, there was no significant sex difference in ever use of cannabis. Although there were no consistent sex interactions across ExtB problems, conduct problems tended to predict cannabis use more strongly among boys than girls. Also, daily smoking predicted cannabis more strongly among boys than among girls. Interestingly, familial loading to substance use and ExtB as such increased the risk of cannabis use significantly among girls, but not among boys. To understand the mechanisms underlying such sex interactions remains a challenge for further studies, but one potential explanation is that familial influences may be less important for males in this context.

Concerning moderating effects, i.e. smoking x ExtB interactions, we found only one significant interaction. Oppositional problems did not influence cannabis use when looking at never smoking girls, whereas for girls who had smoked there was almost a two-fold increased risk for the likelihood of trying cannabis. This means that among girls the influence of oppositional problems is actually conditional on smoking status. We are not aware of similar findings in any other studies.

An important strength of our study was that we included information from both parents and adolescents. A further strength is a longitudinal prospective design allowing assessment of children throughout different developmental stages – even before substance use initiates. Our sample seems to be representative with regard to tobacco and cannabis use prevalence rates in the Netherlands: the national prevalence of ever smoking by the age of 16 was 57%, while in the TRAILS sample this was 56% at T3 (42). Those rates of ever cannabis use were 28% and 31%, respectively.

A potential limitation is the use of a DSM-IV oriented scale rather than actual DSM diagnoses. Another limitation is that we investigated substance use initiation only and we have no information on how smoking and ExtB problems could be related to substance abuse or dependence. Moreover, we mostly included the rating of the mother instead of the father, on problem behaviors. This may have limited our understanding of their adolescent's ExtB, although there is evidence for a rather strong agreement between mother's and father's ratings on their child's behavior (44). Finally, our sample did not represent the full range of ethnic diversity existing in the Netherlands, but included mostly adolescents of Dutch origin.

To conclude, several associations of ExtB problems with cannabis use were mediated through smoking. Similar to the earlier findings among Finnish adolescents, early onset cigarette smoking was a powerful predictor of later cannabis use among Dutch adolescents as well. This early smoking influence seems to be relatively independent of ExtB problems. Such a consistent finding across two countries has implications for prevention. Although ExtB problems are important as a starting point for substance use trajectories, early onset

smoking should be identified as an important marker of cannabis use risk. Interventions to reduce ExtB may still be useful in reducing the onset of cannabis use, but the mechanism might be indirect via reducing early smoking onset.

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Chapter 5

Are Adolescents Gambling With Cannabis Use? A Longitudinal Study of Observed and Reported Impulsivity Measures in Relation to Adolescent Substance Use. The TRAILS Study

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ABSTRACT

Purpose: This study examined 1) the predictive value of observed versus reported measures of impulsivity on the onset of cannabis use, and to determine if lifetime tobacco and cannabis users can be differentiated by their level of impulsivity, and 2) the predictive value of observed versus reported measures of impulsivity on repeated cannabis use, and to determine if repeated tobacco and cannabis users can be differentiated by their level of impulsivity.

Methods: The present study involves 667 (50.5% female) adolescents assessed at two time points of the TRacking Adolescents' Individual Lives Survey (TRAILS) study. Adolescents in our study participated in the Bangor Gambling Task (BGT), as well as completed self-report questionnaires assessing cannabis use behavior (mean age 16.11 years) and the Behavioral Inhibition System (BIS)/Behavioral Activation System (BAS) questionnaire (mean age 13.56 years).

Results: Higher levels of BAS functioning increased the likelihood that adolescents would ever use substances such as tobacco or cannabis during their lifetime. In contrast, low BIS functioning increased the likelihood of repeated cannabis use. Repeated tobacco users did not significantly differ from lifetime users by their BIS functioning. The BGT measures were not significant in relation to lifetime or repeated use of cannabis or tobacco.

Conclusion: High BAS seems to be more important for experimental substance use, whereas low BIS seems to be more important for progression into regular cannabis use specifically. In contrast to the BIS/BAS, our laboratory test of impulsivity, the BGT, is not correlated with early onset tobacco/cannabis use. Furthermore, the BGT is not correlated with the BIS/BAS measures.

Introduction

Adolescence and young adulthood are the lifespan periods in which experimentation with substances, such as cannabis, is most likely to begin (1-4). According to the European School Survey Project on Alcohol and Other Drugs (ESPAD), about a third of adolescents have tried cannabis at least once by the age of 16 years (5) Although many adolescents experiment with cannabis without incurring any major consequences (6), cannabis use has been associated with specific detrimental consequences (7, 8) such as neurological deficits (Pope 2003), and an increased risk for dependence later in life (2, 9, 10). Furthermore, adolescents who reported regular cannabis use possess a higher likelihood of encountering these risks than their "curious" peers who briefly or ever experiment with cannabis (11, 12).

In an attempt to identify specific risk factors and mechanisms that place adolescents at an increased risk to use cannabis, many researchers have examined specific personality and temperamental characteristics such as impulsivity (13-15). Impulsivity is generally thought to be comprised of novelty seeking, sensation seeking, disinhibition, and a deficit in (lack of) forethought (16, 17). Findings from previous studies suggest that adolescents who are more impulsive have an increased likelihood to use cannabis recreationally as well as repeatedly. The manifestation of impulsive and disinhibited behavior has been related to the functioning of the Behavioral Activation System (BAS) and the Behavioral Inhibition System (BIS), which are proposed to be the two neurological and motivational systems that underlie much of our behaviors and personality (18, 19). The BAS is proposed to be sensitive to signals of reward and non-punishment, and relates to approach-oriented behavior, the BIS is sensitive to signals of punishment and non-reward, and relates to avoidance or withdrawal behavior. According to Gray (1981), particularly an overactive BAS is associated with impulsivity. However, a hypoactive BIS is associated with a reduced capacity to inhibit behavior that leads to negative or painful outcomes, resulting also in predominantly reward-seeking behavior (20). Individuals with high levels of BAS (20, 21) and low levels of BIS (22, 23) are more likely to engage in problematic behaviors. Likewise, BIS/BAS functioning has also been associated with substance use. For instance, individuals with high levels of BAS have been found to be more likely to experiment with licit (24) substances, illicit substances (25, 26), and to develop substance misuse (27, 28). Similarly, low BIS functioning has been associated with, for instance, cannabis use (29). Therefore, the BIS/BAS system measures approach and inhibition, which is also referred to as trait impulsivity in our study.

Observed measures of impulsive behaviors, such as decision-making state impulsivity (e.g. gambling tasks), have also been linked to an increased likelihood to use substances, including cannabis. For example, Whitlow and colleagues (26) found that long-term adult cannabis users made more decisions that led to larger immediate gains despite the more costly losses than controls on the Iowa gambling task. However the authors were unsure if these deficits are the result of marijuana use or pre-existing differences.

As yet, very few studies have taken into account both observed and reported measures of impulsivity, which is very important in understanding the "true nature" of impulsivity in adolescence (30). For instance, Steinberg and colleagues (2004) found that when examining self-reported questionnaire data, adolescents and adults were very similar in their information processes needed to perceive and deal with impulsive risk taking events. For

example, when presented with hypothetical risky situations, adolescents and adults answered similarly as to how they would react in the situation. In contrast, adolescents differed greatly in their ability to make decisions during "heat of the moment situations" in that they were more likely to make rash and risky decisions, such as choosing to sneak out of the house in the middle of the night and throw rocks at a girlfriend's window or not to stop to put on a condom during sex, when compared to adults. Similarly, adolescents were more likely to make risky/impulsive "heat of the moment" decisions during a simulated driving experiment especially when peers are present (30). In the current study we measured impulsivity as behavior directed towards short-term reward with disregard to the negative consequences.

Furthermore, it is well known that cannabis use is often accompanied by either early onset, recreational and/or repeated tobacco use (31-33). It is of importance to understand how cannabis users may be differentiated from those who only use tobacco by focusing on specific risk factors. More insight into the functioning of both observed and reported impulsivity during adolescence can assist health care professional in their pursuit to pinpoint at risk cannabis users, and make it possible to differentiate cannabis users from tobacco smokers.

Using data from the TRacking Adolescents' Individual Lives Survey (TRAILS), a general population study, we aimed to investigate the predictive value of observed, state impulsivity, and reported, train impulsivity, measures of impulsivity on lifetime and repeated cannabis use. In order to determine if associations were specific for cannabis use, rather than for general smoking behavior, we additionally aimed to determine if tobacco and cannabis users can be differentiated by their level of impulsivity.

Methods

Participants and procedure

The present study is embedded within the Tracking Adolescents' Individual Lives Survey (TRAILS), a large prospective population study of Dutch adolescents with bi- or triennial measurements from age 11 to at least age 25. The three assessments waves finished so far ran from, respectively, March 2001 to July 2002 (T1) (mean age 11.09 years, SD 0.55, 50.8% girls), September 2003 to December 2004 (T2) (mean age 13.56 years, SD 0.53, with 51.0% girls), and September 2005 to December 2007 (T3) (mean age 16.27 years, SD 0.73, with 52.3% girls). At T1, 2230 children were enrolled in the study (response rate 76.0%, see (34) of whom 1816 (81.4%) participated at T3. Adolescents were assessed at school (or other test locations), where they completed questionnaires, in groups, under the supervision of one or more TRAILS assistants during all three measurements (T1, T2 and T3). Before each measurement wave, informed consent was obtained from all adolescents and their guardian(s) after the nature of the study had been fully explained. Furthermore, the Central Committee on Research Involving Human subjects (CCMO) approved all of the TRAILS study protocols.

The aims of the present study were addressed using a focus sample of TRAILS. During T3, 744 adolescents were invited to perform a series of laboratory tasks (hereafter referred to as the Experimental Session (ES) that was included in addition to the usual assessments, of

which 715 (96.1%) agreed to participate. Adolescents with missing data on cannabis use, tobacco use, or BIS/BAS were excluded leaving a sample of 667 adolescents (mean age 16.11, SD = 0.59, 50.4% female) for analysis.

The ES, during which the participants' were asked to participate in a spatial orienting task, a gambling task, a startle reflex task, and a social stress test, took place on weekdays, in soundproof rooms with blinded windows at selected locations in the participants' residence town. The sessions lasted about 3 hours and 15 minutes, and started between 8:00 a.m. and 9:30 p.m. (morning sessions, 49%) or between 1:00 p.m. and 2:30 p.m. (afternoon sessions, 51%). We asked the participants to refrain from smoking, using coffee, milk, chocolate, and other sugar containing foods in the 2 hours before the session. The test assistants, 16 in total, received extensive training in order to optimize standardization of the experimental session. At the start of the session, the test assistant, blind to the participants' risk status, explained the procedure and administered a short checklist on current medication use, quality of sleep, and physical activity in the last 24 hours, and attached the equipment for heart rate and blood pressure measurements. Next, participants filled out four computerized questionnaires. The participants were asked to relax until 35 minutes after the start of the session. Subsequently, the challenges (i.e., laboratory tasks) were administered in the before-mentioned order. Every task was followed by a short break, during which participants reported subjectively experienced arousal. Following the social stress test, the participants were debriefed about the experiment and could relax for about 15 minutes (for more information please refer to Bouma 2009).

Measures

Dependent Variables

Assessment of Lifetime and Repeated Cannabis Use (T3)

Cannabis use was assessed at 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 other questions, participants were asked to report the frequency of cannabis use ever and in the past year. Answers on these questions were dichotomized in order to achieve a measure of lifetime cannabis use, defined as ever use of cannabis, and repeated cannabis use, defined as the use of cannabis on at least five occasions in the past year (5, 35).

Assessment of Lifetime and Repeated Tobacco Use (T3)

Lifetime and repeated tobacco use was assessed via self-report questionnaires, which were filled out at school or home, supervised by trained TRAILS assistants. The following questions were asked: "Have you ever smoked a cigarette?" "If yes, how many cigarettes (or hand rolled cigarettes) have you had in the last four weeks?"). The options were as follows: *0= I have never smoked, 1=one time, 2=two or three times, 3=four through six times, 4= seven or more times*. Furthermore, adolescents were asked: "How many cigarettes do you smoke per day?". Based on these questions, we created binary measures of ever, weekly

and daily use. Subsequently, we defined repeated tobacco use as at least 50 or more cigarettes during their lifetime in addition to either daily or weekly use during T3 (36).

Independent Variables

Assessment for Self-reported Impulsivity (T2)

BIS/BAS was measured using the Dutch version of the 20-item Carver and White scales (37, 38), which consists of the following four subscales: 1) BIS, a seven item scale reflecting concern and fear about the possibility of a non-pleasurable occurrence, or sensitivity to an occurrence, 2) BAS-reward responsiveness (BAS-RR), a five item scale reflecting responsiveness to reward, 3) BAS-drive (BAS-D), a four item scale reflecting the tendency to act quickly in pursuit of appetitive goals, and 4) BAS-fun seeking (BAS-FS), a four item scale reflecting the tendency to seek out new potentially rewarding experiences. Given that the alpha for the three BAS subscales was low (BAS-RR: α=0.64, BAS-D: α=0.65, BAS-FS: α=0.44) and to minimize the amount of analyses, we chose to combine BAS-RR, BAS-D, and BAS-FS to reflect a total BAS combined scale (BAS-CS). The alpha values for the current study are: BIS: α=0.68, BAS-CS: α=0.76. Various studies have confirmed the reliability of the Carver and White scales (37-39).

Assessment for Observed Impulsivity (T3)

The Bangor Gambling Task (BGT) was one of a battery of tests administered during the Experimental Session (ES)at T3. The BGT (40) involves a deck of 100 playing cards, with 38 'high' cards (Jack, Queen, King, Ace) and 62 "low" cards (between 2 and 10). High cards produce financial gain, whereas the low cards produce financial loss. Each card was labeled on the face/number side with the monetary loss or gain, corresponding to one of four values (win €0.40, win €0.20, loss €0.40, loss €0.20). The deck of 100 cards consists of five blocks of 20 cards, with increasing probabilities of loss (40). To prevent the adolescent from predicting when the game would end, fifty random cards were placed at the bottom of the deck.

At the start of the game the participants were given € 5.00, and told that they may keep any winnings that remained after the game was completed. Participants were informed that the deck of cards was not a regular deck of cards, but instead contained a unique variety of cards chosen specifically for the present gambling task. Participants were then presented with 25 €0.20 cent coins and instructed that the purpose of the game was to try to win as much money as possible. They would be given the option to "gamble" or "not gamble" before the experimenter would turn over a card. They could choose to gamble or not gamble as often as they would like. If they chose not to gamble, regardless of the card, they would not incur any consequences or benefits. If they chose to gamble and received a card with a positive amount on the face of the card then they would win that amount, whereas if they received a card with a negative amount then they would lose that amount. Unlike the Bowman study (40) in which the adolescents were given more money if they depleted their funds before the 100 cards were completed, participants in our study participated in the gambling task until they reached the maximum of 100 cards or until their money was

depleted. In our study all adolescents were able to complete at least 71 cards before their funds were depleted.

Performance on the task was calculated in two manners A) *BGT 71*, similar to the Bowman study, was calculated as the number of non-gambling choices – number of gambling choices. Unlike the Bowman study (40) we only took the first 71 cards into account instead of the total 100 cards given that not all of our participants finished the total 100 cards before their funds were depleted. B) *Percent gambled* was calculated as number of times gambled / total cards played (e.g. until their money was depleted or 100 cards were finished). Low scores on the BGT 71 and high scores on Percent gambled reflect more impulsive behavior during gambling tasks.

Confounding variables

Assessment of Alcohol Use during the Past Month (T3)

Monthly Alcohol use was assessed via self-report questionnaires, which were filled out during T3 at school or home, supervised by trained TRAILS assistants. The following question was asked: "Number of alcoholic drinks you have consumed in the last four weeks." The options were as follows: *0= 0, 1= 1, 2= 2, 3= 3 with the scale continuing until 13= 40 or more.* We dichotomized alcohol use during the past month use as 0= no use of alcohol in the past month and 1= use of alcohol in the past month.

Experimental Session (ES) Selection Stratum (T3)

Adolescents with a slightly increased risk of mental health problems had a greater chance of being selected for the ES. An increased risk was defined based on baseline temperament (high scores on frustration and fearfulness, low scores on effortful control), parental psychopathology (depression, anxiety, addiction, psychoses, or antisocial behavior), and environmental risk (living in a single-parent family) (41). The degree of increased risk is best indicated by the proportion of the total sample that was recruited for the focus cohort (approximately 10 out of 25).

Assessment of Socioeconomic status (SES) (T1)

Socio-economic status was measured with five indicators: educational level father/mother, five levels ranging from 'Elementary education' to 'University', occupation (father/mother, nine levels of the International Standard Classification of Occupations ranging from 'Elementary Occupations' to Legislators, Senior Officials and Managers', and family income (< €600/month to > €3,500/month in 9 steps). Each of the variables was standardized (z-scores), and the mean of the five standardized variables was used as the score of socio-economic status score (42, 43). The internal consistency was satisfactory (Cronbach's alpha 0.84), indicating that these variables can be considered to represent the socio-economic status of the family. The lowest 25% of scores were considered to be low socio-economic status; the highest 25% to be high socioeconomic status, and the rest were labeled middle socioeconomic status.

Assessment of Intelligence (IQ) (T1)
Intelligence was individually assessed at T1 by the Vocabulary and Block Design subtests (44) of the Revised Wechsler Intelligence Scales for Children (WISC-R).

Statistical Analysis
The analyses were conducted using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL), version 15. Means of and correlations between substance use, BIS, BAS, Bangor variables, and confounding variables were calculated using bivariate correlation analyses.

In order to establish whether reported (BIS/BAS) and/or observed (Bangor) impulsivity predict ever cannabis use as well as repeated cannabis when compared to tobacco smokers and never users, we conducted multiple multinomial logistic regressions using two different reference groups for each analysis: a) abstainers and b) cigarette smokers. In the first multinomial regression analysis, lifetime cannabis users (lifetime tobacco users *not* excluded) and lifetime tobacco users (lifetime cannabis users *were* excluded) were compared to lifetime abstainers (no lifetime cannabis or lifetime tobacco use). After that, lifetime cannabis users (lifetime tobacco users *not* excluded) were compared to lifetime tobacco users (lifetime cannabis users *were* excluded). In the second multinomial regression analysis, repeated cannabis users (lifetime tobacco users *not* excluded) and repeated tobacco users (no repeated cannabis users) were compared to lifetime users (repeated tobacco or cannabis users were excluded). Subsequently, repeated cannabis users (lifetime tobacco users *not* excluded) were compared to repeated tobacco users. All models controlled for sex, IQ, ES risk group status, monthly alcohol use, and age at BGT.

Results
Lifetime and repeated cannabis use
Descriptive analyses demonstrated that 35.0% of the participants reported ever use of cannabis. Of these adolescents, 93% also had at least some experience with smoking tobacco (Figure 5.1). 28.0% of the adolescents reported ever using tobacco without having any experience with cannabis use. When the focus was on repeated use, 25.4% reported repeated cannabis use and 32.4% of the adolescents reported repeated tobacco use (repeated cannabis users excluded). Correlations between the variables are shown in Table 5.1. Mean scores and SD of the variables can be found in Figure 5.1.

Observed and reported measures of impulsivity predicting lifetime use of cannabis
When the focus was on reported measures of impulsivity, our findings indicate that higher levels of BAS significantly predicted lifetime use (Table 5.2) of cannabis (OR = 2.29, CI = 1.39-3.79, $p<0.01$). Similarly, higher levels of BAS also significantly increased the chances of lifetime use of tobacco (OR = 1.79, 95% CI = 1.09-2.94, $p<0.05$). Lifetime tobacco and cannabis users could not be differentiated based upon their reported levels of BAS, indicating that BAS-functioning was not specifically associated with cannabis use. In contrast, BIS functioning did differ among lifetime tobacco users, lifetime cannabis users and non-users. The BGT measures were not significant in relation to lifetime cannabis, lifetime tobacco use or never users.

Table 5.1 Bivariate associations between variables used in this study

	1	2	3	4	5	6	7	8	9	10	11	12
1. Lifetime use of tobacco [a]	-	.										
2. Lifetime use of cannabis	n/a [c]	-										
3. Repeated tobacco Use [b]	**0.48**	n/a	-									
4. Repeated cannabis use	n/a	**0.60**	n/a	-								
5. Sex *(0= female, 1= male)*	-0.04	0.02	-**0.11**	*0.08*	-							
6. IQ	*-0.12*	-0.01	-**0.13**	-0.00	0.07	-						
7. ES risk group status	-0.04	0.04	0.06	0.05	0.01	-0.12	-					
8. Monthly alcohol use	**0.23**	**0.31**	**0.22**	**0.21**	0.00	**0.08**	*-0.09*	-				
9. BGT 71	-0.08	0.00	*-0.08*	-0.00	-0.00	0.09	*-0.09*	0.02	-			
10. Percent Gambled	0.05	0.03	*0.09*	0.04	0.02	*-0.09*	0.05	-.012	**-0.79**	-		
11. BAS	0.09	0.08	-0.00	0.05	0.06	0.03	0.08	-.001	-0.04	0.07	-	
12. BIS	0.02	*-0.09*	0.0 1	- **0.14**	- **0.26**	-0.02	0.02	**-0.10**	-0.03	0.02	**0.18**	-

Bold values = significant at the p< 0.01 level, Italic values = significant at the p<0.05, [a] Lifetime cannabis users not included, [b] Repeated cannabis users not included, [c] n/a given that cannabis use was excluded in one of the variables.

Figure 5.1 Mean scores, n and SD

	Lifetime abstainers (n=245) Mean (SD)	Lifetime tobacco users [c] (n=190) Mean (SD)	Lifetime cannabis users [d] (n=232) Mean (SD)
Behavioral Inhibition System (BIS)	2.55 (0.53)	2.58 (0.49)	2.48 (0.51)
Behavioral Activation System (BAS)	2.83 (0.42)	2.90 (0.39)	2.94 (0.40)
BGT Percent Gambled [a]	0.44 (0.13)	0.47(0.12)	0.46 (0.15)
BGT 71 [b]	2.49 (4.48)	1.64 (4.53)	2.14 (4.96)

	Lifetime tobacco or cannabis users (n=422) Mean (SD)
Behavioral Inhibition System (BIS)	2.52 (0.50)
Behavioral Activation System (BAS)	2.92 (0.34)
BGT Percent Gambled [a]	0.46 (0.14)
BGT 71 [b]	1.93 (4.78)

	Repeated tobacco users [c] (n=138) Mean (SD)	Repeated cannabis users [d] (n=106) Mean (SD)	Lifetime tobacco or cannabis users [e] (n=178) Mean (SD)
Behavioral Inhibition System (BIS)	2.56 (0.48)	2.39 (0.50)	2.57 (0.50)
Behavioral Activation System (BAS)	2.89 (0.38)	2.94 (0.42)	2.94 (0.39)
BGT Percent Gambled [a]	0.48 (0.13)	0.47 (0.14)	0.45 (0.14)
BGT 71 [b]	1.35 (4.78)	2.11 (4.69)	2.24 (4.81)

[a] Bangor Gambling Task (BGT) Percent Gambled: number of times gambled / total cards played, [b] Bangor Gambling Task (BGT) 71: non-gambling choices – number of gambling choices taking the first 71 cards into account, [c] Tobacco users only (cannabis users excluded), [d] lifetime tobacco users *not* excluded [e] Repeated users excluded

Table 5.2 Multinomial regression of reported and observed impulsivity measures predicting lifetime and repeated cannabis and tobacco use

LIFETIME USERS		
Lifetime tobacco users [c] versus lifetime abstainers *(reference)*	OR	95% CI
Behavioral Inhibition System (BIS)	1.16	(0.78 - 1.75)
Behavioral Activation System (BAS)	1.79*	(1.09 - 2.94)
BGT Percent Gambled [a]	3.80	(0.88 - 16.46)
BGT 71 [b]	0.96	(0.92 - 1.00)
Lifetime cannabis users versus lifetime abstainers *(reference)*	OR	95% CI
Behavioral Inhibition System (BIS)	0.89	(0.59 - 1.33)
Behavioral Activation System (BAS)	2.29**	(1.39 - 3.79)
BGT Percent Gambled [a]	2.91	(0.69 - 12.25)
BGT 71 [b]	0.98	(0.94 - 1.02)
Lifetime cannabis users versus lifetime tobacco users [c] *(reference)*	OR	95% CI
Behavioral Inhibition System (BIS)	0.76	(0.51 - 1.13)
Behavioral Activation System (BAS)	1.28	(0.78 - 2.09)
BGT Percent Gambled [a]	0.76	(0.18 - 3.22)
BGT 71 [b]	1.02	(0.98 - 1.06)
REPEATED USERS		
Repeated tobacco users versus Lifetime tobacco or cannabis users [d] *(reference)*	OR	95% CI
Behavioral Inhibition System (BIS)	0.79	(0.49 - 1.29)
Behavioral Activation System (BAS)	0.76	(0.42 - 1.36)
BGT Percent Gambled [a]	5.19	(0.96 - 28.21)
BGT 71 [b]	0.96	(0.92 - 1.01)
Repeated cannabis users versus Lifetime tobacco or cannabis users [d] *(reference)*	OR	95% CI
Behavioral Inhibition System (BIS)	0.48*	(0.28 - 0.83)
Behavioral Activation System (BAS)	1.01	(0.53 - 1.91)
BGT Percent Gambled [a]	2.80	(0.47 - 16.89)
BGT 71 [b]	0.99	(0.94 - 1.05)
Repeated cannabis users versus repeated tobacco use *(reference)*	OR	95% CI
Behavioral Inhibition System (BIS)	0.61	(0.35 - 1.05)
Behavioral Activation System (BAS)	1.33	(0.69 - 2.57)
BGT Percent Gambled [a]	0.54	(0.08 - 3.53)
BGT 71 [b]	1.03	(0.98 - 1.09)

[a] Bangor Gambling Task (BGT) Percent Gambled: number of times gambled / total cards played, [b] Bangor Gambling Task (BGT) 71: non-gambling choices – number of gambling choices taking the first 71 cards into account, [c] Tobacco users only (cannabis users excluded), [d] Repeated users excluded ** p<0.01, * p<0.05

Observed and reported measures of impulsivity predicting repeated cannabis use
When compared to lifetime ever users, repeated cannabis users had lower levels of BIS (OR = 0.48, CI = 0.28-0.83, p<0.05) (Table 5.2). Repeated tobacco users and lifetime tobacco or cannabis users did not significantly differ in their levels of BIS. BAS functioning did not significantly differ among repeated cannabis or tobacco users and lifetime ever non-users. The BGT measures were not significant in relation to repeated use of cannabis or tobacco.

Discussion
In general, results from the present study suggest that reported levels of impulsivity are more useful for predicting lifetime and repeated substance use than observed levels of impulsivity. More specifically, high BAS increases the risk of lifetime experimental tobacco and cannabis use during adolescence, whereas low BIS increases the risk for progression into regular cannabis use during adolescence. Therefore, BIS appears to be a specific predictor for repeated cannabis use. These findings are in line with results from previous studies, which found that individuals with high levels of BAS (20-21) and low levels of BIS (22, 23) are more likely to engage in problematic behaviors, such as substance use or misuse. In addition to the findings of these studies, our study demonstrates that repeated cannabis users can be differentiated from lifetime users based upon their lower BIS functioning, even when controlling for additional confounders such as monthly alcohol use. Adolescent lifetime users of cannabis or tobacco did not differ significantly from repeated tobacco users on measures of BIS functioning. This result suggests that BIS is not a very good indicator of ever use or repeated tobacco use, but may be a better and specific indicator of more deviant behaviors such as cannabis use in adolescence.

Our findings suggest that adolescents who have a higher sensitivity to reward may be more likely to seek out different types of substance use experiences, but either quit or move on to other types of rewarding experiences instead of becoming repeated users. In contrast, adolescents with lower sensitivity to punishment, as seen in adolescents with low BIS functioning, are particularly vulnerable to cannabis use.

As mentioned before, repeated cannabis users, lifetime users, and non-users could not be differentiated based upon their performance on the BGT, whereas the self-reported measures, the BIS/BAS, were able to do so. In addition, although we had expected that high BAS and low BIS would be related to more risky behavior on the BGT, no such correlations were found. In contrast, the BIS/BAS questionnaire had less variation from the mean, suggesting that perhaps reported measures of impulsivity, such as the BIS/BAS questionnaires, have a higher ecological validity given that it correlates more with the participants' actual real life behavior. Given these findings, it is important to mention that young adults may have a higher correlation between observed and reported impulsivity. Indeed, in young adults, a significant, moderate correlation has been found between state and trait impulsivity (45-48).

The lack of significant findings between adolescent cannabis use and observed gambling behavior, the BGT, may also be explained by findings from previous research, which suggest that impulsive behavior is domain specific, the five domains of risk being: financial,

health/safety, recreational, ethics, and social, and does not remain consistent among different types of risk taking experiences (47, 49). For example, Weber and colleagues found that females, who were risk-aversive in most domains, did show more impulsive, risk taking behavior in social domains. Similarly, Kirby and colleagues (2010) mention that impulsivity may vary across types of reward. For example, some individuals may exhibit more impulsive behaviors with food whereas other may be more likely to act in an impulsive manner with money. Perhaps adolescent cannabis use may fall into a different type of risk taking domain, such as social or health/safety, than our observed measure of impulsivity, the BGT, which may fall under more recreational risk taking.

Contradictory to our findings, other gambling studies have found that substance users are more likely to exhibit impulsive behaviors (50, 52). The differences may be due to the fact that our population does not include addicted or long-term heavy substance users, given that the TRAILS study is a population-based non-clinical study. Furthermore, gathering information from all one hundred cards, such as in the Bowman study (2004), may yield different results.

Our findings suggest that adolescents with low BIS functioning are at an increased risk to use cannabis repeatedly, yet impulsivity cannot differentiate what type of substance adolescents are more likely to choose. Given that adolescent cannabis use poses unique neurological, cognitive, social and societal, health and addiction risks, the identification of adolescents who are at a risk for initiating cannabis use is of the utmost importance for developing successful intervention programs. To further differentiate lifetime onset cannabis users from other substance users and non-users, we suggest that researchers should look for characteristics and mechanisms which are more reliable than gambling behavior in adolescence to predict the onset and transition to repeated use of cannabis. Furthermore, the high occurrence of comorbid substance use complicates the endeavor of developing a "risk profile" that would be able to detect adolescents at risk for cannabis use and dependency. For intervention programs to be the most effective, vulnerable adolescents need to be targeted during adolescence (6). Findings from this study support that adolescents with a lower functioning BIS comprise a specific vulnerability group. Perhaps, similar to findings in high risk-taking gamblers (53, 54), low BIS functioning predisposes adolescents to become repeated cannabis users in that they are less sensitive to the types of punishment linked to cannabis use. For example, the adolescents mentioned above may be prone to take more risks because they are less sensitive to the consequences and punishment that are attached to the risk. Future research, which focuses on physiological characteristics, such as cortisol function and/or heart rate data, collected during risk taking situations, may help us to better understand this unique vulnerability group. For instance, according to the self-medication hypothesis, individuals who experience negative emotional states seek out specific substances that will help to alleviate those symptoms (55). Therefore, investigating the physiological profiles of adolescent tobacco users both prior to and after the initiation of cannabis use, in a longitudinal study, may provide a very important piece for understanding the difference between cannabis and tobacco users. Given that early onset cannabis users, late onset cannabis users and non-users could be differentiated

based upon their morning cortisol levels (56), further research focusing on HPA-axis functioning among cannabis and tobacco users may be a step in the right direction.

Strength and Limitations

To the best of our knowledge, this is the first study to take both reported and observed measures into account in a non-clinical adolescent prospective population with both cannabis and non-cannabis users, which we consider to be a major strength of our study. Furthermore, our study used two separate methods, reported and observed, of assessing impulsivity. In contrast, the present study is not without limitations. For instance, our study used an altered version of the BGT, therefore limiting our ability to view the gambling behavior of all adolescents throughout the total five blocks (100 cards), as in the Bowman study (40). Furthermore, the BIS/BAS was measured during T2, whereas the BGT was measured during T3, although the BIS/BAS correlates well with other behavioral measures collected during T3 (e.g. externalizing and internalizing behavioral problems). Finally, the measures (BIS/BAS and BGT) used in our study are a proxy of impulsive behavior/short term reward.

Implications

Impulsivity, as measured by the BIS/BAS and the Bangor Gambling Task, in itself is not specific enough to predict lifetime cannabis use during adolescence. Health care interventions should concentrate on more tangible goals to decrease cannabis use initiation such as educating parents to better understand as well as deal with the general impulsive nature that is characteristically a part of adolescence.

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Chapter 6

HPA axis Reactivity to Social Stress and Adolescent Cannabis Use: The TRAILS Study

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ABSTRACT

Aims: To investigate the relationship of lifetime and repeated cannabis use with hypothalamic–pituitary–adrenal (HPA) axis reactivity to social stress in a general population sample of adolescents.

Design: Adolescents who reported lifetime or repeated cannabis use, lifetime or repeated tobacco use, and never use of either cannabis or tobacco were compared with respect to their HPA axis reactivity during the Groningen Social Stress Task (GSST), which was based on the Trier Social Stress Task.

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

Participants: 591 adolescents (51% male) who participated in the GSST, which was an additional measurement during the third assessment wave.

Measurements: HPA axis stress reactivity was indexed by four cortisol samples collected before, during and after the GSST. Furthermore, all adolescents in our study completed self-reported questionnaires on lifetime and repeated cannabis and tobacco use. Models were adjusted for sex, recent alcohol use, experimental session risk status, socioeconomic status, mood, and time of the experimental session.

Findings: Lifetime cannabis users had significantly lower stress reactivity levels when compared to abstainers (OR = 0.68, CI = 0.55-0.85, $p<0.01$) and lifetime tobacco users (OR = 0.79, CI = 0.64-0.98, $p<0.05$). In addition, repeated cannabis users also exhibited lower stress reactivity levels when compared to lifetime ever users of either tobacco or cannabis (OR = 0.74, CI = 0.53-0.98, $p<0.05$).

Conclusions: Lower HPA-axis stress reactivity in adolescents is specifically related to lifetime and repeated cannabis use.

Introduction

Experimenting with cannabis during adolescence has been found to increase the risk of developing a cannabis use disorder later in life (1), later psychosis (2) as well as unemployment and higher school dropout rates (3). Furthermore, repeated cannabis use during adolescence further increases the likelihood of persistent use in adulthood (4). Given that cannabis use during adolescence is associated with a myriad of consequences, detecting adolescents at risk for cannabis use is imperative.

In their attempts to pinpoint adolescents that have a higher likelihood to initiate and repeatedly use cannabis, researchers have recently started to focus on hypothalamic-pituitary–adrenal (HPA) axis reactivity (5-7). The HPA axis is part of the human neuroendocrine system that regulates various bodily processes, and is a central component of the body's neuroendocrine response to stress. Individual differences in HPA axis response to stress can be measured during basal functioning (i.e. daily rhythm) or during stressful situations, which is a reflection of stress reactivity of the HPA axis. The end-product of the HPA axis, cortisol, has been shown to affect both behavior and emotions (8, 9)There is an increasing recognition that HPA axis reactivity is somehow involved in processes that may lead to substance use (10) and abuse (11-13). For example, the stimulation-seeking theory suggests that adolescents with a lower HPA axis reactivity/functioning are more likely to take risks and seek out sensation seeking experiences, such as drug use, to increase their level of arousal.

When examining HPA axis basal functioning in an adolescent population, Huizink and colleagues (5) found some evidence to support a link between HPA axis hypo-activity at awakening and early onset of cannabis use compared to late onset use. This might indicate an increased risk for early onset users of seeking stimulation to restore arousal levels by using substances. This finding is in line with animal studies in which rats with low HPA axis activity were more likely to initiate self-administered drug use (14). Interestingly, when examining basal cortisol levels in *tobacco* users, Huizink et al. (2009) found that higher HPA axis basal functioning increases the risk of initiating tobacco use during adolescence. This might suggest that HPA axis functioning has differential associations with various types of substances.

When examining HPA axis stress reactivity during stressful situations, Moss and colleagues found that adolescent sons of substance dependent fathers (diagnosed using the DSM-III-R) had a relatively low cortisol response to an anticipated stressor (6). In addition, their findings demonstrated that boys with low cortisol stress reactivity were more likely to initiate cannabis use at an early age (6, 7).

The current study is the first to address the link between changes in HPA axis stress reactivity, as indicated by an increase in cortisol level following a social stress task, and lifetime and repeated cannabis use in a population based cohort of adolescents. Because of our interest in cannabis use, rather than in the often accompanied use of tobacco (15-17), we additionally focused on the differentiation between cannabis users and tobacco smokers. The present study examined a) if adolescent lifetime cannabis users, lifetime tobacco users, and nonusers of both tobacco and cannabis differ with respect to their HPA axis stress reactivity during a social stress task and b) if adolescent repeated cannabis users, repeated

tobacco users, and ever users of either tobacco or cannabis differ with respect to their HPA axis stress reactivity during a social stress task. Based upon previous findings with regard to functioning of the HPA axis in relation to cannabis use (6), we hypothesized that lower cortisol stress reactivity is related to cannabis use during adolescence.

Methods

Participants and Procedure

The present study is embedded within the Tracking Adolescents' Individual Lives Survey (TRAILS), a large prospective population study of Dutch adolescents with bi- or triennial assessments from age 11 to at least age 25. The three assessments waves finished so far ran from, respectively, March 2001 to July 2002 (T1) (mean age 11.09 years, SD 0.55, 50.8% girls), September 2003 to December 2004 (T2) (mean age 13.56 years, SD 0.53, with 51.0% girls), and September 2005 to December 2007 (T3) (mean age 16.27 years, SD 0.73, with 52.3% girls). At T1, 2230 children were enrolled in the study (response rate 76.0%, see (18)), of whom 1816 (81.4%) participated at T3. Adolescents were assessed at school or other test locations, where they completed questionnaires, in groups, under the supervision of one or more TRAILS assistants during all three assessments (T1, T2 and T3). Before each assessment wave, informed consent was obtained from all adolescents and their guardian(s) after the nature of the study had been fully explained. Furthermore, all of the TRAILS study procedures were approved by the International ethical committee 'Central Committee on Research Involving Human Subjects (CCMO)' in the Netherlands.

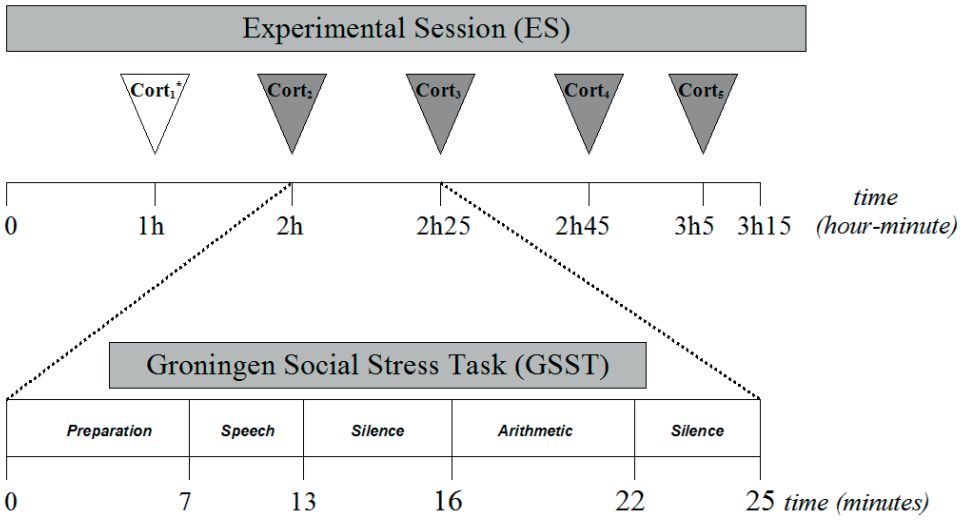
The aims of the present study were addressed using a focus (increased risk) sample of TRAILS. During T3, 744 participants were invited to perform a series of laboratory tasks (hereafter referred to as the Experimental Session (ES)), on top of the usual assessments. Of these adolescents, 715 (96.1%) agreed to participate. Adolescents with one or more risk factors for mental health problems had a greater chance of being selected for the ES. The risk factors were defined based on the three following three indicators: (a) Temperament, which was assessed with the Early Adolescent Temperament Questionnaire (EATQ) at T1. High scores ($\geq 90^{th}$ percentile) on frustration, fear, or low scores ($\leq 10^{th}$ percentile) on effortful control, were indicated as an increased risk, (b) Parental psychopathology, which was indicated if the participant had at least one parent with psychopathology (depression, anxiety, addiction, psychoses or antisocial behavior). This was assessed during a parental interview administered at T1, and (c) Environmental risk, which was indicated if at lest one of the biological parents is not living with the participant (19). In total, 66.0% of the focus sample had at least one of the above-described risk factors; the remaining 34.0% were selected randomly from the "low-risk" TRAILS participants. Please note that the focus sample still represented the range of problems seen in a normal population of adolescents. Adolescents who reported medical use of corticosteroid or selective serotonin reuptake inhibitors (N=7) were excluded from the analyses. Furthermore, adolescents with missing data on cannabis use, tobacco use, or cortisol were excluded leaving a sample of 591 adolescents (mean age 16.10, SD = 0.56, 50.9% male) for analysis. The inclusion of adolescents in our study was independent of both tobacco use at T2 ($p>0.05$) and cannabis use at T2 ($p>0.05$).

The Experimental Session (ES)

The ES, during which the participants' were asked to participate in a spatial orienting task, a gambling task, a startle reflex task, and a social stress test, which took place on weekdays, in sound-proof rooms with blinded windows at selected locations in the participants' residence town. The sessions lasted about 3 hours and 15 minutes, and started between 8:00 a.m. and 9:30 a.m. (morning sessions, 49%) or between 1:00 p.m. and 2:30 p.m. (afternoon sessions, 51%). We asked the participants to refrain from smoking, using coffee, milk, chocolate, and other sugar containing foods in the 2 hours before the session. The test assistants, 16 in total, received extensive training in order to optimize standardization of the experimental session. At the start of the session, the test assistant, blind to the participants' risk status, explained the procedure and administered a short checklist on current medication use, quality of sleep, and physical activity in the last 24 hours. Next, participants filled out four computerized questionnaires. The participants were asked to relax until 35 minutes after the start of the session. Afterwards, the first cortisol sample ($Cort_1$) was collected. Subsequently, the challenges (i.e., laboratory tasks) were administered during which the additional cortisol samples ($Cort_2$, $Cort_3$, $Cort_4$, $Cort_5$) were collected (Figure 6.1). Every task was followed by a short break, during which participants reported subjectively experienced arousal. Following the social stress test, the participants were debriefed about the experiment and could relax for about 15 minutes, after which subjective and physical arousal were assessed again (19).

The Groningen Social Stress Test (GSST)

The GSST was one of a battery of tests administered during the Experimental Session (ES) at T3 (Figure 6.1). The GSST is a standardized protocol, inspired by the Trier Social Stress Task (20), designed to induce moderate performance-related social stress. Similar tasks have proven to trigger a substantial stress response (21, 22). Participants were instructed to prepare a 6-minutes speech about themselves and their lives and deliver this speech in front of a video camera. They were told that their videotaped performance would be judged on content of speech as well as on use of voice and posture and rank-ordered by a panel of peers after the experiment. Participants had to speak continuously for the whole period of 6 minutes. The test assistant watched the performance critically, without showing empathy or encouragement. After 6 minutes of speech, the participants were told that there was a problem with the computer and they had to sit still and be quiet. After the interlude, participants were instructed to subtract 17 repeatedly, starting with 13,278. This difficult task was meant to induce a sense of uncontrollability. Uncontrollability was further provoked by negative feedback by the test assistant, including remarks such as, "No, wrong again, begin at the number 13,278", "Stop wiggling your hands" or "You are too slow, be as quick as you can, we are running out of schedule"(19).



* $Cort_1$ was not included in the analyses.

Figure 6.1 Timeline detailing when cortisol (Cort) was collected during the Experimental Session (adapted from Bouma et al., 2010).

Measures

Dependent Variables

Lifetime and Repeated Cannabis Use

All substance use measures were assessed at T3 by self-report questionnaires filled out at school or home, 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. The following questions were asked: "Have you ever smoked cannabis (weed or hash) in your life?" and "How many times have you smoked cannabis in the last four weeks?". The options were as follows: *0= I have never smoked cannabis, 1=one time, 2=two times, 3=three times…13= forty times or more*. Answers on these two questions were dichotomized in order to achieve a measure of lifetime cannabis use, defined as ever use of cannabis, and repeated cannabis use, defined as the use of cannabis on at least five occasions in the past year (23, 24).

Lifetime and Repeated Tobacco Use

Tobacco use was assessed with the following questions: "Have you ever smoked a cigarette?" "If yes, how many cigarettes (or hand rolled cigarettes) have you smoked in the last four weeks?". The options were as follows: *0= I have never smoked, 1=one time, 2=two or three times, 3=four through six times, 4= seven or more times*. Furthermore, adolescents were asked: "How many cigarettes do you smoke per day?". Based on these questions, we created dichotomous measures of ever, weekly and daily use. Subsequently, we defined lifetime tobacco use as ever use of tobacco, and repeated tobacco use as ever use of at least 50 or more cigarettes during their lifetime in addition to either daily or weekly use during T3 (25).

Independent Variables

HPA Axis Stress Reactivity

HPA axis responses to the GSST were assessed by four cortisol samples, referred to as $Cort_2$, $Cort_3$, $Cort_4$ and $Cort_5$. $Cort_2$ was taken just before the start of the GSST. There is a delay of approximately 20 min between the production of cortisol by the adrenal glands and the detectability of representative levels of cortisol in saliva. The first cortisol sample, $Cort_1$, taken right at the start of the experimental session (approximately one hour before the start of the GSST and reflecting HPA axis activity before the actual experimental session) could not be used as a pretest sample in the analyses because of relatively high cortisol levels, probably reflecting anticipation stress before the actual stress procedure (for further details on the procedure please see Bouma et al. 2009). $Cort_2$ hence reflects HPA axis activity 20 minutes earlier than the beginning GSST, and is considered a pretest measure. $Cort_3$ was collected directly after the end of the GSST and reflects HPA axis responses during speech. $Cort_4$ and $Cort_5$, collected 20 respectively 40 min after the end of the GSST are considered measures of post-stress activity of the HPA axis. In order to calculate the response to the GSST we first calculated the peak cortisol production (indicated by $Cort_3$, $Cort_4$ or $Cort_5$). The Maximum Increase was computed by subtracting $Cort_2$ (pretest) from this peak (19).

Confounding Variables

Since some variables are related with both cannabis use and HPA axis functioning, and might thus interfere in the relationship between the two, these variables were considered as putative confounders. The following variables were considered:

Past Month Alcohol Use

Past month alcohol use was assessed using the question: "What is the number of alcoholic drinks you have consumed in the last four weeks." The options were as follows: *0= 0, 1= 1, 2= 2, 3= 3 with the scale continuing until 13= 40 or more*. We dichotomized alcohol use during the past month as 0= never use of alcohol in the past month and 1= use of alcohol in the past month.

ES Selection Stratum

Since adolescents with one or more risk factors for mental health problems were overrepresented in the sample, we controlled for the presence of one or more risk factors (0= no risk factor, 1= one or more risk factors for mental health problems).

ES Time of Day

Although morning and afternoon levels of cortisol during stress experiments have been reported to be comparable (26), it is still important to control for the effect of time. For the purpose of the study, time of day was dichotomized as 0 = morning session and 1 = afternoon session.

Assessment of Mood

Current depressed mood was assessed at the start of the experimental session, by means of the Dutch version of the short Profile of Mood Scale (27). The scale includes eight items describing current mood, which could be rated on a 5-point scale (1 = not at all, 2 = a little, 3 = partly, 4 = kind of, 5 = very much).

Use of Oral Contraceptive in Females (OC)

Current use of OC was assessed at the day of the experiment, while type and name of the pill were asked as part of a questionnaire that was assessed previously, at school. We dichotomized oral contraceptives use as no= 0 and yes= 1.

Assessment of Socioeconomic Status

SES (28) was calculated as the average of income level, educational level, and occupational level of each parent at T1, using the International Standard Classification for Occupations (29) and was categorized in low, average and high SES.

Statistical Analysis

The analyses were conducted using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL), version 15. For descriptive purposes, means and standard deviations were calculated for Maximum Increase for abstainers, lifetime and repeated tobacco and cannabis

users. Correlations between cannabis use, tobacco use, Maximum Increase and confounding variables were calculated using bivariate correlation analyses. Cortisol data were log transformed (using the natural logarithm) to approach a normal distribution before analysis.

In order to establish whether Maximum Increase is associated with lifetime as well as repeated cannabis use when compared to lifetime and repeated tobacco use and nonuse, we performed multiple multinomial logistic regressions using two different reference groups for each analysis. In the first multinomial regression analysis, lifetime cannabis users and lifetime tobacco users (with no lifetime cannabis use) were compared to lifetime abstainers (no lifetime cannabis or lifetime tobacco use). After that, lifetime cannabis users were compared to lifetime tobacco users. In the second multinomial regression analysis, repeated cannabis users and repeated tobacco users (no repeated cannabis users) were compared to lifetime users (lifetime but no repeated use of tobacco or cannabis). Subsequently, repeated cannabis users were compared to repeated tobacco users. In all models we controlled for sex, age at the ES, ES Selection Stratum, ES time of day, past month alcohol use, SES, use of oral contraceptives, and mood (Table 6.1).

Results

Lifetime and repeated cannabis use

Descriptive analyses demonstrated that 204 of the 591 included adolescents reported ever use of cannabis (Figure 6.2). Of these adolescents, 188 had at least some experience with smoking tobacco. 168 of the adolescents reported ever using tobacco without having any experience with cannabis use. When only lifetime users of tobacco or cannabis were considered, 90 of the adolescents reported repeated cannabis use and 120 of the adolescents reported repeated tobacco use (repeated cannabis users excluded) (Figure 6.2). Mean scores and SD of the Maximum Increase per group can be found in Figure 6.2.

HPA axis stress-reactivity and lifetime cannabis use

Our findings indicated that a smaller increase in cortisol-level (a lower Maximum Increase, thus lower HPA-axis stress reactivity) during the GSST, was significantly associated with lifetime use of cannabis when compared to both abstainers (OR = 0.68, CI = 0.55-0.85, $p<0.01$) and lifetime tobacco users (OR = 0.79, CI = 0.64-0.98, $p<0.05$) (Table 6.2). Lifetime tobacco users could not be differentiated from tobacco abstainers based upon their Maximum Increase, indicating that lower HPA axis stress reactivity was uniquely associated with lifetime cannabis use.

HPA axis stress reactivity and repeated cannabis use

When compared to lifetime ever users of tobacco or cannabis, repeated cannabis users had a significantly smaller increase in cortisol-level during the GSST (a lower Maximum Increase; OR = 0.74, CI = 0.53-0.98, $p<0.05$, Table 6.2). Repeated tobacco users did not significantly differ in their Maximum Increase from lifetime tobacco or cannabis users, nor from repeated cannabis users.

Table 6.1 Bivariate associations between variables used in this study

	1	2	3	4	5	6	7	8	9	10	11	12
1. Lifetime use of tobacco [a]	-	.										
2. Lifetime use of cannabis	n/a	-										
3. Repeated tobacco use [b]	**0.49**	**0.40**	-									
4. Repeated cannabis use	n/a	**0.59**	n/a	-								
5. Max Increase T3	-0.09	**-0.13**	**-0.14**	*-0.10*	-							
6. Sex	-0.03	0.02	*-0.10*	0.06	**-0.20**	-						
7. SES	*-0.10*	0.08	*-0.10*	0.01	0.06	0.02	-					
8. ES Selection Stratum	-0.06	-0.01	0.07	0.04	0.01	0.01	**-1.21**	-				
9. Alcohol use (current month)	**0.22**	**0.31**	**0.24**	**0.20**	0.08	0.02	**0.17**	**-0.13**	-			
10. Age at GBE	0.06	*0.10*	0.05	0.04	0.01	-0.01	0.03	-0.03	0.07	-		
11. Depression Risk	0.04	**0.12**	0.08	0.02	-0.04	**0.22**	0.08	0.02	0.02	0.06	-	
12. GSST Time	-0.05	0.04	0.04	-0.01	-0.07	*-0.09*	*0.10*	-0.02	-0.01	-0.02	*0.10*	-

Bold values = significant at the p< 0.01 level, *Italic values* = significant at the p<0.05, [a] Lifetime cannabis users not included, [b] Repeated cannabis users not included

	Lifetime abstainers n=219 Mean (SD)	Lifetime tobacco users [a] n=168 Mean (SD)	Lifetime cannabis users n=204 Mean (SD)
Maximum Increase	2.48 (3.26)	1.89 (2.84)	1.43 (2.46)

	Lifetime tobacco or cannabis users n=372 Mean (SD)
Maximum Increase	1.92 (2.65)

	Repeated tobacco users [a] n=120 Mean (SD)	Repeated cannabis users n=90 Mean (SD)	Lifetime tobacco or cannabis users [b] n=162 Mean (SD)
Maximum Increase	1.43 (2.60)	1.44 (2.74)	1.92 (2.65)

[a] Tobacco users only (cannabis users excluded), [b] Repeated users excluded.

Figure 6.2. Mean scores, n and SD

Table 6.2 Multinomial regression of Maximum Increase (T3) predicting lifetime and repeated cannabis and tobacco use

LIFETIME USERS		
	OR	95% CI
Lifetime tobacco users [a] versus lifetime abstainers (reference)		
Maximum Increase (T3)	0.87	0.68 – 1.12
Lifetime cannabis users versus lifetime abstainers (reference)		
Maximum Increase (T3)	0.68 **	0.55 – 0.85
Lifetime cannabis users versus lifetime tobacco users [a] (reference)		
Maximum Increase (T3)	0.79 *	0.64 – 0.98
REPEATED USERS		
	OR	95% CI
Repeated tobacco users versus Lifetime tobacco or cannabis [b] users (reference)		
Maximum Increase (T3)	0.85	0.63 - 1.16
Repeated cannabis users versus Lifetime tobacco or cannabis [b] users (reference)		
Maximum Increase (T3)	0.74*	0.53 - 0.98
Repeated cannabis users versus repeated tobacco users [a] (reference)		
Maximum Increase (T3)	0.85	0.62 - 1.18

[a] Tobacco users only (cannabis users excluded), [b] Repeated users excluded ** p<0.01, * p<0.05

Discussion

The aim of the present study was to investigate the relationship of HPA-axis stress reactivity during a social stress task and lifetime and repeated cannabis in the TRAILS general population sample of adolescents. We found that lifetime adolescent cannabis users exhibited lower HPA axis stress reactivity in response to a social stressor when compared to both never users of either tobacco or cannabis and lifetime tobacco only users. In addition, repeated adolescent cannabis users exhibited a lower HPA axis stress reactivity when compared to lifetime ever users of either tobacco or cannabis. These findings suggest that particularly adolescents that use/have used cannabis, rather than those who smoke/have smoked tobacco, are characterized by low cortisol stress reactivity. Furthermore, findings suggest that adolescents that repeatedly use cannabis can be differentiated from more experimental users by their lower levels of HPA axis stress reactivity.

The finding that low stress reactivity is associated with adolescent lifetime or repeated cannabis use in a non-clinical sample of adolescents extends previous findings from Moss et al. (7), who demonstrated that low cortisol reactivity in sons of substance dependent fathers was associated with early onset cannabis use (6, 7). When looking at alcohol consumption, Evans and colleagues (30) show that adolescents who begin *drinking* at an earlier age also show an attenuated HPA axis reactivity. This link between low HPA axis reactivity to stress and adolescent substance use might be partially explained by the stimulation-seeking hypothesis. Given that acute intake of cannabis and alcohol causes increases in cortisol level (31-33), individuals with low HPA axis stress reactivity might use these substances to stimulate their HPA-axis activity. In addition, adolescents might use cannabis as a means to increase their responses to everyday activities (34), thus allowing them to better experience sensation or novelty. Interestingly, the current study is clearly able to differentiate adolescent cannabis users from tobacco users based upon their lower HPA axis stress reactivity. In contrast to cannabis users, lifetime tobacco users did not differ from abstainers, and repeated tobacco users did not differ from lifetime ever users with regard to their HPA axis reactivity. In an earlier study based on TRAILS data, Huizink and colleagues (2009) demonstrated that frequency of tobacco use was predicted by moderately higher, instead of lower, basal cortisol levels (5). These findings suggest that adolescents may be involved in certain types and patterns of substance use based upon a specific physiological profile or need.

The present study is not without limitations. In Europe, it is common to smoke cannabis with a small amount of tobacco mixed in the joint. Therefore, our cannabis users also inhaled tobacco. Given that we were able to compare our cannabis use group to a “pure” tobacco use group and no significant findings were associated with tobacco use and HPA axis reactivity, we feel that the construction of our tobacco and cannabis user groups is justified. Furthermore, since HPA axis reactivity and cannabis use were measured at the same assessment wave, we cannot make any conclusive statements about the directionality of their association. Based on findings from previous research (6) we expect that low HPA axis reactivity to stress increases the risk of (repeated) cannabis use. However, although rates of cannabis use were generally low in our adolescent population, we cannot exclude the possibility that the use of cannabis might have affected HPA axis reactivity. Dysregulation of

the HPA axis leading to deficient cortisol reactivity to stressors has indeed been reported following persistent nicotine and alcohol use (32). However, although acute intake of cannabis has been found to cause increases in cortisol level (31-33), we are not aware of any studies that have demonstrated dysregulation of HPA-axis stress reactivity as a result of cannabis use.

In conclusion, the present findings in a nonclinical sample, suggest that a lower HPA axis stress reactivity increases the likelihood of both lifetime and repeated *cannabis use*. In line with the findings of the current study, combined with the findings from Evans and colleagues (30), we suggest that future research should focus on the HPA axis stress reactivity of users of both cannabis and alcohol during adolescence, with a special focus on binge drinkers and regular cannabis users. Particularly research in which HPA axis stress reactivity is assessed prior to the initiation of substance use, and thus before any dysregulation of the HPA axis due to substance use may occur, is recommended. In addition, neuroimaging studies have taught us more about the acute effects of cannabis use in that cannabis is associated with changes in brain activity (35-38). A neuroimaging study within an adolescent population, before and after the onset of recreational or acute cannabis use, may be able to provide more information about the effects of cannabis use. In order to further elucidate the mechanisms behind the development of cannabis abuse and dependence, future research should aim to investigate further HPA (re)activity as an endophenotype predictive of cannabis use.

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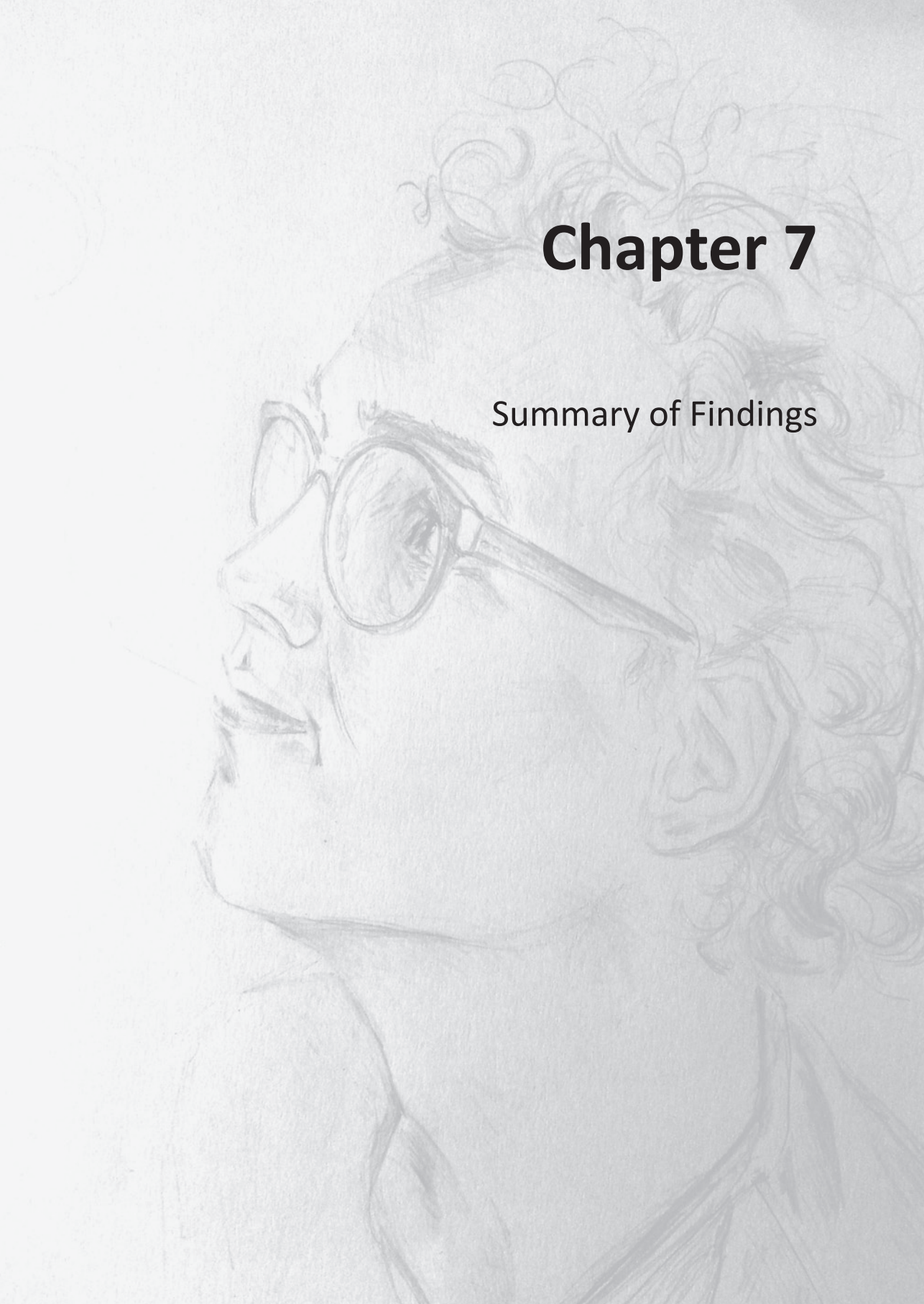
Chapter 7

Summary of Findings



Summary of Findings

The main objective of this thesis was to provide a better understanding of which factors predict cannabis use among adolescents, and to examine which of these factors are able to differentiate cannabis users from tobacco users. Given that Dutch adolescent cannabis users often combine cannabis use with tobacco use, through the preferred *method of intake* by smoking a 'joint', one can expect that several risk factors for tobacco use and cannabis use are shared. However, not all smokers of tobacco progress to cannabis use. Hence, some specific characteristics of individuals who do start using cannabis and maintain their use over time may shed light on which factors hold promise for preventive efforts targeting adolescent cannabis use. For studying several research questions related to this objective, data from TRAILS, a large, general population study of Dutch adolescents, were analyzed. In this chapter, a summary of the main findings is presented first. In the next chapter, a general discussion of the findings is provided, including limitations and strengths of this research. Finally, implications for (clinical) practice and recommendations for future research are given.

Summary of Main Findings

Which model best predicts cannabis use during adolescence: the Gateway Model, the Common Liability Model and/or the Route of Administration Model?

Chapter 2 describes the findings of a survival analysis with TRAILS data, in which the associations between early onset smoking, early onset alcohol use and subsequent cannabis use initiation were examined. Several models were compared: the Gateway Hypothesis, the Common Liability Model, and the Route of Administration Model. In short, the Gateway Hypothesis proposes that drug consumption progresses in a stage-like sequence, that is, use of licit drugs such as tobacco and alcohol precedes cannabis use, which in turn is followed by use of other illicit drugs like cocaine. The Common Liability Model proposes that using both licit and illicit drugs may be due to the influence of a common liability. This liability may include a genetic and individual vulnerability, such as proneness to deviancy and familial liability to addiction. Alternatively, the Route of Administration Model suggests that the shared route in which substances are administered (e.g. through inhalation) may account for the future initiation of other types of substance use, which share that method of intake. We found that early onset tobacco use did not pose a significantly higher risk of initiating cannabis use than early onset alcohol use. Therefore, we could rule out the Route of Administration Model for initiation of cannabis use. This model assumes a stronger relationship between smoking tobacco and smoking cannabis as compared to drinking alcohol and smoking cannabis. Similarly, we could partly rule out the Gateway Hypothesis given that this model could not explain our finding that adolescents who reported early onset combined use of both tobacco and alcohol have a higher likelihood to initiate cannabis use than adolescents who have tried either tobacco or alcohol. In addition, we found that parental vulnerability to psychopathology and externalizing behavior were also significantly

related to cannabis use. Given these findings, we concluded that the Common Liability Model was the most robust model to predict cannabis use.

Is early onset smoking and/or drinking related to an increased likelihood of developing cannabis use disorder during adolescence?

By following the same adolescents within the TRAILS study over time, from 9 until 19 years of age, we could further examine the pathway from early onset smoking and/or drinking to more progressed forms of cannabis use during adolescence. With a structured interview, the Composite International Diagnostic Interview 3.0 (CIDI), symptoms of cannabis use disorders (Table 7.1) could be assessed at the fourth data wave of TRAILS (T4).

Table 7.1 Criteria for a DSM-IV Cannabis Use Disorder

Criteria for Cannabis Abuse

1) Failure to fulfill major role obligations
2) Continued use despite trouble with friends or family
3) Use in hazardous situations
4) Legal problems/getting arrested

Cannabis abuse= Endorsement of one or more of the abovementioned criteria

Criteria for Cannabis Dependence

1) Trying to stop or cut down use of drug (More than once)
2) Spent time getting or using drug
3) Tolerance
4) Use of drug despite health/psychological problems
5) Give up or cut down on important activities
6) Using larger amounts/for longer than intended

Cannabis Dependence= Endorsement of three or more of the abovementioned criteria of cannabis dependence within a period of 12 months

Findings from these analyses are described in ***Chapter 3***. We found that both early onset tobacco use and continuous use of tobacco increased the likelihood of developing a cannabis use disorder (CUD), whereas early onset and continued alcohol use did not. When taking the findings of this chapter in account together with the findings of chapter 2, we conclude that the Common Liability Model seems to be the best model to predict the onset of substance use, i.e. alcohol, tobacco and cannabis use, whereas for continued/more progressed forms of substance use the ROA model seems to provide an adequate description of our findings, because specifically early onset tobacco use and continued use of tobacco increased the risk

for CUD, and both forms of substance use share their method of administration: through inhalation.

How can the interplay between externalizing behavior and early onset smoking as predictors of adolescent cannabis use be described?

To further understand the relation between early onset smoking and cannabis use in adolescents, ***Chapter 4*** focused on the interplay between externalizing behavior and early onset smoking, before the age of 12 years, as predictors of cannabis use. As externalizing behavior has been found to be linked to any substance use, including tobacco use and cannabis use, some findings suggest that externalizing behavior may underlie the link between tobacco use and cannabis use that we reported in Chapter 2 and 3. Our findings in Chapter 4 show that all associations of parent-rated externalizing behavior problems (conduct, attention deficit hyperactivity, and oppositional problems) with adolescent cannabis use were mediated by early onset smoking. In contrast, none of the associations between the self-reported externalizing behavior problems) and cannabis use were mediated by smoking except the influence of self-reported conduct problems in girls. In sum, we found that, even after adjusting for externalizing problems, early onset smoking independently and consistently predicted cannabis use. Our findings challenge the view that externalizing behavior problems directly predict cannabis use initiation. In addition, externalizing behavior problems did not explain the link between tobacco use and cannabis use in our study. Rather, our findings indicate early smoking onset as a powerful predictor of later cannabis initiation independent of preceding externalizing behavior problems.

What is the predictive value of observed versus reported measures of impulsivity on the onset of cannabis use and repeated cannabis use in adolescence? Can impulsivity measures differentiate between cannabis users and tobacco users?

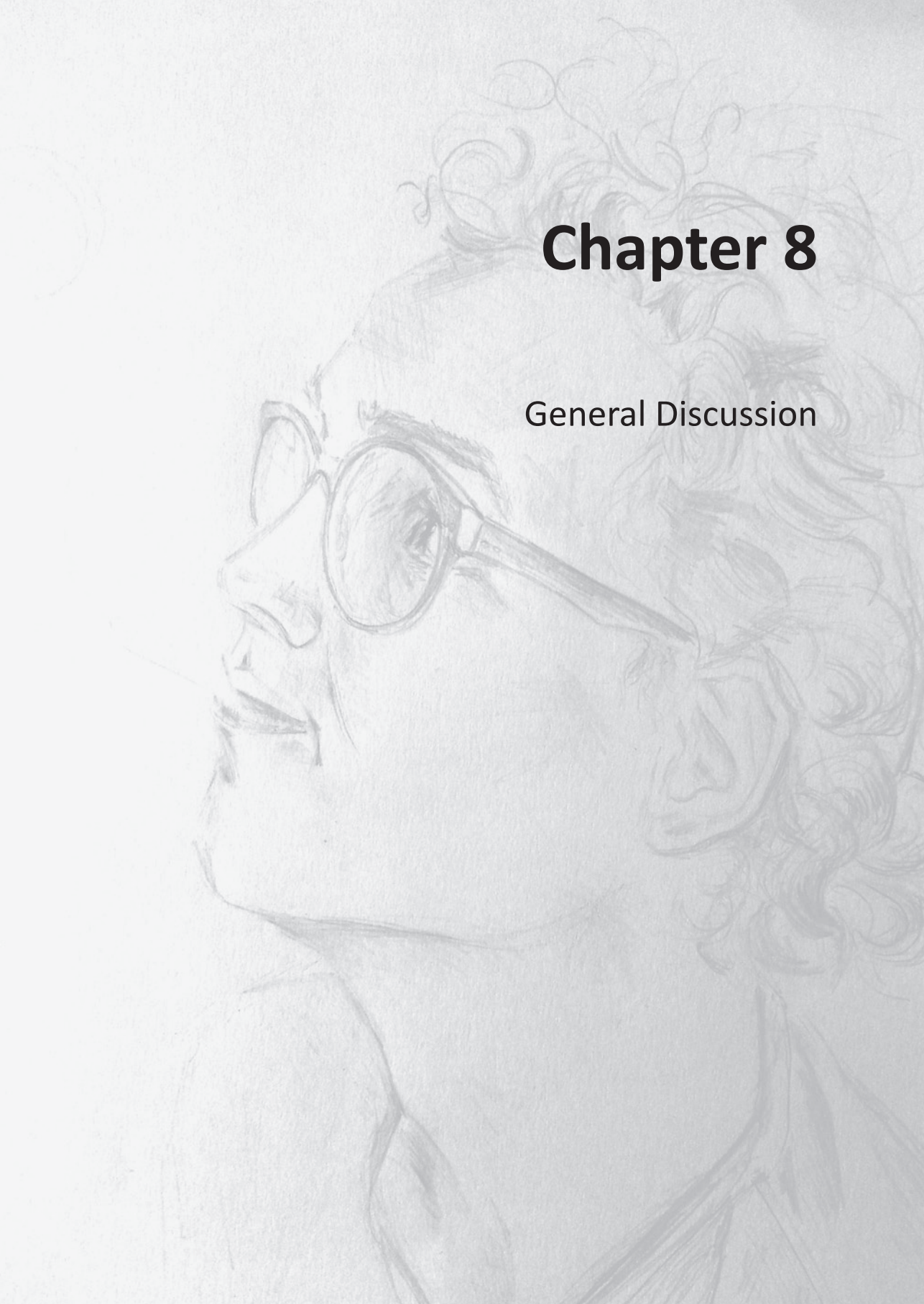
In ***Chapter 5*** it was examined whether a specific individual characteristic, namely impulsivity, is able to differentiate between cannabis users and tobacco users. In order to do so, we first focus on the assessment of impulsivity in adolescents. We chose to investigate both observed and reported measures of impulsivity in relation to tobacco and cannabis use. The Bangor Gambling Task (BGT), a card/gambling task using real money, was administered during a behavior experiment to *observe* impulsive behavior. The BGT involves a deck of 100 playing cards, with 38 'high' cards (Jack, Queen, King, Ace) and 62 'low' cards (between 2 and 10). High cards produce financial gain, whereas the low cards produce financial loss. Each card was labeled on the face/number side with the monetary loss or gain, corresponding to one of four values (win €0.40, win €0.20, loss €0.40, loss €0.20). A *self-report* questionnaire assessed the functioning of the Behavioral Inhibition System (BIS) and the Behavioral Activation System (BAS). BIS and BAS are proposed to be the two neurological and motivational systems that underlie much of our behaviors and personality. BIS is sensitive to signals of punishment and non-reward, and relates to avoidance or withdrawal behavior, whereas BAS is proposed to be sensitive to signals of reward and non-punishment, and

relates to approach-oriented behavior. Findings showed that the observed levels of impulsivity were not associated with lifetime or repeated use of cannabis or tobacco. Interestingly, self-reported measures of impulsivity did predict cannabis and tobacco use: higher levels of BAS functioning increased the likelihood that adolescents would ever use substances such as tobacco or cannabis during their lifetime. Furthermore, BIS functioning was related to cannabis use only: low levels of BIS functioning increased the likelihood of repeated cannabis use.

Is any and repeated cannabis use related to hypothalamic-pituitary-adrenal (HPA) axis reactivity to a social stressor? Can different patterns of HPA axis reactivity be found for cannabis users versus tobacco users?

Finally, in ***Chapter 6***, we examined whether individual variation in stress sensitivity is related to any use of cannabis and repeated cannabis use. Additionally, we examined whether this individual endophenotypic characteristic can differentiate between cannabis users and tobacco users. The Groningen Social Stress Task (GSST), inspired by the Trier Social Stress Task, was used to measure stress sensitivity. During the GSST, participants were instructed to give a speech about themselves and to conduct a mathematical task in front of a camera to induce stress. Furthermore, cortisol levels were measured before, during and after the GSST. Cortisol is the end-product of the HPA axis and has been shown to affect both behavior and emotions. Moreover, research suggests that HPA axis reactivity is somehow involved in processes that may lead to substance use and abuse.

We found that lifetime cannabis users had significantly lower stress reactivity levels of the HPA axis, reflected by lower cortisol levels, when compared to abstainers as well as lifetime tobacco users. Furthermore, repeated cannabis users exhibited lower stress reactivity levels when compared to lifetime ever users of either tobacco or cannabis. Therefore, we conclude that lower HPA axis stress reactivity in adolescents is specifically related to lifetime and repeated cannabis use. Our findings further suggest that by measuring HPA axis reactivity in youth, we are able to differentiate between tobacco users and cannabis users.



Chapter 8

General Discussion

The frequently observed co-occurrent or subsequent use of tobacco and cannabis provided the starting point of several studies described in this thesis. As these studies used data from TRAILS (1), in which adolescents were followed from mean age 11.09 (T1) until age 19.20 (T4), the main focus was on first expressions of adolescent substance use, including initiation of use, particularly at early ages, repeated use, and symptoms of cannabis use disorder. The latter symptoms were assessed at the fourth data wave.

Tobacco use and Cannabis use Associations in Adolescence

In a recent review, Agrawal and colleagues (2) presented some epidemiological data from the US population aged 12 years and older, collected by the National Household Survey on Drug Use and Health (NSDUH) in 2009 regarding co-occurrence of tobacco use and cannabis use. A striking percentage of smokers (57.9%) also reported any cannabis use during their lifetime, as compared to 11.9% of non-smokers. Additionally, almost all cannabis users (90%) reported being or having been a cigarette smoker. Although these figures originate from a very diverse age group, including young adolescents and older adults, they clearly show that cannabis use and tobacco use frequently co-occur.

Within our adolescent population, we also focused on this co-occurrence and did so in a temporal way. That is, we examined whether early onset of cigarette smoking was predictive of cannabis use onset (Chapter 2), and, because of the longitudinal design of TRAILS, it could also be tested whether early onset smoking predicted cannabis use disorder several years later (Chapter 3). It became clear that early onset smoking was related to a higher risk of initiating cannabis use. However, this prediction was not restricted to early onset smoking only, because a similar association was found between early onset alcohol use and cannabis use. These findings are therefore not in line with the Route of Administration Model, postulated by Agrawal and Lynskey in 2009, that was based on their finding that adults using smoked forms of tobacco were more likely than adults who used tobacco in a non-smoking fashion (e.g. chewing tobacco) to report cannabis use (3). This finding suggested that inhaling a substance, like tobacco, could somehow facilitate progression to inhaling another substance, like cannabis. Our findings fit with the Common Liability Model, in which individuals with a (inherited) vulnerability for substance use may first use so-called licit drugs, which are more easily available, and then progress to other substances such as cannabis. By prospectively tracking the adolescents over time, we could also examine if early onset of tobacco and/or alcohol use was predictive of cannabis use disorder (CUD) several years later. In line with the findings reported in Chapter 2, we found that early initiation and continued use of tobacco could predict CUD in late adolescence. However, alcohol use, early onset and continuation, was no longer related to CUD.

The liability found in this group of adolescent tobacco users, i.e. leading to problem use of cannabis, are in line with Agrawal's ROA theory. For example, Agrawal and colleagues (3) further suggested that regularly smoking a cigarette may serve as a cue to want to inhale other substances. Therefore, individuals who experienced inhaling tobacco smoke as pleasurable may reflect back to those moments of giddiness, happiness, relaxation and or pleasure when they are inhaling another substance such as cannabis (4-6). Perhaps,

adolescents need to have a certain amount of experience with a substance, such as tobacco, before the pleasurable connection is made. Another explanation for this relation between regular smoking and risk of developing a CUD could be a genetic vulnerability to addictive behavior (2, 7, 8) as both types of behavior reflect aspects such as externalizing behavior problems, sensation seeking, behavioral disinhibition and impulsive behavior (9, 10). Finally, continued tobacco smokers may experience more positive/rewarding sensations to cannabis use (4, 6, 11). It is of interest to further examine this specific pathway from continued, or regular smoking, to cannabis use progression in youth.

The Role of Behavior

Both externalizing behavior problems and impulsive behavior have been linked to an increased risk to initiate and maintain substance use in adolescence (12-15). For externalizing behavior problems, including conduct disorder (CD), attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), it seems common knowledge to most clinicians and researchers that these disorders are co-morbid with substance use disorders among youth. Yet, externalizing behavior problems and substance use disorders may occur simultaneously in mostly male clinical populations, such co-occurrence may be less prevalent among general populations of adolescents including both genders. In itself, it seems logical to assume that a general behavioral tendency to break or not comply with rules, to exhibit impulsive behavior and have a lack of self-control, as core elements of externalizing behavior problems or more generally, impulsive behavior, is related to experimenting with (illegal) substances and continued use as well. This thesis includes studies that focus on the role that externalizing behavior plays in the described relation between early onset smoking and cannabis use (Chapter 4), and whether different levels of observed or reported impulsive behavior differentiate between smokers and cannabis users (Chapter 5). In other words, both studies examine whether either externalizing behavior problems or impulsive behavior represent a common individual vulnerability to engage in early stages of adolescent substance use, irrespective of the type of substance used (i.e. tobacco or cannabis), or, alternatively, whether these behavioral patterns do differentiate between individuals who smoke only tobacco and those that progress to smoking cannabis as well.

The findings reported in Chapter 4 challenge the common viewpoint that externalizing behavior problems directly predict cannabis use initiation. A direct impact of externalizing behavior problems on smoking initiation was found, with particularly high odds for conduct disorder. Yet, when smoking initiation was regarded as predictor of cannabis use initiation alongside externalizing behavior problems, the effect of externalizing behavior problems was clearly attenuated in most models. Particularly early onset smoking remained as a strong predictor of cannabis use initiation, as we also noted in the previous chapters of this thesis. Thus, externalizing behavior problems may enhance the risk of experimentation with smoking tobacco, which by itself could then lead to a cascade of substance use in which cannabis use is the next step. Rather than being a common vulnerability factor, explaining both smoking and cannabis use, externalizing behavior problems may trigger the offset of a substance use pathway, from smoking to cannabis use.

Impulsivity may be regarded as a trait or individual characteristic that may predict risk-taking behavior in general (16, 17), including smoking and cannabis use, also in general populations of adolescents (18). In Chapter 5 we specifically focused on two aspects of impulsive behavior, also framed as the functioning of the Behavioral Activation System (BAS) and the Behavioral Inhibition System (BIS). Both represent neurological and motivational systems that may underlie part of our behavior and personality (19-21). Individuals with deficits in the BIS or BAS systems (e.g. high levels of BAS and low levels of BIS) have an increased likelihood to engage in risk-taking behaviors and engage in substance use (22, 23).

In addition to self-reported levels of BAS and BIS, we also observed impulsive behavior in a subsample of TRAILS adolescents using the Bangor Gambling Task (24). We presented these adolescents with a deck of 100 cards. These cards were sectioned into five 20-card blocks. With each block, the probability of losing, if the adolescent chose to gamble, would increase. Thus, adolescents who are more impulsive would be more likely to lose all of their money, because they could not resist the urge to gamble. In this study, we used both these reported (BIS/BAS) and observed (Bangor Gambling Task) measures of impulsive behavior, and examined their (specific) relation with cannabis use. The results of the study reported in Chapter 5 showed that BAS functioning was not sufficient to differentiate between tobacco smokers and cannabis users, or more specifically, higher levels of BAS functioning predicted both tobacco use and cannabis use. Combined with results from the study described in Chapter 4, one could assume that BAS functioning and expressions of externalizing behavior share some common ground and are both linked to any substance use in early adolescence. For example, research has shown that adolescents with high BAS are more likely to exhibit externalizing behavior problems and these adolescents are in turn more likely to initiate and continue tobacco use. Given the findings mentioned in this thesis, we know that tobacco use is a strong predictor of cannabis use, therefore the BAS system may be useful in identifying an early at risk group before any substance use has been initiated. As such, BAS functioning are not specific or important predictors of cannabis use.

In contrast, lower BIS functioning seemed to be a more specific predictor of particularly repeated cannabis use. As lower BIS functioning is assumed to reflect a reduced capacity to inhibit behavior that leads to negative or painful outcomes, BIS functioning may be important in predicting cannabis abuse as well. Future studies may focus on the role BIS functioning has in several transitions from (early) onset of cannabis use, to regular use, to CUD. Based on our findings, one could expect that BAS influences the onset of a pathway of substance use, similar to externalizing behavior problems, while BIS could enhance the transition from any use to regular use and so forth.

Interestingly, and in contrast to our expectations, observed measures of impulsivity did not predict tobacco smoking or cannabis use. Perhaps, we were unable to pinpoint impulsive behavior, especially in the age group that we measured (mean age 16.27 years), because at this age most adolescents exhibit some form of impulsive behavior. Therefore, it is hard to separate a normative group from a deviating group in terms of impulsivity. Dahl and colleagues (18) discuss this idea, that most adolescents are commonly confronted in daily life situations with the fact that when they have to make ‘heat of the moment’ decisions, they quite often take the impulsive path instead of the ‘rational’ path (18). On the other

hand, our outcome may be due to our testing method. Unlike Bowman and colleagues (24), who chose to give the adolescents more money if they ran out before the end of the 100 cards, our lab chose to stop the game once the money ran out. Both options have their positive and negative points. The Bowman group was able to have a picture of all 100 cards for each subject, whereas our group had various stop points. Similarly, logic behind not giving extra money is that we did not want the adolescents to think that the money was an endless source. This in itself may contribute to more compulsive gambling choices for all adolescents.

In sum, only BIS functioning appears to be a specific predictor of (repeated) cannabis use, while BAS functioning and externalizing behavior problems may be more general predictors of any substance use and could trigger the onset of a pathway of substance use, starting with (early) onset of tobacco use, progressing to onset of cannabis use.

Hypo-arousal in Response to a Social Stressor

Abundant studies have examined how stress may be related to substance use. Most of the studies were performed in either animals (25, 26), clinical populations (27-30) or substance dependent adults (31-34). Findings suggest that stress, cortisol reactivity, is linked to an increased likelihood to use and abuse drugs. For example, in a population of adolescent boys with a paternal history of substance abuse, low cortisol reactivity was found to be linked to early onset of cannabis use. It has been suggested that adolescents who have a hyporeactive HPA axis are initiating drug use, such as cannabis, to try to compensate for their underaroused system, as a way of self-medication to restore 'normal' levels of arousal (28, 35-37). Yet, this suggestion still lacks clear empirical evidence. An alternative explanation, to be examined, would be that individuals with low arousal levels lack a physiological break, which would make it easier for them to cross boundaries and exhibit rule breaking behavior. In other words, they do not suffer from bodily discomfort usually associated with anxiety or stress caused by increased physiological arousal levels when they perform dangerous or rule breaking behavior.

Only few scholars looked at stress and the onset of substance use in adolescence. The few studies that are currently available among adolescent populations seem to imply a hypo-arousal of the HPA axis in adolescent substance users (38, 40-42), rather than the often found hyperarousal of this stress system in adult substance users/abusers (43-45). Results from the study reported in Chapter 6 are also in line with this phenomenon of hypo-arousal of the HPA axis in response to a social stressor, in average 16-year-olds who have an increased risk of lifetime and repeated cannabis use. Importantly, this pattern of a smaller increase in cortisol after exposure to a social stressor, which may be especially salient for adolescents (46-48), differentiated lifetime cannabis users from tobacco users and abstainers, and repeated cannabis users from lifetime cannabis or tobacco users. Repeated cannabis users could not be differentiated from repeated tobacco users in terms of HPA axis reactivity. Thus, hypo-arousal of the HPA axis may be specifically associated with initiation of cannabis use, but prolonged use of other substances, like tobacco, may affect the HPA axis in such a way that repeated cannabis users can no longer be distinguished from repeated tobacco users with this pattern of cortisol responses.

In sum, it seems that stress response patterns represent a promising tool to identify adolescents at risk of onset and continuation of cannabis use. However, given that effects of initial substance use on HPA axis functioning cannot be ruled out, no conclusions can be drawn regarding the potential of stress-reactivity as a predictor or indicator for adolescent cannabis use. It would be very interesting to address this issue. Furthermore, it may be worthwhile to test whether low BIS functioning is related to hypo-arousal of the HPA axis in adolescents, and examine whether these two factors are interactively or additively predictive of several phenotypes or transitions of cannabis use patterns in adolescence.

Strengths and Limitations

The strengths of this thesis include the following. First, we had longitudinal data available from a large and representative group of youth in the Netherlands, with rates of substance use that are rather similar to that of youth in other parts of the Netherlands. Second, because of our longitudinal designed study that started early in (pre)adolescence, we were able to examine the first expressions of cannabis use. This is an asset, as most other studies examined cannabis use in adolescents (and adults) only once problematic use/problems were identified. In these studies, most of the information is obtained from individuals once they are addicted or have a long pattern of excessive cannabis use. The TRAILS data used for this thesis provided a very strong and unique opportunity to examine a cohort of (pre)adolescents before the onset of cannabis and other types of substance use. Finally, during this important developmental period, we were able to utilize multiple resources such as physiological tests, questionnaires, experimental and interviews which were collected using a longitudinal design in a nonclinical adolescent population.

Nevertheless, this thesis is not without limitations. First, in the Netherlands, it is common to mix a small amount of tobacco with cannabis. Therefore it is rare to find “pure” cannabis users. We compared cannabis users with tobacco users in several studies, but it would be more precise to state that we compared between cannabis + tobacco users and tobacco-only users. Furthermore, we used a general population cohort for our study, which is a strength of our design (given its representativeness), but a limitation at the same time. Although quite a number of youth included in the TRAILS Study reported symptoms of CUD, severe patterns of cannabis abuse were seldom in our group. This implies that some of our findings may not generalize to higher risk populations, such as youth with parents with severe addiction problems, youth with psychiatric disorders, and so on. Particularly in these groups, the HPA axis may function differently, as a result of prolonged stress exposure or a genetically different pattern of stress reactivity (40, 49). Furthermore, our sample is rather homogeneous, in that it does not have a very capacious ethnic background. The majority of our participants are from Dutch descent, which may not generalize to adolescents with a non-Western background. For example, in adolescents with a non-Western background, religion may serve as a protective mechanism against cannabis and other substance use, whereas differential peer and parental interactions may pose a unique risk (50, 51, 52).

Implications

The major findings of this thesis suggest that adolescents who initiate tobacco and alcohol use before the age of thirteen years are at an increased risk to initiate cannabis use. Additionally, early onset tobacco users and continued tobacco users in particular were more likely to develop a cannabis use disorder. These findings suggest that intervention program should try to curb a) early onset, before the age of 13 years, tobacco use and alcohol use, and b) continued use of tobacco. Moreover, programs that help adolescents to stop smoking tobacco may also be beneficial to decrease the number of adolescents who develop a cannabis use disorder. In their efforts to prevent tobacco and cannabis use, intervention programs should target impulsivity (BIS/BAS functioning) and externalizing behavior problems. For instance, they could teach children and adolescents adaptive strategies to deal with these behavioral patterns, and provide their parents with information and advice to prevent early substance use in their children.

Recommendations for Future Research

Although we have answered several questions with this dissertation, still other questions remain to be examined. Some suggestions for future research arise from our findings that were based on a general population cohort of youth. It would be very informative to test our hypothesis in high-risk youth and clinical populations as well. For instance, hypo-arousal patterns of the HPA axis may be more prevalent in youth with chronic family adversities or with genetic vulnerability to addiction, whereas youth with internalizing psychiatric disorders may show an opposite pattern, with a hyperarousal of the HPA axis. It would be of interest to test whether the finding of low arousal of HPA axis in relation to cannabis use in our general population of youth holds in these high risk populations, or that different – and psychopathology-specific – patterns will be found.

We showed that the HPA axis reactivity is important in predicting cannabis use in youth. Future research could extend these findings to the autonomic nervous system (ANS), and focus on the combined reactivity patterns of the HPA axis and the ANS in predicting more advanced forms of cannabis use. The combined action of both HPA axis and ANS may represent an endophenotype of individuals at risk for (continuing) cannabis use during adolescence. Yet, little is known on how ANS reactivity to stressful situations is related to cannabis use patterns in youth, and therefore, studies could first focus on this stress system alone, before examining the combined action of HPA and ANS.

Little is known about the impact of first (irregular) use of tobacco and cannabis on the HPA axis functioning in youth. To examine this, HPA axis reactivity could be tested repeatedly, prior to onset of use and during periods of first use of tobacco and cannabis. These HPA axis measures could then be compared to those of abstainers of any substance use over time, to see whether a different pattern of HPA axis reactivity emerges as a result of substance use exposure, in a dose-dependent manner.

If resources were limitless, it would be very interesting to a) have parental stress reactivity measures, as measured via our behavioral experiment with the adolescents, given that current research emphasizes the importance of genetic vulnerabilities leading to cannabis addiction, and b) measure the HPA axis reactivity of substance users (tobacco,

alcohol, or cannabis) when the participant is also able to use their substance of choice before the experiment. Measuring the effect of substance use may provide us with a physiological map of what is actually occurring, which is especially interesting in individuals with low functioning HPA reactivity. Furthermore, if the data is collected over a period of time, we could also get a better picture of the effects continued substance use has on the HPA axis system, especially in developing adolescents.

Finally, it is recommended that future research could ask more detailed questions about the type and amount of cannabis used as well as how it is smoked. This will not only allow us to better understand cannabis use, but hopefully we could get a better understanding of the association between cannabis use and tobacco use. Given that the amount of THC is so much stronger in the Netherlands, and that various types of cannabis are available which also have different amounts of THC, it is hard to compare the exact THC intake of cannabis users. Furthermore, it would also be interesting to test if adolescents who mix tobacco with their cannabis are more likely to increase tobacco use when compared to their peers who smoke pure cannabis. A more standardized questionnaire would add a lot of beneficial information to the field of substance use, such as cannabis use, misuse, and abuse.

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Dutch Summary

De studies die beschreven worden in dit proefschrift zijn uitgevoerd om meer inzicht te krijgen in voorspellers van cannabisgebruik onder adolescenten. Omdat jongeren die cannabis gebruiken vaak ook roken en cannabis bovendien vaak gebruikt wordt in combinatie met tabak, is er mogelijk sprake van gedeelde risicofactoren voor cannabisgebruik en roken. Echter, lang niet alle rokende jongeren gaan ook cannabis gebruiken. Inzicht in verschillen tussen jongeren die wel de stap zetten naar cannabisgebruik in vergelijking met jongeren die het houden bij het roken van sigaretten, of die zich onthouden van middelengebruik, kan bijdragen aan de preventie van cannabisgebruik onder adolescenten.

Voor de studies die beschreven worden in dit proefschrift zijn gegevens gebruikt van de eerste vier meetmomenten van TRAILS (TRacking Adolescents' Individual Lives Survey), een groot, prospectief, algemeen bevolkingsonderzoek onder Nederlandse adolescenten. Tijdens het eerste meetmoment waren de deelnemers 10-12 jaar en zij werden gevolgd met tussenpozen van 2 à 3 jaar. Onderstaand volgt een samenvatting van de belangrijkste resultaten uit dit proefschrift.

Welk van de volgende modellen geeft de beste voorspelling van cannabisgebruik tijdens de adolescentie: het Gateway Model, het Common Liability Model en/of het Route of Administration Model?

In Hoofdstuk 2 wordt het verband onderzocht tussen het vroegtijdig beginnen met roken en drinken, dat wil zeggen beginnend vóór de leeftijd van 13 jaar, en daaropvolgend (experimenteel) cannabisgebruik. Drie modellen werden vergeleken: het Gateway Model, het Common Liability Model en het Route of Administration Model. Volgens het Gateway Model verloopt drugsgebruik in een stapsgewijze volgorde: legaal drugsgebruik, zoals roken en alcoholgebruik, gaat vooraf aan cannabisgebruik, wat vervolgens leidt tot het gebruik van illegale middelen zoals cocaïne. In het Common Liability Model wordt uitgegaan van de hypothese dat het gebruik van zowel legale als illegale middelen wordt veroorzaakt door dezelfde onderliggende kwetsbaarheid. Deze kwetsbaarheid kan liggen in genetische en individuele vatbaarheid voor verslaving, familiaire oorzaken van verslaving of bijvoorbeeld de neiging tot grensoverschrijdend gedrag. Het Route of Administration Model gaat uit van het idee dat het gebruik van een bepaald middel de kans op toekomstig gebruik van andere middelen, die op dezelfde manier worden ingenomen (bijvoorbeeld door inhalatie), vergroot.

Uit ons onderzoek komt naar voren dat adolescenten die vroegtijdig beginnen met roken niet vaker beginnen met het gebruik van cannabis dan adolescenten die vroeg beginnen met het drinken van alcohol. Daarmee kunnen we het Route of Administration Model uitsluiten als verklaring voor beginnend cannabisgebruik. Vanuit dit model zou immers verwacht worden dat er een sterker verband is tussen roken en cannabisgebruik dan tussen alcohol- en cannabisgebruik. Uit ons onderzoek komt verder naar voren dat jongeren die vroegtijdig beginnen met zowel roken als drinken vaker beginnen met het gebruik van cannabis dan jongeren die vroegtijdig één van beide middelen gebruiken. Deze bevinding

kan niet verklaard worden vanuit het Gateway Model, waardoor dit model deels verworpen kan worden als verklaring voor de samenhang tussen roken, drinken en cannabisgebruik. De gevonden samenhang tussen vroegtijdig roken, drinken en het gebruik van cannabis past het best bij het Common Liability Model. Ofwel, vroegtijdig roken, drinken en het gebruik van cannabis lijken voort te komen uit een gedeelde onderliggende kwetsbaarheid.

Is roken en/of het gebruik van alcohol op vroege leeftijd gerelateerd aan een verhoogde kans op het ontwikkelen van problematischcannabisgebruik tijdens de adolescentie?

Omdat de deelnemers aan TRAILS over een lange tijd gevolgd worden, is het mogelijk om de ontwikkeling van roken en alcoholgebruik op jonge leeftijd naar meer gevorderde vormen van cannabisgebruik in kaart te brengen. Tijdens de vierde meting van TRAILS werden door middel van een gestructureerd interview, het Composite International Diagnostic Interview 3.0 (CIDI),de DSM-IV symptomen van problematisch cannabisgebruik, gedefinieerd als cannabismisbruik of -afhankelijkheid gemeten (Tabel 7.1).

Tabel 7.1 Criteria voor problematisch cannabisgebruik volgens DSM-IV

Cannabismisbruik

1) Belangrijke verplichtingen worden niet nageleefd door het gebruik
2) Het gebruik wordt voortgezet ondanks problemen met familie of vrienden
3) Herhaaldeijk gebruik in situaties waarin het fysiek gevaarlijk is
4) Er zijn legale problemen (arrestatie)

Cannabismisbruik = Wanneer aan één van de hierboven genoemde criteria wordt voldaan

Cannabisafhankelijkheid

1) Herhaalde poging(en) om te stoppen of minderen met het middel
2) Er wordt veel tijd besteed aan het verkrijgen of gebruiken van het middel
3) Tolerantie treedt op
4) Het gebruik wordt voortgezet ondanks fysieke of psychologische problemen die door het middel worden veroorzaakt of verergerd
5) Belangrijke activiteiten worden opgegeven of verminderd voor het middelengebruik
6) Er wordt meer van het middel gebruikt of het wordt vaker gebruikt dan voorgenomen

Cannabisafhankelijkheid = Wanneer drie of meer van de bovengenoemde criteria voorkomen binnen een periode van 12 maanden

De resultaten van deze analyses worden beschreven in ***Hoofdstuk 3***. Onze bevindingen laten zien dat jongeren die vroeg beginnen met roken en jongeren die doorgaan met roken significant vaker problematisch cannabisgebruik ontwikkelen. Voor jongeren die vroeg beginnen met het drinken van alcohol en doorgaan met het drinken van alcohol wordt dit verhoogde risico op problematisch cannabisgebruik niet gevonden. Op basis van de

resultaten beschreven in dit hoofdstuk en in *Hoofdstuk 2* concluderen wij dat beginnend middelengebruik het beste wordt verklaard door het Common Liability Model, terwijl voor problematisch cannabisgebruik het Route of Administration model de meest adequate beschrijving van onze resultaten geeft.

Hoe kan de wisselwerking tussen externaliserend gedrag en vroegtijdig roken als voorspellers van cannabisgebruik worden beschreven?

Het onderzoek beschreven in ***Hoofdstuk 4*** is gericht op het verband tussen externaliserend gedrag (zoals agressief of antisociaal gedrag), vroegtijdig roken, en cannabisgebruik. Uit eerder onderzoek is gebleken dat externaliserend gedrag het risico op middelengebruik, waaronder roken en cannabisgebruik, vergroot. De rol van externaliserend gedrag in het eerder gevonden verband tussen roken en cannabisgebruik is echter nog onduidelijk. De resultaten in ***Hoofdstuk 4*** laten zien dat het verband tussen door de ouders gerapporteerd externaliserend gedrag en cannabisgebruik wordt gemedieerd door vroegtijdig roken. Dit houdt in dat meer externaliserend gedrag leidt tot een verhoogd risico op vroegtijdig roken, wat dan weer kan leiden tot cannabisgebruik. Dit geldt voor zowel jongens als meisjes. Echter, het verband tussen door de jongeren *zelfgerapporteerd* externaliserend gedrag en cannabisgebruik wordt niet gemedieerd door roken. Ofwel, op basis van zelfrepportages van externaliserend gedrag is het verband met cannabisgebruik onafhankelijk van het verband tussen roken en cannabisgebruik. Een uitzondering hierop betreft de zelfgerapporteerde oppositionele en gedragsproblemen bij meisjes, waarvan de invloed op cannabisgebruik wel gemedieerd wordt door vroegtijdig roken. Samengevat blijkt uit onze resultaten dat vroegtijdig beginnen met roken een sterke voorspeller is van cannabisgebruik, en de invloed van externaliserend gedrag op cannabisgebruik veelal via dit vroegtijdige roken loopt. Onze bevindingen verwerpen daarmee ten dele het idee dat externaliserend gedrag een directe voorspeller is van cannabisgebruik. Bovendien lijkt externaliserend gedrag geen rol te spelen in het verband tussen roken en cannabisgebruik.

Wat is de voorspellende waarde van geobserveerde versus gerapporteerde impulsiviteit op beginnend en gecontinueerd cannabisgebruik gedurende de adolescentie? Verschillen rokers en cannabisgebruikers wat betreft impulsiviteit?

In ***Hoofdstuk 5*** is onderzocht of er een verschil is in impulsiviteit tussen jongeren die sigaretten roken en jongeren die cannabis gebruiken. Hiervoor hebben we zowel geobserveerde als gerapporteerde maten van impulsiviteit in relatie tot roken en cannabisgebruik onderzocht. De Bangor Gambling Task (BGT), een kaart-/goktest waarmee echt geld gewonnen of verloren kan worden, werd afgenomen bij de TRAILS deelnemers om impulsief gedrag te *observeren*. De BGT werkt met een kaartspel met 100 speelkaarten, waarvan 38 'hoge' kaarten (Boer, Koningin, Koning, Aas) en 62 'lage' kaarten (tussen 2 en 10). Hoge kaarten leveren financieel gewin op, terwijl lage kaarten tot een financieel verlies leiden. Elke kaart was aan de symboolkant gelabeled met de geldelijke winst of het verlies, corresponderend met één van vier waarden (€0.40 winst, €0.20 winst, €0.40 verlies, €0.20

verlies). Voor een gerapporteerde maat van impulsiviteit werd een zelfrapportage vragenlijst afgenomen, waarmee het functioneren van het activitatie (BAS)- en inhibitiesysteem (BIS) in ons brein gemeten werd. BIS en BAS zijn twee neurologische systemen die deels ten grondslag liggen aan onze gedragingen en persoonlijkheidskenmerken. Het BIS is gevoelig voor straf en negatieve feedback en staat in verband met ontwijkings- en terugtrekkingsgedrag. Het BAS is daarentegen gevoelig voor beloning en positieve feedback en staat in verband met toenaderingsgedrag. Uit onze studie komt naar voren dat er geen significant verband is tussen de BGT-maten, oftewel de geobserveerde impulsiviteit, en het gebruik van cannabis of roken. Een opvallend resultaat is echter dat de gerapporteerde impulsiviteit wel significant samenhangt met roken en cannabisgebruik: een hogere BAS werking verhoogt de kans dat adolescenten sigaretten roken of cannabis gebruiken. De werking van het BIS lijkt daarentegen specifiek voor cannabisgebruik in onze studie: een lage BIS werking verhoogt de kans op herhaaldelijk cannabisgebruik.

Is er een verband tussen eenmalig en herhaaldelijk cannabisgebruik en de reactiviteit van de hypothalamus-hypofyse-bijnieras op sociale stress? (Hieronder zal HPA, afkorting van de engelse term hypothalamic-pituitary-adrenal gebruikt worden in verwijzingen).

Tenslotte hebben we in ***Hoofdstuk 6*** onderzocht of er een verband bestaat tussen individuele variatie in stressgevoeligheid en eenmalig en herhaaldelijk cannabisgebruik. Bovendien hebben we onderzocht of rokers en cannabisgebruikers verschillen wat betreft stressgevoeligheid. Als maat voor stressgevoeligheid hebben we cortisol gemeten. Cortisol is het eindproduct van de HPA-as en beïnvloedt zowel gedrag als emotie. Bovendien duidt onderzoek er op dat de reactiviteit van HPA-as betrokken kan zijn bij de processen die leiden tot middelengebruik en middelenmisbruik.
De Groningen Social Stress Task (GSST), geïnspireerd op de Trier Social Stress Task (1), werd gebruikt om stressgevoeligheid te meten. Voor de GSST werden deelnemers geïnstrueerd om voor de camera een voordracht te geven over henzelf en vervolgens een wiskundige test te doen, beide bedoeld om stress uit te lokken. Verder werd het cortisolniveau gemeten voor, tijdens en na de GSST. Onze resultaten laten zien dat cannabisgebruikers een significant lagere stress-respons hebben, dat wil zeggen: een lager cortisol-niveau, dan rokers en dan jongeren die niet roken of cannabis gebruiken. Bovendien hadden herhaaldelijk cannabisgebruikers een lagere stress-respons dan gebruikers die ooit gedurende het leven gerookt of cannabis gebruikt hebben. Daarom concluderen wij dat een lagere HPA-as stress-respons bij adolescenten specifiek in verband staat met ooit en herhaaldelijk cannabisgebruik. Dit houdt in dat de HPA-as-respons gezien kan worden als een risicofactor voor middelengebruik in de adolescentie.

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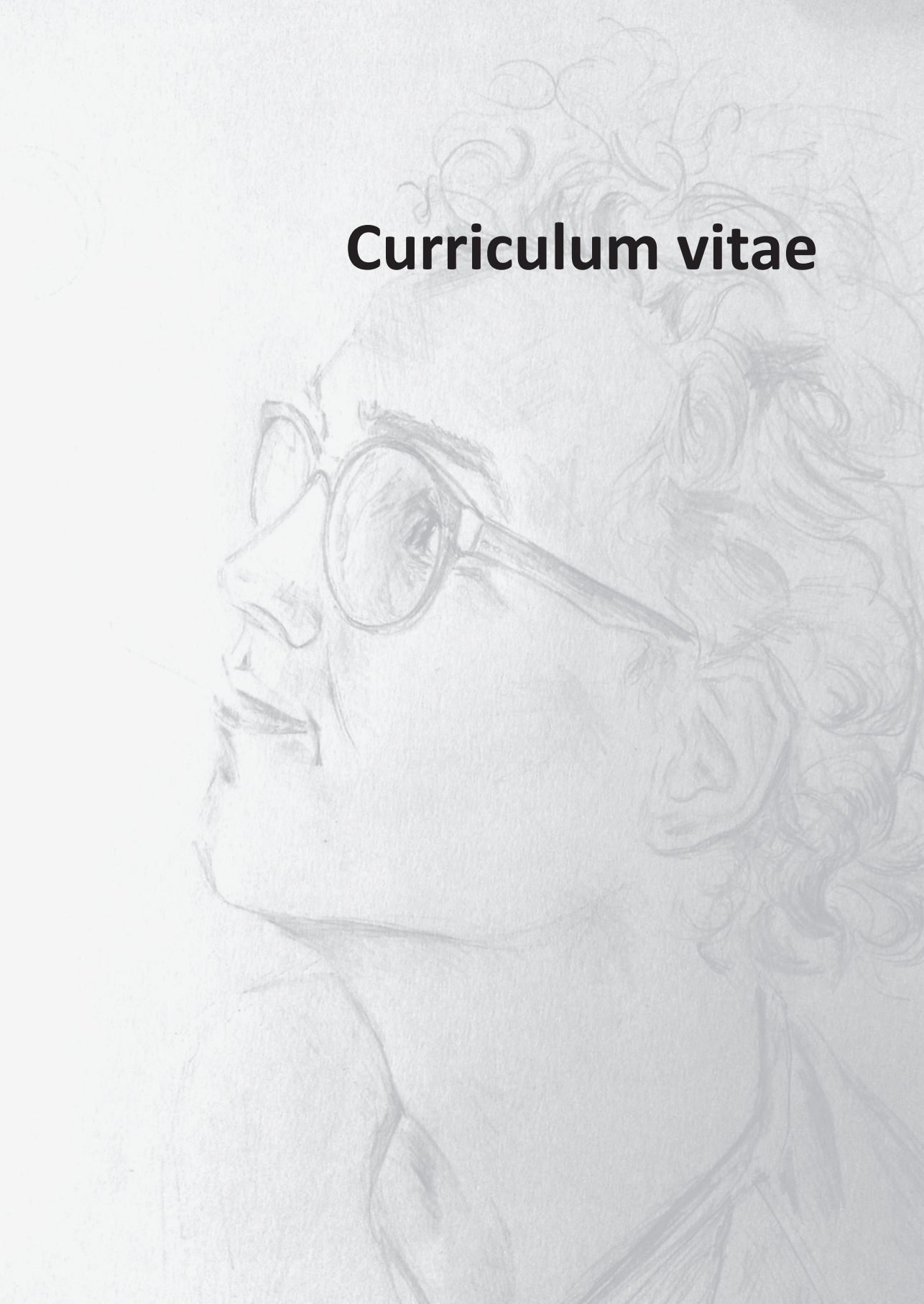
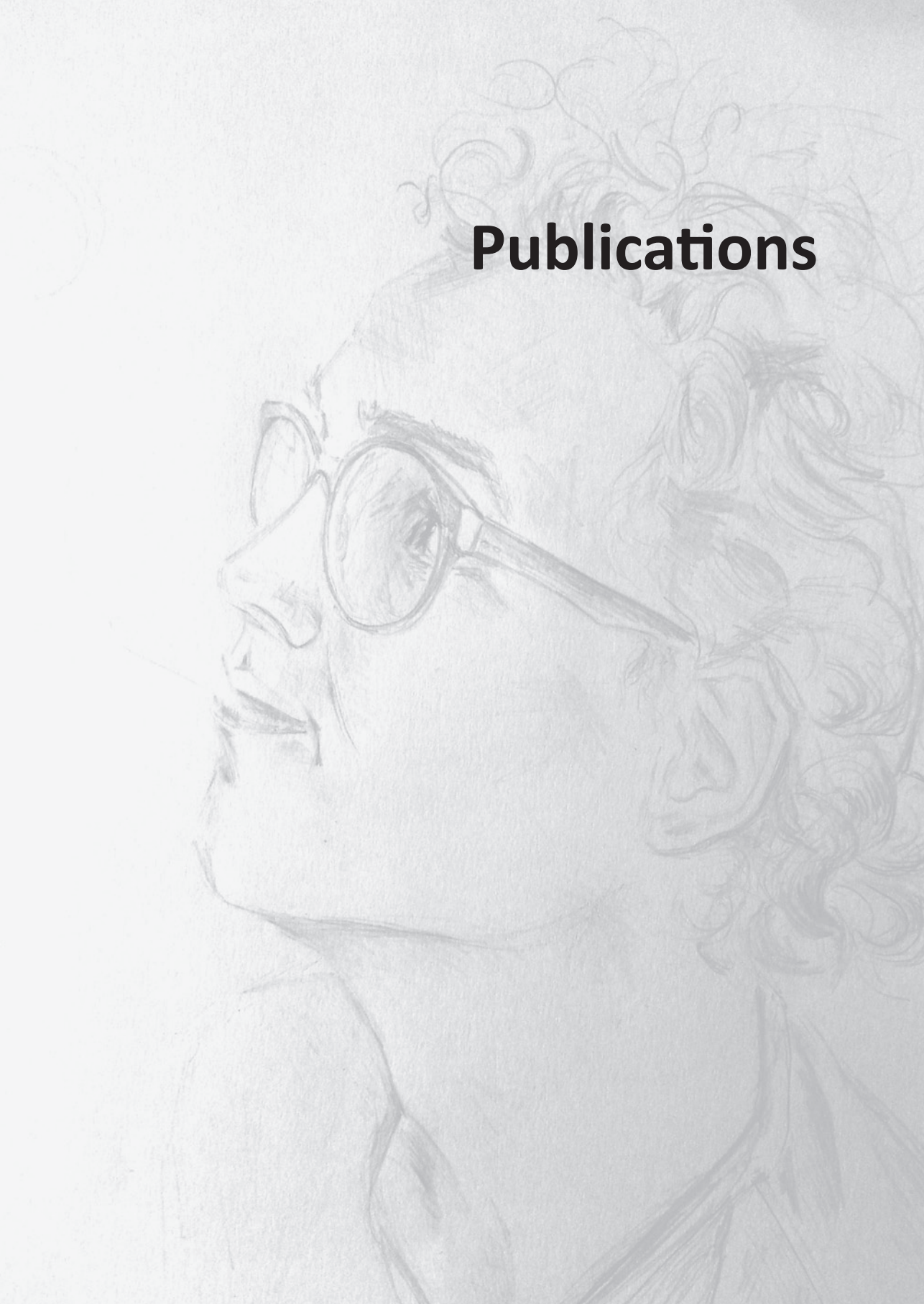
Curriculum vitae



Andrea Prince van Leeuwen was born on the 12th of November 1977 in Princeton, West Virginia. Andrea moved to Gainesville, Florida where she received her Bachelors Degree at the University of Florida from the Department of Psychology. During this time, she taught at the English Language Institute. Teaching students from all corners of the world inspired her to travel through Central America, where she later volunteered to work with drug addicted street children and adolescents.

The course Integrative Physiological Psychology, during her Bachelor Studies, inspired Andrea to enter the Behavior Neuroscience Program under the supervision of Graduate Research Professor Emeritus Philip and Osnat Teitelbaum. During this time, Andrea worked on a project to detect Autism before the first year of age in children, using the Teitelbaum Tilt Test. Furthermore, she worked with the Eshkol Wachman Movement Notation to detect movement disturbances in individuals diagnosed with Autism. After researching in the Graduate Program with the Teitelbaums, Andrea moved to the Netherlands to work with Professor Anja Huizink and Professor Frank Verhulst. The research carried out in The Netherlands is the focus of this thesis, which investigates vulnerabilities of initiating cannabis use. Andrea lived in Groningen during her data collection/analyzing time with TRacking Adolescents' Individual Lives Survey (TRAILS) study under the supervision of Dr. Andrea de Winter. After the data collection period, Andrea had the opportunity to work with colleagues at the Department of Child and Adolescent Psychiatry and Psychology at the Erasmus University Medical Center Sophia Children's Hospital, at Amsterdam University and at the Department of Public Health in Helsinki Finland.

Publications



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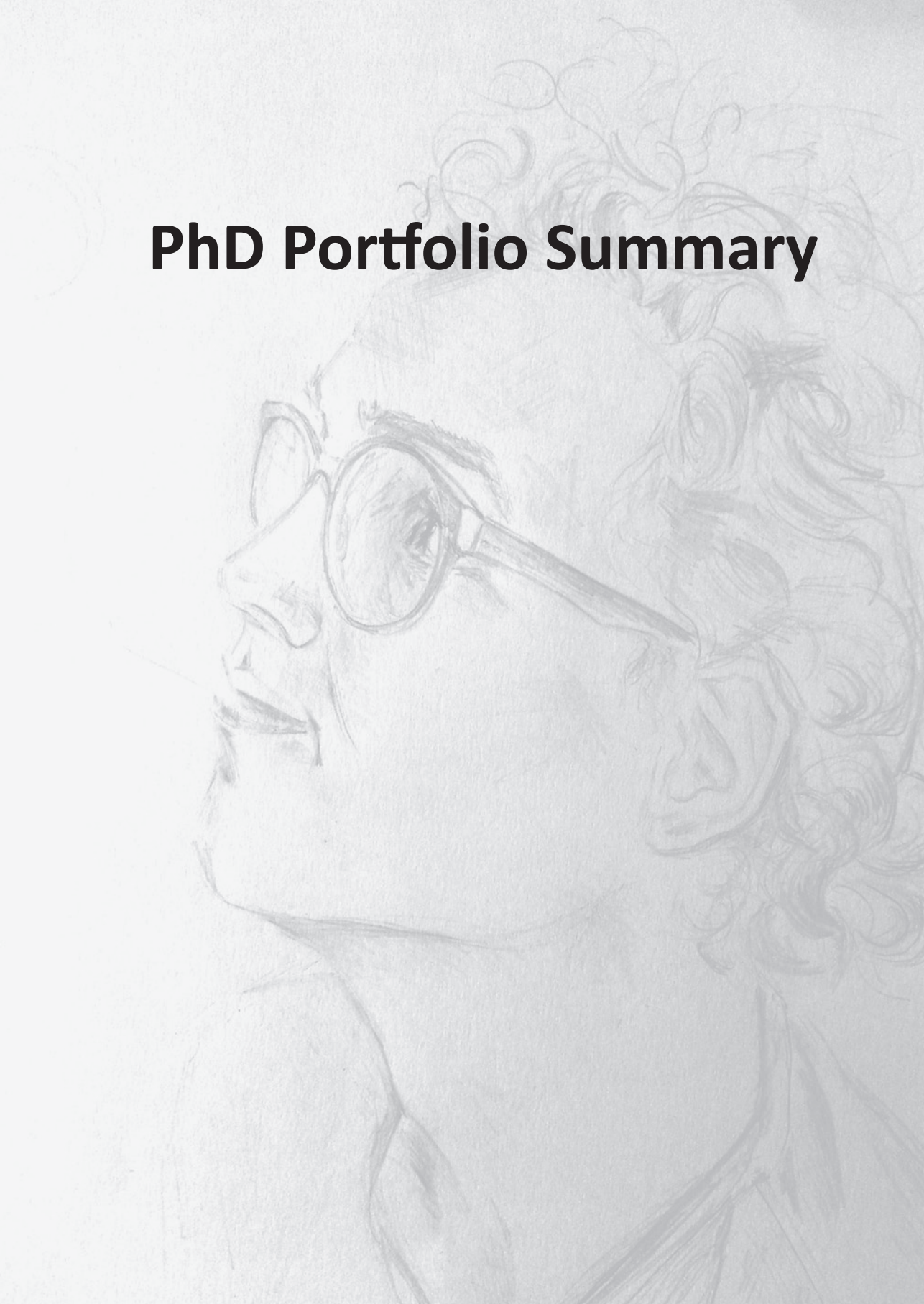
PhD Portfolio Summary



PhD Portfolio Summary

Summary of PhD training, teaching, and responsibilities

Name PhD Student	Andrea Prince van Leeuwen
PhD Period:	2007-2013
Erasmus MC Department	Child and Adolescent Psychiatry
Promotor(s)	Prof. Dr. A.C. Huizink
	Prof. Dr. F.C. Verhulst

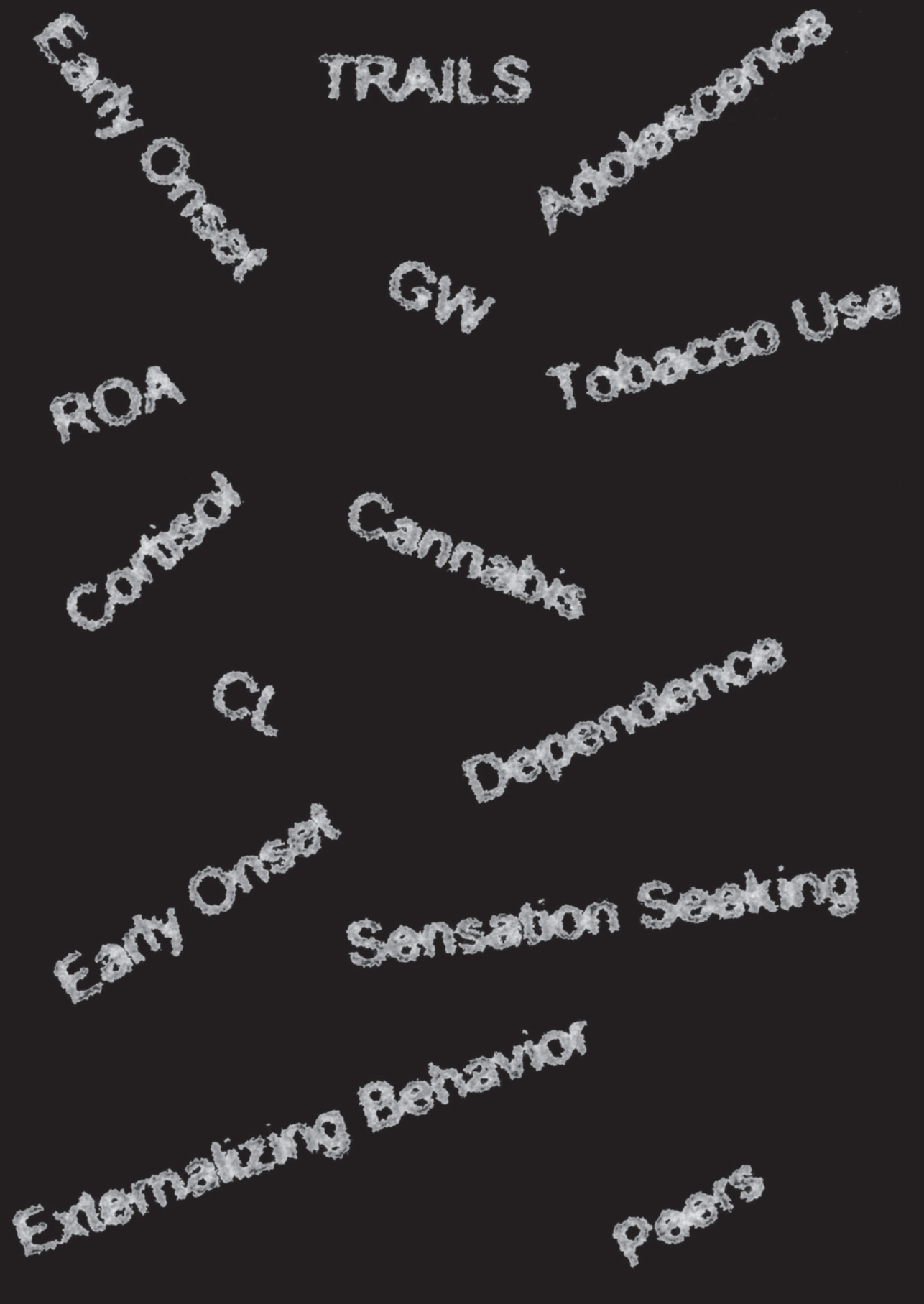
PhD training

Courses	**Year**	**Workload (ECTS)**
Genetics and Behavior, UMCG Groningen	2007	6.0
Investigating Impulsivity during Adolescence, UVA Amsterdam	2010	6.0
Multilevel Statistics, UVA, Amsterdam	2010	6.0
Netherlands Organization for Scientific Research PhD Training Day	2010	0.2
Composite International Diagnostic Interview (CIDI) Interviewer Course University Medical Centrum Groningen	2011	1.4

Conferences and symposia	**Year**	**Workload (ECTS)**
Symposium Epidemologie, Rotterdam	2009	0.2
Sumposium Drug Use, Helsinki Finland, Oral presentation	2009	0.2
College on Problems of Drug Dependence, Arizonia USA, Oral presentation	2010	2.0
International Forum of the National Institute on Drug Abuse, Arizona USA, Poster Presentation		0.6
Geestelijke Gezondheids Zorg Kennisdag, Amsteram, Oral presentation	2010	2.0
Forum Alcohol and Drug Research, Utrecht, Oral presentation	2010	0.2

Teaching and Responsibilities	***Year***	***Workload (ECTS)***
Lecturer, Developmental Psychology, Rotterdam	2009	1.0
TRAILS Substance Use Data Manager and Forum Organizer	2008-2010	3.0
PhD President, Amsterdam University	2009-2011	3.0
Lecturer, Substance Use and Addiction, Amsterdam	2010-2011	1.0

Other	***Year***	***Workload (ECTS)***
Research visit to the University of Helsinki, Department of Public Health Helsinki	2008	4


TRAILS
Early Onset
Adolescence
GW
Tobacco Use
ROA
Cortisol
Cannabis
CL
Dependence
Early Onset
Sensation Seeking
Externalizing Behavior
peers