HIGH TIMES

The role of temperament and other risk factors in the onset and continuation of cannabis use during adolescence

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Colophon

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TURBULENTE TIJDEN

De rol van temperament en andere risicofactoren in het beginnen met en continueren van cannabisgebruik in de adolescentie

Proefschrift

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CONTENT

CHAPTER 1

General Introduction

BACKGROUND

Adolescence is a period of increased risk for the onset of a wide range of emotional and behavioral problems [1]. In the last few years, scientists have provided us with new knowledge about brain development that helps us understand this increased vulnerability during adolescence. For instance, there is growing evidence that brain maturation continues well through adolescence. In addition, the maturation of arousal and motivational systems seems to precede the development of an adolescent's regulatory competence [1]. These changes might explain why adolescents are more prone to emotionally influenced behavior, which can lead to disregard for potential risks and consequences. Because trajectories that are set during adolescence can have a major impact later in life, and because altering negative trajectories prior to adulthood seems to be more effective than interventions later in life [2], a focus on adolescent development is indicated.

One type of behavioral problems that often has developmental roots in adolescence is problem use of substances, including cannabis. During adolescence, many individuals are exposed to cannabis. In the Netherlands for example, the proportion of adolescents that has used cannabis at least once during their lifetime increases from 2.3% at age 12 to 43.1% at age 17-18 [3]. Although there are large differences between countries, the position of the Netherlands with regard to the prevalence of lifetime cannabis use among adolescents seems somewhat above the center of the distribution [4, 5].

While cannabis has generally been perceived to be a relatively harmless drug, the growing number of cannabis clients in addiction care [3, 6] indicates that the use of cannabis is not as harmless as was once considered. For adolescent users, it has been estimated that 18 to 20 percent develop a cannabis use disorder within ten years from initiation of use [7, 8]. Particularly adolescents that started using cannabis at an early age, or that use cannabis on a regular or persistent basis, are at risk of developing a cannabis use disorder [7-9]. With regard to the former, research has indicated that the rate of drug-related problems is highest among those who initiated illicit drug use at age 12 or younger, and declines with increased age of initiation [10]. In addition to cannabis-related risks, various patterns of cannabis involvement have been prospectively related to several other adverse outcomes, including illicit drug use [11], poor school performance and early school leaving [12], affiliations with deviant peers [13], and mental health problems such as depression, suicidal ideation, delinquency and psychosis [14-17]. Again, younger cannabis users have been found to be more susceptible for most of these outcomes than older users [15].

Taken together, the harmful effects of cannabis use create a threat to public health, especially for adolescent users. Research on the determinants of early onset and continuation of cannabis use during adolescence can improve our understanding of predictors and mechanisms that are related to the development of potentially hazardous patterns of cannabis use. This knowledge might contribute to the early identification of at-risk individuals and might provide entry points for health promotion interventions. Because adolescence is the developmental period in which individuals usually initiate cannabis use, and in which they are most vulnerable to develop subsequent problems, a focus on this developmental period is essential.

Temperament as a risk factor of adolescent cannabis use

Why is it that some adolescents start using cannabis at a very early age, or progress to regular patterns of use, while others never use cannabis or experiment with it only once or twice? Longitudinal studies have focused on several risk factors of initiation and frequency of cannabis use in adolescents and young adults. These factors have been broadly categorized in socio-environmental factors, substance related factors, interpersonal factors, and intrapersonal factors such as personality and temperamental attributes [18, 19]. The focus of the present thesis is on the role of temperament in the onset and continuation of cannabis use during adolescence. Because temperamental characteristics appear early in life, and are assumed to have reasonable stability over time [20], they might be valuable for the early identification of individuals at-risk for adverse outcomes of cannabis use.

Temperament refers to the behavioral style that individuals use when they relate to other persons and to the environment. Many researchers have investigated the dimensional structure of adolescent temperament and have defined different dimensions of temperament according to the theoretical framework they focused on [21-24]. One of these frameworks is the biologically oriented temperament model developed by Rothbart and colleagues. In this model, temperament is defined as constitutionally based individual differences in reactivity and self-regulation, which are influenced over time by heredity, maturation, and experience [25]. In order to model temperament, Rothbart and colleagues developed the Early Adolescent Temperament Questionnaire (EATQ) [22], later revised into the EATQ-R [26, 27]. The Dutch translation of the EATQ-R incorporates the six empirically verified temperament dimensions High-intensity pleasure: the pleasure derived from activities involving high-intensity or novelty; Shyness: behavioral inhibition to novelty and challenge, especially social; Fear: worrying and unpleasant affect related to the anticipation of distress; Frustration: negative affect related to interruption of ongoing tasks or

goal blocking; Effortful control: the capacity to voluntarily regulate behavior and attention; and Affiliation: the desire for warmth and closeness with others [28].

When temperament is studied in relation to adolescent cannabis use, specific dimensions of temperament seem relevant. Most previous research has focused on temperamental traits that reflect one's reaction to, and seeking of novel and rewarding stimuli, including for instance sensation seeking, novelty seeking, and high-intensity pleasure. Individuals with high levels on these constructs are characterized by a tendency towards frequent exploratory activity and increased susceptibility to the reinforcing effects of novel and pleasurable stimuli. Their behavior is consequently more oriented towards approach, which increases the likelihood of engaging in risk-taking activities, such as substance use. While novelty seeking and high-intensity pleasure mainly reflect the excitement in response to novel stimuli and the tendency towards exploratory behavior, the construct of sensation seeking also incorporates characteristics of behavioral disinhibition [29]. According to Zuckerman, high sensation seekers appraise risk as smaller than low sensation seekers do, even for activities they have never tried, and they experience less anxiety in such situations [30]. As a consequence, they show less avoidance in novel or potentially hazardous situations. Behavioral disinhibition is conceptually and inversely related to the EATQ-R dimensions shyness and fearfulness, and to Cloninger's construct of harm avoidance. The latter reflects the tendency to respond intensely to aversive stimuli and to avoid novel stimuli, punishment and non- reward. According to Cloninger, particularly the combination of high novelty seeking and low harm avoidance places an individual at increased risk of substance use problems [31, 32].

In addition to indicators of novelty or sensation seeking, two other dimensions of temperament seem of particular relevance with respect to adolescent cannabis use. First, temperament dimensions related to negative affectivity or negative emotionality, sometimes referred to as difficult temperament, have been suggested to predict adolescent cannabis and general substance use [33, 34]. Negative affectivity reflects the tendency to easily become frustrated and irritated and to become intensely upset. It is indicated by measures of, for instance, frustration and, particularly in younger individuals, fearfulness. It has been suggested that irritation and anger in reaction to blocked goals make highly frustrated individuals prone to health-risk behaviors, including cannabis abuse [35]. Second, characteristics related to task orientation, attention control or effortful control, reflecting the ability to regulate attention and behavior and to follow through to completing a task, have been related to a lower likelihood of adolescent general substance use, including the use of cannabis [34]. Individuals with high effortful control are expected to be at

a decreased risk of potentially hazardous substance use because they are more likely to consider the, sometimes long-delayed, consequences of their actions.

Multiple risk factors, multiple pathways

Given the aforementioned multifactorial nature of cannabis use and abuse, and the likelihood of associations between temperament and other risk factors of cannabis use, multiple pathways might relate temperament to adolescent cannabis use. First, as depicted in Figure 1.1 (arrow A), temperament might directly, independent from other risk factors, affect the risk of early onset and/or continuation of cannabis use.

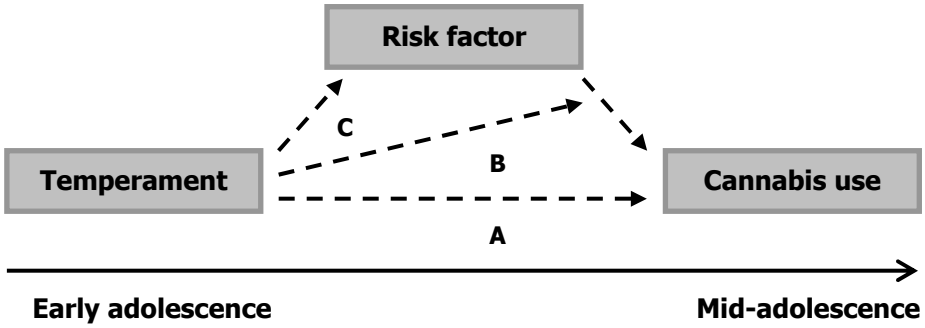

Figure 1.1 Schematic presentation of suggested pathways relating temperament to cannabis use.

However, when temperament is considered next to certain other risk factors of cannabis use, direct associations between temperament and cannabis use lose strength or disappear. Apparently, different risk factors explain an overlapping part in the prediction of cannabis use. As such, the relationship between temperament and cannabis use seems more complicated than straightforward associations between specific traits and particular patterns of cannabis use, and likely includes interrelations with other risk factors of cannabis use. One possible interrelation is moderation, indicated by arrow B in Figure 1.1. This pathway implies that the impact of a risk factor depends on the temperamental make-up of an individual. For instance, adolescents with a high tendency towards exploratory behavior might be more negatively affected by a family environment characterized by low parental monitoring than less exploratory adolescents. Consequently, adolescents in the former group will be relatively more likely to initiate the use of cannabis at an early age, or to progress into regular patterns of cannabis use. A "moderation" pathway would explain why, given equal exposure to other risk factors, some individuals do initiate or continue the use of cannabis use while others do not. In addition to the direct and moderation

pathway, a third pathway is proposed (Figure 1.1, arrow C) in which the relationship between temperament and cannabis use is mediated by another risk factor of cannabis use. In such a pathway, temperament affects the risk to start or continue the use of cannabis because it predisposes an individual towards other risk factors of cannabis use. For instance, adolescents that are easily frustrated might be more inclined to select deviant and substance-using friends than less irritable adolescents. By affiliating with substance-using friends they put themselves at an increased risk of initiating or continuing the use of cannabis.

Temperament in relation to other risk factors of cannabis use

While some studies have examined the interrelation between temperament and other risk factors of adolescent substance use, most of these focused on a composite measure of alcohol, tobacco, and cannabis use. The fact that cannabis use is generally considered more deviant than alcohol consumption and cigarette smoking, and that it frequently marks the transition from legal substance use to the use of soft and illicit drugs [36], implies that a specific focus on the determinants of cannabis use is of importance. In the present thesis, various pathways will be examined to determine the role of temperament, and the interrelation between temperament and other risk factors, in the onset and continuation of cannabis use during adolescence.

First, although several studies assessed the prospective, direct relationship between indicators of sensation seeking and cannabis use during adolescence, conceptual and methodological differences between studies make it difficult to draw conclusions on the actual presence and nature of such associations. Factors that complicate comparison among studies include, for example, characteristics of the study samples, the variety in instruments and definitions of temperamental constructs and cannabis use measures, and differences between studies with regard to the inclusion of additional risk factors or confounders. Furthermore, studies may encounter various biases, such as selective attrition, resulting in limited validity and generalizability of their findings. In this thesis, we established the evidence for direct, prospective relationships between indicators of sensation seeking and various measures of adolescent cannabis use. To this end, we systematically searched and evaluated relevant papers, and summarized their findings while taking methodological and conceptual strengths and weaknesses into account.

Second, characteristics of disruptive behavior, including hyperactivity, impulsivity and conduct problems, have been associated with adolescent onset of cannabis and general substance use [37, 38]. While previous research has shown a link between temperamental indicators of sensation seeking and

disruptive behavior [39-41], their interrelation in predicting the onset of cannabis use remains unclear. In the present thesis we examine several plausible pathways that connect high-intensity pleasure, disruptive behavior, and onset of cannabis use. First, higher levels of high-intensity pleasure and disruptive behavior might be independently associated with onset of cannabis use. Alternatively, a higher level of high-intensity pleasure might place certain individuals with disruptive behavior at increased risk to initiate the use of cannabis. Finally, a higher level of high-intensity pleasure might predispose an individual toward disruptive behavior that subsequently predicts onset of cannabis use. An additional issue that is explored in the present thesis involves the specificity of the interrelation between high-intensity pleasure and various subtypes of disruptive behavior – attention-deficit hyperactivity (ADH), oppositional problems (OPs), and conduct problems (CPs) – in predicting onset of cannabis use. As discussed previously, high-intensity pleasure refers to the excitement in response to novel and high-intensity activities. As such, it mainly reflects the approach component of sensation seeking. Within the framework of Gray's behavioral inhibition system (BIS) and behavioral activation system (BAS), it has been suggested that approach-oriented behavior results from high BAS activity [42]. After all, high behavioral activation is reflected in heightened sensitivity to cues for reward, which increases behavior towards more rewards. Experimenting with the use of cannabis might be such a rewarding experience. Whereas oppositional defiant disorder and conduct disorder have also been associated with high BAS activation [43], attention-deficit hyperactivity disorder has been associated with low BIS activation [44, 45]. Individuals with a hypoactive BIS experience less negative affect in response to pain, punishment, failure, loss of reward or novelty [46], and therefore display less inhibition of behavior that leads to negative outcomes. The aforementioned associations between BIS/BAS, high-intensity pleasure and subtypes of disruptive behavior suggest an interrelation among high-intensity pleasure, oppositional problems and conduct problems, but not attention-deficit hyperactivity, in the prediction of onset of cannabis use.

Third, as mentioned previously, the risk of future cannabis-related problems is highest among those adolescents that initiate the use of cannabis at a very early age, e.g. at age 12 or younger [10]. Previous research has indicated that early onset of cannabis use is most frequently preceded by alcohol and cigarette use, and that particularly early cigarette smoking predicts subsequent cannabis use [47-49]. As yet, little is known about the role of temperamental traits in this sequence. For instance, certain temperamental traits might make early onset of cannabis use more likely by predisposing an adolescent toward early onset of cigarette use that subsequently predicts cannabis use. Alternatively, certain

temperamental traits might affect the risk of transition from cigarette smoking to cannabis use. In the present thesis, we explore the role of different temperamental traits at these two points along the trajectory from early onset cigarette smoking to early onset of cannabis use.

Fourth, it has been demonstrated that belonging to a deviant and/or substance-using peer group is a strong predictor of adolescent cannabis use [19, 50]. Possible explanations for this association include the acquirement of norms and behaviors favorable to using drugs, and the increased availability of substances in peer groups characterized by deviant behavior and substance use [51, 52]. Findings from previous studies suggest that affiliation with substance-using peers mediates the association between various temperamental traits and cannabis or general substance use among adolescents [53-55]. That is, certain temperamental traits affect a person's risk to use cannabis by predisposing the individual to select or withhold from deviant peers. In this thesis, we examine the association between various temperamental traits, affiliation with cannabis-using peers, and lifetime and regular cannabis use. Unlike previous studies, we focus on regular cannabis use, and on affiliation with peers that specifically use cannabis and not on affiliation with a broader group of deviant peers and/or licit substance-using peers. This focus enables us to get more insight in a specific subgroup of cannabis users that has a high risk of adverse outcomes.

Finally, individual differences in both novelty seeking and substance use disorders have been associated with the functioning of the dopaminergic system [56]. More specifically, it has been suggested that individuals with a lack of D2 dopamine receptors (DRD2) are more likely to seek rewarding experiences, including substance use, in order to compensate for a reduced sense of reward [57]. Specific genes have been related to the reduced number of DRD2 in brain structures linked to reinforcement, including the DRD2/ANKK1 TaqIA polymorphism [58]. However, the very small number of studies that assessed differential substance use patterns in adolescent carriers of the A1 allele of the TaqIA polymorphism has yielded inconsistent results. In addition to direct effects of TaqIA, TaqIA by parenting interactions have been studied in relation to substance use. For instance, there is some evidence that the A1 allele is associated with increased alcohol consumption only when parents are permissive toward alcohol use [59]. However, it remains undetermined if general parenting behaviors also modify the actual expression of the A1 allele in adolescent substance use. Moreover, we are not aware of any studies that assessed a gene by parenting interaction with respect to adolescent cannabis use. In the present thesis, we therefore address the association between the A1 allele of the TaqIA polymorphism and regular alcohol and cannabis use during adolescence. In addition, we determine whether measures of general parenting

modify the expression of a genetic liability for regular alcohol or cannabis use. Various aspects of parenting have been prospectively related to a spectrum of adolescent externalizing problem behaviors, including substance use [60-63]. In the present study we focus on the influence of parental rejection, overprotection, and emotional warmth.

Aim & research questions

The aim of the present thesis is to extend the existing knowledge on the aetiology of potentially hazardous patterns of adolescent cannabis use. More specifically, the aim is to gain more insight in the role of temperament in the early onset and continuation of cannabis use during adolescence, and on the interrelation between temperament and other risk factors in predicting adolescent cannabis use.

The main research questions of this thesis are:

1. Does the available literature provide evidence for a direct, prospective relationship between indicators of sensation seeking and adolescent cannabis use?
2. What is the nature of the interrelation between high-intensity pleasure, disruptive behavior and onset of cannabis use? Which subtypes of disruptive behavior interrelate with high-intensity pleasure in predicting the onset of cannabis use?
3. Is the relationship between temperament and early onset of cannabis use mediated by early onset of cigarette smoking? Do temperamental traits modify the risk of transition from cigarette smoking to cannabis use?
4. Is the relationship between temperament and lifetime cannabis use mediated by affiliation with cannabis-using peers? Are associations of temperament and affiliation with cannabis-using peers with lifetime cannabis use also applicable to the development of regular cannabis use?
5. Is the A1 allele of the TaqIA polymorphism (rs1800497) associated with the development of regular alcohol and cannabis use? Does general parenting behavior modify the expression of TaqIA in regular alcohol and cannabis use?

Sample & methods

The study described in this thesis was embedded within the TRacking Adolescents' Individual Lives Survey (TRAILS) [64, 65]. TRAILS is a large,

prospective cohort study of Dutch young adolescents initially aged 10-12 years, who are followed biennially, until the age of 24. 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. For the present thesis, data from the first (2001-2002), second (2003-2004), and third (2005-2007) assessment waves were used. 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 (n=2,230, mean age 11.09 years, SD 0.55, 50.8% girls). 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 [64]. At the second assessment wave, information was obtained from 96.4% of those who participated at the first assessment wave (n=2,149, mean age 13.56 years, SD 0.53, 51.0% girls). T3 was completed with 81.4% of the original number of participants (n=1816, mean age = 16.27 years, SD 0.73, 52.3% girls). The number of individuals that were included in the analyses differs for the separate chapters of this thesis, depending on the availability of complete data on the measures that were used in the analyses.

Outline

The role of temperament in adolescent cannabis use, as well as the interplay between temperament and other risk factors of cannabis use is investigated in several ways. In ***chapter 2***, we provide an overview of the findings of general population studies that addressed the prospective relationship between indicators of sensation seeking and adolescent cannabis use. While taking the methodological and conceptual strengths and weaknesses of the included studies into account, evidence for the associations between these indicators and future cannabis use is evaluated. In ***chapter 3,*** we examine the mechanism by which high-intensity pleasure, disruptive behavior and future onset of cannabis use interrelate. Our focus is on a) the nature of the interrelation (independent effects, moderation, mediation), and on b) which subtypes of disruptive behavior – attention deficit hyperactivity (ADH), oppositional problems (OP), and conduct problems (CP) – interrelate with high-intensity pleasure in predicting the onset of cannabis use. In ***chapter 4***, we address the risk of transition from

early onset of cigarette smoking to early onset of cannabis use, and determine the role of temperamental traits at two points along the trajectory from cigarette smoking to cannabis use. In ***chapter 5,*** we investigate the mediating role of affiliation with cannabis-using peers in the pathways from various dimensions of temperament to lifetime cannabis use, and determine if these characteristics also contribute to the development of regular cannabis use. In ***chapter 6,*** we examine the direct effect of the A1 allele of the TaqIA polymorphism (rs1800497) on regular alcohol and cannabis use, and assess whether parenting modifies the expression of a genetic liability for regular alcohol and cannabis use. Finally, in ***chapter 7,*** the main findings and conclusions of chapters 2-6 are presented and discussed. This thesis concludes with some implications for clinical practice and recommendations for future research.

CHAPTER 2

Temperamental risk factors for adolescent cannabis use: a systematic review of prospective general population studies

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ABSTRACT

In order to establish the evidence for prospective relationships between temperamental and personality indicators of behavioral undercontrol and adolescent cannabis use, we systematically searched relevant papers published through April 2008. We assessed and evaluated 14 studies, of which only four were considered of high quality. Using best-evidence synthesis, we found weak to moderate evidence for prospective relations between a combination of high approach and low avoidance and several measures of cannabis use. Limitations are noted. This review provides suggestions and recommendations for future studies in this area.

INTRODUCTION

The use of cannabis has been associated with various risks, especially for adolescent users. Lynskey and colleagues found elevated odds of subsequent illicit drug use in early cannabis users when compared to their non-early-using co-twins [11]. In addition to substance use related risks, increasing levels of cannabis use in adolescence have been associated with affiliations with delinquent and substance-using peers, an unconventional lifestyle, poor educational performance, higher school dropout rates and difficulties in interpersonal relationships [12]. In addition, cannabis use has been associated with psychiatric problems, such as depression, suicidal behavior, and psychosis, for which adolescent users may be especially vulnerable [15-17]. Taken together, the harmful effects of cannabis use create a threat to public health.

In order to develop effective programs that focus on the prevention of problems related to cannabis use, it is important to gain more knowledge about predictors and mechanisms that are associated with cannabis use. This systematic review focuses exclusively on temperamental predictors of adolescent cannabis use. More specifically, our focus is on temperamental or personality indicators of behavioral undercontrol. These indicators, for example high risk-taking or low constraint, reflect difficulty in the inhibition of behavioral impulses. Because temperamental characteristics appear early in life, and are considered to have reasonable stability over time [20], they might be valuable for the early identification of individuals at-risk of future cannabis use. Because adolescence is the developmental period in which individuals usually initiate cannabis use, and in which they are most vulnerable to develop subsequent problems, a focus on this developmental period is essential.

Our aim is to provide an overview of the findings of general population studies that have addressed the prospective relationship between temperamental and personality indicators of behavioral undercontrol in childhood and adolescence and cannabis use. While taking the methodological and conceptual strengths and weaknesses of the different studies into account, evidence for the associations between these indicators and future cannabis use will be evaluated.

Before we review relevant studies, we provide a short overview of theoretical concepts and assessment of temperament, and subsequently discuss temperamental and personality indicators of behavioral undercontrol.

General concepts and assessment of temperament

In general, temperament refers to the behavioral style with which individuals relate to others and to the environment. According to Thomas and Chess, who

pioneered the work on temperament in infancy and childhood, temperament is the 'how' of behavior, and is the product of innate characteristics and environmental influences [66]. Thomas and Chess constructed the Dimensions of Temperament Survey (DOTS) [23], which has been revised by Windle and Lerner (R-DOTS) for use with respondents from early childhood to early adulthood [24]. Since Thomas and Chess, many others have defined temperament, based on different frameworks that yielded diverse concepts of temperament. Buss and Plomin focused on the heritable component of temperament [21]. Others suggested a neurobiological substrate of temperament [67, 68]. Cloninger theoretically relates his biosocial model of personality to Gray's behavioral approach or activation system (BAS) and behavioral inhibition system (BIS) [67]. The BAS is activated by stimuli associated with reward or relief from punishment. Greater BAS sensitivity is, in case of exposure to cues of future reward, supposed to be reflected in greater proneness to move towards goals and to experience positive feelings. The BIS is activated by novel stimuli or by stimuli associated with punishment or non-reward, and generates negative affect and inhibition of behavior that may lead to negative outcomes [42]. Cloninger developed the Tridimensional Personality Questionnaire to assess three dimensions of personality that are associated with BAS and BIS sensitivity. Another biological approach to temperament is provided by Rothbart and Derryberry, who regarded temperament as individual differences in reactivity and self-regulation, which are influenced over time by heredity, maturation, and experience [25]. Rothbart and colleagues developed the Early Adolescent Temperament Questionnaire (EATQ) to model temperament [22].

Temperamental characteristics associated with substance use

The aforementioned authors have provided researchers with general instruments to assess temperament. When the focus of temperamental research is on substance use, specific aspects instead of general concepts have often been used. Most of these aspects are personality or temperamental indicators of behavioral undercontrol. One of these indicators is Sensation Seeking, defined by Zuckerman as "the seeking of varied, novel, complex, and intense sensations and experiences, and the willingness to take several risks for the sake of these experiences" [29]. The Sensation Seeking Scale (SSS), a self-report questionnaire for adults, is a popular measure of the sensation seeking trait, and has gone through a number of stages in its development. The most widely used version is the SSS–V, which consists of the four subscales Disinhibition, Thrill and Adventure Seeking, Experience Seeking and Boredom Susceptibility. Versions for children and adolescents have been developed by others [69, 70].

According to Zuckerman, individuals who are high in Sensation Seeking have, because of their neurochemical make-up, an increased susceptibility to the reinforcing effects of pleasurable stimuli [71]. Moreover, they appraise risk as smaller than low sensation seekers do, even for activities they have never tried [30]. Their behavior is consequently more oriented towards approach, which increases the likelihood of engaging in risk-taking activities, such as substance use. The probability to engage in such activities is additionally increased in high sensation seekers because of less anticipated anxiety in risk-taking activities [30]. Cloninger relates this high approach-oriented behavior and low avoidance to a highly sensitive BAS and decreased BIS sensitivity, respectively. According to his theory, the probability of early onset substance use is increased in individuals with high Novelty Seeking, manifested in frequent exploratory activity and intense reactions to reward stimuli; low Harm Avoidance, a reduced tendency to respond intensely to aversive stimuli and to avoid novel stimuli, punishment and non-reward; and low Reward Dependence, that involves decreased maintenance of behavior that induces reward and less reduction of behavior that elicits punishment [31]. A related indicator of behavioral undercontrol is low Constraint. Constraint is defined as a propensity to endorse traditional values, act in a cautious and restrained manner, and avoid thrills. It is measured with the Multidimensional Personality Questionnaire (MPQ; [72] and consists of the three primary scales Control (reflective, cautious; plans activities), Harm Avoidance (avoids danger; prefers safer activities), and Traditionalism (conservative; endorses high moral standards).

METHODS

Study selection

Online searches in PsychINFO and PubMed databases were carried out to identify all studies on the prospective relationship between temperamental and personality indicators of behavioral undercontrol and cannabis use in adolescence. The search of electronic databases included peer-reviewed studies published through April 2008, using the search terms (cannabis OR marijuana OR marihuana), adolescen* and longitudinal, combined with one of the following search terms: temperament, personality and sensation seeking. A total of 173 articles were identified. Abstracts of these articles were examined to select those studies that met the following inclusion criteria: 1) the study used a general population sample, 2) it had a prospective design, 3) personality and temperamental indicators of behavioral undercontrol were used as the predictor variables, and 4) the outcome was cannabis use in adolescence or young adulthood. Because of the limited amount of relevant studies we chose to

include studies predicting cannabis use in young adulthood as well, despite our focus on adolescent use. For the same reason we decided to select not only studies on exclusively cannabis use, but also studies that used a composite measure of substance use, including cannabis. If no abstract of the study was available, or if, based on the abstract, it remained unclear whether a study should be included, the whole article was retrieved and read.

Eight studies met the inclusion criteria listed above. Reference lists of the included studies were checked for relevant studies. This resulted in the additional inclusion of seven studies. Because of overlap in study sample and data-waves, one study was excluded. In that case, only the study that focused on hypotheses that fitted best to the aims of this review was included for quality assessment. This resulted in a total inclusion of 14 studies. Table 2.1 summarizes the characteristics of the studies, including age of the participants at the assessment of temperament and substance use, measure of temperament used, substance use measure, results, and strength of the association (if available).

Quality assessment

In order to evaluate the findings of the included studies in the light of the quality with which they were performed, a checklist was developed to assess the methodological quality of the included studies. Table 2.2 shows the items on this checklist, that consider several areas of potential biases, as described by Hayden et al. [73]. The following issues were added because we considered them essential in the study of the prospective relationship between temperament and cannabis use. In order to exclude the potential influence of cannabis use on temperament, temperamental characteristics should have been assessed before exposure to cannabis took place. In addition, in order to exclude inflation of the association between temperament and cannabis use, items with regard to the use of substances should have been eliminated from the temperamental instrument. Furthermore, in order to determine the prospective association between temperament and cannabis use, misclassification of (the level of) cannabis use should have been minimized. For instance, when a studies' focus is on predicting cannabis use in the past year, it should account for previous use of the substance. If not, former cannabis users might be misclassified as abstainers, which might obscure the association with temperamental predictors. Finally, in order to increase the reliability of the self-reported cannabis use, confidentiality of the study should be emphasized.

For every item in the quality list, two independent reviewers (HEC and ACH) rated each study either positive (+) or negative (-). An item was rated as ambiguous if the paper did not contain sufficient information about this criterion.

Table 2.1 Details of included studies on temperamental characteristics that predict cannabis use in adolescence.

Author (year)	Age at assessment temperament Age at assessment substance use	Temperament construct(s) (Instrument)	Substance use measure	Results	Effectsize
Bates et al. (1986)	15 + 18 + 21	Disinhibition	Past year frequency of use (10-point scale ranging from no use - more than once a day) and quantity of use per occasion	Higher disinhibition predicted using marijuana more frequently or in greater quantities.	β = .25 β = .17
	15 + 18 + 21	Change in disinhibition (Sensation Seeking Scale)		Change in disinhibition predicted increased frequency and quantity of use.	β = .18 β = .13
Block et al. (1988)	¾	Item: 'Inhibited and constricted'	Frequency of use (never - 1/2 - occasionally - once a month - once a week - more than once a week)	'Is inhibited and constricted' was negatively correlated to future CU in boys.	r = -.36
	14	Item: 'Curious, eager to learn, open to new experiences' (California Child Q-sort)		'Is curious and exploring' was not significantly related to future CU.	
Brook et al. (1999)	13, 15, 21, 26 13, 15, 21, 26	Conventionality (composite index of intolerance of deviance, rebelliousness, self-deviance and sensation seeking)	Initiation of marijuana use	Youngsters who are unconventional were at a higher risk of marijuana initiation.	OR 2.07

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Table 2.1 Details of included studies on temperamental characteristics that predict cannabis use in adolescence *(continued)*.

Author (year)	Age at assessment temperament Age at assessment substance use	Temperament construct(s) (Instrument)	Substance use measure	Results	Effectsize
Crawford et al. (2003)	Middle school (Waves 1-4)	Level of sensation seeking	Frequency of and increase in weekly marijuana use	SS predicted initial level of marijuana use in high school in one sample. SS predicted the rate of increase in marijuana use in high school in both samples.	β = .14 β = .21
	Middle and high school (Waves 1-8)	Change in sensation seeking (based on 2 items of the Sensation Seeking Scale: 'Do you like to take chances?' and 'Is it worth getting into trouble if you have fun?')		The rate of increase in SS during middle school predicted rate of increase of marijuana use during high school in both samples.	β = .46
Donohew et al. (1999)	8th, 9th, 10th grade 8th, 9th, 10th grade	Sensation Seeking (24-items of Sensation Seeking Scale)	Frequency of past year marijuana use (7-point scale ranging from 1 (none) to 7 (40 times or more))	SS, in the context of the remaining variables, failed to predict frequency of marijuana use.	
Elkins et al. (2006)	16-18 16-18, 19-22	Constraint (Multidimensional Personality Questionnaire)	Onset of illicit substance use disorder (including cannabis)	Low constraint predicted the onset of illicit drug disorder by follow-up.	OR = 1.76

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Table 2.1 Details of included studies on temperamental characteristics that predict cannabis use in adolescence *(continued).*

Author (year)	Age at assessment temperament Age at assessment substance use	Temperament construct(s) (Instrument)	Substance use measure	Results	Effectsize
Höfler, et al. (1999)	14-17 14-17 and at on average 19.7 months later	Behavioral inhibition - Fear Factor Behavioral inhibition - Social Factor (Retrospective Self-Report of Inhibition)	Lifetime frequency of cannabis use (1=no use ever, 2=one-time use, 3=repeated use (2-4 times), 4=regular use (five times and more))	High behavioral inhibition (fear factor) was associated with increased frequency of cannabis use.	COR 1.20 (1.09-1.31)
Krueger (1999)	18	Harm avoidance	Substance dependence disorder (alcohol and/or marijuana) in past 12 months	Harm avoidance was not significantly related to substance dependence disorder.	
	18, 21	Constraint (Multidimensional Personality Questionnaire)		(Low) constraint predicted substance dependence disorder and predicted higher substance dependence scale scores.	OR = .66 ß = -.12
Lerner & Vicary (1984)	1, 3, 5, adolescence, adulthood early and late adolescence / young adulthood	Difficult temperament – composite of low rhythmicity, low adaptability, withdrawal responses, negative mood, high intensity of reactions (Thomas & Chess Parental, Teacher & Subject Interview)	Level of marijuana use (5-point scale ranging from no use to severe use)	Difficult temperament predicted severity of future marijuana use.	R^2 = .20

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Table 2.1 Details of included studies on temperamental characteristics that predict cannabis use in adolescence *(continued).*

Author (year)	Age at assessment temperament Age at assessment substance use	Temperament construct(s) (Instrument)	Substance use measure	Results	Effectsize
Mâsse & Tremblay (1997)	6,10	Novelty- Seeking	Onset of cannabis or other illegal substance use	Novelty seeking at age 6 and 10 predicted the onset of substance use.	0.18 and 0.18 (Wald χ^2 = 16.75 and 14.46)
	11, 12, 13, 14, 15	Harm Avoidance		(Low) harm avoidance at age 6 and 10 predicted the onset of substance use.	-0.16 and -0.13 (Wald χ^2 = 16.85 and 10.29)
		Reward Dependence (Preschool Behavior Questionnaire, Prosocial Behavior Questionnaire)		Reward dependence did not predict the onset of substance use.	
Pedersen (1991)	16-18 and at follow-up(20 months later)	Experience Seeking	Level of cannabis use (moderate <30 times, heavy use >30 times)	Higher experience seeking predicted both moderate and heavy cannabis use in boys.	OR 1.8 OR 2.3
	at follow-up	Thrill and adventure Seeking		Thrill and adventure seeking was not related to use.	
		Disinhibition (Sensation Seeking Scale 18)		Higher disinhibition predicted moderate cannabis use in girls and heavy cannabis use in boys.	OR 3.3 OR 2.3

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Table 2.1 Details of included studies on temperamental characteristics that predict cannabis use in adolescence *(continued).*

Author (year)	Age at assessment temperament Age at assessment substance use	Temperament construct(s) (Instrument)	Substance use measure	Results	Effectsize
Shedler & Block (1990)	7, 11, 18	Item: 'Inhibited and constricted'	Stage of marijuana use (abstainers, experimenters (maximal use of once a month) and frequent users (use once a week or more))	At age 7 and 11: 'Inhibited and constricted' was lower in experimenters as compared to abstainers.	Not available
	18	Item: 'Curious, eager to learn, open to new experiences' (California Child Q-sort, California Adult Q-sort)	*Abstainers and frequent users were compared to experimenters.*	'Curious, eager to learn, open to new experiences' was, at age 7, lower in frequent users as compared to experimenters and, at age 11, higher in experimenters as compared to frequent users and abstainers.	
Teichman et al. (1989)	14-17	Sensation Seeking (Sensation Seeking Scale)	Initiation and continuation of marijuana use (abstainers, initiators (no use at T0 – use at T1) and users (use at both times)) and frequency of substance use, including marijuana	Groups differed significantly in baseline SS with highest level in users, followed by initiators.	F = 66.33, d.f. = 2/1198
	14-17 and on average 12 months later			SS predicted frequency of current substance use, including marijuana use, at ages 15, 16 and 17, but not at age 18.	R^2 = .02, R^2 = .02 R^2 = .01

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Table 2.1 Details of included studies on temperamental characteristics that predict cannabis use in adolescence *(continued).*

Author (year)	Age at assessment temperament Age at assessment substance use	Temperament construct(s) (Instrument)	Substance use measure	Results	Effectsize
Von Sydow et al. (2002)	14-24	Behavioral inhibition - Fear Factor	Onset of cannabis use, frequency of cannabis use, and progression to cannabis abuse and dependence	Fear factor predicted onset of cannabis use.	OR 1.4 (1.3-1.6)
	14-24 and at on average 42 months later	Behavioral inhibition - Social Factor (Retrospective Self-Report of Inhibition)		Social factor predicted frequency of use in former non-users.	IRR 0.6 (0.5-0.7)
				Progression into cannabis abuse was not associated with behavioral inhibition.	
				Social factor and fear factor predicted progression into cannabis dependence.	OR 1.7 (1.1-2.6) OR 1.8 (1.1-2.8)

'+'= different age groups; '/'= composite score of different assessments; ','= separate assessments for each individual ; '-'= age-range.

Scores of the two reviewers were compared and, if inconsistent, were discussed in order to reach consensus. A study was judged of high quality if it, for at least 50%, satisfied the criteria of each of the domains of potential bias [73]. Based on this criterion, four of the 14 studies were rated of high quality. Table 2.3 shows the results of the quality assessment of the included studies.

Table 2.2 Criteria list for the quality assessment of studies on temperamental risk factors for cannabis use in adolescence.

Criteria
1. Study purpose
A Description of a specific, clearly stated purpose of the study.
2. Study participation
The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results.
B Description of the key characteristics of the study population (distribution by age, gender and ethnicity).
C The sampling frame and recruitment are described, including characteristics of the place of recruitment.
D Inclusion and exclusion criteria are described.
E Adequate participation at baseline.
3. Study attrition
Loss to follow up is not associated with key characteristics, sufficient to limit potential bias.
F Adequate response rate.
G There are no important differences in key characteristics between completers and dropouts.
4. Predictor measurement
The predictor variables are adequately measured in study participants to sufficiently limit potential bias.
H A clear definition or description of the measure of temperament or personality is provided.
I The assessment of temperament or personality is adequately valid and reliable to limit misclassification bias (includes: assessment at age 10 or younger by adult informants; assessment at age 10+ by self-report; absence of or adjustment for substance related items in questionnaires).
J Temperament or personality was assessed prior to the first use of cannabis.

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Table 2.2 Criteria list for the quality assessment of studies on temperamental risk factors for cannabis use in adolescence (*continued)*.

	Criteria
5.	*Outcome measurement* *The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.*
K	A clear definition of the measure of cannabis use is provided.
L	The measure of cannabis use is adequately valid to limit misclassification.
M	The method used is adequately reliable to limit under-reporting (e.g. efforts were made to increase reliable reporting of substance use; additional use of a biological marker of cannabis use).
6.	*Confounding measurement* *Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.*
N	Age and gender are accounted for in the analysis.
7.	*Analysis and data presentation*
O	The selected model is appropriate for the design of the study.
P	Presentation of the data is sufficient to assess the adequacy of the analysis.
Q	The number of cases in the multivariate analysis is at least ten times the number of independent variables in the analysis.

Categories of temperamental and personality indicators of undercontrol

In order to increase comparability among the findings of the included studies, temperamental and personality indicators of behavioral undercontrol were divided into categories. As shown in Table 2.4, we suggested that the various indicators fall into three categories. These categories were called 1) indicators of approach, referring to temperamental characteristics that regard openness to new experiences, 2) indicators of avoidance, referring to measures that assess the inhibition or disinhibition of behavior, and 3) indicators of combined high approach and low avoidance.

Table 2.3 Results of the quality assessment of studies on temperamental risk factors for cannabis use in adolescence.

Issue	**1**	**2**				**3**		**4**			**5**			**6**	**7**			
Criterium	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	***b***
Bates (1986)	+	-	+	+	-	+	?	+	-	-	+	-	+	+	+	-	+	**1**
Block (1988)	+	+	+	-	?	+	?	-	-	+	+	+	+	-	-	+	-	**3**
Brook (1999)	+	+	+	+	?	?	?	+	-	+	+	+	+	+	+	+	+	**1**
Crawford (2003)	+	+	+	-	+	+	?	+	+	-	+	+	+	+	+	+	+	**0**
Donohew (1999)	+	+	+	+	?	+	?	+	+	-	+	+	+	-	+	+	+	**1**
Elkins (2006)	+	+	+	+	+	+	-	+	+	-	+	+	?	+	+	+	+	**0**
Höfler (1999)	+	+	+	-	?	+	?	+	+	-	+	+	+	-	+	+	+	**1**
Krueger (1999)	+	-	+	+	+	+	+	+	+	-	+	-	?	-	+	+	+	**2**
Lerner (1984)	+	+	+	-	?	+	-	+	+	+	-	-	?	-	-	-	+	**3**
Mâsse (1997)	+	+	+	+	?	-	+	+	+	+	+	+	?	+	+	+	+	**0**
Pedersen (1991)	+	-	+	-	?	+	?	+	+	-	-	-	+	-	+	-	+	**3**
Shedler (1990)	+	+	+	-	?	+	?	-	+	+	+	+	+	-	-	+	-	**2**
Teichman (1989)	+	+	+	-	+	-	-	+	+	+	+	+	+	-	+	+	+	**2**
Von Sydow (2002)	+	+	+	-	?	+	?	+	+	+	+	+	+	+	+	+	+	**0**

1, 2, A, B, C, etc. refer to the issues and quality criteria listed in Table 2.2, '*b*' refers to the total number of biases. Bias is defined as negative or ambiguous ratings on more than 50% of the criteria for a specific issue. '+'= study was rated positive on criterium; '-'= study was rated negative on criterium; '?'= study was rated ambiguous on criterium.

Best-evidence synthesis

Because of considerable variation among studies we performed a best-evidence synthesis, instead of meta-analysis, to determine the evidence for the investigated prospective relations between temperament and cannabis use. As can be seen in Table 2.5, the evidence for a factor was determined by taking into account the number of studies evaluating this factor, the methodological quality of these studies, and the consistency of these studies findings [74]. Four levels of evidence, based on Sackett et al. [75], were defined (Table 2.5).

Table 2.4 Categories of temperamental and personality indicators of behavioral undercontrol.

Category name	Temperament or personality construct
Indicators of approach	Novelty seeking
	Experience seeking
	Thrill and adventure seeking
	'Open to new experiences'
Indicators of avoidance	Harm avoidance
	Behavioral inhibition
	'Inhibited and constricted'
	Difficult temperament
	Disinhibition *R*
Indicators of combined high approach and low avoidance	Sensation seeking
	Constraint *R*
	Conventionality *R*

'*R*' refers to *reversed.*

Table 2.5 Definitions of levels of evidence (Sackett et al., 2000).

Level of evidence	
Strong	Consistent findings (≥ 75%) in at least 2 high quality cohorts
Moderate	Consistent findings (≥ 75%) in one high quality cohort and at least one low quality cohort
Weak	Findings in one high quality cohort or consistent findings (≥ 75%) in at least 3 or more low quality cohorts
Inconclusive	Inconsistent findings irrespective of study quality, or less than 3 low quality cohorts available

(≥ 75%): at least 75% of the findings of studies investigating a specific relation between temperament and cannabis use had to agree on existence and direction of the relation.

RESULTS

Temperamental indicators of approach

Two studies, one of which was considered of high quality, described the relationship between indicators of approach and onset of cannabis or substance use. As shown in Table 2.6, findings indicated that the evidence for this relationship was inconclusive. Mâsse and Tremblay found that high approach at ages 6 and 10 predicted the onset of substance use before the age of 15 [32].

In addition, Shedler and Block found that the level of approach at age 11 was higher in individuals that experimented with the use of cannabis at age 18 when compared to abstainers. However, when measured at age 7, this indicator did not differentiate experimental users from abstainers [76].

With regard to frequency of cannabis use, evidence for a relationship with indicators of approach remained also inconclusive. Findings of three low quality studies on this subject were inconsistent. According to Shedler and Block approach at age 7 was higher in experimental users when compared to frequent users at age 18. However, when measured at age 4, this indicator was not associated with frequency of cannabis use at age 14 [77]. Moreover, Pedersen et al. found that one measure of high approach, e.g. experience seeking, at age 16-18 was related to both moderate and heavy cannabis use two years later, but only in boys. In the same study, another measure of approach, e.g. thrill and adventure seeking did predict neither moderate nor heavy cannabis use [78].

Temperamental indicators of avoidance

Nine studies investigated the prospective relationships between various indicators of avoidance and different measures of cannabis use. With regard to onset of cannabis use, the evidence for a prospective relationship with indicators of avoidance remained inconclusive. While two studies, one of which was considered of high quality, found that low avoidance in childhood predicted the onset of cannabis and substance use in adolescence [32, 76], a third study found opposite effects. In the third study that was also considered of high-quality, high avoidance in adolescence and young adulthood predicted future onset of cannabis use [19].

Evidence with regard to the relationship between indicators of avoidance and frequency of cannabis use remained also inconclusive. Two studies, one of which was considered of high quality, found an association between low avoidance in adolescence and young adulthood and increased frequency of future cannabis use [19, 79]. Findings of two studies indicated gender differences in the relationship between low avoidance and frequency of cannabis use. Findings of one study were consistent with previous findings, but only for boys [77]. Another study found that low avoidance predicted moderate but not heavy cannabis use in girls, and heavy but not moderate cannabis use in boys [78]. Contradictorily, two studies found an association between indicators of high avoidance and increased frequency of cannabis use in adolescence and young adulthood [33, 50]. Finally, one study found that level of avoidance did not differentiate experimenters from abstainers or frequent users [76]. One low quality study also investigated the relationship between change in avoidance

and frequency of cannabis use and found that a decrease in avoidance predicted a higher frequency of use [79].

With regard to the development of substance use disorders, findings were inconsistent. Two studies, one of which was considered of high quality, investigated the role of avoidance in the development of substance use disorder. Von Sydow et al. found that progression into cannabis dependence, but not abuse, was associated with high avoidance [19]. Krueger et al. did not find a relationship between avoidance and substance use disorder [80]. The prospective relationship between indicators of avoidance and the development of substance use disorders remained therefore inconclusive.

Indicators of combined high approach and low avoidance

Six studies investigated the relationship between indicators of combined approach and avoidance characteristics and cannabis use.

With regard to onset of cannabis use, two studies, one of which was considered of high quality, found that a combination of high approach and low avoidance in adolescence predicted future onset of cannabis use [81, 82]. Evidence for this relationship was therefore moderate.

With regard to frequency of cannabis use, evidence for a prospective association with an indicator of high approach and low avoidance was inconclusive. Findings from two high-quality studies indicated that a higher level of this indicator predicted increased frequency of use [82, 83]. In one of these studies, substance use at age 15, 16, and 17, but not at age 18, were predicted by high approach and low avoidance [82]. In a study by Donohew et al. frequency of marijuana use was not predicted by this indicator [53]. Crawford et al. also found that the increase in frequency of marijuana use in high school was positively related to the level of high approach and low avoidance in middle school, as well as to the change in this level during middle school [83]. Because the latter findings were based on only one high-quality study, evidence for these relationships was weak.

Two studies, one of which was considered of high quality, investigated an indicator of combined approach and avoidance in relation to substance use disorder, including cannabis. Findings indicated that a combination of high approach and low avoidance in adolescence predicted substance abuse and dependence in young adulthood [80, 84]. Evidence for this relationship was therefore moderate.

Table 2.6 Overall level of evidence.

	Temperament characteristics	Measure	Outcome	+/-/?	AQ/TS	Level of evidence
Indicators of approach						
	Novelty seeking "Curious, eager to learn and open to new experiences"	Level	Onset of cannabis or other illegal substance use	?	1/2	Inconclusive
	"Curious, eager to learn and open to new experiences" Experience seeking Thrill and adventure seeking	Level	Frequency of cannabis use	?	0/3	Inconclusive
Indicators of avoidance						
	Harm avoidance "Inhibited and constricted" Behavioral inhibition	Level	Onset of cannabis or other illegal substance use	?	2/3	Inconclusive
	Disinhibition *R* Behavioral inhibition "Inhibited and constricted" Difficult temperament	Level	Frequency of cannabis use	?	1/7	Inconclusive
	Disinhibition *R*	Change	Frequency of cannabis use	-	0/1	Inconclusive
	Behavioral inhibition Harm avoidance	Level	Substance use disorder	?	1/2	Inconclusive
Indicators of high approach and low avoidance						
	Conventionality *R* Sensation seeking	Level	Onset of cannabis use	+	1/2	Moderate
	Sensation seeking	Level	Frequency of cannabis use	?	2/3	Inconclusive
	Sensation seeking	Level	Change in frequency of marijuana use	+	1/1	Weak
	Sensation seeking	Change	Change in frequency of marijuana use	+	1/1	Weak
	Constraint *R*	Level	Substance use disorder including cannabis	+	1/2	Moderate

AQ/TS: number of relevant studies of high quality / total number of studies on that relationship; +/-/?: nature of relationship, respectively (+) positive, (-) negative, (?) inconsistent findings.

DISCUSSION

The aim of this review was to establish the evidence for prospective relationships between temperamental and personality indicators of behavioral undercontrol and adolescent cannabis use. Studies on this subject were searched for. Because of the limited amount of studies that answered our inclusion criteria, we decided to include studies in which cannabis use was assessed in young adulthood, and in which a composite measure of substance use, including cannabis, was used. The methodological quality of the included studies was assessed using a checklist. According to our criteria, only four out of 14 studies were considered of high quality. Studies published in the last decade demonstrated an improvement in quality when compared to previously published studies, especially with regard to the analyses and presentation of the data, and in accounting for confounders. Findings were summarized and, in order to facilitate comparison among studies, were categorized according to 1) the nature of the temperamental or personality construct, e.g. indicator of high approach, indicator of low avoidance, or indicator of combined high approach and low avoidance, and 2) the measure of cannabis use, e.g. onset, frequency, or substance use disorder. Subsequently, levels of evidence for relationships between indicators of behavioral undercontrol and various measures of future cannabis use were determined. Due to the small number of studies, the lack of quality of the included studies, and heterogeneity among studies, convincing evidence in favor or disfavor of the investigated relations was absent.

Findings indicated that, irrespective of the measure of cannabis use, evidence for the prospective relationships between indicators of either approach or avoidance and cannabis use remained inconclusive. Evidence for the prospective relationships between indicators of combined approach and avoidance and various measures of cannabis use was weak to moderate. Findings indicated that a combination of high approach and low avoidance in adolescence was associated with an increased risk of both onset of cannabis use and developing a substance use disorder [80-82, 84]. In addition, the level of high approach and low avoidance in middle school, as well as the change in this level during middle school were positively related to the increase in frequency of marijuana use during high school [83]. Studies that confirmed a prospective relationship between indicators of behavioral undercontrol and cannabis or substance use demonstrated considerable variation in the sizes of the effects. Because of heterogeneity in statistical approach and in accounting for additional risk factors, comparability of effect sizes was limited.

Our findings underline that it is the combination of high approach and low avoidance, rather than the individual indicators, which increases the risk for

cannabis use or substance use disorder in adolescence and young adulthood. This conclusion is in agreement with the theories proposed by Zuckerman and Cloninger, who both describe mechanisms of approach and avoidance in relation to substance use vulnerability [30, 31, 71].

The total absence of evidence for the relationships between indicators of either approach or avoidance and cannabis use can be alternatively explained by heterogeneity among studies on these subjects in combination with their lack of quality. Because, due to heterogeneity, not all the investigated associations could be reasonably categorized and compared, various associations have been described that were addressed by only few low quality studies. Heterogeneity within categories might explain the high degree of inconsistent findings. Though associations were categorized according to overlap in predictors and outcomes, conceptual differences between predictors and differences in reliability of the constructs might account for the inconsistent findings. In addition, due to the small number of studies, we were not able to categorize findings according to the developmental phase in which the study had been performed. Therefore, age-specific relationships between indicators of undercontrol and cannabis use might have caused the discrepancies in findings. Indeed, within some samples included in this review, findings on the prospective relation between indicators of avoidance and substance use were age-specific [19, 50, 76, 77].

Besides the answers to the aims of this review, the findings of the included studies offer some interesting additional information that provides directions for future research. While the majority of studies focussed on the univariate effects of temperament or personality on future cannabis or substance use, some studies used a multivariate approach, investigating the additional contribution of other risk factors. In those studies, the association between temperament and future substance use was reduced or disappeared after adding other risk factors to the model. Apparently, different constructs explain an overlapping part in the prediction of substance use. This indicates the existence of an association between different risk factors for substance use. Donohew et al. for instance, investigated the complementary effect of sensation seeking and social influences on marijuana use. Findings indicated that there was no direct relationship between sensation seeking and marijuana use [53]. In the discussion of their findings, Donohew et al. suggest that the association between sensation seeking and marijuana use might have been mediated by friendship selection. Besides mediator effects, moderation has been suggested by others. Wills et al. found that the influence of parent-child conflict, parental substance use, and impact of peer substance use on adolescent substance use was moderated by the temperamental make-up of the individual [85]. In conclusion, studies indicate that the relationship between temperament and future substance use goes

beyond a direct one, and interrelates with the influence of other risk factors. Future research is needed to disentangle the interplay between various predictors of adolescent cannabis use.

An additional interesting finding refers to the stability of temperamental characteristics as predictors of cannabis use. As discussed earlier, some findings on the prospective relation between indicators of avoidance and substance use were age-specific. Moreover, two studies found a relation between an increase in levels of disinhibition and sensation seeking throughout adolescence and frequency of cannabis use [79, 83]. These findings suggest that the nature of the relationship between indicators of behavioral undercontrol and cannabis use is not static, but that it depends on the developmental periods at which it is investigated. A change in the level of some temperamental or personality characteristics throughout adolescence, accompanied by a shift in importance of environmental risk factors such as peer substance use, might explain this phenomenon. Future research should attend to these considerations.

Limitations

There are some aspects of the present review that could be noted as limitations. First, our search for papers was restricted to papers that were included in electronic databases that are considered relevant for the topic of our review. Therefore, we may have missed studies that do not fulfil these requirements and that were not identified during our additional reference checking. Second, in order to reduce arbitrariness in the quality appraisal of the studies and in the levels of evidence for the various relations between temperamental or personality indicators and future substance use, we based our definitions on recommendations by Hayden et al. and Sackett et al. [73, 75]. However, any system for defining level of quality or evidence will be subject to some randomness.

Conclusion

We found moderate and weak evidence for a prospective relationship between a combination of high approach and low avoidance in adolescence and increased risk of onset of cannabis use, substance use disorder and increase in frequency of cannabis use during adolescence. Strong evidence for prospective relations between temperamental and personality indicators of behavioral undercontrol and cannabis use in adolescence and young adulthood is lacking. Well-conducted, prospective studies on this subject are needed in order to determine the existence of such relations.

CHAPTER 3

Predicting onset of cannabis use in early adolescence: The interrelation between high-intensity pleasure and disruptive behavior. The TRAILS Study

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ABSTRACT

Background/Aims: Increased knowledge about the mechanisms by which some individuals are at-risk of early onset of cannabis use might contribute to the improvement of prevention efforts. We focus on the roles of early-adolescent high-intensity pleasure, disruptive behavior, and their interplay in the prediction of onset of cannabis use two years later.
Methods: Data from 81% (N=1804) of the participants (51.9% girls) of the Tracking Adolescents' Individual Lives Survey (TRAILS), a prospective general population study in the north of the Netherlands, were analyzed. Measures included parent-reported high-intensity pleasure (Early Adolescent Temperament Questionnaire; EATQ-R), and parent- and self-reported general disruptive behavior, attention-deficit hyperactivity (ADH), oppositional problems (OP) and conduct problems (CP) (Child Behavior Checklist/6-18 and Youth Self-Report) at age 10-12. Onset of cannabis use was assessed at age 12-14 by means of self-reports. Analyses were carried out in Mplus.
Results: Early adolescent high-intensity pleasure and disruptive behavior, mainly CP and to some extent ADH, predicted the onset of cannabis use in adolescence. Although we found some mediation by general disruptive behavior, CP and ADH, the contribution of high-intensity pleasure in predicting the onset of cannabis use was found to be mainly independent from disruptive behavior.
Conclusions: The unique contribution of both high-intensity pleasure and disruptive behavior points in the direction of different pathways towards onset of cannabis use.

INTRODUCTION

Early onset of cannabis use is associated with increased risks for future substance use, abuse and dependence [9]. Moreover, the rate of drug-related social, legal, emotional and health problems is highest among those who initiated illicit drug use at age 12 or younger, and declines with increased age of initiation [10]. Therefore, more insight in the mechanism behind early onset of cannabis use is important and might contribute to early identification of at-risk individuals and to the development of prevention programs.

Previous studies have found prospective associations between certain temperamental and behavioral characteristics and onset of cannabis and illicit substance use in adolescence. The majority of these temperamental characteristics, such as sensation seeking [82] and novelty seeking [32], are associated with one's reaction to and seeking of novel and rewarding stimuli. While the construct of sensation seeking also incorporates characteristics of behavioral disinhibition [29], the construct of novelty seeking reflects mainly the excitement in response to novel stimuli and the tendency towards exploratory behavior [31]. Certain behavioral characteristics that have been associated to onset of cannabis and other illicit substance use, such as hyperactivity, impulsivity and conduct behavior [37, 38], can be classified as disruptive behavior. While previous research has shown a link between temperamental indicators of sensation seeking and disruptive behavior [39-41], their interrelation in predicting the onset of cannabis use remains unclear. In order to increase the insight in the mechanism behind early onset of cannabis use, we need to understand the roles of sensation seeking characteristics, disruptive behavior, and their interrelation.

When the focus is on temperamental indicators of sensation seeking, disruptive behavior and future onset of cannabis use, various mechanisms seem plausible. Sensation seeking and disruptive behavior might independently contribute to an increased risk of onset of cannabis use in adolescence. This way, an individual with both sensation seeking characteristics and disruptive behavior would be most vulnerable to the early onset of cannabis use. Alternatively, the increased vulnerability for onset of cannabis use in adolescents with disruptive behavior might be due to their increased level of sensation seeking. In this model, sensation seeking modifies the relationship between disruptive behavior and onset of cannabis use. A third possibility is that sensation seeking and disruptive behavior are different points at a same continuum. In this case, the relationship between sensation seeking characteristics and onset of cannabis use might be mediated by a higher level of disruptive behavior.

Another question with respect to the mechanism behind early onset of cannabis use regards the specific subtypes of disruptive behavior that interrelate with sensation seeking characteristics in predicting early onset of use. Within the framework of Gray's behavioral inhibition system (BIS) and behavioral activation system (BAS) [42], it has been suggested that sensation seeking characteristics reflect the activation of the BAS [86]. High behavioral activation is reflected in heightened sensitivity to cues for reward, which increases behavior towards more rewards. Experimenting with the use of cannabis might be a rewarding experience for those with high BAS functioning. This way, increased BAS activity might explain why certain adolescents are at increased risk to initiate the use of cannabis when compared to others. Whereas oppositional defiant disorder and conduct disorder have been associated with high BAS activation [43], attention deficit/hyperactivity disorder has been associated with low behavioral inhibition [44, 45]. These findings suggest an interrelation between sensation seeking characteristics and oppositional problems (OPs) and conduct problems (CPs), but not attention-deficit-hyperactivity (ADH), in the prediction of onset of cannabis use.

The Tracking Adolescents' Individual Lives Survey (TRAILS) is a general population study that offers the possibility to find out which of the mechanisms described above underlie the early onset of cannabis use. One of the strengths of TRAILS is that information about its participants is gathered from multiple informants. Because of differences in contexts and perspective, different informants provide partly unique information about the participants' behavior [87]. Moreover, observation by different informants rules out common method variance as an interpretation of the findings.

The aims of the present study are to prospectively investigate 1) the predictive value of both high-intensity pleasure – a temperament dimension based on the construct of sensation seeking that emphasizes physical and social thrill seeking [22] – and disruptive behavior in early adolescence on the onset of cannabis use in adolescence, and 2) the mechanism by which high-intensity pleasure, disruptive behavior and future onset of cannabis use interrelate. Our focus is on 2a) the nature of the interrelation (independent effects, moderation, mediation), and on 2b) which subtypes of disruptive behavior – attention deficit hyperactivity (ADH), oppositional problems (OP), and conduct problems (CP) – interrelate with high-intensity pleasure in predicting the onset of cannabis use.

METHODS

Sample

The present study reports data from the first (T1) and second (T2) assessment wave of TRAILS, which ran from March 2001 to July 2002 and from September 2003 to December 2004, respectively. A detailed description of the sampling procedure and methods is provided in De Winter et al. [64].

Briefly, the TRAILS target sample involved all 10- to 11-year-old children living in the three largest cities and some rural areas in the North of the Netherlands. Of the eligible children, 76.0% (n=2230, mean age 11.09, *SD*=0.55, 50.8% girls) were enrolled in the study (i.e., both child and parent gave informed consent 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 [64].

Of the 2230 baseline (T1) participants, 96.4% (n=2149, 51.2% girls) participated in the first follow-up assessment (T2), which was held 2-3 years after T1 (mean number of months 29.44, *SD*=5.37). Mean age at T2 was 13.55 (*SD*=0.54). For the analyses of the present study, subjects who reported onset of cannabis use before the assessment of temperament had taken place were eliminated from the analyses (n=14). Furthermore, only subjects were included only when complete data on the measures outlined below were available (n=1804). Included participants had a somewhat higher intelligence (t=7.96, 2219 df, $p<.001$), a lower level of self-reported conduct problems (t=-2.22, 2196 df, $p<.05$), a higher socioeconomic status (χ^2 (1 df, n=2188) = 81.88, $p<.001$), and were less likely to have a parent with a history of substance use disorder (χ^2 (1 df, n=2176) = 13.69, $p< .05$), when compared with the excluded participants (n=426).

Data collection

At T1, one of the parents or guardians (preferably the mother) was asked to fill out a written questionnaire. Besides the questionnaire, well-trained interviewers visited the parent at their homes to administer an interview covering a wide range of topics, including parental psychopathology. Children were assessed at school, where they filled out questionnaires, in groups, under the supervision of one or more TRAILS assistants. In addition, neurocognitive tasks, intelligence, and a number of biological parameters were assessed individually. Teachers were asked to fill out a brief questionnaire for all TRAILS children in their class.

T2 involved only questionnaires, to be filled out by the adolescents, their parents and their teachers. As in T1, the adolescents filled out their

questionnaires at school, supervised by TRAILS assistants. Confidentiality of the study was emphasized.

Measures

Behavior, temperament and cannabis use

Disruptive behavior at T1 was assessed by the Child Behavior Checklist (CBCL) [88] and Youth Self-Report [89]. Both instruments contain a list of behavioral and emotional problems, which parents and children, respectively, can rate as being not true, somewhat or sometimes true, or very or often true in the past 6 months. For both parent and self-reports, we constructed a composite scale of "general disruptive behavior". This measure represents the mean of the standardized ratings on the DSM-oriented problem scales attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder (CBCL: 29 items, Cronbach's α=0.90, YSR: 27 items, Cronbach's α=0.84), which correspond to the clinical diagnostic categories [90, 91]. In addition to this composite measure, we used the mean standardized ratings on the individual scales attention-deficit/hyperactivity disorder (CBCL: 7 items, Cronbach's α=0.84, YSR: 7 items, Cronbach's α=0.72), oppositional defiant disorder (5 items, Cronbach's α=0.71, YSR: 5 items, Cronbach's α=0.62), and conduct disorder (17 items, Cronbach's α=0.78, YSR: 15 items, Cronbach's α=0.72). None of the problem scales included items that regarded the use of substances.

High-intensity pleasure, defined as "the pleasure derived from activities involving high intensity or novelty" was assessed at T1 by the parent version of the short form of the Early Adolescent Temperament Questionnaire – Revised (EATQ-R) [27]. The dimension high-intensity pleasure was based on the Zuckerman construct of sensation seeking [22, 29]. Although the Sensation Seeking Scale Form V, the most widely used version of the Sensation Seeking Scale, differentiates the four subscales Disinhibition, Thrill and Adventure Seeking, Experience Seeking, and Boredom Susceptibility, the construct of high-intensity pleasure of the EATQ emphasizes physical and social thrill seeking only. It consists of items (e.g. "wouldn't be afraid to try a risky sport, like deep sea diving"; "expresses a desire to travel to exotic places when s/he hears about them") that are largely covered by the subscales Thrill and Adventure Seeking and Experience Seeking of the Sensation Seeking Scale Form V. We used the parent version, because its factor structure was superior to that of the child version in our sample [39]. The Dutch version of the EATQ-R identifies 6 temperament dimensions, including high-intensity pleasure (6 items, Cronbach's α=0.77) [28].

Onset of cannabis use was assessed at T2 by self-report questionnaires. Adolescents were asked to report the age at onset of cannabis use. Answers

were dichotomized into "use" and "no use". Although reliability of self-reports on substance use has been subject of debate, previous research has concluded that, when anonymity is assured, self-report measures of substance use have acceptable reliability [92].

Confounding variables

Intelligence was assessed at T1 by the Vocabulary and Block Design subtests [94] from the Revised Wechsler Intelligence Scales for Children (WISC-R) [94, 95].

Socioeconomic status (SES) 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 [96], and scored on 3-point scale.

Onset of tobacco use was assessed at T2 by self-report questionnaires. Adolescents were asked to report the age at onset of tobacco use. Answers were dichotomized into "use" and "no use".

Statistical approach

Means of and correlations between variables were calculated, and gender differences in means and percentages were analyzed by t-tests and χ^2-tests, respectively. All continuous variables were standardized to a mean of 0 and a standard deviation of 1 to obtain internally comparable regression coefficients. All paths were controlled for the possible effects of gender, age, SES, and intelligence. Intelligence and SES were initially tested as potential confounders, but being not significantly related to cannabis use were excluded from the models. As onset of tobacco use is a strong predictor for onset of cannabis use [98], it was added as an outcome variable (multivariate model). In this way, we controlled for the possibility that associations between temperament, disruptive behavior and cannabis use were spurious due to a shared link with tobacco use. Thus, onset of tobacco use was included as an outcome variable in order to test the unique association between the predictor variables and onset of cannabis use, and was not an outcome of interest.

Subsequent analyses were conducted in three phases and for self- and parent reports separately. First, we aimed to test the predictive value of both early adolescent high-intensity pleasure and general disruptive behavior on onset of cannabis use by specifying an additive model. A multiple regression model, in which both high-intensity pleasure and general disruptive behavior at age 10-12 predicted the onset of cannabis use at age 12-14, was fitted. As cannabis use was treated as a dichotomous variable, a (multinomial) logistic regression model was used. The odds ratios (OR) describe the increase in odds

of early onset of cannabis use per increase by one standard deviation in the predictor variable.

Second, we aimed to investigate the possible interrelation between both predictors by specifying two separate models. We started of with an interaction-model to test whether high-intensity pleasure served as a modifier in the prospective relationship between general disruptive behavior and onset of cannabis use. Then, we specified a mediation model to test whether the relationship between high-intensity pleasure and onset of cannabis use was mediated by general disruptive behavior. In order to test mediation, we first specified a direct model, in which onset of cannabis use at age 12-14 was regressed on high-intensity pleasure, in addition to regressing the general disruptive behavior score on high-intensity pleasure. This was done to ascertain that direct effects of high-intensity pleasure to both general disruptive behavior and cannabis onset were present. The direct path from general disruptive behavior to cannabis onset was not specified. We then specified a full mediation model by allowing for the direct path from general disruptive behavior to onset of cannabis use. To test for an indirect effect from high-intensity pleasure to onset of cannabis use via general disruptive behavior, a joint significance test of the indirect paths was used [98-100].

In order to determine which of the three models (additive, moderation, mediation) was the best representation of the interrelation between high-intensity pleasure, general disruptive behavior and onset of cannabis use, model fit was compared using chi-square difference tests for WLSMV and MLMV [101].

In the final phase of the analyses, we examined whether the results of the optimal model from step 1 and 2 (using a general disruptive behavior score) held for each of the subtypes of disruptive behavior (ADH, OP, and CP). To account for comorbidity between ADH, OP, and CP, we adjusted for the correlation between the constructs. Thus, we assessed their independent association with onset of cannabis use. All models were tested in Mplus 5.0 [101].

RESULTS

Descriptive statistics

At age 12-14, 6.3% of the adolescents (n=114) reported onset of cannabis use. Onset of cannabis use was more likely in boys than in girls (χ^2 (1 df, n=1804) = 4.72, p=.030). Percentages or mean scores of the variables, and gender differences in percentages and means are shown in Table 3.1. Correlations between the variables are shown in Table 3.2.

Table 3.1 Descriptive statistics.

	Boys	**Girls**	**Gender difference**		
	Mean (SD)	**Mean (SD)**	**t**	***df***	**p**
Onset of cannabis use T2	7,60%	5,10%	χ^2=4.72	1	0,03
High-intensity pleasure T1	3.42 (0.92)	3.21 (0.93)	4,99	1802	0
Parent report					
Disruptive behavior	0.37 (0.26)	0.27 (0.21)	8,67	1682[a]	0
ADH	0.64 (0.48)	0.48 (0.43)	7,59	1736[a]	0
OP	0.63 (0.44)	0.54 (0.39)	4,73	1747[a]	0
CP	0.17 (0.18)	0.10 (0.13)	9,4	1540[a]	0
Self-report					
Disruptive behavior	0.39 (0.23)	0.33 (0.19)	6,12	1683[a]	0
ADH	0.59 (0.38)	0.58 (0.34)	0,58	1747[a]	0,565
OP	0.47 (0.36)	0.42 (0.33)	3,31	1744[a]	0,001
CP	0.27 (0.21)	0.19 (0.15)	10,33	1588[a]	0

[a] Degrees of freedom not equal to n-1 due to correction for unequal variances.

Table 3.2 Correlation matrix of T1 high-intensity pleasure, T1 disruptive behavior and T2 onset of cannabis use.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Onset of cannabis use									
2. High-intensity pleasure	.09[a]								
Parent report									
3. Disruptive behavior	.14[a]	0,1							
4. ADH	.12[a]	0,08	0,88						
5. OP	.11[a]	0,09	0,84	0,6					
6. CP	.14[a]	0,09	0,87	0,59	0,67				
Self-report									
7. Disruptive behavior	.13[a]	0,12	0,31						
8. ADH	.08[a]	0,08		0,31			0,81		
9. OP	.11[a]	0,09			0,29		0,81	0,53	
10. CP	.14[a]	0,13				0,29	0,86	0,47	0,6

[a] Point biserial correlations for associations between a continuous and a dichotomous variable; all associations were significant at p<.001.

The predictive value of high-intensity pleasure and general disruptive behavior with regard to onset of cannabis use

In the additive models, higher levels of both high-intensity pleasure (OR=1.17, 95%CI=1.05-1.31, p<.01) and general disruptive behavior (self-reports OR=1.30, 95%CI=1.18-1.43, p<.001 and parent reports OR=1.30, 95%CI=1.19-1.42, p<.001) were associated with a significantly higher risk of onset of cannabis use two years later. When both predictors were entered into the model, we found a small reduction in the predictive value of high-intensity pleasure, indicating some interrelation between high-intensity pleasure and general disruptive behavior.

The interrelation between high-intensity pleasure and general disruptive behavior in the prediction of onset of cannabis use

Results from the moderation analyses indicated that high-intensity pleasure did not modify the relationship between general disruptive behavior and onset of cannabis use. In other words, the predictive value of general disruptive behavior with regard to the onset of cannabis use did not depend on the level of high-intensity pleasure.

Results from the mediation analyses indicated that high-intensity pleasure was associated with a higher level of general disruptive behavior according to both self-reports (β =0.10, 95%CI=0.06-0.15, p<.001) and parent reports (β =0.10, 95%CI=0.06-0.14, p<.001). When allowing for the indirect path, findings indicated that there was a small indirect relationship between high-intensity pleasure and onset of cannabis use via general disruptive behavior (self-reports OR=1.03, 95%CI=1.01-1.04, p<.001; parent reports OR=1.02, 95%CI=1.01-1.04, p<.001). The direct path from high-intensity pleasure to onset of cannabis use remained almost unchanged (self-reports OR=1.16, 95%CI=1.05-1.29, p<.01; parent reports OR=1.17, 95%CI=1.05-1.29, p<.01).

Because the additive as well as the mediation model yielded significant results, chi-square difference testing was used to determine which of the models fitted the data best. The mediation model was superior to the additive model according to self-reports (χ^2 = 18.73, 1 df, p < .001) and parental reports (χ^2 = 21.21, 1 df, p < .001). This indicated that three pathways explained the onset of cannabis use; two direct paths from high-intensity pleasure and general disruptive behavior, and a small indirect path from high-intensity pleasure via general disruptive behavior.

Table 3.3 Effects of high-intensity pleasure and disruptive behavior on onset of cannabis use.

	Onset of cannabis use vs. no onset			
	Parent report		**Child report**	
	Odds ratio	**95% CI**	**Odds ratio**	**95% CI**
Additive model				
High-intensity pleasure	1.17*	1.05-1.31	1.17*	1.05-1.31
Disruptive behavior	1.30**	1.19-1.42	1.30**	1.18-1.43
Moderation model				
High-intensity pleasure	1.19*	1.06-1.34	1.18*	1.05-1.33
Disruptive behavior	1.31**	1.20-1.43	1.31**	1.18-1.45
High-intensity pleasure X disruptive behavior	0,96	0.89-1.05	0,98	0.88-1.08
Mediation model				
High-intensity pleasure to outcome	1.17*	1.05-1.29	1.16*	1.05-1.29
Disruptive behavior to outcome	1.28**	1.18-1.38	1.29**	1.19-1.40
High-intensity pleasure to disruptive behavior	β = 0.10**	0.06-0.14	β = 0.10**	0.06-0.15
High-intensity pleasure to disruptive behavior to outcome	1.02**	1.01-1.04	1.03**	1.01-1.04

All continuous variables were standardized to mean zero and standard deviation 1. All values were adjusted for the influence of gender and age, and for spurious associations due to a shared link with onset of tobacco use (multivariate models). * p< .01, ** p< .001, CI= Confidence Interval.

The interrelation between high-intensity pleasure, ADH, OP, and CP in the prediction of onset of cannabis use

In the third phase, we aimed to study whether the results for the general disruptive behavior score held for each subtype of disruptive behavior (ADH, OP, and CP). Correlations between subtypes were taken into account. In the direct models, a higher level of high-intensity pleasure was significantly associated with higher levels of ADH, OP and CP, according to both self- and parent reports. Betas ranged from 0.07 to 0.10. Subsequently, for each of the informants separately, an indirect model was specified, allowing for the direct paths from ADH, OP and CP to onset of cannabis use, and for the indirect path from high-intensity pleasure to cannabis onset via ADH, OP and CP.

According to self-reports, and when controlling for the influence of other subtypes of disruptive behavior, ADH and OP did not predict onset of cannabis use. These predictors were therefore excluded from the model. In the final

model, CP predicted the onset of cannabis use (OR=1.29, 95%CI=1.19-1.40, p<.001) and partially mediated the relationship between high-intensity pleasure and onset of cannabis use (OR=1.02, 95%CI=1.01-1.04, p<.01). The direct path from high-intensity pleasure to cannabis onset was left nearly unchanged (OR=1.17, 95%CI=1.05-1.29, p<.01).

According to parent reports OP did not predict onset of cannabis use. This problem scale was therefore excluded from the final model, in which ADH (OR=1.17, 95%CI=1.06-1.28, p<.01) and CP (OR=1.14, 95%CI=1.05-1.23, p<.01) predicted onset of cannabis use. Both partially mediated the relationship between high-intensity pleasure and onset of cannabis to a very small extent. Again, the significance of the direct path from high-intensity pleasure to onset of cannabis use remained nearly unchanged (OR=1.17, 95%CI=1.05-1.29, p<.01).

Although the values of the indirect paths were very small, chi-square difference testing indicated that allowing for the indirect paths significantly contributed to the model fit of both the model based on child reports (χ^2 (1) = 14.77, p<.001) and the model based on parent-reports (χ^2 (1) = 18.10, p<.001).

Table 3.4 Effects of T1 high-intensity pleasure and subtypes of disruptive behavior on onset of cannabis use at T2.

	Onset of cannabis use vs. no onset			
	Parent report		**Child report**	
	Odds ratio	**95% CI**	**Odds ratio**	**95% CI**
High-intensity pleasure to outcome	1.17**	1.05-1.29	1.17**	1.05-1.29
ADH to outcome	1.17**	1.06-1.28		
CP to outcome	1.14**	1.05-1.23	1.29***	1.19-1.40
High-intensity pleasure to ADH	β = 0.08***	0.04-0.13		
High-intensity pleasure to CP	β = 0.08***	0.04-0.13	β = 0.10***	0.05-0.14
High-intensity pleasure to ADH to outcome	1.01*	1.00-1.02		
High-intensity pleasure to CP to outcome	1.01*	1.00-1.02	1.02**	1.01-1.04

All continuous variables were standardized to mean zero and standard deviation 1. All values were adjusted for the influence of gender and age, and for spurious associations due to a shared link with onset of tobacco use (multivariate models). * p<.05, ** p< .01, *** p< .001.

DISCUSSION

The first aim of the present study was to examine the predictive value of a temperamental and a behavioral manifestation of disinhibition at age 10-12 with regard to the onset of cannabis use two years later. According to self- and parent reports both high-intensity pleasure and general disruptive behavior predicted the onset of cannabis use.

Our findings on temperament are in line with previous studies that investigated the prospective relationship between overlapping measures of temperament - novelty and sensation seeking - and onset of cannabis or illicit substance use in adolescence. In a study of Mâsse and Tremblay [32], novelty seeking in 6-year-old boys predicted the onset of illicit substance use in early and mid-adolescence. Teichman and colleagues [83] found a prospective relationship between sensation seeking in mid-adolescence and onset of cannabis use in late adolescence. Altogether, these findings suggest that the relationship between one's reactive style towards rewarding and novel stimuli and onset of cannabis use persists from at least early childhood to late adolescence.

Our findings on the prospective association between general disruptive behavior and onset of cannabis use are also in line with previous studies. Findings from the Minnesota Twin Family Study indicate that not only clinical levels of externalizing behavior at age 11 predict onset of cannabis and other substance use at age 14, but symptom dimensions of attention-deficit/hyperactivity disorder, oppositional defiant disorder and conduct disorder as well [102]. Also, Pedersen and colleagues [38] found that a subclinical level of conduct problems at age 13 predicts the onset of cannabis use two years later. These findings show that children and adolescents with symptoms of disruptive behavior, and therefore not only those with clinical diagnoses, are at increased risk to initiate the use of cannabis.

Our second aim was to examine the interplay between high-intensity pleasure and general disruptive behavior in the prediction of onset of cannabis use. Again the findings from self- and parent reports converged. Our results indicated that a mediation model described the interrelation between high-intensity pleasure, general disruptive behavior and onset of cannabis use best. In this model there were three pathways to the onset of cannabis use, two direct pathways from high-intensity pleasure and general disruptive behavior, and an indirect pathway from high-intensity pleasure to onset of cannabis use via general disruptive behavior. The coefficient of this latter path indicated that only a very small part of the relationship between high-intensity pleasure and onset of cannabis use was due to a higher level of general disruptive behavior.

Although temperamental characteristics and psychopathology are sometimes viewed as different points on the same continuum, our findings indicate mainly independent contributions to the risk of early onset of cannabis use.

Our third aim was to investigate whether the associations between high-intensity pleasure, general disruptive behavior and onset of cannabis use held for a specific subtype of disruptive behavior (i.e. ADH, OP, and CP), corrected for the overlap between subtypes. This time, findings from parent and self-reports diverged. According to self-reports, only CP predicted the onset of cannabis use, while according to parent reports both CP and ADH predicted onset of cannabis use. To some extent these findings are in line with the study of Elkins and colleagues [37] who found that, after adjustment for the overlap between subtypes, both hyperactivity and conduct symptoms at age 11 increased the odds of trying an illicit drug at age 14 by respectively 29% and 60%. In their study, symptom scores were created by combining mother- and self-reports. This methodological difference might explain the divergence with our findings that are based on separate analyses of self- and parent reports. While we found very high agreement between self- and parent reports on the general disruptive behavior scale, agreement was somewhat lower when subtypes of disruptive behavior were considered. In our sample, parents reported a lower level of CP and a somewhat higher level of ADH when compared to self-reports. This might have affected the reciprocal influence between ADH and CP in the association with onset of cannabis use, and might explain why ADH predicted onset of cannabis use only according to parent-reports. Discrepancy in findings between parent and self-reports might be explained by differences between informants in the context and perspective in which they observe behavior, and is in line with previous research [103]. For instance, parents might perceive hyperactive symptoms in their children as more disturbing than children do, which might explain the higher rate of ADH in parent reports. The lower level of CP in parent reports might be explained by the fact that parents might be unaware of the rule-breaking behavior of their children. Disruptive behavior may be less apparent at home and, in addition, as teenagers become more autonomous most of them confide less in their parents [104]. Conclusively, CP and to some extent ADH predicted the onset of cannabis use.

Finally, we aimed to examine if CP and/or ADH mediated the prospective relationship between high-intensity pleasure and onset of cannabis use. We expected CP to mediate this relationship, as increased BAS functioning in both novelty seeking characteristics and conduct problems [43, 86] might explain their relationship with onset of cannabis use. According to both self- and parent reports, a very small part of the relationship between high-intensity pleasure

and onset of cannabis use was indeed mediated by CP. This finding suggests that increased BAS functioning might underlie the onset of cannabis use. Contrary to our expectations, we also found some mediation by ADH, only according to parent reports. Although the predictive value of this indirect path was very small, an explanation for this finding might be considered. As BIS and BAS functioning are assumed to be mutually inhibitory [42] and independent [42, 43], different combinations of high and low BIS and BAS are possible. Thus, even though ADH is associated with decreased BIS functioning [45] there is also a certain level of BAS functioning. The latter might explain the mediating role of ADH in the relationship between high-intensity pleasure and onset of cannabis use. On the other hand, although high-intensity pleasure has been associated with increased BAS sensitivity, it also contains a certain level of BIS sensitivity. Therefore, the relationship between high-intensity pleasure, ADH, and onset of cannabis use might indicate a role of the behavioral inhibition system in the onset of cannabis use. Associations between behavioral (dis)inhibition and frequency and onset of cannabis and substance use have been found in previous studies [19, 32, 50, 78, 79]. Conclusively, findings indicate mainly independent contributions for high-intensity pleasure, CP and to some extent ADH in predicting onset of substance use, and a very small indirect relationship between the constructs.

In conclusion, early adolescent high-intensity pleasure and disruptive behavior predicted the onset of cannabis use in adolescence. Although we found some mediation by general disruptive behavior, the contribution of high-intensity pleasure in predicting the onset of cannabis use was found to be mainly independent from disruptive behavior. When subtypes of disruptive behavior were considered, we found that particularly the conduct and attention deficit hyperactivity characteristics were related to onset of cannabis use, and that both mediated a very small part of the relationship between high-intensity pleasure and onset of cannabis use.

The present study is not without limitations. First, because temperamental characteristics, such as high-intensity pleasure, are assumed to appear early in life, and to have reasonable stability over time [20], we assumed high-intensity pleasure to predate the manifestation of disruptive behavior. However, in this study, high-intensity pleasure and disruptive behavior were assessed at the same age. Therefore, based on the currently available data, we were not able to investigate the relation in time between high-intensity pleasure and disruptive behavior, nor could we exclude the possibility that behavioral problems might have affected high-intensity pleasure. Second, behavior problems were based on questionnaire data that do not represent one-to-one counterparts with the DSM-IV criteria of attention deficit hyperactivity disorder, oppositional defiant

disorder, and conduct disorder. Third, a general population sample is characterized by low prevalence rates of cannabis use, especially because of our young age groups. Fourth, even though confidentiality of the study was emphasized, participants might have underreported their use of cannabis. This may have influenced the results. However, because of the importance of studying predictors of cannabis use at an early age, our results contribute to understanding the mechanism behind onset of cannabis use.

Our findings have implications for future research. The unique contribution of both high-intensity pleasure and disruptive behavior points in the direction of different pathways towards onset of cannabis use. These pathways might be differentially affected by genetic liability, might diverge in the progression towards substance abuse, and interactions with other risk factors of substance use, such as peer influence and parenting practices, might differ among pathways. In order to increase the insight in the mechanism behind early onset of cannabis use, we recommend future research in this area to address these matters.

CHAPTER 4

The role of temperament in the relationship between early onset of tobacco and cannabis use. The TRAILS study

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ABSTRACT

Background: While temperamental characteristics have been related to the onset of cannabis use, it is not clear at what point(s) along the trajectory from early onset of tobacco use (EOT) to early onset of cannabis use (EOC) these characteristics exert their impact. This study examined if 1) temperamental characteristics predispose to EOT that on its turn predisposes to EOC, and 2) temperament moderates the importance of EOT on the progression to EOC.
Methods: Data from 1848 (83%) participants in the TRacking Adolescents' Individual Lives Survey (TRAILS), a prospective population study of Dutch adolescents, were analyzed. We used parent-reports on the Early Adolescent Temperament Questionnaire to assess the dimensions of high-intensity pleasure, frustration, effortful control, shyness and fearfulness at age 10-12. EOT and EOC were defined as use at least once before the ages of 12 and 13 years, respectively, assessed by means of self-reports. We performed mediation and moderation analyses in Mplus.
Results: High levels of high-intensity pleasure predisposed to entrance in the trajectory from EOT to EOC. Once tobacco use had been initiated at early age, low levels of shyness and high levels of high-intensity pleasure increased the risk of progression to EOC.
Conclusions: Besides a common liability for EOT and EOC based on temperament, the risk of transition from tobacco to cannabis use is modified by temperamental characteristics. Differences in interplay with other risk factors may explain the impact of temperament on distinct points along the substance use trajectory.

INTRODUCTION

The use of cannabis has been associated with various risks, especially for adolescent users [12, 105]. Particularly adolescents who initiate cannabis use before the age of 13 may be at risk for adverse substance use outcomes [106, 107]. These adolescents are characterized by relatively low scores on school performance and commitment, parent-child relationship, and peer-pressure resistance when compared to late-onset and non-users [108]. More insight into the mechanisms behind early initiation of cannabis use would contribute to the identification of at-risk individuals and provide better entry points for health promotion interventions.

Legal substance use has been found to predict cannabis use [49, 97, 109]. The exact sequence of the use of specific substances, as well as the impact of these substances on the use of other substances, has been a source of debate [110-112]. The most likely sequence is from legal to semi-legal or illegal substances, as access to legal substances is generally easier compared to access to cannabis or other illicit drugs in adolescence. Previous research has indicated that particularly cigarette smoking, rather than alcohol use, is associated with elevated odds of subsequent cannabis use [49]. Moreover, early initiators of cigarette smoking have a particularly high risk for subsequent use of cannabis [47-49].

As yet, little is known about the mechanisms underlying the progression from onset of cigarette smoking to cannabis use. More specifically, one undetermined aspect is the role of temperamental characteristics in this sequence. While personality and temperamental characteristics have been related to the onset of either cigarette smoking or cannabis use in adolescence [34, 113], it is not clear at what point(s) along the trajectory towards onset of cannabis use these characteristics are influential. Based on the common liability model, which suggests a common underlying factor for use of various substances, one would expect that the same temperamental characteristics predispose to onset of both cigarette smoking and cannabis use. Thus, given the most frequent developmental sequence of drug involvement, these temperamental characteristics would predispose to early tobacco use and subsequently to experimentation with cannabis as opportunities arise. However, the common liability model does not explain why some early tobacco users do not progress to early experimentation with cannabis. Moreover, it remains undetermined whether temperamental characteristics affect the risk of transition to cannabis use once the chain of substance use has been initiated.

When temperament is studied in relation to substance use, specific aspects of temperament, instead of general concepts, have often been used. First,

indicators of sensation seeking, manifested in frequent exploratory activity, intense reactions to reward and difficulty inhibiting behavioral impulses, has been found to predict onset of cannabis use in adolescence (for a review see [114]. In addition, negative affectivity or negative emotionality, reflecting the tendency to easily become frustrated and irritated and to become intensely upset, has been associated with substance use [34]. A dimension often termed task orientation, attentional control or effortful control, which reflects the ability to regulate attention and behavior and to follow through to completing the task, has been related to a lower likelihood of substance use [34].

Using data from the TRacking Adolescents' Individual Lives Survey (TRAILS), a general population study, we investigated the roles of temperamental characteristics in the relationship between early onset of cigarette smoking and early onset of cannabis use. Strengths of the TRAILS study are that information about its participants is gathered from multiple informants, and the possibility to control for important correlates, such as alcohol initiation, parental licit substance use, and parenting factors. Aims of the present study were to examine 1) the risk of transition from early onset of tobacco use (EOT) to early onset of cannabis use (EOC), 2) whether temperamental characteristics that predict EOC first predispose to early cigarette smoking that subsequently predicts EOC (mediation), and 3) whether temperament modifies the risk of transition from EOT to EOC (moderation).

METHODS

Sample and participants

The present study reports data from the first (T1) and second (T2) assessment waves of the TRAILS, which ran from March 2001 to July 2002 and from September 2003 to December 2004, respectively. A detailed description of the sampling procedure and methods is provided in De Winter et al. [64]. 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. The sample selection involved two steps. First, the selected municipalities were asked to provide names and addresses of all inhabitants born between October 1, 1989 and September 30, 1990 (first two municipalities) or October 1, 1990 and September 30, 1991 (last three municipalities). Second, primary schools (including schools for special education) within these municipalities were simultaneously approached with the request to participate. School participation was a prerequisite for eligible children and their parents to be approached by the TRAILS staff. Of all the selected inhabitants (n=3483), 90.3% attended a school that was willing to participate (n=3145). 6.7% were excluded because of

incapability or language problems. Of the remaining 2935 children, 76.0% (n=2230, mean age = 11.09, *SD* = 0.55, 50.8% girls) were enrolled in the study (i.e., both child and parent agreed to participate). Responders and non-responders did not differ with respect to the prevalence of teacher-rated problem behavior nor the associations between sociodemographic variables and mental health indicators [64].

Of the 2230 T1 participants, 96.4% (n=2149, 51.2% girls) participated in T2, which was held 2-3 years after T1 (mean interval 29.4 months, *SD*=5.4). The mean age at T2 was 13.55 years (*SD*=0.54). For the analyses of the present study, subjects who reported EOC before EOT were excluded from the analyses (n=5). Only subjects were included of which complete data on temperament, onset of cigarette smoking and onset of cannabis use were available (n=1848). The participants included in the current study had a somewhat higher intelligence (see below for more details) (t=6.68, *df*=2228, $p<0.001$), a higher socioeconomic status (χ^2 (2, n=2188) = 69.20, $p<0.001$), and were less likely to have a family history of substance abuse or antisocial behavior (t=-2.61, *df*=2163, $p<0.01$), when compared to the excluded subjects.

Measures

Temperament and substance use

Early adolescent temperament was assessed at T1 by the parent version of the short form of the Early Adolescent Temperament Questionnaire–Revised (EATQ-R) [27], preferably completed by the mother. The Dutch version of the EATQ-R identifies 6 temperament dimensions and 2 behavioral dimensions [28]. Of interest for the present study were the dimensions 1) high-intensity pleasure, defined as the pleasure derived from activities involving high intensity or novelty (6 items, α = 0.77), 2) frustration, defined as negative affect related to the interruption of ongoing tasks or blocked goals (5 items, α = 0.74), 3) shyness, referring to behavioral inhibition to novelty and challenge, especially social (4 items, α = 0.84), 4) fearfulness, manifested in worrying and unpleasant affect related to the anticipation of distress (5 items, α = 0.63), and 5) effortful control, defined as the capacity to voluntarily regulate behavior and attention (11 items, α = 0.86). For the dimensions high-intensity pleasure and frustration we expected that high levels on these measures would be associated with a higher risk of early onset of cannabis use. For the dimensions effortful control, shyness and fearfulness we expected a negative association with early onset of substance use. Factor analyses show that these measures are statistically distinct and that the risk and protective factors are inversely but not strongly correlated (ranging from 0.05 to 0.40).

Tobacco and cannabis use were assessed at T1 and T2 by self-report questionnaires filled out at school, supervised by TRAILS assistants. Confidentiality of the study was emphasized. At T1, adolescents were asked in separate questions whether or not they had ever used tobacco or cannabis. At T2 they were asked to report the age of onset (in years) of any tobacco and cannabis use. EOT was defined as onset of use before the age of 12 years [115]. EOC was defined as onset of use before the age of 13 years [18, 106, 107]. Although the reliability of self-reports on substance use has been a subject of debate, previous research has concluded that, when anonymity is assured, self-report measures of substance use have acceptable reliability [92].

Confounding variables

Intelligence was individually assessed at T1 by the Vocabulary and Block Design subtests [93] of the Revised Wechsler Intelligence Scales for Children (WISC-R) [94, 95].

Lifetime alcohol consumption was assessed at T1 by self-reports. Responses were dichotomized into never and ever lifetime alcohol intake.

Perceived parental emotional warmth was assessed with the EMBU-C [116], the child version of the EMBU (a Swedish acronym for My Memories of Upbringing, developed by Perris et al. [117]). The scale of emotional warmth contains 18 items (α = 0.91 for both parents). Because the associations for father and mother were high ($r=0.79$, $p<0.001$) we combined them into a single measure, which was based on only one informant when information from one parent was missing.

Parental substance use was assessed during the parental interview at T1. In most cases, mothers were asked about their own and their partners' cigarette smoking and alcohol use. For both parents, responses were categorized into low (smoking less than daily and drinking less than one glass a week), moderate (smoking 1-9 cigarettes a day or 1-10 drinks a week), and high parental substance use (smoking 10 or more cigarettes a day or drinking 11 or more drinks a week). Maternal and paternal scores were combined and divided by two to achieve an average score of parental substance use. When information on one parent was missing this composite score was based on only one informant.

Socioeconomic status (SES) 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 [96], and was categorized into low, average and high SES.

Pubertal development at T1 was based on parent ratings on schematic drawings of secondary sex characteristics associated with the five standard Tanner stages of pubertal development [118]. Tanner stages are a widely

accepted standard for assessment of physical development, and have demonstrated good reliability, validity and parent-child agreement [118, 119]. Children were classified into five stages of puberty, in which stage 1 corresponds to infantile and stage 5 to complete puberty [120].

Statistical approach

Statistical analyses were performed using the Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc. Chicago, IL) and Mplus 5.1 [101]. Temperamental scale scores were standardized to a mean of 0 and a standard deviation of 1. Means of variables and correlations between them were calculated, and gender differences in means and proportions were analyzed by t-tests and χ^2-tests, respectively. All paths towards EOC were adjusted for sex, pubertal development, intelligence, SES, parental substance use, and perceived parental emotional warmth. When EOT was included as a predictor of EOC, we additionally adjusted for alcohol initiation. In order to make the final model as parsimonious as possible we excluded all non-significant covariates. Model fit was determined using the comparative fit index (critical value = 0.95) and the root mean square error of approximation (critical value = 0.08) [121, 122].

First, we conducted logistic regressions to address the risk of EOC in early onset cigarette smokers, as compared to never smokers.

Second, we assessed whether the relationship between temperamental characteristics and EOC was mediated by the influence of temperament on EOT. We started with separate regression analyses with each of the standardized temperamental scale scores as the predictor and EOC as the outcome. We included the significant predictors together with EOT in an additive model to test the independent effects of the various predictors. In order to test mediation, we first specified a direct model, in which EOC was regressed on the temperamental characteristics of the final model, in addition to regressing EOT on these characteristics. This was done to ascertain that direct effects of the same temperamental characteristics to both EOT and EOC were present. Both paths were adjusted for all aforementioned covariates except alcohol initiation. We then specified a full mediation model by allowing for the direct path of EOT to EOC, additionally adjusting for alcohol initiation. To test for an indirect effect from temperament to EOC via EOT, a joint significance test of the indirect paths was used [98-100]. In order to determine whether the mediation model was a better representation of the data when compared to the final additive model, model fit was compared using the Chi-square difference tests for weighted least squares means and variance adjusted (WLSMV) and maximum likelihood means and variance adjusted (MLMV) estimation [101].

Finally, we tested whether temperament modified the transition from EOT to EOC. We specified separate logistic regression models for each of the temperamental scale scores, in combination with EOT, and the interaction between the two. To control for the possibility that associations between temperament and cannabis use were spurious due to a shared link with tobacco use, tobacco use was added as an outcome variable (multivariate logistic model) that was regressed on the same temperamental scale score. To facilitate the interpretation of the significant interaction effects, we performed descriptive analyses to assess the proportion of early initiators of cannabis use in subgroups based on temperament and early onset of tobacco use.

RESULTS

Risk of early onset cannabis use in early onset smokers

18.9% (n=350) of the participants fulfilled the criteria for early onset of tobacco use and 2.8% (n=52) reported early onset of cannabis use. Percentages or mean scores of the variables, and gender differences in percentages and means are shown in Table 4.1. Correlations between the variables are shown in Table 4.2.

As expected, adolescents who reported early onset of tobacco use were more likely to have initiated the use of cannabis at an early age (OR=4.14, 95%CI=3.03-16.28, $p<0.001$). When EOT was included as a predictor, the covariates intelligence, alcohol initiation, SES, parental substance use, and perceived parental emotional warmth were not significantly related to EOC. Therefore, the most parsimonious model included only sex and pubertal development as covariates. A non-significant sex by EOT interaction ($p=0.81$) indicated that there was no difference in risk of transition between boys and girls.

Is the relationship between temperament and early onset cannabis use mediated by early onset of tobacco use?

We carried out separate regression analyses to assess the associations between temperamental characteristics at age 10-12 and EOC. When adjusted for the significant covariates sex, pubertal development and perceived parental emotional warmth, high-intensity pleasure significantly predicted EOC (OR=1.22, 95%CI=1.05-1.41, $p<0.01$). Although a low level of shyness was a nearly significant predictor of EOC (OR=0.86, 95%CI=0.74-1.01, $p=0.06$), this effect was attenuated when the independent effects of high-intensity pleasure and shyness were assessed in an additive model, indicating only an independent effect of high-intensity pleasure. None of the other temperamental

Table 4.1 Descriptive statistics of the TRAILS sample.

	Boys (n=900) Mean (SD)	**Girls (n=948) Mean (SD**	**Gender difference T/ χ^2**	***df***	**p**
Tobacco use before age 12	19,70%	18,20%	0,6	1	0,44
Cannabis use before age 13	3,80%	1,90%	5,96	1	<.05
High-intensity pleasure	3.43 (0.92)	3.21 (0.92)	5,12	1846	<.01
Frustration	2.84 (0.68)	2.75 (0.64)	2,92	1822*	<.01
Effortful Control	3.10 (0.69)	3.35 (0.65)	-7,96	1823*	<.01
Shyness	2.41 (0.88)	2.59 (0.87)	-4,3	1846	<.01
Fearfulness	2.34 (0.69)	2.49 (0.75)	-4,42	1846	<.01

* Degrees of freedom not equal to n-1 due to correction for unequal variances.

Table 4.2 Correlation matrix of T1 temperament, early onset of tobacco use and early onset of cannabis use.

	1.[1]	**2.**[1]	**3**	**4**	**5**	**6**
1. Tobacco use before age 12						
2. Cannabis use before age 13	.29**[2]					
3. High-intensity pleasure	.10**	.07**				
4. Frustration	.09**	0,04	-0,01			
5. Effortful control	-.13**	-.05*	.05*	-.40**		
6. Shyness	-.07**	-.06*	-.29**	.09**	-0,02	
7. Fearfulness	0,03	0,03	-.19**	.31**	-.24**	.14**

[1] Point biserial correlations for associations between a continuous variable and a dichotomous variable. [2] Tetrachoric correlation; * p<.05, ** p<.01.

characteristics was significantly related to EOC. Non-significant sex by temperament interactions (all p-values >0.46) indicated that there were no differences between boys and girls pertaining to the influence of temperamental characteristics on early onset of cannabis use.

Subsequently, we included high-intensity pleasure and EOT in an additive model. In this model, high-intensity pleasure was no longer a significant predictor of EOC (OR=1.18, 95%CI=0.99-1.41, p=0.07), while EOT remained a significant predictor (OR=4.10, 95%CI=2.97-5.64, p<0.001). The change in

significance of high-intensity pleasure indicated a certain degree of overlap between the predictors.

In order to test mediation, we regressed EOC on high-intensity pleasure in addition to regressing EOT on high-intensity pleasure. This was done to ascertain the presence of a direct effect between high-intensity pleasure and EOT. As can be seen in Table 4.3, high-intensity pleasure was significantly associated with EOT. When the direct path from EOT to EOC was allowed, findings showed that the relationship between temperament and EOC was completely mediated by EOT, rendering the direct effect of high-intensity pleasure non-significant. The fit indices for this model were comparative fit index (CFI) 0.99 and root mean square error of approximation (RMSEA) 0.02. Chi-square difference testing indicated that fit of the mediation model was significantly better when compared to the fit of the additive model (χ^2 (1) = 11.39, p<0.001).

Table 4.3 Final mediation model.

		Step 1		**Step 2**	
Predictor	**Outcome**	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
High-intensity pleasure	EOT	1.17***	1.09 – 1.25	1.13***	1.05 – 1.21
High-intensity pleasure	EOC	1.22*	1.05 – 1.43	1,1	0.94 – 1.27
EOT	EOC			2.02***	1.82 – 2.23
High-intensity pleasure -> EOT -> EOC				1.09**	1.03 – 1.15

Step 1 refers to a direct model in which early onset tobacco use (EOT)and early onset cannabis use (EOC) were regressed on high-intensity pleasure. In the final model, EOC was adjusted for sex and pubertal development, EOT was adjusted for pubertal development, intelligence, SES, parental substance use, and perceived parental emotional warmth. Step 2 refers to a full mediation model that allowed for an additional direct path from EOT to EOC. In the final model, EOC was adjusted for pubertal development, EOT was adjusted for intelligence, initiation of alcohol use, SES, and perceived parental emotional warmth. All continuous variables were standardized to mean zero and standard deviation 1. * p<.05, ** p< .01, *** p< .001, CI= Confidence Interval.

Does temperament modify the risk of transition from early onset of tobacco use to early onset of cannabis use?

Findings of the temperament by EOT interactions indicated that the levels of high-intensity pleasure (OR=1.48, 95%CI=1.03-2.12, p<0.05) and shyness (OR=0.61, 95%CI=0.41-0.92, p<0.05) modified the risk of transition from EOT

use to EOC. Whereas main effects of EOT remained significant, there were no main effects of temperament. The fit indices indicated almost sufficient fit for the model with high-intensity pleasure (CFI: 0.92, RMSEA: 0.06) and shyness (CFI: 0.88, RMSEA: 0.07) as moderating variables. None of the other temperamental scales modified the risk of transition from EOT to EOC. Three-way temperament by EOT by sex interactions indicated no significant gender differences (all p-values >0.28).

To facilitate the interpretation of the interaction effects, we performed descriptive analyses in order to assess the proportion of early initiators of cannabis use in subgroups based on high and low levels of high-intensity pleasure and shyness, and on EOT-status. Findings are presented in Figure 4.1, and indicate that the risk of transition from EOT to EOC was higher in adolescents with low levels of shyness and high levels of high-intensity pleasure when compared to adolescents with opposite levels on these temperamental constructs.

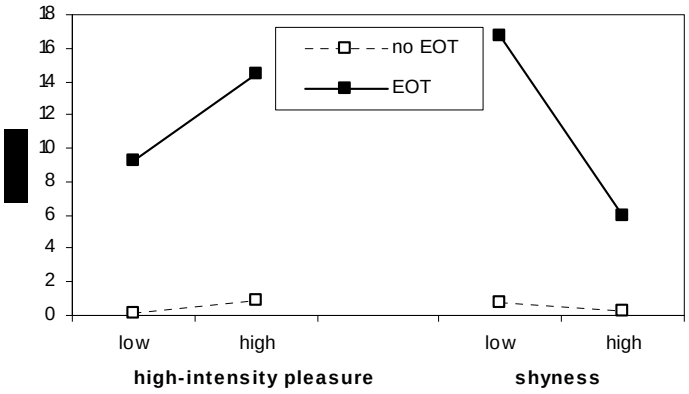

Figure 4.1 Graphical presentation of the interactions of either high-intensity pleasure and shyness and early onset tobacco use (EOT) in relation to early onset of cannabis use (EOC).

DISCUSSION

The findings of the present study indicate that the risk of EOC was more than four times as high in individuals who initiated the use of tobacco at an early age when compared to individuals who did not smoke cigarettes this early in life. This finding is in line with results of previous studies that found a higher incidence of cannabis use among early initiators of tobacco use [47-49], and

indicates that the onset of smoking before the age of 12 signals an increased risk of entrance into a sequence of adverse behaviors.

By means of mediation and moderation models we investigated at what point(s) along the trajectory from EOT to EOC temperamental characteristics exerted their impact. Results from our mediation analyses suggest a common liability for tobacco and cannabis use with regard to the temperamental dimension high-intensity pleasure. A high level of high-intensity pleasure predisposed to EOT which in turn increased the risk of EOC. While prospective associations between related measures of novelty seeking and either tobacco or cannabis use have been identified before [32, 123], this is, to the best of our knowledge, the first study that assessed the interrelationship between these factors by applying a mediation model. An indication for some interrelation between sensation seeking and smoking in relation to marijuana use has been provided by Siqueira and Brook (2006). In their study, the odds of daily cigarette smoking in mid-adolescence that predicted marijuana use 2 years later decreased when sensation seeking had been taken into account, indicating some overlap between the constructs [124].

In addition to illustrating a common liability for EOT and EOC based on a high level of high-intensity pleasure, moderation analyses showed that the levels of high-intensity pleasure and shyness determined the risk of transition from tobacco to cannabis use. When adolescents had used tobacco before the age of 12, high levels of high-intensity pleasure and low levels of shyness were associated with an increased risk of progression to the use of cannabis. Thus, while a high level of high-intensity pleasure predisposes to tobacco use which in turn predisposes to cannabis use, its level also determines one's subsequent risk of making this transition. These common and specific effects might involve differential interplay between high-intensity pleasure and other risk factors of substance use. For instance, high levels of high-intensity pleasure might influence the selection of peers who share risk-taking tendencies, including the use of substances. However, once a substance has been used, high levels of high-intensity pleasure might influence interest in trying other substances of abuse. As expected, low shyness, defined as behavioral inhibition to novelty and challenge, particularly in the social domain, was associated with a higher risk of transition from tobacco to cannabis use. Measures of low behavioral inhibition in late childhood and early adolescence have previously been associated with early onset of cannabis use [32, 76]. However, the observation that not all adolescents with certain temperamental characteristics will initiate the use of substances at an early age, suggests the influence of other factors, such as attitudes towards the use of substances, the presence of behavioral problems, peer use, and family factors. For instance, the findings of Kellam et al. [125]

indicate that whereas moderate or severe shyness was associated with lower cannabis use frequencies 10 years later, it was associated with the highest rate of cannabis use in a subgroup with additionally moderate or severe levels of aggressiveness. We posit that interplay between temperament and other risk and protective factors of substance use might explain our finding that the level of shyness affects the risk of transition from EOT to EOC, rather than the risk of early onset of EOC via EOT.

In our study, fearfulness, frustration, and effortful control were not related to EOC. Whereas the absence of significant findings might be due to the differences in conceptualization of the temperamental constructs when compared to previous studies, and to the relatively low reliability of the subscale fearfulness (α = 0.63), it is speculated that the influence of these temperament dimensions might depend on developmental phase and substance use measure. Rather than being associated with early onset of use, fearfulness, frustration and effortful control may affect the risk of regular substance use or abuse.

The present study is not without limitations. First, because of the characteristics of our sample and our focus on EOT and EOC, temperamental characteristics were assessed at or around the same age as early onset of use. Therefore, we were not able to investigate the temporal relation between temperament and onset of cigarette and cannabis smoking. Second, EOT and EOC were based on reported age at onset in years. While we could determine that EOT preceded EOC for the majority of participants, 17 participants reported the same year of onset for both events. Because the use of tobacco generally precedes the use of cannabis, we did not exclude these participants from our analyses. As a consequence, some participants that used cannabis before the use of tobacco, albeit in the same year, might have been included in the sample. Finally, though confidentiality of the study had been emphasized, participants might have underreported their use of cannabis, which may have influenced the results. However, because of the importance of studying adolescent substance use, our results contribute to understanding the mechanisms underlying early onset of cannabis use in a general population of adolescents.

In conclusion, our findings indicate that high levels of high-intensity pleasure predispose to entrance and continuation in the trajectory from tobacco to cannabis use and that levels of shyness and high-intensity pleasure determine the impact of EOT on EOC. Besides our specification of the mechanisms by which temperament and smoking interrelate, this paper contributes to the current knowledge due to our focus on characterizing at-risk individuals based on early onset of substance use. Risk-taking behavior, including the use of substances, is inherently related to adolescence because of an increased interest in risk-taking behavior in combination with developing self-regulatory capacities

[126]. Temperamental factors appear to contribute to the risk of progression from licit to illicit drugs, most likely in interaction with other risk or protective factors. Given the yet immature self-regulatory competence of adolescents, the efficiency of educational interventions in this developmental phase is likely to be limited. It may be more effective to focus on the interplay of temperament and interpersonal characteristics, such as peer influence and parental monitoring [19, 54, 123], and contextual factors that influence the availability of substances.

CHAPTER 5

Predicting lifetime and regular cannabis use during adolescence; the roles of temperament and peer substance use. The TRAILS study

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ABSTRACT

Aims: The aim of the present study was to determine the mediating role of affiliation with cannabis-using peers in the pathways from various dimensions of temperament to lifetime cannabis use, and to determine if these associations also contributed to the development of regular cannabis use.
Methods: Objectives were studied using data from 1300 participants of the Tracking Adolescents' Individual Lives Survey (TRAILS), a large, general population study of Dutch adolescents. We used parent-reports on the Early Adolescent Temperament Questionnaire to assess the dimensions high-intensity pleasure, shyness, fearfulness, frustration, and effortful control at age 10-12. By means of self-reports, lifetime and regular cannabis use were determined at age 15-18, and proportion of substance-using peers was determined at ages 12-15 and 15-18. Models were adjusted for age, sex, intelligence, and parental cannabis use.
Results: High-intensity pleasure (OR=1.09, 95%CI=1.05-1.13) and effortful control (OR=0.92, 95%CI=0.89-0.96) affected the risk for lifetime cannabis use through their influence on affiliation with cannabis-using peers. Shyness affected this risk independent from peer cannabis use. Only the pathway from effortful control was additionally associated with the development of regular cannabis use (OR=0.93, 95%CI=0.89-0.98).
Conclusions: Peer cannabis use and, to a lesser extent, certain temperamental characteristics affect an adolescent's risk of cannabis use, and should be considered in prevention programs. We recommend future research to focus on factors that potentially modify the association between temperament, affiliation with cannabis-using peers and cannabis use.

INTRODUCTION

While cannabis has generally been perceived to be a relatively harmless drug, the growing number of cannabis clients in addiction care indicates that the use of cannabis is not as harmless as was once considered [3, 6]. For adolescent users, it has been estimated that 18 to 20 percent develop a cannabis use disorder within ten years from initiation of use [7, 8]. Particularly adolescents that started using cannabis at an early age, or that use cannabis on a regular or persistent basis, are at risk of developing a cannabis use disorder [8, 9]. Research on the determinants of cannabis use during adolescence can improve our understanding of which factors are related to adolescent cannabis use and to the development of regular patterns of cannabis use.

Longitudinal studies have focused on several risk factors of cannabis use in adolescents and young adults, including intrapersonal factors, for instance temperamental attributes, and interpersonal variables, such as belonging to a deviant and/or substance-using peer group [19, 50]. With regard to the latter, social learning has been one of the proposed mechanisms to explain the association between peer and own substance use: through associations with peers the adolescent acquires certain norms and behaviors that are favorable of or opposed to using drugs [51]. In addition, peers might encourage substance use by making drugs available [52]. When temperament is considered in relation to cannabis use, some studies have demonstrated prospective associations between specific temperament dimensions and cannabis use. For instance, higher levels of sensation seeking have been prospectively related to lifetime cannabis use and extent of cannabis use in middle and late adolescence [54, 82, 83]. In addition, indices of negative affect or negative emotionality have been linked to substance use, including cannabis, and to increased growth in substance use during adolescence [127-130]. In contrast, indicators of attentional control have been found to buffer against initiation and increasing levels of substance use [34, 130]. Interestingly, when temperament is considered next to other risk factors of cannabis use, such as affiliation with deviant peers, direct associations between temperament and cannabis use are less obvious [50]. For instance, Donohew and coworkers found that sensation seeking, in the context of factors related to peer substance use, failed to predict frequency of cannabis use two years later [53]. This finding points in the direction of a mediated pathway from sensation seeking to frequency of cannabis use through affiliation with substance-using peers. Indeed, findings from a longitudinal study by Hampson et al. indicate that affiliation with peers that display general disruptive behavior mediated the effect of sensation seeking on extent of marijuana use [54]. In addition, findings from a study by Wills and

Cleary indicate that difficult temperament and poor self-control are related to affiliation with substance-using peers that subsequently predicts initial level and frequency on a composite measure of tobacco, alcohol and cannabis use [55].

In order to extend the findings from previous research, we aimed to determine the mediating role of affiliation with cannabis-using peers in the pathways from various dimensions of temperament to lifetime and regular cannabis use, the latter defined as the use of cannabis on at least four occasions in the past four weeks. Because the use of cannabis is generally considered more deviant than legal substance use in this age group, we focused on affiliation with specifically cannabis-using peers, rather than affiliation with a broader group of deviant and/or licit substance-using peers. Based on findings from previous research we selected indicators of the temperament dimensions sensation seeking, negative affectivity and attentional or effortful control. Within the biologically-oriented temperament model developed by Rothbart and colleagues [25], the broad dimension surgency, manifested as orientation to and exploration of novelty, is indexed by the temperament dimensions high-intensity pleasure, (low) shyness and (low) fearfulness [27]. High-intensity pleasure is based on the Zuckerman construct of sensation seeking [22, 29]. Within the same framework, frustration is, in adolescents, the main indicator of the broad temperament factor negative affectivity [27]. Effortful control is the sole indicator of the similarly named broad dimension, and is related conceptually to task attentional orientation that has been linked previously to adolescent substance use [34, 130]. While we expected risk-enhancing effects of high-intensity pleasure and frustration on affiliation with cannabis-using peers and cannabis use, we expected risk-buffering effects of shyness, fearfulness and effortful control.

METHODS

Sample and participants

The present study reports data from the first (T1), second (T2) and third (T3) assessments of TRAILS, which ran from 2001 to 2002, 2003 to 2004, and 2005 to 2007, respectively. A detailed description of the sampling procedure and methods is provided in De Winter et al. [64]. 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 percent of the target population (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 [64]. At T2, 96.4% of these participants (n=2149, mean age 13.56 years; *SD* 0.53, 51.0% girls) were re-assessed, including the collection of peer nominations in a subsample of TRAILS participants and their classmates. This subsample consisted of 3312 students (mean age 13.60, *SD* = 0.66, 49.4% girls), including 1007 regular TRAILS participants. Peer nominations were assessed in classrooms with at least three regular TRAILS participants. The school classes were almost equally divided among levels of education: low education (60 school classes), middle education (53 school classes), and high education (59 school classes). A detailed description of the assessment of the peer nominations is provided in Dijkstra et al. [131]. T3 was completed with 81.4% of the original number of participants (n=1816, mean age = 16.27 years, *SD* 0.73, 52.3% girls).

To answer the aims of the present study we composed a subgroup based on available data with regard to temperament at T1, affiliation with cannabis-using peers at T3 and cannabis use at T3 (n=1300). Participants included in this subgroup were more likely to be female (χ^2 (1 df, n=2230) = 28.45, $p<.001$), to have a higher socioeconomic status (χ^2 (2 df, n=2230) = 92.11, $p<.001$), and to have a higher intelligence (t=10.58, 2228 df, $p<.001$) when compared to the excluded participants (n=930). When compared to participants with available data on T3 cannabis use that were excluded due to missing information on temperament or peer cannabis use (n=340), included participants were equally likely to report lifetime (χ^2 (1 df, n=1640) = 0.11, $p=.74$) and regular cannabis use at T3 (χ^2 (1 df, n=1640) = 2.55, $p=.11$).

Using data from the peer-nominations collected at T2 we were able to verify that affiliation with substance-using peers preceded cannabis use in a subsample consisting of 697 of the 1300 participants. Included and excluded participants did not differ in terms of T3 lifetime (χ^2 (1 df, N=1300) = 0.29, $p=.59$) and regular (χ^2 (1 df, n=1300) = 0.03, $p=.85$) cannabis use, and affiliation with cannabis-using peers at T3 (t=-.08, 1298 df, $p=.94$).

Measures

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 four weeks. Answers on these questions were dichotomized in order to achieve a measure of lifetime cannabis use, defined as any cannabis use ever, and regular cannabis use, defined as the use of cannabis on at least four occasions in the past four weeks.

The *proportion of cannabis using peers at T3* was assessed from a self-report questionnaire in which participants were asked to name up to seven friends, and to report for each of these friends in separate questions whether they ever used cigarettes, alcohol, soft drugs and hard drugs. In the Netherlands, the term soft drug usually refers to cannabis. The proportion of cannabis-using peers was acquired by dividing the number of soft drug-using friends by the total number of friends. Data from the peer nominations at T2 did not provide specific information about peer cannabis use. Alternatively, substance use ('who drinks alcohol and/or uses soft drugs on a regular basis?') was assessed for all classmates. In addition, the number of best friends (unlimited) within the class ('which classmates are your best friends?') was assessed. *Proportion of substance-using peers at T2* was acquired by dividing the number of substance-using friends by the total number of friends. To obtain a T3 measure that was comparable to the proportion of substance-using peers at T2, the number of alcohol- and/or soft drug-using friends at T3 was divided by the total number of friends reported at T3.

Early adolescent temperament was assessed at T1 by the parent version of the short form of the Early Adolescent Temperament Questionnaire – Revised (EATQ-R) [27]. The Dutch translation of the EATQ-R identifies six temperament dimensions and two behavioral dimensions [28]. For the present study we used the dimensions: 1) high-intensity pleasure, defined as the pleasure derived from activities involving high intensity or novelty (6 items, α = 0.77); 2) shyness, referring to behavioral inhibition to novelty and challenge, especially in social situations (4 items, α = 0.84); 3) fearfulness, manifested in worrying and unpleasant affect related to the anticipation of distress (5 items, α = 0.63); 4) frustration, defined as negative affect related to the interruption of ongoing tasks or goals blocking (5 items, α = 0.74), and 5) effortful control, defined as the capacity to voluntarily regulate behavior and attention (11 items, α = 0.86).

Covariates

Parental cannabis use was assessed at T3. In most cases, mothers completed a questionnaire about their own and their partners' lifetime and past year cannabis use. For both parents, responses were categorized into never, ever (used cannabis but not in the past year), and past year cannabis use. Maternal and paternal scores were summed to achieve a composite score of parental cannabis use.

Socioeconomic status (SES) 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 [96], and was categorized in low, average and high SES.

Intelligence was individually assessed at T1 by the Vocabulary and Block Design subtests [93] from the Revised Wechsler Intelligence Scales for Children (WISC-R) [94, 95].

Statistical approach

Statistical analyses were performed using the Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc. Chicago, IL) and Mplus 5.1 [101]. All continuous variables were standardized to a mean of 0 and a standard deviation of 1. Means of variables were calculated, and gender differences in means and proportions were analyzed by t-tests and χ^2-tests, respectively. Models were initially adjusted for age, sex, intelligence, SES, and parental cannabis use. In order to achieve the most parsimonious models, non-significant covariates were excluded from the models by backward exclusion.

First, we tested the hypothesized associations between temperament, affiliation with cannabis-using peers, and lifetime cannabis use by comparing lifetime cannabis users and abstainers. We tested the predictive power of each of the temperament dimensions by performing separate logistic regressions with lifetime cannabis use as the outcome variable. Based on these crude associations, we included all significant temperament dimensions in the next model, which was specified to assess the independent prediction by the different dimensions of temperament. The final temperament model included only the dimensions that remained significant. Next, we specified a logistic regression model to assess the association between the proportion of cannabis-using peers and lifetime cannabis use. In order to test mediation, we first specified a direct path model in which lifetime cannabis use was regressed on the temperament dimensions of the final model, in addition to regressing the proportion of cannabis-using peers on these dimensions. This was done to ascertain that direct associations between temperament and both proportion of cannabis-using peers and lifetime cannabis use were present. Subsequently, we specified a full mediation path model by additionally allowing for the direct path from proportion of cannabis-using peers to lifetime cannabis use. To test for an indirect relation from temperament to lifetime cannabis use via proportion of cannabis-using peers, a joint significance test of the indirect paths was used [98-100]. In order to determine if the identified mechanisms also contributed to the development of regular patterns of cannabis use, tests of the significant associations were repeated in a subgroup including regular and less regular cannabis users. Model fit was determined using the comparative fit index (CFI, critical value = 0.95) and the root mean square error of approximation (RMSEA, critical value = 0.08) [121, 122]. In order to determine whether the mediation model was a better representation of the data when compared to an additive

model, model fit was compared using the chi-square difference tests for weighted least squares means and variance adjusted (WLSMV) and maximum likelihood means and variance adjusted (MLMV) estimation [101]. To determine the prospective relation between proportion of substance-using peers and lifetime and regular cannabis use, we additionally performed two hierarchical logistic regression models in which lifetime and regular cannabis use at T3 were regressed on the significant covariates in the first step, on proportion of substance-using peers at T3 in the second step, and on proportion of substance-using peers at T2 in the final step. For this final analysis we used the subsample with available data on the peer nominations (n=697).

RESULTS

Descriptive statistics

At age 15-18, lifetime and regular cannabis use were reported by, respectively, 30.2% and 5.6% of the adolescents. Whereas boys and girls did not differ in the prevalence of lifetime cannabis use, boys were more likely than girls to be regular cannabis users (χ^2 (1 df, n=1300) = 27.71, p<.001). Means of the unstandardized scores or percentages of the variables used are shown in Table 5.1.

Table 5.1 Descriptive statistics.

n=1300	**Boys (n=579) Mean (SD)**	**Girls (n=721) Mean (SD)**	**Gender difference T/ χ^2**	***df***	**p**
Lifetime cannabis use	30,90%	29,80%	0,18	1	0,67
Regular cannabis use	9,50%	2,50%	27,71	1	<0.001
Proportion of cannabis-using peers T3	0.22 (0.31)	0.16 (0.26)	3,27	1123*	<0.01
High-intensity pleasure	3.44 (0.92)	3.23 (0.90)	4	1288	<0.001
Shyness	2.40 (0.86)	2.58 (0.87)	-3,65	1288	<0.001
Fearfulness	2.35 (0.70)	2.47 (0.72)	-3,05	1288	<0.01
Frustration	2.84 (0.68)	2.72 (0.63)	3,32	1288	<0.01
Effortful control	3.11 (0.71)	3.38 (0.65)	-7,09	1288	<0.001

Continued on next page

Table 5.1 Descriptive statistics *(continued).*

n=697	**Boys (n=306) Mean (SD)**	**Girls (n=391) Mean (SD)**	**Gender difference T/ χ^2**	***df***	**p**
Lifetime cannabis use	33%	29,90%	0,76	1	0,38
Regular cannabis use	10,50%	2,30%	20,62	1	<0.001
Proportion of substance-using peers T2	0.11 (0.24)	0.09 (0.21)	1,21	695	0,23
Proportion of substance-using peers T3	0.76 (0.33)	0.75 (0.33)	0,27	695	0,79

* Degrees of freedom not equal to n-1 due to correction for unequal variances.

Table 5.2 Associations between temperament, proportion of cannabis-using peers at T3 and lifetime and regular cannabis use at T3.

	Lifetime cannabis users versus abstainers (n=1300)				**Regular users versus less regular users (n=394)**	
	Crude associations		**Multivariate model**		**Crude associations**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
High-intensity pleasure	1.20***	1.11 – 1.29	1.18***	1.08-1.28	1,04	0.87 – 1.24
Shyness	0.87**	0.81 – 0.94	0.90*	0.83-0.98	0,97	0.81 – 1.14
Fearfulness	0,99	0.91 – 1.06				
Frustration	1.10*	1.02 – 1.18				
Effortful control	0.88**	0.82 – 0.96	0.87**	0.80-0.94	0.83*	0.70 – 0.98
Proportion of cannabis-using peers T3	2.35***	2.14 – 2.58			1.59***	1.38 – 1.84

Multivariate model refers to a model including all significant temperament dimensions as predictors. The most parsimonious n=1300 models were adjusted for age, intelligence and parental cannabis use, the most parsimonious n=394 models were adjusted for sex. All continuous variables were standardized to mean zero and standard deviation 1. * p<.05, ** p< .01, *** p< .001, CI= Confidence Interval.

Lifetime cannabis use

As presented in Table 5.2, findings from the separate logistic regression analyses indicated that high-intensity pleasure and frustration tended to enhance the risk of cannabis use, whereas effortful control and shyness buffered this risk. Fearfulness was not significantly related to cannabis use. Findings from the multivariate model indicated independent predictive power for high-intensity pleasure, shyness and effortful control. Proportion of cannabis-using peers at T3 was significantly associated with cannabis use. The most parsimonious models included age, intelligence, and parental cannabis use as covariates.

In order to test mediation, we first ascertained the presence of direct associations between the temperament dimensions of the final model and proportion of cannabis-using peers. Whereas high-intensity pleasure (β=0.13, 95%CI=0.07-0.19, p<0.001) and effortful control (β=-0.13, 95%CI=-0.18 to -0.07, p<0.001) were prospectively related to proportion of cannabis-using peers, shyness was not (β=-0.06, 95%CI=-0.11-0, p=0.06).

Subsequently, a full mediation model was specified including the paths from each of the three temperament dimensions and proportion of cannabis-using peers to lifetime cannabis use, from high-intensity pleasure and effortful control to proportion of cannabis-using peers, and the indirect paths from high-intensity pleasure and effortful control to lifetime cannabis use through proportion of cannabis-using peers. Findings indicated that proportion of cannabis-using peers mediated the pathways from high-intensity pleasure (OR=1.09, 95%CI=1.05-1.13, p<0.001) and effortful control (OR=0.92, 95%CI=0.89-0.96, p<0.001) to lifetime cannabis use. The direct paths from high-intensity pleasure (OR=1.08, 95%CI=1.01-1.16, p<0.05) and effortful control (OR=0.94, 95%CI=0.88-1.01, p=0.09) to life-time cannabis use were attenuated. Whereas the path from effortful control to lifetime cannabis use failed to reach significance, suggesting (largely) full mediation, the association between high-intensity pleasure and cannabis use was partially mediated by proportion of cannabis-using peers. The CFI=0.99 and RMSEA=0.05 indicated a good fit. Chi-square difference testing indicated that the mediation model fitted significantly better than an additive model with the temperament dimensions and proportion of cannabis-using peers as predictors (χ^2 (1) = 280.53, p<0.001). The full mediation model is depicted in Figure 5.1.

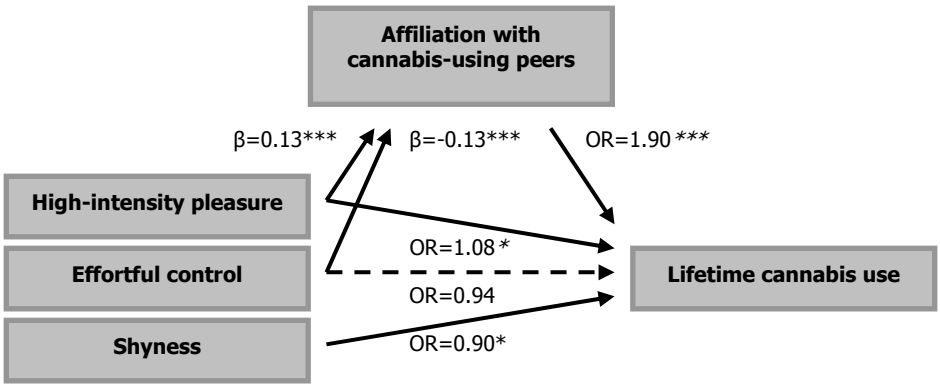

Figure 5.1. Final mediation model lifetime cannabis use.
The most parsimonious model was adjusted for age, intelligence and parental cannabis use. All continuous variables were standardized to mean zero and standard deviation 1. * p< .05, *** p< .001, OR = Odds Ratio.

Regular cannabis use

When tests of the significant associations were repeated in a subgroup including only lifetime cannabis users (n=394), divided in regular and less regular users, crude associations demonstrated that regular cannabis users were characterized by lower levels of effortful control at T1 and by a higher proportion of cannabis-using peers at T3. Regular and less regular users could not be differentiated by their levels of high-intensity pleasure or shyness (Table 5.2). Findings from the mediation model, depicted in Figure 5.2, indicated that effortful control buffered against the development of regular cannabis use through its buffering effect on affiliation with cannabis-using peers (OR=0.93, 95%CI=0.89-0.98, p<0.01). The direct path from effortful control to regular cannabis use did not remain significant (OR=0.89, 95%CI=0.76-1.04, p=0.13), indicating (largely) full mediation. In these models, sex was the only significant covariate. The CFI=0.95 and RMSEA=0.07 indicated a sufficient fit. The mediation model fitted significantly better than an additive model with effortful control and proportion of cannabis-using peers as predictors (χ^2 (1) = 36.71, p<0.001).

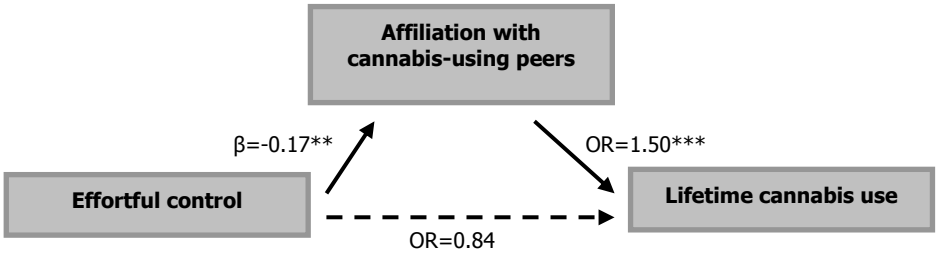

Figure 5.2. Final mediation model regular cannabis use.
The most parsimonious model was adjusted for sex. All continuous variables were standardized to mean zero and standard deviation 1. ** p< .01, *** p< .001, OR = Odds Ratio.

The prospective relation between affiliations with substance-using peers and cannabis use

Findings from the hierarchical logistic regression model in a subsample of the TRAILS population (n=697) ascertained the prospective relation between affiliation with substance-using peers and lifetime cannabis use. In the final model, adjusted for the covariates age, parental cannabis use, SES, and for proportion of substance-using peers at T3, proportion of substance-using peers at T2 predicted lifetime cannabis use (OR=1.33, 95%CI=1.12-1.58, p<0.01). Proportion of substance-using peers did not predict regular cannabis use (OR=1.05, 95%CI=0.78-1.40, p=0.76).

DISCUSSION

Using data from a large, longitudinal, general population sample of adolescents, we had the unique opportunity to examine the mediating role of exposure to cannabis-using peers in the pathways from various dimensions of temperament to lifetime and regular cannabis use. Crude associations indicated that proportion of cannabis-using peers was most strongly associated with lifetime and regular cannabis use. Particularly in adolescence, the association between peer factors and substance use outcomes becomes increasingly powerful [132]. We found, in agreement with prior studies [32, 55, 76, 83], risk-enhancing effects of high-intensity pleasure and risk-buffering effects of shyness and effortful control. While effortful control also appeared to buffer one's risk to progress into regular cannabis use, high-intensity pleasure and shyness were not prospectively related to regular cannabis use. Although previous studies have demonstrated prospective associations between related temperament dimensions, e.g. sensation seeking and behavioral inhibition, and frequency of use in young adolescents [77, 82], we do not know of any studies that investigated their association with specifically regular cannabis use. This combination of findings suggests that characteristics related to sensation seeking and behavioral inhibition contribute to one's risk to initiate and continue the use of cannabis, but that regular users constitute a specific subgroup that is less influenced by these temperamental traits. Contrary to our expectations, fearfulness and frustration were not (independently) associated with lifetime and regular cannabis use. The former might be due to the relatively low reliability of the subscale fearfulness (α = 0.63), or to moderation by other risk factors that may influence the presence and direction of the association between fearfulness and cannabis use. More specifically, fearfulness was expected to be associated with a reduced risk of cannabis use because of its buffering influence on impulsive and risk-taking behaviors. However, adolescents with high levels of

fearfulness might also be more likely to use cannabis in order to reduce negative affect. Yet, Swaim et al. have suggested that theories that view adolescent drug use as providing negative affect reduction might be more applicable to later stage substance abuse than to adolescent substance use [133]. This might also explain the absence of a significant relationship between frustration and cannabis use.

Findings from the mediation analyses indicated that temperament affected the risk of lifetime and regular cannabis use mainly by influencing the adolescents' tendency to affiliate with cannabis-using peers. These findings add to prior cross-sectional and longitudinal evidence of associations between related temperament dimensions and lifetime and frequency of cannabis and other substance use [53, 54, 129, 134]. The exception was the temperament dimension shyness. While shyness was expected to buffer the risk of cannabis use by making affiliation with cannabis-using peers less likely, the association between shyness and affiliation with cannabis-using peers failed to reach significance at the $p<0.05$ level. Thus, the hypothesized pathway might hold for some individuals, but may be modified by other factors, including exposure to or coping with peer pressure. When allowing for the indirect paths through affiliation with cannabis-using peers, effortful control appeared to be only indirectly related to lifetime and regular cannabis use. This is in line with the primary socialization theory [135], according to which personal characteristics and personality traits affect drug use only indirectly through their effect on association with primary socialization agents, such as peers. However, high-intensity pleasure remained also directly related to lifetime cannabis use. Although this is in line with the cross-sectional findings by Yanovitzky et al., other studies have found only indirect effects between sensation seeking and frequency of cannabis use through affiliation with deviant or sensation-seeking peers [53, 54, 134].

In agreement with findings from previous studies using various measures of substance use [55, 136, 137], our findings provided support for a prospective relation between affiliation with substance-using peers and lifetime cannabis use. Having relatively more substance-using peers is likely to promote the adoption of attitudes favorable towards drug use and to increase the number of opportunities to use drugs, resulting in a higher likelihood of own substance use. However, affiliation with substance-using peers was not related to regular cannabis use. This might however be explained by our measure of peer substance use, indicated by peer alcohol and cannabis use. We expect that specifically peer cannabis use, rather than the more common use of alcohol, is associated with the development of regular patterns of cannabis use. Own cannabis use might also precede the selection of a substance-using peer group.

Although previous studies have yielded inconsistent findings with regard to this latter mechanism, i.e. peer selection [55, 138, 139], findings from recent studies are consistent with this hypothesis [13, 140].

The present study is not without limitations. At T2 we did not assess the proportion of cannabis-using peers. As an alternative, we composed a variable based on information about peer use of 'alcohol or soft drugs' that was collected in a subsample (n=1007). Because the use of this variable placed restrictions on sample size and on the ability to study cannabis-specific associations between peer and own cannabis use, we used this measure only to ascertain a prospective association between proportion of substance-using peers and lifetime and regular cannabis use. As our findings provided support for this assumption with regard to lifetime cannabis use, we felt it was justified to model peer cannabis use at T3 as a mediator in the pathway from temperament at T1 to cannabis use at T3. However, our findings did not support the presence of a prospective association between affiliation with substance-using peers and regular cannabis use. Moreover, given the cross-sectional nature of the information on affiliation with cannabis-using peers and own cannabis use, the temporal precedence between the variables could not be established. Finally, as is common in large surveys, information about some factors, i.e. cannabis use, affiliation with cannabis-using peers, and parental cannabis use, was obtained using single or several items, rather than more extensive instruments.

Conclusions

In conclusion, this study showed that effortful control and high-intensity pleasure affected the risk for lifetime cannabis use through their influence on affiliation with cannabis-using peers: whereas adolescents with higher levels of effortful control were less likely to select cannabis-using peers, those with higher levels of high-intensity pleasure affiliated more with cannabis-using peers. Shyness seemed to affect this risk independent from peer cannabis use. Only the pathway from effortful control was additionally associated with the development of regular cannabis use. These findings contribute to the current knowledge about adolescent lifetime and regular cannabis use, which have been associated with an increased risk of developing a cannabis use disorder [7, 8].

Implications for future research and prevention

Some of our findings lead us to suggest that the impact of temperamental characteristics on affiliation with cannabis-using peers, and on lifetime and regular cannabis use is modified by other risk factors, such as parenting behaviors and coping strategies. In order to further understand the relation between temperament and adolescent cannabis use, and given the potential of

modifying factors for improving prevention efforts, we recommend future research to address the interplay between temperament and other risk factors of cannabis use. Given the fact that temperamental characteristics, with the exception of effortful control, seem to relate differently to lifetime and regular cannabis use, we recommend these studies to focus on specific and potentially hazardous patterns of cannabis use, rather than on cannabis use in general. Our findings also offered some interesting information that provides additional directions for future research. Although cross-sectional in nature, the covariate parental cannabis use was significantly associated with a higher risk of regular cannabis use and with more affiliation with cannabis-using peers. In order to explore the influence of parental cannabis use on the selection of cannabis-using peers and on the development of regular cannabis use, we recommend future prospective research in this area.

The results of this study have implications for prevention work. Our findings emphasize the importance of peers in adolescent cannabis use. They therefore indicate that prevention programs should include modules designed to enhance skills to resist social influences to engage in substance use. Prior research has suggested that, at least for programs teaching social competency skills, targeting high risk youths may yield stronger effects than targeting the general population [141]. Findings from the present study suggest that particularly adolescents with high levels of high-intensity pleasure and low levels of effortful control and shyness should be targeted, because these individuals are at increased risk of affiliation with cannabis-using peers and potentially hazardous patterns of cannabis use. As temperament or personality factors are expected to predict substance use by influencing specific motivational processes underlying substance use [142], we also suggest that prevention programs should include cognitive behavioral components aimed at enhancing the development of healthy coping strategies.

CHAPTER 6

DRD2/ANKK1 in relation to adolescent alcohol and cannabis use: does parenting modify the impact of genetic vulnerability? The TRAILS study

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ABSTRACT

Aims: The aims of the present study were to determine the direct effect of the A1 allele of the TaqIA polymorphism (rs1800497), and its interaction with parenting (i.e. rejection, overprotection and emotional warmth), on the development of regular alcohol and cannabis use in a large, general population sample of Dutch adolescents.

Methods: Information was obtained by self-report questionnaires. Perceived rejection, overprotection and emotional warmth were assessed at age 10-12. Regular alcohol and cannabis use were determined at age 15-18 and defined as the consumption of alcohol on 10 or more occasions in the past four weeks, and the use of cannabis on 4 or more occasions in the past four weeks. In the vast majority of cases, DNA was extracted from blood samples. Models were adjusted for age, sex, and parental alcohol or cannabis use.

Results: Carrying the A1 allele was not related to regular alcohol or cannabis use, neither directly nor in interaction with perceived parenting. Main effects for parenting indicated that overprotection increased the risk of regular alcohol use, and that the risk of cannabis use was enhanced by parental rejection and buffered by emotional warmth.

Conclusions: Our findings do not support a genetic predisposition for regular alcohol and cannabis use in adolescent carriers of the A1 allele of the TaqIA polymorphism. Given the substance-specific influences of rejection, overprotection and emotional warmth, these parenting factors might be promising candidates for prevention work.

INTRODUCTION

Persistent substance use during adolescence has been associated with various adverse outcomes, including an increased risk of developing substance use disorders and delinquent behaviors [8, 143, 144]. Research on the determinants of persistent substance use in this developmental phase can improve our understanding of liability to substance use disorders.

Twin studies have established that genetic influences contribute to the etiology of substance abuse and dependence [110]. These studies have reported heritability estimates that range from 50-70% for alcohol abuse/dependence and from 34-78% for cannabis dependence. While genetic influences have generally been found to be strongest for these heavier stages of substance use [145], the role of genetic factors on initiation, use, and non-diagnostic problem use of substances has also been established [146, 147]. For the latter, the influence of shared environmental influences is relatively stronger. Findings from twin studies assessing multiple stages of substance involvement suggest, at least partly, common genetic and environmental risk factors for substance use and misuse among adolescents and adults [148-150].

In substance use research, the genetic influences estimated in twin studies represent the composite variance explained by multiple genes, each of which is assumed to contribute to the liability to substance use disorders. Candidate gene association analysis is one of the available strategies to identify specific genes that influence this liability. One of the candidate genes implicated in substance use disorders is the ANKK1 TaqIA polymorphism (rs1800497, previously reported as located in the D2 dopamine receptor (DRD2) gene) [58]. Individuals carrying the A1 allele of the TaqIA polymorphism have a reduced number of D2 dopamine receptors in brain structures linked to reinforcement, particularly in the striatum [151-153]. Functioning of the dopaminergic system, especially in the striatum, has been associated with individual differences in reward-related traits, such as impulsivity and novelty seeking [67], and to disorders that involve enhanced reward-seeking, including substance use disorders [56]. As such, it has been suggested that individuals with a lack of D2 receptors, including those carrying the A1 allele of the TaqIA polymorphism, are more likely to manifest drug-seeking behavior in order to compensate for their reduced sense of reward [57].

Although the A1 allele of the TaqIA polymorphism has indeed been associated to, among others, alcohol-related phenotypes, smoking and illicit substance abuse, other studies have failed to replicate such associations or have found opposing links (for a review see Noble, 2003 [154]). Only few studies have examined the genetic effects of the A1 allele on substance use and abuse

during adolescence. When the focus of these studies was on alcohol consumption, results are inconsistent. Whereas sons of alcoholics with the A1 allele have been found to try and get intoxicated on alcohol more often [155], community and clinical studies have identified no other direct genetic effects on quantity of alcohol consumption per episode [156], frequency of alcohol consumption [59, 157] and early onset alcohol use disorder [158] in adolescents younger than 19 years old. In older adolescents and young adults (age 19-26 years), the A1 allele has been associated with a higher quantity of alcohol consumption per episode [156], but also with a decreased frequency of alcohol consumption in the past 12 months [157]. To the best of our knowledge, only one study assessed the association between adolescent cannabis use and the A1 allele. In a high-risk sample consisting of 48 adolescent sons of alcoholics, Conner and colleagues found that boys with this allele were not more likely to initiate the use of cannabis, although they experienced their first marijuana high at a younger age when compared to boys without this allele [155]. In the aforementioned study by Sakai et al., 93% of the adolescents with early onset alcohol use disorder also reported comorbid cannabis abuse or dependence, suggesting absence of effects of the A1 allele on comorbid alcohol and cannabis use disorder [158]. In conclusion, a small number of studies assessing the direct effects of the A1 allele of the TaqIA polymorphism on various alcohol and cannabis-related phenotypes during adolescence and young adulthood have yielded inconsistent results. Particularly in adolescents younger than 19 years old few direct effects have been found.

One of the explanations for the lack of direct effects of the A1 allele on adolescent substance use is the relative independent importance of environmental factors in this developmental stage, including for instance peer and parental influences [146, 157]. The expression of a genetic predisposition has been shown to vary as a function of environmental factors [159, 160]. This latter so-called gene-environment interaction implies that environmental stimuli modify the importance of genetic influence on substance use. Parenting has been suggested as such an environmental factor. Various aspects of parenting, most of which can be categorized into one of the two key dimensions parental warmth and control [161], have been prospectively related to a spectrum of adolescent externalizing problem behaviors, including onset and frequency of substance use [60, 61, 63, 162-167]. Parental monitoring and parental rule-setting toward substance use have also been associated with adolescent substance use [168, 169]. When compared to alcohol and tobacco use, relatively little prospective research is available on parenting in relation to cannabis use. In the present study we focus on the influence of parental rejection, overprotection, and emotional warmth on the risk of regular alcohol

and cannabis use. Parental rejection is characterized by hostility, punishment, and blaming of the child. Given a person's need for warmth and belongingness [170], a family environment characterized by rejection is likely to increase the risk of behavior problems. Indeed, associations of rejection with behavior problems and substance use have been reported [63, 167, 171]. As such, we expect that high levels of rejection enhance the risk of regular alcohol and cannabis use. Overprotection denotes fearfulness and anxiety for the child's safety, guilt engendering, and intrusiveness. It is suggested that such an overly restrictive parental environment, which might hinder the adolescent in achieving a sense of autonomy, is linked to greater misbehavior, including substance use, among adolescents. Although we do not know of any studies that assessed the influence of overprotection on alcohol or cannabis use, this parenting behavior has been found to increase the risk of externalizing behavior problems in the sample that we use here [63]. Therefore, we expect that adolescents that perceive high levels of overprotection are also more likely to use alcohol or cannabis on a regular basis. Finally, parental emotional warmth is likely to contribute to a persons need for warmth and belongingness. Most previous studies that examined indicators of parental warmth have found risk buffering effects on problem behavior and substance use [61, 63, 163, 165]. We therefore expect that this parenting factor, characterized by giving special attention, praising approved behavior, showing unconditional love, and being supportive and affectionately demonstrative, buffers the risk of regular alcohol and cannabis use. Besides direct risk enhancing or buffering effects on substance use, we hypothesize that these parenting factors modify the expression of a genetic predisposition for regular alcohol and cannabis use. Related gene by parenting interactions have been identified with respect to adolescent substance use [59, 164], indicating that a genetic liability increases the likelihood of substance use or abuse only when specific parenting styles are applied. With regard to the TaqIA polymorphism, findings by van der Zwaluw and coworkers show that adolescents carrying the A1 allele AND who have parents that are highly permissive towards alcohol consumption, use significantly more alcohol over time than adolescents without these characteristics [59]. However, it remains undetermined if general parenting also affects the actual expression of this A1 allele in substance-related phenotypes. Moreover, we are not aware of any studies that assessed a gene by parenting interaction with respect to adolescent cannabis use.

Using data from the Tracking Adolescents' Individual Lives Survey (TRAILS), a large, general population sample of Dutch adolescents, we have tested 1) for a direct effect of the A1 allele of the TaqIA polymorphism (rs1800497) on alcohol and cannabis use, and 2) whether parenting modifies the expression of a

genetic liability for alcohol and cannabis use. The focus of the present study is on regular patterns of alcohol and cannabis use in young adolescents, defined as the use of alcohol on at least 10 occasions in the past four weeks [5, 172], and the use of cannabis on at least four occasions in the past four weeks. This focus enabled us to get more insight in specific subgroups of alcohol and cannabis users that have a high risk of adverse outcomes. Based on findings from previous studies, we did not expect direct effects of the A1 allele on regular alcohol and cannabis use. Instead, we expected that the risk-enhancing effects of parental rejection and overprotection and the risk-buffering effect of emotional warmth would moderate the effect of the A1 allele on regular alcohol and cannabis use.

METHODS

Sample and participants

The present study reports data from the first (T1) and third (T3) assessments of TRAILS, which ran from 2001 to 2002, and from 2005 to 2007, respectively. A detailed description of the sampling procedure and methods is provided in De Winter et al. [64] and Huisman et al. [65]. 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 percent of the target population (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 [64]. T3 was completed with 81.4% of the original number of participants (n=1816, mean age = 16.27 years, *SD* 0.73, 52.3% girls).

For the analyses of the present study, all Dutch subjects with complete data on predictors and outcome were included in the analyses. Of the fourteen pairs of siblings within the TRAILS-sample, one of the siblings was randomly excluded. This resulted in a final sample of n=1197. Included participants were equally likely to be male/female (χ^2 (1 df, n=2230) = 3.67, $p>.05$), more likely to have a higher socioeconomic status (χ^2 (2 df, n=2230) = 107.55, $p<.001$), had a higher intelligence (t=10.02, 2169 df, $p<.001$), and were less likely to have initiated cannabis use at the second assessment of TRAILS (mean age 13.56 years; *SD* 0.53) (χ^2 (1 df, n=2230) = 6.60, $p<.05$) when compared to the excluded participants.

Measures

Alcohol and cannabis use

Frequency of alcohol and 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 and alcohol use ever, in the past year, and in the past four weeks. Response options ranged from 0-13, with 0-10 corresponding to the equivalent number of times, and 11, 12 and 13 corresponding to, respectively, 11-19, 20-39, and at least 40 times. In order to create comparable measures of regular alcohol and cannabis use, both were defined according to the number of occasions of use. Regular alcohol consumption was defined as drinking on 10 or more occasions in the past four weeks [5, 172]. Regular cannabis use was defined as the use of cannabis on at least four occasions in the past four weeks. When averaged, this reflects weekly or more frequent than weekly use of cannabis.

In order to minimize the possibility of including substance-related phenotypes in the comparison groups, regular users were compared to abstainers. For cannabis use, abstainers were those that reported never to have used cannabis. Because hardly any adolescents reported no alcohol consumption ever, alcohol abstainers were those that reported no consumption of alcohol in the past year. In addition, to make sure that the addressed associations were specific for regular use, rather than for substance use in general, regular users were also compared to experimental users. Experimental cannabis users were those that reported lifetime use of cannabis though on less than four occasions in the past four weeks. Less regular alcohol consumers were those that reported past year alcohol use though on less than 10 occasions in the past four weeks.

Parenting

Perceived parenting behavior was assessed at T1 with the EMBU-C [116], the child version of the EMBU (a Swedish acronym for My Memories of Upbringing, developed by Perris et al [117]. The EMBU-C contains the factors Rejection, Overprotection, and Emotional Warmth. Rejection (12 items, α = 0.84 for fathers and α = 0.83 for mothers) is characterized by hostility, punishment (physical and abusive), derogation, and blaming of subject (e.g. "Does your father/mother sometimes punish you even though you haven't done anything wrong?", "Does your father/mother treat you harsh and unfriendly?"). Overprotection (12 items, α = 0.70 for fathers and α = 0.71 for mothers) is characterized as fearfulness and anxiety for the child's safety, guilt engendering,

and intrusiveness (e.g. "Do you feel that your father/mother is extremely anxious that something will happen to you?", "Do you feel guilty when your father/mother is sad?"). Emotional Warmth (18 items, α = 0.91 for both parents) is characterized by giving special attention, praising for approved behavior, unconditional love, and being supportive and affectionately demonstrative (e.g. "Do your parents make it obvious that they love you?"). Subjects were asked to rate all items on a 5-point scale from never, sometimes, often, about always, to always. Because the scores for fathers and mothers on all parenting behaviors were highly correlated (*r*s = 0.67 for Rejection, 0.80 for Overprotection, and 0.78 for Emotional Warmth), they were averaged into a single measure of parental Rejection, Overprotection and Emotional Warmth. For 30 participants, these measures were based on only one parent because information about the other parent was missing.

Taq1A genotyping

DNA was extracted from blood samples or (in a few cases) buccal swabs (Cytobrush®) using a manual salting out procedure as described by Miller and colleagues [173]. Genotyping was performed on the Illumina BeadStation 500 platform (Illumina Inc., San Diego, CA, USA) by laboratory personnel blinded to the identity of the individual samples. We used an assay which was designed within the framework of various research questions of the TRAILS study. Scan data were analyzed and genotyped in BeadStudio 3.0 (Illumina Inc., San Diego, CA, USA). Rs1800497 could be genotyped in 99.9% of the TRAILS participants and call rate was 100%. Genotyping accuracy was 100% as determined by concordance between DNA replicates. Allele frequencies were calculated and analyzed for deviations from Hardy-Weinberg equilibrium (HWE) using χ^2-tests. No deviations from HWE were detected (P=0.31).

Intelligence

Intelligence was individually assessed at T1 by the Vocabulary and Block Design subtests [93] of the Revised Wechsler Intelligence Scales for Children (WISC-R) [94, 95].

Socioeconomic status (SES)

Socioeconomic status 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 [96], and was categorized in low, average and high SES.

Parental substance use

Parental alcohol and cannabis use were assessed at T3. In most cases, mothers completed a questionnaire about their own and their partners' substance use. Parental alcohol use was measured as the total number of consumed alcoholic drinks in a regular week, during weekdays and weekends. Parental cannabis use was measured as the frequency of cannabis use and in the past year. Because involvement in cannabis use was low among parents, responses were categorized into never, ever (used cannabis but not in the past year), and past year cannabis use. Maternal and paternal scores were summed to achieve a composite score of parental alcohol and cannabis use.

Statistical approach

Statistical analyses were performed using the Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc. Chicago, IL). All parenting measures were standardized to a mean of 0 and a standard deviation of 1.

Means of and correlation between variables were calculated, and gender differences in means and proportions were analyzed by t-tests and χ^2-tests, respectively.

Subsequent analyses were conducted separately for regular alcohol and cannabis use. Because of the absence of the A1A1 genotype in regular cannabis users (Table 6.1), genotypes were not examined by the conservative genotype approach (A2A2 vs A1A2 vs A1A1). Instead, we collapsed the A1A1 and A1A2 genotype, as has been done in many previous studies (A2A2 vs A1A2/A1A1) [59, 155, 158]. Models were initially adjusted for age, sex, intelligence, SES, and – depending on the outcome of interest – parental alcohol or cannabis use. In order to achieve the most parsimonious models, non-significant covariates were excluded from the models by backward exclusion.

First, we compared regular users and abstainers. To test the direct effect of the A1 allele of the TaqIA polymorphism, we performed logistic regression analyses. In order to test whether parenting modified the influence of the A1 allele on regular alcohol and cannabis use, we specified hierarchical regression models including the main effects of the A1 allele and one of the parenting measures in the first step, and the interaction between the two in the second step. To make sure that the addressed associations were specific for regular use, rather than for substance use in general, analyses were repeated comparing regular users to experimental or less regular users.

RESULTS

Descriptive statistics

At age 15-18, regular alcohol and cannabis use were reported by, respectively, 12.3% and 6.3% of the adolescents. Boys were more likely than girls to be regular users of alcohol (χ^2 (1 df, n=1197) = 10.78, p<.01) and cannabis (χ^2 (1 df, n=1197) = 21.92, p<.001). Genotype frequencies of the ANKK1 TaqIA polymorphism are depicted in Table 6.1. Mean scores or percentages of the variables used are shown in Table 6.2. For descriptive purposes, we presented the mean of the unstandardized scores. Correlation analyses indicated only a few significant associations: regular alcohol use was related to overprotection (Spearman's rho=0.07, p<0.05), and regular cannabis use was related to parental rejection (Spearman's rho=0.07, p<0.05) and emotional warmth (Spearman's rho=-0.08, p<0.01). Pearson correlations between the parenting measures ranged from -0.35 to 0.42, all at the p<0.01 level.

Table 6.1 Genotype frequencies of the ANKK1 TaqIA polymorphism.

	Total	**Alcohol consumption**			**Cannabis use**		
		Regular alcohol users	**Less regular alcohol users**	**Alcohol abstainers**	**Regular cannabis users**	**Experi-mental cannabis users**	**Cannabis abstainers**
N	1197	147	796	254	73	304	820
A2A2	747 (62.4%)	90 (61.2%)	505 (63.4%)	152 (59.8%)	47 (64.4%)	199 (65.5%)	501 (61.1)
A1A2	404 (33.8%)	54 (36.7%)	261 (32.8%)	89 (35.0%)	26 (35.6%)	96 (31.6%)	282 (34.4)
A1A1	46 (3.8%)	3 (2%)	30 (3.8%)	13 (5.1%)	0 (0%)	9 (3.0%)	37 (4.5)

Regular alcohol use was defined as use on at least ten occasions in the past four weeks. Less regular alcohol use was defined as past year alcohol use though on less than ten occasions in the past four weeks. Alcohol abstainers were those that had not consumed alcohol in de past year. Regular cannabis use was defined as use on at least four occasions in the past four weeks. Experimental cannabis use was defined as any cannabis use though on less than four occasions in the past four weeks. Cannabis abstainers were those that had never tried the use of cannabis.

Table 6.2 Descriptive statistics.

	Total n=1197 Percentage	**Boys n=565 Percentage**	**Girls n=632 Percentage**	**Gender difference**		
				χ^2	***df***	**p**
Regular cannabis use	6.3	9.7	3.2	21.92	1	<.001
Regular alcohol use	12.3	15.6	9.3	10.78	1	<.01
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**T**	***df***	**p**
Rejection	1.49 (0.30)	1.53 (0.32)	1.45 (0.28)	4.86	1112*	<.001
Overprotection	1.85 (0.36)	1.87 (0.38)	1.83 (0.35)	1.73	1195	0.08
Emotional warmth	3.24 (0.48)	3.18 (0.49)	3.30 (0.45)	-4.67	1147	<.001

* Degrees of freedom not equal to n-1 due to correction for unequal variances.

Direct effects of ANKK1 TaqIA on regular alcohol and cannabis use

The univariate analyses (not depicted in a Table) showed that the A1 allele of the ANKK1 TaqIA polymorphism had no direct effect on regular alcohol (OR=0.95, 95%CI=0.62-1.46, p=0.81) or cannabis use (OR=0.87, 95%CI=0.52-1.46, p=0.60).

Moderation by parenting

Gene by parenting measure interactions did not yield any significant associations, indicating that rejection, overprotection, and emotional warmth did not modify the effect of the A1 allele on regular alcohol or cannabis use (see Table 6.3a and b). However, substance-specific main effects for the various parenting behaviors were found. With regard to alcohol consumption, findings demonstrated a higher risk of regular alcohol consumption among adolescents that perceived higher levels of overprotection, either when compared to abstainers as to less regular users. Rejection and emotional warmth were not prospectively related to regular alcohol consumption. With respect to cannabis use, results demonstrated that regular cannabis use was more likely in adolescents that felt rejected by their parents. On the other hand, adolescents that perceived higher levels of emotional warmth were less likely to develop a regular pattern of cannabis use. The associations of parental rejection and emotional warmth with regular cannabis use disappeared when regular cannabis

users were compared to experimental users. This indicates that these parenting factors were associated with general use of cannabis, rather than with specifically regular cannabis use. Overprotection was not related to adolescent cannabis use.

The most parsimonious models included sex, age, and parental alcohol or cannabis use as covariates. Because adjusting for parental substance use might have ruled out part of the variance explained by genetic factors, analyses were repeated without adjusting for parental substance use. These analyses yielded comparable results.

Table 6.3a Associations between the A1 allele, parenting, and regular alcohol consumption.

	Regular alcohol users (n=147)	
	Versus past year abstainers (n=254)	**Versus less regular users (n=796)**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**
TaqIA (1=A2A2)	0.95 (0.62 – 1.46)	1.12 (0.78 – 1.62)
Rejection	1.03 (0.84 – 1.25)	1.08 (0.91 – 1.29)
TaqIA x Rejection	0.83 (0.54 – 1.26)	0.92 (0.63 – 1.32)
TaqIA (1=A2A2)	0.94 (0.61 – 1.45)	1.16 (0.80 – 1.68)
Overprotection	1.22* (1.01 – 1.46)	1.31** (1.10 – 1.56)
TaqIA x Overprotection	0.72 (0.49 – 1.06)	0.93 (0.65 – 1.34)
TaqIA (1=A2A2)	0.95 (0.62 – 1.46)	1.12 (0.78 – 1.61)
Emotional warmth	0.99 (0.81 – 1.22)	0.99 (0.83 – 1.18)
TaqIA x Emotional warmth	1.20 (0.80 – 1.81)	0.93 (0.65 – 1.35)

Parenting measures were standardized to mean zero and standard deviation 1. All analyses were adjusted for sex, age, and parental cannabis or alcohol use. * p<.05, ** p<.01, CI = Confidence Interval.

Table 6.3b Associations between the A1 allele, parenting, and regular cannabis use.

	Regular cannabis users (n=73)	
	Versus lifetime abstainers (n=819)	**Versus experimenters (n=304)**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**
TaqIA (1=A2A2)	0.87 (0.51 – 1.46)	1.24 (0.71 – 2.19)
Rejection	1.41** (1.13 – 1.76)	1.19 (0.94 – 1.51)
TaqIA x Rejection	0.81 (0.51 – 1.28)	0.98 (0.58 – 1.66)
TaqIA (1=A2A2)	0.87 (0.52 – 1.46)	1.20 (0.69 – 2.11)
Overprotection	1.03 (0.80 – 1.31)	0.91 (1.69 – 1.19)
TaqIA x Overprotection	1.04 (0.63 – 1.72)	1.12 (0.59 – 2.11)
TaqIA (1=A2A2)	0.85 (0.50 – 1.44)	1.18 (0.67 – 2.07)
Emotional warmth	0.72** (0.56 – 0.91)	0.83 (0.65 – 1.06)
TaqIA x Emotional warmth	0.70 (0.42 – 1.16)	0.82 (0.49 – 1.37)

Parenting measures were standardized to mean zero and standard deviation 1. All analyses were adjusted for sex, age, and parental cannabis or alcohol use. * p<.05, ** p<.01, CI = Confidence Interval.

Power

To rule out the possibility that the absence of significant gene by environment interactions was due to inadequate power to detect such associations, power analyses were computed using QUANTO [174]. Power was computed for the comparisons between regular alcohol or cannabis users and either abstainers or irregular users, resulting in four separate power analyses. With regard to regular alcohol use, these analyses supported that we had adequate power (>80%) to detect the risk of regular alcohol use conferred by gene by parenting interactions (assuming A1 allele frequency of 0.23 as documented in dbSNP (www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1800497), regular alcohol use prevalence of 0.37 in the first analysis and 0.16 in the second analysis, 147 cases versus 254 abstainers or 796 irregular users, relative risks ranging from ORs 1.0–3.0, and alpha of 0.05). Similarly, power to detect the risk of regular cannabis use conferred by gene by parenting interactions was adequate (assuming A1 allele frequency of 0.23 as documented in dbSNP, regular alcohol use prevalence of 0.37 in the first analysis and 0.16 in the second analysis, 147 cases versus 254 abstainers or 796 irregular users, relative risks ranging from ORs 1.0–3.0, and alpha of 0.05).

DISCUSSION

The aim of the present study was to determine the effects of the TaqIA polymorphism and its interaction with parenting on the risk for regular alcohol and cannabis use in a large, general population sample of Dutch adolescents. We did not find support for a direct association between the A1 allele and regular alcohol and cannabis use. With respect to alcohol use, this finding is in line with most previous studies that assessed the direct effects of the A1 allele and various alcohol-related phenotypes expressed during mid-adolescence [59, 156, 157, 158]. The present study is, to the best of our knowledge, the first study that reports on the association between TaqIA and cannabis use in a general population sample of adolescents. Some explanations for the absence of significant associations between the A1 allele and regular alcohol and cannabis use should be considered. First, although twin studies suggest that genetic influences on substance use disorders overlap with genetic influences on earlier stages of substance use [145, 149], it has been suggested that the TaqIA A1 allele is more prevalent with increasing severity of substance use disorders, at least with respect to alcohol use disorders [154, 175]. A second important issue involves the reference groups used, e.g. those adolescents that did not use alcohol or cannabis. By comparing regular users to abstainers, we tried to minimize the possibility that alcohol- or cannabis use related phenotypes were included in the comparison groups. However, because genetic effects related to DRD2 have been associated with a broad range of reward-related disorders [56], the absence of significant differences between regular users and abstainers might be due to the inclusion of adolescents with reward-related phenotypes in the comparison groups. However, Sakai and colleagues assessed the direct effect of TaqIA on early onset alcohol use disorders in an adolescent sample with a high prevalence of comorbid cannabis use disorder and conduct disorder. Even when controls were selected for the absence of other substance use disorders and conduct disorder, no significant association between the A1 allele and early onset alcohol disorder was found [158]. Thus, even when "severe" alcoholics are compared to controls selected for the absence of related phenotypes, there seems to be no direct association between the A1 allele and adolescent substance abuse.

However, the presence of the A1 allele might not always lead to increased levels of substance use, but only in conjunction with an unfavourable environment. We expected that the risk-enhancing effects of parental rejection and overprotection and the risk-buffering effect of emotional warmth would moderate the effect of the A1 allele on regular cannabis and alcohol use. Although our findings provide support for prospective associations between

overprotection and alcohol consumption, and between rejection and emotional warmth and cannabis use, these parenting behaviors do not seem to moderate the actual expression of the A1 allele in regular alcohol or cannabis use. While no previous studies have reported TaqIA by parenting interactions with respect to cannabis use, findings by van der Zwaluw et al. indicate that low parental rule-setting toward alcohol consumption is associated with more alcohol use over time, particularly in adolescents that carry the A1 allele [59]. This inconsistency in findings might be explained by the difference between the studies in alcohol-related phenotypes used (regular alcohol use versus frequency of alcohol consumption). Alternatively, we suggest that substance-specific rule-setting might be more strongly associated with subsequent adolescent substance use when compared to general parenting behaviors, and might therefore more easily trigger the actual expression of a genetic predisposition.

In general, our findings of risk enhancing effects of parental rejection and overprotection, and a risk buffering effect of emotional warmth on substance use, are in the same direction as most previous findings on the associations between general parenting behaviors and adolescent substance use [60, 61, 163, 176, 177]. What is interesting, however, is that we found substance-specific main effects. While regular alcohol use was more common in adolescents that perceived their parents as overprotective, the risk of cannabis use was enhanced by parental rejection and buffered by emotional warmth. Apparently, being blocked in the pursuit of autonomy (indicated by overprotection) is more likely to result in alcohol consumption, whereas a family environment characterized by rejection and little warmth places an adolescent at risk for future cannabis use. We suggest that these substance-specific associations might be explained by distinct reactions to the different parenting behaviors in combination with higher parental permissiveness towards alcohol versus cannabis use. More specifically, children of overprotective parents might more easily react to the restrictive behavior of their parents by using alcohol rather than cannabis, keeping thereby closer within the substance use boundaries defined by their overprotective parents. In contrast, adolescents that feel rejected by their parents might feel less restricted by parental rules that prohibit the use of cannabis, and might be more likely to use cannabis in their search for acceptance by peers. Finally, adolescents that experience a warm relationship with their parents may be more likely to adopt parental rules, which are expected to be less permissive towards cannabis use when compared to alcohol use. It should be noted, however, that the absence of an association between parental warmth and regular alcohol use contrasts previous findings of a negative relation between indicators of parental warmth or support and adolescent alcohol use [61, 163]. An additional consideration is that, instead of

affecting the risk of regular substance, parenting behavior might also be influenced by a child's problem behavior [178], including (early onset of) substance use. Since relatively little research is available on parenting in relation to illicit substance use, and on the specific role of parenting across different classes of substances, we recommend future research in this area. Such research might address other factors, for instance the acceptance of parental rules and affiliation with substance-using peers, which may explain the relationship between parenting behaviors and adolescent substance use. In addition, given that some parenting behaviors are subject to change during adolescent development [179] and in reaction to the behavior of the child [178], we recommend future studies to focus on the change in parenting behaviors during adolescence and on the interplay between parenting and child characteristics.

A final consideration regards the specificity of the associations between parenting and regular versus less regular alcohol and cannabis use. While perceived overprotection was highest among regular alcohol users when compared to less regular alcohol users, regular and experimental cannabis users did not differ with regard to their levels of perceived rejection and emotional warmth. Thus, these latter parenting behaviors enhanced and buffered, respectively, the risk of general cannabis use but did not predict the progression into a regular pattern of use. Apparently, once cannabis use has been initiated, other risk factors have more impact on the progression to regular cannabis use than parental rejection and emotional warmth.

The present study is not without limitations. First, although retention rates in TRAILS are relatively high, our sample suffered from some selective attrition, indicated by higher levels of intelligence and socio-economic status, and, at the second assessment wave, a lower likelihood of cannabis use in included subjects. Second, although confidentiality of the study had been emphasized, self-reports of substance use may be subject to over- or underreporting of alcohol and cannabis use. However, previous research has concluded that, when anonymity is assured, self-report measures of substance use have acceptable reliability [92].

In conclusion, this study showed that carrying the A1 allele is not related to regular alcohol or cannabis use, neither directly nor in interaction with perceived parenting. Our findings do indicate substance-specific prospective associations between parenting and substance use; while overprotection was associated with an increased risk of regular alcohol use, the risk of cannabis use was enhanced in adolescents that perceived parental rejection and buffered in adolescents that experienced emotional warmth. These findings contribute to the current knowledge about risk factors for persistent alcohol and cannabis use during

adolescence, which have been associated with various adverse outcomes [8, 143, 144]. In their effort to minimize the development of malignant patterns of substance use, prevention workers might focus on relevant parental factors. Findings from the present study suggest that these factors are substance-specific, and that both carriers and non-carriers of the A1 allele of the TaqIA polymorphism might benefit from such efforts.

CHAPTER 7

General Conclusions and Discussion

GENERAL CONCLUSIONS

The aim of the present thesis was to extend the existing knowledge on the aetiology of potentially hazardous patterns of adolescent cannabis use. More specifically, the purpose was to gain more insight in the role of temperament in the early onset and continuation of cannabis use during adolescence, and in the interrelation between temperament and other risk factors in predicting adolescent cannabis use. Objectives were studied in TRAILS, a large, general population study of Dutch adolescents.

In this chapter, an overview of cannabis use in the TRAILS-population is provided. After that, the main results and conclusions of this thesis are summarized. Subsequently, a general discussion of the findings is presented, and limitations and strengths of this research are discussed. This chapter concludes with implications for clinical practice and recommendations for future research.

Cannabis use in TRAILS

During the first assessment wave (T1, mean age 11.09, SD 0.55), cannabis use was very uncommon among TRAILS-participants. The overall prevalence of lifetime cannabis use increased from 1.3% at T1 to 30.4% at the third assessment wave of TRAILS (T3, mean age = 16.27, SD 0.73). Although at younger ages boys were more likely than girls to have tried cannabis, boys and girls were equally likely to have experimented with cannabis at T3. Of those who had initiated the use of cannabis at the second assessment wave (T2, mean age 13.56, SD 0.53), 48% reported to have used once or twice, 38% three to ten times, and 14% on more than ten occasions. At T3, these numbers were 25%, 35%, and 40%, respectively.

The past month prevalence rates usually indicate a more or less regular use [172]. In TRAILS, the likelihood of cannabis use in the past four weeks was higher among boys than among girls, particularly with increasing age. The prevalences of lifetime and any past month use of cannabis in the TRAILS population seem not to diverge from national estimates [3]. Table 7.1 depicts the prevalence rates of lifetime, past year and past four weeks cannabis use at the different assessment waves of TRAILS.

In addition to these measures of cannabis use, the present research focused on early onset of cannabis use as indicated by the onset of use before the age of 13, and on regular cannabis use, defined as the use on at least 4 occasions in the past 4 weeks. In TRAILS, early onset cannabis use was prevalent in 2.8% of the adolescents. Regular cannabis use at T3 was reported by 5.6% of the sample. Both early onset and regular use were more likely among boys.

Table 7.1 The prevalence of various patterns of cannabis use on each of the assessment waves. Numbers depend on available data.

	T1		**T2**		**T3**	
	mean age 11.09		**mean age 13.56**		**mean age 16.27**	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Lifetime cannabis use	2.10%	0.40%	8.30%	6.20%	31.70%	29.10%
Past year cannabis use			6.30%	5.20%	27.30%	22.10%
Past month cannabis use			3.60%	2.90%	17.90%	8.80%

T1, T2, and T3 refer to, respectively, assessment wave 1, assessment wave 2, and assessment wave 3.

Summary of main results and conclusions

Chapter 2 provided a review of the available prospective, general population studies that examined the relation between indicators of sensation seeking and adolescent cannabis use. A systematic search of the literature resulted in the inclusion of 14 studies on this subject. According to our quality assessment only four were considered of high quality. In order to facilitate comparison among studies, findings were categorized according to 1) the nature of the indicator of sensation seeking, e.g. indicator of high approach, indicator of low avoidance, or indicator of combined high approach and low avoidance, and 2) the measure of cannabis use, e.g. onset, frequency, or disordered use. Subsequently, levels of evidence for relationships between the different indicators and measures of cannabis use were determined. Results indicated weak to moderate evidence for associations of indicators of combined approach and avoidance with onset of and increase in cannabis use, as well as with substance use disorders. Evidence for prospective associations between indicators of either approach or avoidance and any of the measures of cannabis use remained inconclusive. Although these findings suggest that the combination of high approach and low avoidance is most important with respect to future cannabis use, the overall absence of convincing evidence is surprising. This might however be explained by the small number of studies, by the relatively low quality of most included studies, and by heterogeneity among studies with regard to population characteristics and measures. Moreover, the inclusion of additional risk factors in some studies resulted in an attenuated association between indicators of sensation seeking and cannabis use. In such studies, different constructs seemed to explain an overlapping part in the prediction of cannabis use, which points in the direction

of an interrelation between indicators of sensation seeking and other risk factors for adolescent cannabis use.

In ***chapter 3*** we examined the nature of the interrelation between the temperament dimension high-intensity pleasure and disruptive behavior in predicting onset of cannabis use in early adolescence (T2). To this end, we tested an additive model, a moderation model, and a mediation model. Our results indicated that the mediation model, including direct paths from high-intensity pleasure and disruptive behavior to onset of cannabis use, and an indirect path from high-intensity pleasure via disruptive behavior, represented the interrelation best. Although part of the relation between high-intensity pleasure and onset of cannabis use was mediated by disruptive behavior, this was only a very small part. In other words, the role of high-intensity pleasure in predicting the onset of cannabis use was found to be mainly independent from the role of disruptive behavior. An additional aim addressed in this chapter was to examine whether the associations between high-intensity pleasure, disruptive behavior and onset of cannabis use held for a specific subtype of disruptive behavior, i.e. attention-deficit hyperactivity (ADH), oppositional problems (OPs), and conduct problems (CPs). When self-reports of disruptive behavior were considered, only CPs were associated with onset of cannabis use and, accordingly, mediated a small part of the relationship between high-intensity pleasure and onset of cannabis use. According to parent-reports, both ADH and CPs were related to cannabis use and mediated the pathway from high-intensity pleasure to onset of cannabis use. The interrelation between high-intensity pleasure and CPs was in agreement with our expectations, which were based on mutual associations with the functioning of the behavioral activation system (BAS) [43, 86]. The interrelation between high-intensity pleasure and ADH was against our expectations, as particularly the functioning of the behavioral inhibition system (BIS), rather than the BAS, has been associated with ADH characteristics [45]. These divergent findings are discussed in the light of the simultaneous functioning of the BIS and the BAS.

The aim of ***chapter 4*** was to determine the roles of various temperamental traits on different points along the trajectory from early onset of cigarette smoking (before the age of 12) to early onset of cannabis use (before the age of 13). In our sample, the risk of early cannabis use was more than four times as high in individuals who initiated smoking cigarettes at an early age when compared to individuals who did not smoke cigarettes this early in life. Our findings indicated that predominantly high-intensity pleasure was associated with early onset of cannabis use. While a high level of high-intensity pleasure was related to early onset of cannabis use by predisposing the individual to early cigarette smoking, it also increased one's subsequent risk of making the

transition from early cigarette smoking to early cannabis use. Low shyness, defined as behavioral inhibition to novelty and challenge, particularly in the social domain, was also associated with a higher risk of transition from early tobacco to cannabis use. The influence of other risk or protective factors of substance use, as well as the interplay between temperamental traits and other risk or protective factors are suggested to explain the influence of temperamental traits on distinct points along the trajectory from cigarette smoking to cannabis use. Fearfulness, frustration, and effortful control were not related to early onset cannabis use.

In ***chapter 5*** we investigated the mediating role of affiliation with cannabis-using peers in the pathways from various dimensions of temperament to lifetime cannabis use in middle adolescence. In addition, we determined if these characteristics also contribute to the development of regular cannabis use, defined as the use of cannabis on at least four occasions in the past four weeks. Findings indicated that the risk of lifetime cannabis use was enhanced in adolescents with high levels of high-intensity pleasure, and buffered in adolescents with high levels of shyness and effortful control. Whereas shyness seemed to affect this risk independent from peer cannabis use, high-intensity pleasure and effortful control affected the risk for lifetime cannabis use through their association with the proportion of cannabis-using peers: adolescents with higher levels of high-intensity pleasure and effortful control were respectively more and less likely to affiliate with cannabis-using peers. These findings are discussed in relation to the primary socialization theory [135], according to which personality traits affect drug use only indirectly through their effect on association with primary socialization agents, such as peers. Effortful control was the only temperament dimension that was also associated with the development of regular cannabis use, again through its influence on affiliation with cannabis-using peers. Our findings suggest that characteristics related to sensation seeking and behavioral inhibition contribute to one's risk to experiment with the use of cannabis, but that regular users constitute a specific subgroup that is less influenced by these temperamental traits. Frustration and fearfulness were not prospectively related to lifetime or regular cannabis use. Significant findings of chapter 3 to 5 are presented in Figure 7.1.

Finally, in ***chapter 6*** we examined if the A1 allele of the TaqIA polymorphism, which has been associated with a reduced number of D2 dopamine receptors in brain structures linked to reinforcement [151-153], is related to regular alcohol and cannabis use in middle adolescence. In addition, we tested whether general parenting behaviors modify the expression of a genetic liability for regular alcohol and cannabis use. Our findings indicated that carrying the A1 allele was not related to regular alcohol or cannabis use, neither

directly nor in interaction with perceived parenting. Overall, substance-specific associations between parenting and substance use were demonstrated; while overprotection was associated with an increased risk of regular alcohol use, the risk of cannabis use was enhanced in adolescents that perceived parental rejection and buffered in adolescents that experienced emotional warmth. These latter parenting behaviors affected the risk of general cannabis use but did not predict the progression into a regular pattern of use. Apparently, once cannabis use has been initiated, other risk factors have more impact on the progression to regular cannabis use.

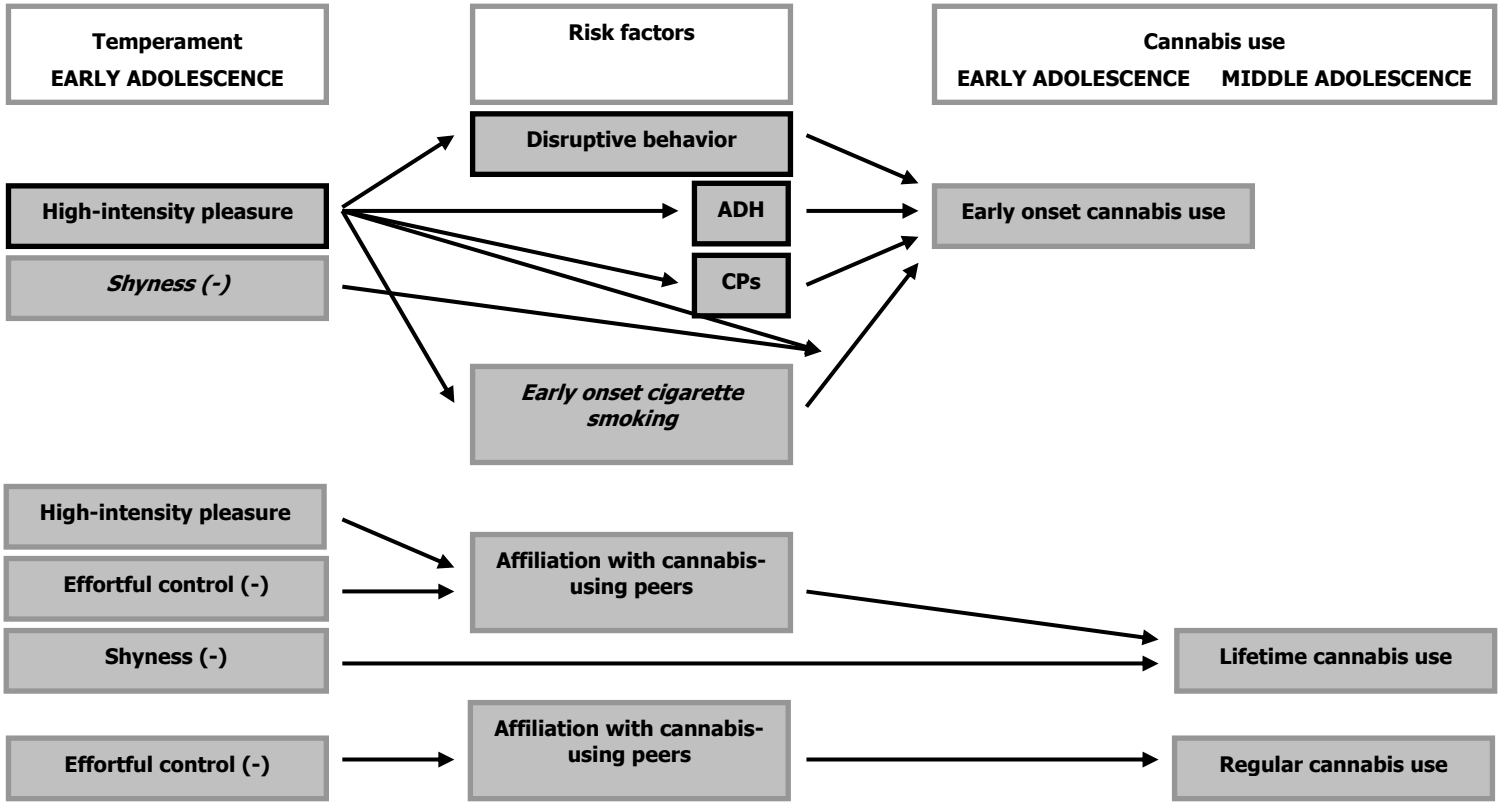

Figure 7.1 The role of temperament in relation to other risk factors of cannabis use among TRAILS-adolescents (significant associations). Early onset cannabis use is defined as onset of use before the second assessment wave, or onset of use before age 13. Lifetime cannabis use is defined as any use of cannabis before the third assessment wave. Regular cannabis use is defined as the use of cannabis on at least four occasions in the past four weeks. ADH refers to attention deficit hyperactivity problems, CPs refer to conduct problems. Risk factors in boxes with dark borders have been tested in chapter 3; risk factors in italics have been tested in chapter 4; associations in the lower half of the figure have been tested in chapter 5.

GENERAL DISCUSSION

Does temperament explain why some adolescents start using cannabis at a very early age, or progress to regular patterns of use, while others never use cannabis or experiment with it only once or twice? In the present thesis, we try to answer this question by focussing on prospective associations between specific temperament dimensions and potentially hazardous patterns of cannabis use, e.g. early onset and regular cannabis use. Moreover, the pathways by which these temperament dimensions, as well as the TaqIA allele, are related to cannabis use have been examined in relation to other risk factors of cannabis use, e.g. disruptive behavior, legal substance use, affiliation with cannabis-using peers, and parenting behaviors.

Direct relations between temperamental traits and cannabis use

In general, the present research demonstrates that temperament contributes to some extent to an adolescent's vulnerability to develop potentially hazardous patterns of cannabis use. Briefly, findings from the univariate analyses indicate that high-intensity pleasure, shyness, frustration, and effortful control in early adolescence are associated with specific measures of cannabis use. When the contributions of several temperamental traits are considered simultaneously, some of these associations lose strength or significance. Apparently, different temperamental traits explain an overlapping part of the variance in cannabis use. For instance, when high-intensity pleasure and shyness are considered simultaneously as predictors of early onset cannabis use, the nearly significant association between low levels of shyness and an increased risk of early onset cannabis use disappears. When adjusted for the influence of other temperamental traits, independent risk-enhancing effects of high-intensity pleasure and risk-buffering effects of shyness and effortful control are demonstrated. Although either high-intensity pleasure, shyness, and effortful control affect the risk of lifetime cannabis use in middle adolescence, stage- and/or age-specific associations seem to exist between these temperamental traits and early onset and regular cannabis use: whereas early onset of cannabis use is most likely in adolescents with high levels of high-intensity pleasure, the risk of progression into regular patterns of use seems particularly affected by the adolescent's level of effortful control.

High-intensity pleasure, shyness, and fearfulness

High-intensity pleasure, as described earlier, refers to the pleasure derived from activities involving high-intensity or novelty and, as such, mainly reflects the approach component of sensation seeking. Zuckerman and Cloninger,

introduced in the first chapter of this thesis, proposed that individuals characterized by both high levels of approach and low levels of avoidance are most vulnerable for substance use and abuse [29-31]. In agreement with their theories, the literature review in chapter 2 concludes that most evidence is available for the presence of associations between indicators of combined high approach and low avoidance and various patterns of use, including onset and increase in cannabis use and the development of substance use disorders. In this thesis, the contributions of the approach, e.g. high-intensity pleasure, and avoidance, e.g. shyness and fearfulness, components of sensation seeking were considered separately. This approach has yielded some interesting results.

First, our findings indicate that the risk to develop regular patterns of cannabis use is not affected by the individual approach or avoidance components. Previous studies that addressed related associations have provided inconclusive evidence for the presence of associations between the individual indicators of approach or avoidance and frequency of cannabis use [114]. Although the absence of established relationships might indicate that these temperamental traits are not involved in this specific stage of cannabis use, it might also provide support for the aforementioned proposition that it is particularly the combination of high approach and low avoidance, rather than their individual contribution, which affects the risk of increasing levels of cannabis use. Alternatively, the overall absence of established relationships between indicators of either approach or avoidance and frequency of cannabis use might be due to the lack of consensus with regard to the appropriate definition of such a measure. As a result, studies that concentrated on repeated, regular, or frequent cannabis use have focussed on very heterogeneous groups that differ in their liability to substance abuse. This might explain the inconsistent findings of such studies. Despite these methodological considerations that affect the comparability of previous studies, the findings of the present research lead us to conclude that indicators of approach or avoidance are not independently related to the development of regular cannabis use, defined as the use of cannabis on at least four occasions in the past four weeks.

Another interesting result concerns the avoidance component shyness, defined as behavioral inhibition to novelty and challenge. Whereas the approach component high-intensity pleasure seems to exclusively affect the risk of very early onset cannabis use, the impact of the avoidance component shyness seems to become more pronounced with increasing age. The shift in cannabis use from being a highly deviant behavioral manifestation in early adolescence towards a somewhat less deviant behavioral pattern in middle adolescence might explain the divergent associations of temperament with onset of cannabis

use in early and middle adolescence. More specifically, one might hypothesize that the small number of adolescents that starts using cannabis at a very early age constitutes a specific group of deviant individuals characterized by particularly a high tendency towards exploratory behavior. Given the growing prevalence of cannabis use with increasing age, the group of cannabis users becomes more heterogeneous and also includes individuals that are generally not considered as deviant as the early onset cannabis users. Consequently, the approach component does no longer exclusively distinguish cannabis users from non-users. Instead, other temperamental traits, including the avoidance component shyness, also differentiate adolescents who have experimented with cannabis from those who abstain from using cannabis.

Finally, according to the findings of this thesis, the avoidance component fearfulness seems not involved in the risk of cannabis use in early and middle adolescence. Although methodological issues, such as the relatively low reliability of this subscale, might explain the absence of significant findings, an alternative explanation should be considered. That is, the concurrent presence of different associations between fearfulness and adolescent cannabis use might have impeded their identification. More specifically, although high fearfulness was expected to be associated with a reduced risk of cannabis use because of its buffering influence on impulsive and risk-taking behaviors, adolescents with high levels of fearfulness might also be more likely to use cannabis in order to reduce negative affect. This way, the existence of subgroups of fearful individuals that differ in their vulnerability to cannabis use might explain the absence of an association between general fearfulness and cannabis use.

Effortful control

A second temperamental trait that seems to become more important in distinguishing cannabis users and abstainers in middle adolescence is effortful control, defined as the capacity to voluntarily regulate behavior and attention. According to the findings in this thesis, the ability to regulate behavior and attention protects adolescents that have abstained from cannabis use in early adolescence from the growing risk to initiate cannabis use with increasing age. In addition to protecting against lifetime cannabis use in middle adolescence, effortful control also buffers the risk of developing regular patterns of cannabis use. In other words, once the use of cannabis has been initiated, high levels of self-regulation protect the adolescent from progressing into regular cannabis use. Probably, the (regular) use of cannabis does not fit into the more goal-directed, compliant and conscientious behavioral pattern of adolescents with high levels of effortful control. Unlike high-intensity pleasure and shyness that primarily reflect emotional responses to stimuli (reactivity), effortful control

reflects temperamentally based self-regulation processes. Such processes have been found to be important for learning, adjustment and social competence [180]. The specific associations between temperamental traits and two potentially hazardous patterns of cannabis use, e.g. early onset and regular cannabis use, suggest that these stages of cannabis use might be driven by different processes: whereas reactive processes seem particularly involved in early onset of use, self-regulatory processes seem of increased importance for the development of regular cannabis use.

Frustration

Within the biologically-oriented temperament model developed by Rothbart and colleagues, frustration is, in adolescents, the main indicator of the broad temperament factor negative affectivity [27]. Although we expected that high levels of negative affectivity would be related to an increased risk of cannabis use, findings indicate that frustration does not independently affect the risk of cannabis use in early and middle adolescence. This might be explained by the possibility that, rather than affecting the risk of initiation of cannabis use, this trait is involved in the progression towards regular patterns of cannabis use and abuse. After all, through self-medication motives, individuals might regularly use cannabis to reduce the negative affect they experience. Indeed, although stress and negative affect regulation models have been linked to adolescent substance use initiation, they have been more commonly associated with later stage substance abuse [127]. Because, particularly in younger adolescents, higher levels of fearfulness also indicate negative affectivity, this might also hold for the association between fearfulness and cannabis use.

The role of temperament in relation to other risk factors of cannabis use

In addition to identifying direct relations between temperamental traits and adolescent cannabis use, we aimed to study the role of temperament in relation to other risk factors of cannabis use. Again, the simultaneous consideration of several risk factors, in this case temperamental traits and either disruptive behavior, legal substance use, or affiliation with cannabis-using peers, resulted in attenuated associations. As such, findings from the empirical studies in this thesis confirm one of the findings of the systematic review presented in chapter 2, namely that the simultaneous consideration of other risk factors leads to a (seemingly) decreased role of temperament. Apparently, temperament and other risk factors explain an overlapping part of the variance, which suggests some kind of interrelation between these factors. Indeed, our findings reported in chapter 3-5 confirm the existence of various pathways through which early

onset, lifetime, and regular use of cannabis are predicted by interrelated temperamental traits and other risk factors.

Mediation pathways

Instead of direct relations, the findings of this thesis indicate that almost all temperamental traits affect the risk of potentially hazardous patterns of cannabis use because of their association with other risk factors. For instance, the relatively high likelihood of (early) initiation of cannabis use in adolescents with high levels of high-intensity pleasure is mediated by their predisposition towards disruptive behavior, cigarette smoking, and affiliation with cannabis-using peers. Furthermore, high levels of effortful control protect against lifetime and regular cannabis use in middle adolescence by buffering the degree to which adolescents affiliate with cannabis-using peers. Given the influence of temperament on numerous aspects in life [181], and given the multifactorial nature of substance use and abuse [19], it is not surprising that the pathways from temperament to cannabis use are mediated by certain other risk factors. However, this research adds to the existing knowledge by identifying pathways from certain temperamental traits to potentially hazardous patterns of cannabis use through specific other risk factors of substance use. This approach teaches us that some risk factors seem to be more important than others in mediating specific pathways from temperamental traits to cannabis use. For instance, while early onset cigarette smoking seems to mediate a relatively large part of the association between high-intensity pleasure and early onset cannabis use, disruptive behavior mediates only a very small part of this association. Thus, at least in early adolescence, high-intensity pleasure and disruptive behavior seem to be mainly independently involved in the initiation of cannabis use. On the same note, although affiliation with cannabis-using peers mediates the pathways from both high-intensity pleasure and effortful control to cannabis use, the direct pathway from effortful control disappears, whereas the direct pathway from high-intensity pleasure remains present. Apparently, distinct mechanisms relate high levels of high-intensity pleasure to an increased risk of cannabis use; one through the selection of cannabis-using peers, and one irrespective from affiliation with cannabis-using peers. Interestingly, affiliation with cannabis-using peers seems involved in each of the established associations between temperamental traits and cannabis use, except for the risk-buffering pathway from shyness to lifetime cannabis use. According to the present research, the level of shyness does not affect the extent to which an individual affiliates with cannabis-using peers. It is hypothesized that individuals with high levels of shyness or behavioral inhibition, as opposed to individuals with high levels of high-intensity pleasure or effortful control, might play a more passive role in the

creation of peer relationships. Not actively approaching or avoiding cannabis-using peers might result in affiliations with both cannabis-using and non-cannabis-using peers. This might explain the absence of an association between shyness and proportion of cannabis-using peers.

Moderation pathways

While certain risk factors seem to mediate the pathways from temperament to cannabis use, their impact on cannabis use might also be affected by temperament. The latter interrelation would explain why, given equal exposure to certain risk factors, certain adolescents are even more likely than others to start or continue the use of cannabis. In this thesis, the moderation hypothesis was tested for the associations of both disruptive behavior and cigarette smoking with early onset cannabis use. Either of these risk factors is, irrespective of temperament, related to an increased risk of cannabis use. For adolescents with higher levels of disruptive behavior, the increased risk of cannabis use seems unaffected by their levels of high-intensity pleasure. Although one might expect that the combination of disruptive behavior and high levels of approach would make an individual even more prone to the initiation of cannabis use than either of the individual factors, this does not seem to hold for early onset cannabis use. Apparently, the influence of high-intensity pleasure on disruptive behavior is mainly of a predisposing nature, rather than that it additionally affects the impact of this risk factor on early onset cannabis use. Interestingly, when the focus is on early onset cigarette smoking, certain temperamental traits do seem to influence the increased risk of cannabis use. More specifically, early onset cigarette smokers that are characterized by higher levels of high-intensity pleasure are even more likely to also start early with the use of cannabis. Contrarily, adolescents with higher levels of shyness are less likely to progress from early onset cigarette smoking to early onset cannabis use. Apparently, high-intensity pleasure affects the risk of early onset cannabis use on different points along the most commonly followed sequence from cigarette smoking to cannabis use. The level of shyness, in contrast, does not affect the risk of early onset cannabis use until the substance use trajectory has been initiated. Based on the combination of these findings and the established direct relations between temperament and cannabis use, one might extend the aforementioned hypothesis that high levels of high-intensity pleasure seem particularly involved in the very early initiation of cigarette smoking and cannabis use, and that, with increasing age or experience with tobacco use, the ability to voluntarily (effortful control) and involuntarily (shyness or behavioral inhibition) control one's behavior becomes of additional importance in determining the risk of cannabis use.

As illustrated for shyness, moderation effects can impede the detection of associations between risk factors and cannabis use that apply to specific subgroups of individuals, in this case early onset cigarette smokers. As such, moderation by other risk factors might alternatively explain the absence of associations between fearfulness and frustration and cannabis use. The presence of moderation effects might also affect the strength of established associations between for instance temperamental traits and cannabis use. For example, Oldehinkel et al. demonstrated that the effects of fearfulness and frustration on the development of, respectively, internalizing and externalizing behaviors were attenuated by high levels of effortful control [182]. This indicates that, in addition to independent associations of the individual temperamental traits, the interaction between different temperamental traits also affects the risk of behavioral outcomes. Although, based on the present research, the predictive power of temperament seems relatively small, interactions between temperamental traits, or between temperamental traits and other risk factors such as coping strategies or parental rule-setting, might point towards a more pronounced role of temperament in adolescent cannabis use. In addition, the identification of interrelated temperamental or other factors that mutually affect the risk of cannabis use helps us to better understand the mechanisms behind the development of potentially hazardous patterns of cannabis use.

Genetic predisposition and parenting

As proposed by Rothbart and colleagues, genetics play a role in determining an individual's temperamental make-up [25]. In addition, genetics have also been involved in the etiology of substance use, abuse and dependence [58, 145]. One of the candidate genes implicated in both novelty seeking and substance use disorders is the ANKK1 TaqIA polymorphism, which is assumed to be generally associated with the seeking of rewarding experiences in order to compensate for a reduced sense of reward. In an attempt to identify individual differences in the impact of another risk factor of substance use, e.g. parenting behavior, the interplay between this polymorphism and parental rejection, overprotection and emotional warmth was addressed in relation to the development of regular cannabis and alcohol use. While adolescents who perceive high levels of parental rejection and overprotection seem at increased risk of, respectively, cannabis use and regular alcohol use, adolescents who perceive high levels of emotional warmth are less likely to use cannabis. However, the ANKK1 TaqIA polymorphism seems not involved in the regular use of these substances during adolescence, neither directly nor in interaction with parenting. Under the assumption that this polymorphism induces a so-called reward deficiency, the

absence of an association with regular cannabis or alcohol use suggests that regular use of these substances is not grounded in self-medication motives aimed at reducing a reward deficiency. The fact that such an association is also absent in adolescents who experience adverse parenting behaviors contradicts with the findings of a study by van der Zwaluw et al. in which this polymorphism has been found to increase the risk of alcohol consumption only in adolescents who perceive their parents as highly permissive towards alcohol consumption [59]. The combination of findings from the present study and the study by van der Zwaluw suggests that parents of genetically predisposed adolescents influence the expression of a genetic liability to substance abuse in their offspring by placing few restrictions on the consumption of alcohol, rather than by exposing their offspring to adverse parenting behaviors. Although the latter might affect the adolescent's adherence to parental rules, their influence does not seem strong enough in order to elicit the expression of a genetic liability to substance use.

Limitations and strengths of the presented research

The findings of all studies presented in this thesis should be viewed in the light of several limitations and methodological issues. The specific limitations of each study have been discussed in the previous chapters. Therefore, the more general limitations are discussed in this section. Furthermore, several strengths of this research will be outlined.

Limitations

First, although retention rates in TRAILS are relatively high, they decreased from 96.4% at the second assessment wave to 81.4% at the third assessment wave. This attrition was selective, indicated by for instance higher levels of intelligence and socio-economic status in participating subjects when compared to those who dropped out. In addition, participating subjects reported a lower level of conduct problems and were less likely to initiate the use of cannabis at an early age, or to have a parent with a history of substance use disorder. This suggests that the target group of this research, e.g. adolescents at risk for hazardous patterns of cannabis use, is underrepresented in the TRAILS sample as compared to the general population. This might have affected the strength of the associations between risk factors and cannabis use. Second, all studies presented in this thesis rely on self-report measures of substance use. It is thought that self-reports tend to suffer from social desirability bias and fragmented recall, which might lead to over- or underreporting of substance use. However, previous research has concluded that, when anonymity is assured, self-report measures of substance use have acceptable reliability [92].

Third, in a large, longitudinal survey, the measurement of determinants and outcomes cannot always be as elaborate as a researcher would like, taken the burden this would place on the study participants into consideration. Therefore, information about some determinants and outcomes was collected using single or several items, rather than more detailed and validated instruments. In the presented research, this applies to the measurement of cannabis use, affiliation with cannabis using peers, and the covariate parental cannabis use. In addition, due to the lack of consensus with regard to the appropriate definition of risky patterns of cannabis use, these concepts are also subject to some arbitrariness. Finally, predictors were not always assessed before onset of cannabis use or continuation to regular patterns of use had taken place. For this reason, we were not always able to investigate the temporal relation between temperamental traits, mediating risk factors, and potentially hazardous patterns of cannabis use. As such, we cannot exclude the possibility of inverse associations between these factors.

Strengths

In addition to the limitations mentioned above, some strong points of the present research should also be considered. First, the answers to the research questions of this thesis are based on data from a relatively large sample of adolescents, thereby ensuring adequate statistical power and reducing the risk of research error [183]. Second, the questions were addressed in a general population sample. Investigating the development of potentially hazardous patterns of cannabis use in a general population sample including cannabis use abstainers, experimenters, and repeated or regular users makes it possible to further understand the determinants of various patterns of adolescent cannabis use, as well as the mechanisms underlying the associations between the determinants and cannabis use. Third, while parents provided information about temperament, information about substance use was obtained by self-reports. Observation by different informants rules out common method variance as an interpretation of the findings. Fourth, TRAILS is characterized by the breadth of measurement of factors, which makes it possible to control for important correlates, such as alcohol initiation and parental licit substance use. Lastly, numerous studies have investigated a wide variety of risk and protective factors in relation to cannabis and general substance use. However, most previous studies have focussed on individual contributions of the various risk factors, rather than on the underlying mechanisms and interplay between risk factors. The research presented in this thesis adds to the existing knowledge by its focus on the interrelation between temperamental traits and several risk factors of substance use, e.g. disruptive behavior, cigarette smoking, and affiliation with

cannabis using peers, and on the interrelation between genetic liability and general parenting behavior. This approach elucidates that temperamental and other risk factors are not mere independent predictors of cannabis use but act together in determining and adolescent's vulnerability to potentially hazardous patterns of cannabis use.

Implications and recommendations for future research and practice

Future research

The present thesis addressed the role of temperament and several other risk and protective factors, as well as their interrelation, in predicting potentially hazardous patterns of cannabis use during adolescence. However, as mentioned earlier, there is no consensus with regard to the appropriate definition of risky patterns of cannabis use. Because of the importance of investigating subclinical levels of substance use disorders, there is an absolute need for future research aimed at reaching consensus about the optimal operationalization of potentially hazardous patterns of substance use. Next, given the fact that multiple risk and protective factors are involved in the initiation and continuation of cannabis use [18, 19], the breadth and depth of study on this subject matter should be extended in future research. For instance, as some of the findings indicate or suggest that the impact of temperamental traits and other risk factors of substance use is modified by other factors, future studies may further focus on the interplay between temperament and different risk or protective factors. For instance, studies might focus on the interaction between temperamental traits and socio-environmental factors such as socio-economic status or the experience of life-events. In addition, future studies might target the modifying effects of coping strategies or parenting behaviors, given the potential of such factors for improving efforts to prevent the development of problematic cannabis and general substance use. Besides considering the separate effects of, or interactions between, individual temperamental traits, a focus on specific temperamental profiles associated with the development of hazardous patterns of cannabis use might contribute to the identification of at risk individuals and might provide more insight in the mechanisms behind cannabis use and misuse. For instance, adolescents with a temperament profile characterized by high levels of frustration and high-intensity pleasure, and low levels of effortful control, shyness, and fear are expected to be easily bored and irritated, and might experience great difficulty in coping with these states of mind. Furthermore, although temperamental characteristics are assumed to have reasonable stability over time [20], they are influenced by heredity, maturation, and experience [25]. For instance, the capacity to self-regulate behavior and attention continues to develop until early adulthood [126]. Thus, despite the fact

that early adolescent temperamental traits contribute to characterizing adolescents at risk of the initiation and continuation of cannabis use in early and middle adolescence, their development throughout adolescence might be of additional value for understanding the process of adolescent substance use. Therefore, future studies should also focus on developmental trajectories of temperament, and consequently altered interactions with other risk factors of substance use, in relation to the growth in cannabis or general substance use. Finally, according to the findings presented in this thesis, parental rejection and emotional warmth were uniquely related to cannabis use, and not to alcohol use. These findings point in the direction of substance-specific risk and protective factors. As particularly the use of cannabis, rather than the use of alcohol or tobacco, has been associated with an increased risk of illicit drug use, knowledge of factors that specifically influence cannabis use is crucial for any preventive work. Although identifying risk factors of legal substance use is also of the utmost importance, future studies could focus on risk and protective factors that distinguish legal substance users from those that progress into the use of semi-legal or illegal substances.

Prevention & intervention

Although the findings of this thesis are mainly of theoretical relevance, some clinical implications should be considered. First, adolescents who start the use of cannabis at a very early age, or who progress into regular patterns of use, are characterized by certain temperamental traits, but also by higher levels of disruptive behavior, early onset cigarette smoking, affiliation with cannabis-using peers and negative interactions with their parents. Therefore, we suggest that prevention programs aimed at delaying the onset of cannabis use, or preventing the progression towards malignant patterns of cannabis use, should target not only cannabis use but also these concomitant concerns. Second, individuals who begin substance use early appear to be more resistant to preventive interventions [184, 185]. For this reason, prevention programs should consider beginning such interventions at an early age, before the onset of cannabis use has taken place. Prior research has suggested that selective prevention, targeting high-risk youths, generally produces superior results than universal prevention, targeting the general population [141]. Since the findings of the present research indicate that temperament is linked to cannabis use at relatively early ages, they suggest that particularly adolescents with high levels of high-intensity pleasure and low levels of effortful control and shyness should be targeted by such programs. Because most prevention programs are school-based, information about the risk-status of young adolescents might be best obtained from their teachers and/or from self-reports. Ideally, risk-status

information would be based on a valid assessment of several risk and protective factors of substance use, including temperamental traits. Third, as temperament or personality factors are expected to predict substance use by influencing specific motivational processes underlying substance use, including the reduction of negative affect, the avoidance of problems, or the seeking of stimulation [142], we suggest that prevention programs should include cognitive behavioral components aimed at enhancing the development of healthy coping strategies. In addition, since our findings emphasize the importance of peer substance use as a proximal factor for adolescent cannabis use, they indicate that prevention programs should also include modules designed to teach adolescents how to deal with social influences to engage in substance use. Last but not least, prevention work should focus on the influence of parents. According to the findings of this study, parents affect their offspring's substance use by their general parenting styles, as well as by their own substance use. Particularly in the light of the immature self-regulatory competence of adolescents, and their increased tendency to emotionally influenced and risk-taking behavior, adolescents need their parents to protect them against the development of hazardous patterns of cannabis use.

SUMMARY

Adolescents who start using cannabis at an early age, or use cannabis on a regular or persistent basis, are at risk of developing a cannabis use disorder [8, 9]. In addition, these youngsters are more likely to develop other problems, including illicit drug use, dropping out of school, affiliations with deviant peers, and mental health problems [14-17]. Research on the determinants of early onset and regular cannabis use can improve our understanding of predictors and mechanisms that are related to the development of potentially hazardous patterns of cannabis use. Because adolescence is the developmental period when individuals usually initiate cannabis use, and when they are most vulnerable to develop subsequent problems, a focus on this developmental period is essential. More insight in the determinants of adolescent cannabis use might contribute to the early identification of at-risk individuals and might provide entry points for health promotion interventions.

The focus of the present thesis is on the role of temperament in the onset of cannabis use and the progression towards regular use among adolescents. According to Rothbart and colleagues, temperament is defined as a constitutionally based individual difference in reactivity and self-regulation, influenced over time by heredity, maturation, and experience [25]. When temperament is studied in relation to adolescent cannabis use, specific dimensions of temperament seem relevant. First, indicators of sensation seeking or high-intensity pleasure have been positively related to substance use. Individuals with high levels on these indicators are characterized by a tendency towards frequent exploratory activity, resulting in approach-oriented behavior. Sensation seeking, as defined by Zuckerman [30], also incorporates behavioral disinhibition and low fearfulness in novel or potentially hazardous situations, resulting in behavior characterized by low avoidance. Second, indicators of negative affectivity or frustration, reflecting the tendency to become easily frustrated and irritated and to become intensely upset, have been positively related to substance use [33, 34]. Third, indicators of task orientation or effortful control, reflecting the ability to regulate attention and behavior, have been related to a lower likelihood of adolescent substance use [34].

In addition to the role of temperament independent from other risk factors, the research in this thesis addresses the interrelation between temperament and other risk factors in predicting cannabis use. More specifically, moderation and mediation pathways are tested. Moderation by temperament implies that the impact of a risk factor on cannabis use depends on the temperamental make-up of an individual. In a mediation pathway, temperament affects the risk to start or continue the use of cannabis because it predisposes an individual towards other risk factors of cannabis use.

The studies described in this thesis are designed to gain more insight in the role of the aforementioned temperament dimensions in early onset and regular cannabis use, both directly as well as in relation to other risk factors of cannabis use, e.g. disruptive behavior, cigarette smoking and affiliation with cannabis-using peers. In addition, the interplay between a genetic liability to substance use and parenting is addressed. The five main research questions of this thesis were outlined in the general introduction (***Chapter 1***):

1. Does the available literature provide evidence for a direct, prospective relationship between indicators of sensation seeking and adolescent cannabis use?
2. What is the nature of the interrelation between high-intensity pleasure, disruptive behavior and onset of cannabis use? Which subtypes of disruptive behavior interrelate with high-intensity pleasure in predicting the onset of cannabis use?
3. Is the relationship between temperament and early onset of cannabis use mediated by early onset of cigarette smoking? Do temperamental characteristics modify the risk of transition from cigarette smoking to cannabis use?
4. Is the relationship between temperament and lifetime cannabis use mediated by affiliation with cannabis-using peers? Are associations of temperament and affiliation with cannabis-using peers with lifetime cannabis use also applicable to the development of regular cannabis use?
5. Is the A1 allele of the TaqIA polymorphism (rs1800497) associated with the development of regular alcohol and cannabis use? Does general parenting behavior modify the expression of TaqIA in regular alcohol and cannabis use?

In order to answer the first research question, a literature search was completed. ***Chapter 2*** provides a review of 14 prospective, general population studies that examined the relation between indicators of sensation seeking and adolescent cannabis use. Findings of these studies were categorized according to 1) the nature of the indicator of sensation seeking, e.g. indicator of high approach, indicator of low avoidance, or indicator of combined high approach and low avoidance, and 2) the measure of cannabis use, e.g. onset, frequency, or disordered use. Weak to moderate evidence was found for associations of indicators of combined approach and avoidance with onset of and increase in cannabis use, as well as with substance use disorders. Evidence for associations between indicators of either approach or avoidance and any of the measures of

cannabis use remained inconclusive. These findings suggest that the combination of high approach and low avoidance is most important with respect to future cannabis use. The overall absence of convincing evidence might be explained by the small number of studies, by the heterogeneity and the relatively low quality of most included studies, and by the fact that some studies simultaneously assessed the influence of other risk factors. In these studies, different constructs seemed to explain an overlapping part in the prediction of cannabis use, which points in the direction of an interrelation between indicators of sensation seeking and other risk factors of adolescent cannabis use.

Research questions 2-5 were addressed using data from the first three assessment waves of the TRacking Adolescents' Individual Lives Survey (TRAILS), a large, prospective cohort study of Dutch young adolescents initially aged 10-12 years, who are followed biennially. In ***chapter 3*** the second research question is elaborated on. To this end, we tested an additive model, a moderation model, and a mediation model. The mediation model, including direct paths from high-intensity pleasure and disruptive behavior to onset of cannabis use, and an indirect path from high-intensity pleasure via disruptive behavior, represented the interrelation best. Although a small indirect path was demonstrated, the role of high-intensity pleasure in the onset of cannabis use was mainly independent from the role of disruptive behavior. When subtypes of disruptive behavior were considered, e.g. attention-deficit hyperactivity (ADH), oppositional problems (OPs), and conduct problems (CPs), particularly CPs and ADH appeared to mediate a small part of the relationship between high-intensity pleasure and onset of cannabis use. The interrelation between high-intensity pleasure and CPs was in agreement with our expectations, which were based on mutual associations with the functioning of the behavioral activation system (BAS) [43, 86]. The interrelation between high-intensity pleasure and ADH was against our expectations, as particularly the functioning of the behavioral inhibition system (BIS), rather than the BAS, has been associated with ADH characteristics [45].

The aim of ***chapter 4*** was to determine the roles of various temperamental traits on different points along the trajectory from early onset of cigarette smoking (before the age of 12) to early onset of cannabis use (before the age of 13). According to the findings of this study, high levels of high-intensity pleasure were related to early onset of cannabis use by predisposing young adolescents to cigarette smoking, and additionally increased the subsequent risk of making the transition from early cigarette smoking to cannabis use. Low shyness, defined as behavioral inhibition to novelty and challenge (mainly social), was also associated with a higher risk of transition from early tobacco to cannabis use. Fearfulness, frustration, and effortful control were not related to early onset

cannabis use. It is suggested that the influence of other risk or protective factors of substance use, as well as the interplay between such factors and temperamental traits might differentially affect the associations between temperamental traits and cannabis use on distinct points along the trajectory.

The study presented in ***chapter 5***, addressing research question 4, demonstrates that the risk of lifetime cannabis use was enhanced in adolescents with high levels of high-intensity pleasure, and buffered in adolescents with high levels of shyness and effortful control. Whereas shyness seemed to affect this risk independent from peer cannabis use, high-intensity pleasure and effortful control affected the risk for lifetime cannabis use through their, respectively, positive and negative association with the proportion of cannabis-using peers. Effortful control was the only temperament dimension that was also associated with the development of regular cannabis use, again through its influence on affiliation with cannabis-using peers. Our findings suggest that characteristics related to sensation seeking and behavioral inhibition contribute to one's risk to experiment with the use of cannabis, but that regular users constitute a specific subgroup that is less influenced by these temperamental traits. Frustration and fearfulness were not prospectively related to lifetime or regular cannabis use.

In ***chapter 6*** we determined the influence of the A1 allele of the TaqIA polymorphism, which has been associated with a reduced number of D2 dopamine receptors in brain structures linked to reinforcement [151-153], on the development of regular alcohol or cannabis use. Carrying the A1 allele was not related to regular alcohol or cannabis use, neither directly nor in interaction with perceived parenting. Overall, substance-specific associations between parenting and substance use were demonstrated; while overprotection was associated with an increased risk of regular alcohol use, the risk of cannabis use was enhanced in adolescents that perceived parental rejection and buffered in adolescents that experienced emotional warmth. These latter parenting behaviors affected the risk of general cannabis use but did not predict the progression into a regular pattern of use. Apparently, once cannabis use has been initiated, other risk factors have more impact on the progression to regular cannabis use.

In the last chapter of this thesis (***Chapter 7***) the main results of all studies are briefly outlined and implications, shortcomings and strengths of this research are addressed. Furthermore, several recommendations for future research on the role of temperament and other risk factors in the onset and continuation of cannabis use are elaborated on. It is concluded that temperament contributes at least to some extent to an adolescent's vulnerability to cannabis use, and that disruptive behavior, cigarette smoking, and affiliation with cannabis-using peers mediate (part of) the link between temperamental

traits and cannabis use. Whereas high-intensity pleasure seems particularly involved in the very early initiation of tobacco and cannabis use, the ability to voluntarily (effortful control) and involuntarily (shyness or behavioral inhibition) control one's behavior seems to become of additional importance in determining the risk of cannabis use with increasing age or experience with cigarette smoking. Particularly effortful control seems involved in the development of regular cannabis use.

SAMENVATTING

Adolescenten die op jonge leeftijd beginnen met het gebruik van cannabis (*early onset*), of die regelmatig cannabis gebruiken, lopen het risico cannabismisbruik of -afhankelijkheid te ontwikkelen [8, 9]. Deze adolescenten zijn bovendien kwetsbaarder voor het ontwikkelen van andere problemen, zoals het gebruik van illegale genotsmiddelen, vroegtijdig stoppen met school, omgaan met deviante leeftijdsgenoten en geestelijke gezondheidsproblemen [14-17]. Onderzoek naar de determinanten van early onset en regelmatig cannabisgebruik kan ons inzicht in voorspellers van deze risicovolle vormen van cannabisgebruik, en in mechanismen die ten grondslag liggen aan de ontwikkeling hiervan, vergroten. Een focus op de adolescentie is hierbij essentieel, omdat veel cannabisgebruikers tijdens deze ontwikkelingsfase beginnen, en omdat adolescenten kwetsbaarder zijn voor het ontwikkelen van problemen ten gevolge van cannabisgebruik. Meer inzicht in de determinanten van cannabisgebruik in de adolescentie kan bijdragen aan de vroegtijdige herkenning van kwetsbare jongeren en biedt mogelijk aangrijpingspunten voor preventieprogramma's.

Huidig onderzoek legt zich toe op de rol van temperament in cannabisgebruik onder adolescenten. Rothbart en collega's definieerden temperament als constitutioneel bepaald individueel verschil in reactiviteit en zelfregulatie, dat wordt beïnvloed door erfelijkheid, rijping en ervaring [25]. In relatie tot middelengebruik lijken voornamelijk specifieke temperamentkenmerken van belang. Allereerst wordt sensatiezucht of *high-intensity pleasure* in verband gebracht met een hoger risico op middelengebruik en misbruik. Individuen met deze kenmerken neigen naar het actief opzoeken van nieuwe ervaringen, uitdagingen en kicks. Sensatiezucht, zoals bepaald door Zuckerman [30], wordt tevens gekenmerkt door gedragsdisinhibitie en het ervaren van weinig angst in onbekende of mogelijk gevaarlijke situaties. Dergelijke individuen vertonen als gevolg daarvan relatief weinig vermijdingsgedrag. Ten tweede wordt negatieve affectiviteit of frustratie verbonden aan een hoger risico op middelengebruik en misbruik. Personen met een hoge mate van negatieve affectiviteit worden gekenmerkt door emotionele instabiliteit en door de neiging om snel geïrriteerd te raken en/of negatieve emoties te ervaren [33, 34]. Ten slotte worden kenmerken van *effortful control* of aandachtscontrole, die betrekking hebben op de vaardigheid om vrijwillig het eigen gedrag en de eigen aandacht te reguleren, in verband gebracht met een lager risico op middelengebruik in de adolescentie [34].

Naast de onafhankelijke rol van temperament in cannabisgebruik richt huidig onderzoek zich ook op het samenspel van temperament en andere risicofactoren van cannabisgebruik. In het bijzonder wordt hierbij gekeken naar moderatie en mediatie. Wanneer een verband tussen een risicofactor en cannabisgebruik

gemodereerd wordt door temperament, betekent dit dat de invloed van deze risicofactor op cannabisgebruik afhankelijk is van iemands temperament. Met mediatie wordt gekeken of het verband tussen temperament en cannabisgebruik verloopt via een andere risicofactor. In dit geval hangt temperament samen met cannabisgebruik omdat het de kans op een andere risicofactor vergroot of verkleint.

De studies die beschreven worden in dit proefschrift zijn uitgevoerd om het inzicht in de rol van temperament in early onset en regelmatig cannabisgebruik te vergroten. Hierbij wordt zowel gekeken naar de directe, onafhankelijke rol van temperament, als naar de rol van temperament in relatie tot andere risicofactoren, namelijk disruptief gedrag, het roken van sigaretten en het selecteren van deviante vrienden. Tevens wordt het samenspel tussen genetische kwetsbaarheid voor middelenmisbruik en opvoeding onderzocht. De vijf belangrijkste onderzoeksvragen werden beschreven in de algemene introductie (***Hoofdstuk 1***):

1. Biedt de bestaande literatuur bewijs voor een direct, prospectief verband tussen kenmerken van *sensation seeking* en cannabisgebruik door adolescenten?
2. Wat is de aard van het verband tussen *high-intensity pleasure*, disruptief gedrag en cannabisgebruik? Welke subtypes van disruptief gedrag hangen samen met *high-intensity pleasure* in het voorspellen van cannabisgebruik?
3. Wordt het verband tussen temperament en *early onset* cannabisgebruik gemedieerd door *early onset* roken? Modereren temperamentkenmerken het risico op de transitie van roken naar cannabisgebruik?
4. Wordt het verband tussen temperament en cannabisgebruik gemedieerd door het selecteren van cannabisgebruikende vrienden? Zijn de verbanden tussen temperament, het selecteren van cannabisgebruikende vrienden en cannabisgebruik ook van toepassing op regelmatig cannabisgebruik?
5. Is er een verband tussen het A1 allel van het TaqIA polymorfisme (rs1800497) en regelmatig alcohol- en cannabisgebruik? Modereert opvoeding de expressie van genetische kwetsbaarheid voor regelmatig alcohol- en cannabisgebruik?

Teneinde de eerste onderzoeksvraag te beantwoorden werd een literatuuronderzoek uitgevoerd. ***Hoofdstuk 2*** biedt een overzicht van 14 prospectieve, algemene bevolkingsstudies naar de relatie tussen kenmerken van *sensation seeking* en cannabisgebruik door adolescenten. De bevindingen van

deze studies werden gecategoriseerd op 1) de aard van het kenmerk (toenadering, weinig vermijding, of de combinatie hiervan) en 2) de maat van cannabisgebruik (*onset*, frequentie, of verstoord gebruik). Zwak tot bescheiden bewijs werd gevonden voor verbanden tussen de combinatie van toenadering en weinig vermijding en *onset* van cannabisgebruik, groei in frequentie van cannabisgebruik, en verstoord middelengebruik. Er werd geen sluitend bewijs gevonden voor verbanden tussen de individuele maten van toenadering en weinig vermijding en cannabisgebruik. Op basis van deze bevindingen kan gesuggereerd worden dat de combinatie van toenadering en weinig vermijding voornamelijk samenhangt met toekomstig cannabisgebruik. Het algemene gebrek aan overtuigend bewijs zou verklaard kunnen worden door het kleine aantal studies, door de heterogeniteit en de relatief lage kwaliteit van de studies, en door het feit dat sommige studies gelijktijdig keken naar de invloed van andere risicofactoren. In het laatste geval leken verschillende risicofactoren een overlappend deel van de diversiteit in cannabisgebruik te verklaren, hetgeen wijst op verbanden tussen temperament en andere risicofactoren van cannabisgebruik.

Onderzoeksvragen 2-5 werden beantwoord met behulp van gegevens van de eerste drie 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 jaar. ***Hoofdstuk 3*** gaat in op de tweede onderzoeksvraag. Om deze vraag te beantwoorden werd een additief, moderatie-, en mediatiemodel getoetst. Het mediatiemodel, met directe paden van *high-intensity pleasure* en disruptief gedrag naar cannabisgebruik, en met een indirect pad van *high-intensity pleasure* via disruptief gedrag, vormde het beste model. Hoewel er sprake was van een klein indirect pad, bleek de rol van *high-intensity pleasure* voornamelijk onafhankelijk te zijn van de rol van disruptief gedrag. Analyses naar de samenhang tussen *high-intensity pleasure* en subtypes van disruptief gedrag, aandachtstekort met hyperactiviteit (ADH), oppositionele problemen (OPs), en/of antisociale gedragsproblemen (AGPs), toonden aan dat voornamelijk CPs en ADH een klein deel van de relatie tussen *high-intensity pleasure* en cannabisgebruik mediëren. Wat betreft AGPs kwam dit overeen met de verwachtingen gebaseerd op de gemeenschappelijke associaties van *high-intensity pleasure* en AGPs met het functioneren van het activatie-systeem in ons brein [43, 86]. Omdat kenmerken van ADH geassocieerd worden met het functioneren van het inhibitiesysteem, was dit deel van de bevindingen tegengesteld aan de verwachtingen [45].

Hoofdstuk 4 had als doel te bepalen welke temperamentkenmerken invloed uitoefenen op verschillende punten in het traject van *early onset* roken (voor de leeftijd van 12 jaar) naar *early onset* cannabisgebruik (voor de leeftijd van 13 jaar). Volgens de bevindingen van deze studie hangt *high-intensity pleasure* samen met *early onset* cannabis gebruik door enerzijds de kans op *early onset* roken te verhogen, en anderzijds het risico op de transitie van roken naar cannabisgebruik te vergroten. Ook een lage mate van verlegenheid, gedefinieerd als gedragsinhibitie in onbekende of uitdagende (sociale) situaties, was geassocieerd met een groter risico op de transitie van roken naar cannabisgebruik. Kenmerken van angst, frustratie en effortful control bleken niet samen te hangen met *early onset* cannabisgebruik. Mogelijk varieert het belang van andere risico- of beschermende factoren, en van het samenspel tussen dergelijke factoren en temperamentkenmerken, op verschillende punten in het traject van roken naar cannabisgebruik.

In ***hoofdstuk 5*** wordt, als antwoord op onderzoeksvraag 4, aangetoond dat het risico op cannabisgebruik groter is onder adolescenten met een hoge mate van *high-intensity pleasure*, en kleiner is onder adolescenten die in sterkere mate verlegen zijn of over een goede aandachtscontrole beschikken. Hoewel de invloed van verlegenheid of gedragsinhibitie niet samenhing met de proportie cannabisgebruikende vrienden, bleken de verbanden van *high-intensity pleasure* en *effortful control* naar cannabisgebruik gemedieerd te worden door, respectievelijk, een hogere en lagere proportie cannabisgebruikende vrienden. *Effortful control* was het enige temperamentkenmerk dat samenhing met regelmatig cannabisgebruik, wederom via het negatieve verband met de proportie cannabisgebruikende vrienden. Op basis van deze bevindingen kan gesuggereerd worden dat kenmerken van *sensation seeking* en gedragsinhibitie bijdragen aan het risico op experimenteel cannabisgebruik, maar dat regelmatige gebruikers een specifieke subgroep vormen die niet te onderscheiden is op basis van deze temperamentkenmerken. Er werd geen prospectief verband gevonden tussen kenmerken van frustratie en angst en cannabisgebruik.

In de studie beschreven in ***hoofdstuk 6*** werd bepaald of het A1 allel van het TaqIA polymorfisme, dat leidt tot een gereduceerd aantal D2 dopamine receptoren in hersenstructuren voor positieve bekrachtiging [151-153], samenhangt met regelmatig alcohol- of cannabisgebruik. Uit deze studie komt naar voren dat het hebben van dit allel niet samenhangt met het risico op regelmatig alcohol- of cannabisgebruik, en dat er ook geen sprake is van moderatie door opvoeding. In het algemeen wordt aangetoond dat er middelspecifieke verbanden lijken te bestaan tussen opvoeding en alcohol- en cannabisgebruik. Terwijl overbescherming samenhing met een hoger risico op

regelmatig alcoholgebruik, bleek het risico op cannabisgebruik hoger onder adolescenten die zich afgewezen voelden door hun ouders, en lager onder adolescenten die aangaven emotionele warmte van hun ouders te krijgen. Deze laatste opvoedingsgedragingen bepaalden het risico op algemeen cannabisgebruik, maar waren niet gerelateerd aan progressie naar regelmatig gebruik. Wanneer het gebruik van cannabis eenmaal geïnitieerd is, hebben andere risicofactoren mogelijk een sterkere invloed op de overgang naar regelmatig gebruik.

In het laatste hoofdstuk van dit proefschrift (***Hoofdstuk 7***) worden de belangrijkste resultaten kort beschreven en worden implicaties, tekortkomingen, en sterke punten van huidig onderzoek belicht. Tevens komen verschillende aanbevelingen voor toekomstig onderzoek naar de rol van temperament en andere risicofactoren in het beginnen met en continueren van cannabisgebruik in de adolescentie aan bod. Concluderend wordt er gesteld dat temperament in zekere mate bijdraagt aan de kwetsbaarheid voor cannabisgebruik in de adolescentie, en dat disruptief gedrag, roken, en de omgang met cannabisgebruikende vrienden (deel van) het verband tussen temperamentkenmerken en cannabisgebruik mediëren. Terwijl voornamelijk *high-intensity pleasure* lijkt samen te hangen met de zeer *early onset* van cannabisgebruik, lijken de vrijwillige (*effortful control*) en onvrijwillige (verlegenheid of gedragsinhibitie) controle van gedrag een grotere bijdrage te leveren aan het risico op cannabisgebruik in de mid-adolescentie, of na ervaring met roken. Voornamelijk *effortful control* draagt bij aan het risico op regelmatig cannabisgebruik.

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CURRICULUM VITAE

Hanneke Creemers werd op 5 oktober 1979 geboren te Roermond. In 1998 behaalde zij haar VWO-diploma aan Scholengemeenschap Sint Ursula te Horn. In datzelfde jaar startte zij aan de opleiding Psychologie aan de Universiteit van Maastricht. Na het behalen van haar propedeuse in 1999 koos zij voor de afstudeerrichting Biologische Psychologie, en vervolgens voor de afsplitsing Neuropsychologie. In 2002 verrichte zij haar onderzoeksstage naar verstoorde impulscontrole bij alcoholverslaafden en pathologisch gokkers aan de Vrije Universiteit van Amsterdam (VU), afdeling klinische neuropsychologie (gesuperviseerd door Dr. A.E. Goudriaan en Prof. dr. R.W.H.J. Wiers). In 2003 deed zij een facultatieve praktijkstage bij het Centro Italiano di Solidarièta di Roma (CeIs Roma), Italië, waar zij werkzaam was binnen een therapeutische gemeenschap voor drugsverslaafden. In het najaar van 2003 studeerde zij af. Van september 2004 tot en met november 2009 was zij als junior onderzoeker verbonden aan het Erasmus MC – Sophia Kinderziekenhuis te Rotterdam, waar zij een promotieonderzoek uitvoerde binnen de afdeling Kinder- en Jeugdpsychiatrie (Hoofd: Prof. dr. F.C. Verhulst). De eerste twee jaar van dit traject was haar standplaats Groningen, waar zij data verzamelde binnen het TRAILS onderzoek (TRacking Adolescents' Individual Lives Survey, hoofdonderzoekers: Prof. dr. F.C. Verhulst en Prof. dr. J. Ormel). Vanaf september 2006 werkte zij vanuit het ErasmusMC aan het beschrijven van de onderzoeksresultaten van haar studie naar temperament en andere risicofactoren in relatie tot het gebruik van cannabis in de adolescentie (gesuperviseerd door Prof. dr. A.C. Huizink). Tot september 2008 combineerde zij dit met een klinische functie op de polikliniek Kinder- en Jeugdpsychiatrie, daarna was zij fulltime verbonden als onderzoeker. De resultaten van haar promotieonderzoek staan beschreven in dit proefschrift. Vanaf januari 2010 is Hanneke werkzaam als post-doc onderzoeker binnen de afdeling Pedagogiek en Onderwijskunde van de Universiteit van Amsterdam (UvA, leerstoelgroep ontwikkelings- en opvoedingsproblemen, leerstoelhouder: Prof. dr. S.M. Bögels), waar zij onderzoek doet naar de diagnostiek van cannabismisbruik en naar de relatie tussen genetische kwetsbaarheid voor middelenmisbruik en omgevingsfactoren.

PUBLICATION LIST

Publications from this thesis

Creemers, H.E., Verhulst, F.C., & Huizink, A.C. (2009). Temperamental risk factors for adolescent cannabis use: a systematic review of prospective general population studies. *Substance Use & Misuse*, 44, 1833-1854.

Creemers, H.E., van Lier, P.A.C., Vollebergh, W.A.M., Ormel, J., Verhulst, F.C., & Huizink, A.C. (2009). Predicting onset of cannabis use in early adolescence: The interrelation between high-intensity pleasure and disruptive behavior. The TRAILS Study. *Journal of Studies on Alcohol and Drugs*, 70, 850-858..

Creemers, H.E., Korhonen, T., Kaprio, J., Vollebergh, W.A.M., Ormel, J., Verhulst, F.C., & Huizink, A.C. (2009). The role of temperament in the relationship between early onset of tobacco and cannabis use. The TRAILS study. *Drug and Alcohol Dependence*, 104, 113-118.

Creemers, H.E., Dijkstra, J.K., Vollebergh, W.A.M., Ormel, J., Verhulst, F.C., & Huizink, A.C. *(in press).* Predicting lifetime and regular cannabis use during adolescence; the roles of temperament and peer substance use - The TRAILS study. *Addiction.*

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Additional publications

Van der Vlugt, J.J.B., van der Meulen, J.J.N.M., Creemers, H.E., Willemse, S.P., Lequin, L.M., & Okkerse, J.M.E. (2009). The risk of psychopathology in children with craniosynostosis, *Plastic and Reconstructive Surgery*, 124, 2054-2060.

Dick, D.M., Meyers, J., Latendresse, S.J., Creemers, H.E., Lansford, J.E., Pettit, G.S., Bates, J.E., Dodge, K.A., Budde, J., Goate, A., Buitelaar, J.K., Ormel, J., Verhulst, F.C., & Huizink, A.C. *(under revision). CHRM2*, Parental Monitoring, and Externalizing Behavior: A Gene Involved in Biological Sensitivity to Context?.

El Marroun, H., Creemers, H.E., Tiemeier, H., Steegers, E.A., Jaddoe, V.W., Hofman, A., Verhulst, F.C., van den Brink, W., & Huizink, A.C. *(submitted)*. Parental cannabis use during pregnancy and child behaviour problems at 18 months.

Van der Vlugt, J.J.B., van der Meulen, J.J.N.M., Creemers, H.E., Hovius, S.E.R., Verhulst, F.C., & Okkerse, J.M.E. *(submitted)*. Psychopathology in 86 patients with trigonocephaly.

Prince van Leeuwen, A., Creemers, H.E., Verhulst, F.C., Ormel, J., & & Huizink, A.C. *(submitted)*. Are Adolescents Gambling With Cannabis Use? A Longitudinal Study of Observed and Reported Impulsivity Measures in Relation to Adolescent Substance Use. The TRAILS Study.

PORTFOLIO

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio Summary
Summary of all PhD training and teaching activities

Name PhD student: H.E. Creemers Erasmus MC Department: Child- & Adolescent Psychiatry	PhD period: September 2004 – March 2010 Promotor(s): Prof. dr. F.C. Verhulst and Prof. dr. A.C. Huizink Supervisor: Prof. dr. A.C. Huizink

1. PhD training

	Year	Work-load (ECTS)
General courses		
• Biomedical English Writing and Communication, Rotterdam	2007	*1.4*
Specific courses		
• Methodological and Statistical Aspects of Longitudinal Research, Nijmegen	2006	*1.4*
• Latent Variable Modeling with Mplus, Florence, Italy	2007	*1.4*
National and International conferences – participation and presentations		
• TRAILS symposium for parents and teachers, Groningen – Oral presentation	2005	*0.6*
• Forum Alcohol en Drugs Onderzoek (FADO), Utrecht – Oral presentation	2007	*0.6*
• Programmadag ZonMW Verslaving, Amsterdam – Poster presentation	2007	*0.3*
• Congress of the Dutch Association of Psychiatry (NVvP), Amsterdam – Oral presentation	2008	*0.9*
• Forum Alcohol en Drugs Onderzoek (FADO), Utrecht – Oral presentation	2008	*0.6*
• 71st Annual Meeting of the College of Problems on Drug Dependence (CPDD), Reno (NV), United States – Oral presentation	2009	*2*
• International Forum of the National Institute on Drug Abuse (NIDA), Reno (NV), United States – Poster presentation	2009	*2*
• Geestkracht ZonMW, Utrecht – Poster/Oral presentation	2009	*0.6*
• Forum Alcohol en Drugs Onderzoek (FADO), Utrecht – Oral presentation	2009	*0.6*
Other		
• Research visit to the University of Helsinki, Department of Public Health, Helsinki, Finland	2008	*4*
• NIDA Grant Writing Workshop, Reno (NV), United States	2009	

2. Teaching activities		
	Year	**Work-load (ECTS)**
Supervising practicals/tutoring		
• Supervising practicals Child- and Adolescent Psychiatry, ErasmusMC, Rotterdam	2007/ 2008	*1.2*
• Lecturing students, Erasmus University Rotterdam, Department of Psychology	2009	*0.6*
• Lecturing students, University of Amsterdam, Faculty of Behavioral and Social Sciences	2009	*0.6*
• Supervising a research course for 3rd year medical students, ErasmusMC, Rotterdam	2008	*2*
Supervising Master's theses		
• Supervised Didi Kleef, medical student at Erasmus University, Rotterdam. Thesis topic: The association between autonomic stress-reactivity and alcohol consumption among adolescents.	2007	*2.6*
1 ECTS (European Credit Transfer System) is equal to a workload of 28 hrs		