Alcohol use in adolescence

A longitudinal study
of its effect on cognitive functioning

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A longitudinal study of its effect on cognitive functioning

Alcoholgebruik in de adolescentie

Een longitudinale studie naar het effect op het cognitief functioneren

(met een samenvatting in het Nederlands)

Proefschrift

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Contents

1
Introduction

1.1 ADOLESCENT NEUROCOGNITIVE FUNCTIONING AND ALCOHOL USE

During adolescence, alcohol consumption is found to increase significantly, with the prevalence rates of last month alcohol use rising from 16% at age 12 to 85% at age 16 in Dutch adolescents (Verdurmen et al., 2012). Adolescent alcohol use has raised concerns within the society since it has been associated with several negative outcomes regarding serious injuries, impaired judgement, and brain development problems (NIAAA, "Special populations", 2013). The latter concern regarding the neurotoxic effects of alcohol has become more pronounced, since it has been suggested that the developing adolescent brain might be particularly vulnerable to the adverse effects of alcohol (Clark, Thatcher, & Tapert, 2008). However, research on this subject has remained inconclusive thus far.

The first suggestion that the maturation of the human brain, particularly of the prefrontal cortex and cognitive control functions, continues well into the mid-twenties, is relatively recent (Giedd et al., 1999; Gulley & Juraska, 2013). It has triggered societal and scientific interest in the developing adolescent brain and corresponding neurocognitive functions. Intact cognitive and behavioural control facilitates the ability to organise thoughts and behaviour in a goal-directed manner, and it is essential for success in everyday living (Jurado & Rosselli, 2007). This becomes progressively more important during adolescence, since societal demands related to the transition to young adulthood, such as going to college, leaving the parental home, and being financially independent, increase during this stage of life. On the other hand, it has been suggested that an extended developmental trajectory renders brain regions and skills more vulnerable to external disturbances and lesions (Spencer-Smith & Anderson, 2009). From this viewpoint, it is unfortunate that adolescence is also a phase in which risk-taking behaviour such as substance use increases remarkably (Dahl, 2004; Steinberg, 2007). It is hypothesised that during adolescence, brain networks that are sensitive for social and emotional stimuli and reward-processing mature quickly, while the cognitive control functions lag behind. This renders adolescents vulnerable for engaging in risk-taking behaviour and creates a tension field between the drive to engage in sensation-seeking behaviour and the possible harmful consequences of this behaviour.

Societal and scientific concerns about adolescent substance use appear to focus particularly on alcohol use, probably because it is widely available and consumed by adolescents. Moreover, synchronously with increased attention for adolescent neurocognitive development, adolescent alcohol use rates have risen significantly over the last decade. Reports from the European School Survey Project on Alcohol and Other Drugs (ESPAD) in

35 European countries indicate that over the last ten years, lifetime use of alcohol remained roughly the same, but the prevalence of heavy episodic drinking has increased significantly, particularly in females (Hibell et al., 2009). Heavy episodic or binge drinking is a pattern in which larger amounts of alcohol (generally five or more glasses) are consumed on a single occasion (Wechsler & Austin, 1998).

The psychoactive mechanism of alcohol is still not completely understood. Presumably, alcohol acts upon the brain in widespread fashion, thereby disturbing the synaptic activity of both excitatory and inhibitory neurotransmitters and affecting various intracellular processes, such as the influx of calcium ions (Julien, 2001). Since the brain compensates for the suppressive effect of alcohol by compensatory up-regulation of excitatory receptors, sudden alcohol withdrawal leads to excessive excitatory activation in the brain (Julien, 2001), which can lead to increased cell death. Therefore, repeated exposure to and withdrawal from alcohol is hypothesised to be particularly harmful (Ehlers & Criado, 2010). Precisely this binge drinking pattern has increased remarkably in adolescence over the last years. The effects of alcohol on the developing brain are clear when looking at Foetal Alcohol Spectrum Disorders (FASD), where maternal alcohol use during pregnancy has found to have a pronounced influence on general intelligence, memory, visuospatial functioning, attention, and executive functioning (Mattson & Riley, 1998). Furthermore, the consequences of a lifestyle with chronic alcohol use are evident in Wernicke's Korsakoff Syndrome, where vitamin B_1 deficiencies in combination with alcohol use induce severe anterograde amnesia (Koob & Le Moal, 2006).

Given the relevance of the possible effects of alcohol on adolescent neurocognitive functioning, a greater number of studies have investigated this relation in the last decade. Many studies focused on adolescents with alcohol use disorder (AUD), i.e., individuals diagnosed with either alcohol abuse (the recurring use of alcohol despite its negative consequences) or alcohol dependence (the recurring use of alcohol despite its negative consequences and evidence of physical dependence). They found impairments among adolescents with AUD in various neurocognitive domains such as language and general intelligence (Moss, Kirisci, Gordon, & Tarter, 1994), attention and intelligence (Tarter, Mezzich, Hsieh, & Parks, 1995), learning, memory, and visuospatial functioning (Brown, Tapert, Granholm, & Delis, 2000). More recently, heavy drinkers without a diagnosis of AUD have become subjects of studies. However, these population studies have shown only small differences between excessive drinkers and controls in neurocognitive functioning (Schweinsburg, McQueeny, Nagel, Eyler, & Tapert, 2010; Squeglia, Schweinsburg, Pulido,

& Tapert, 2011). It is important to note that all of the abovementioned studies utilised a cross-sectional design. To the best of our knowledge, only three studies have investigated the effects of alcohol use on maturation of neurocognitive functioning using a longitudinal design (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009). One study found differences between heavy drinkers and controls in one out of four neurocognitive domains, and this difference was found for girls only (Squeglia et al., 2009). In the other two studies, fMRI measurements showed differences in brain activation among adolescents who made the transition to heavy drinking while task performance was the same for drinkers and non-drinking controls (Squeglia et al., 2012; Wetherill, Squeglia, Yang, & Tapert, 2013), which has been interpreted as less efficient processing of stimuli in heavy drinkers.

Overseeing the field of research, the findings are inconsistent, and three major gaps in the knowledge on neurocognitive functioning and adolescent alcohol use concern the interpretation of causality, generalizability of findings from adolescents with AUD to the general population, and assessment of covariates and moderators.

1.2 KNOWLEDGE GAPS REGARDING NEUROCOGNITIVE FUNCTIONING AND ALCOHOL USE

The first knowledge gap concerns the causality. Not only is alcohol presumed to have an effect on cognitive and behavioural control functions, but also weaknesses in cognitive and behavioural control could be a risk factor for engaging in heavy drinking. Evidence suggests that cognitive control functions, such as inhibition, attention, and working memory (Grenard et al., 2008; Tapert, Baratta, Abrantes, & Brown, 2002; Tarter et al., 2003) and indices of behavioural control, such as high-intensity pleasure and effortful control, are prospectively related to substance use (Creemers et al., 2009; Willem, Bijttebier, & Claes, 2010; Wong et al., 2006). Therefore, the extent to which differences between alcohol users and controls found in cross-sectional studies preceded alcohol use is unclear, and the results should therefore be interpreted with caution. This calls for longitudinal studies with measures of cognitive and behavioural control before and after the onset of drinking. Such a design facilitates disentangling the reciprocal relation of cognitive and behavioural control with alcohol use.

Second, the results from research conducted among adolescents with AUD are often generalised to the general population, assuming that findings in this at-risk group apply to heavy drinkers in general. It is understandable that studies have focused on subjects with AUD, since they represent not only a group that is clearly at high risk for aversive outcomes,

but are also a group that is easily und unequivocally identified using clinical diagnostic criteria. However, equalizing adolescents with AUD and heavy drinkers can be problematic. First, although adolescents with AUD form a considerable group (i.e., approximately 12% of 17-18 year-olds abuse alcohol and 3% exhibit dependence (Swendsen et al., 2012), this group certainly does not encompass all drinking adolescents. Furthermore, besides engaging in alcohol use, behavioural problems are at the core of the disorder and are strongly associated with behavioural control (according to DSM-IV-criteria (American Psychiatric Association, 2000)). It is therefore not clear whether differences between adolescents with AUD and controls are the result of the alcohol intake or of the psychiatric disorder. Likewise, it furthermore obscures the reciprocal relationship between cognitive and behavioural control and alcohol use. Therefore, heavy drinkers and adolescents with AUD could be studied separately in order to understand whether precursors and aversive outcomes differ across these groups and what the role of quantity of alcohol intake is.

Third, there is insufficient knowledge on relevant covariates and moderators that play a role in the relationship between cognitive and behavioural control and alcohol use. This is related to the fact that, for understandable reasons, sample sizes of the available longitudinal research are relatively small. A relevant covariate is psychiatric comorbidity, which is highly prevalent in AUD (Roberts, Roberts, & Xing, 2007; Rohde, Lewinsohn, & Seeley, 1996). Adolescents with AUD and a comorbid disorder might form a specific risk group since these comorbid disorders are associated with deficits in neurocognitive functioning (Airaksinen, Larsson, & Forsell, 2005; Hammar & Ardal, 2009; Marchetta, Hurks, De Sonneville, Krabbendam, & Jolles, 2008; Pajer et al., 2008). Therefore, comorbid disorders could obscure or explain the effect of AUD on cognitive and behavioural control. Furthermore, gender differences could moderate the relationship of alcohol use with cognitive and behavioural control, since alcohol affects males and females differently. In some studies girls are found to be more vulnerable to the aversive effects of alcohol (Caldwell et al., 2005; National Institutes of Health, 2000; Squeglia et al., 2011), supposedly due to differences in neuromaturation, hormonal fluctuations, and alcohol metabolism (Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007). On the other hand, boys generally experience later onset of puberty (Spear, 2009), opting for a prolonged maturational trajectory of neurocognitive functions and possibly making the development of self-regulation abilities more vulnerable to external influences. Studying these relevant covariates and moderators can provide us with more insights into which alcohol using adolescents are most at risk for negative outcomes. This is facilitated by studies with larger samples sizes.

1.3 THE CURRENT THESIS

Taken together, there is a need for a longitudinal study in population-based cohort with a large sample size in order to assess precursors and outcomes related to cognitive and behavioural control, differentiating between heavy drinking and AUD, taking relevant covariates and moderators into account. The TRacking Adolescents' Individual Lives Survey (TRAILS) meets all these requirements. The main aim of the present thesis was to longitudinally investigate the effect of alcohol use in adolescence on neurocognitive functioning, making use of TRAILS-data. To adequately address this research question, we first studied normal maturation of cognitive control. Subsequently, we addressed the central research question, that is, we investigated whether deviances from this normal maturation where found for heavy drinkers and adolescents with alcohol abuse and dependence. Furthermore, we assessed cognitive and behavioural control precursors of alcohol use in order to identify adolescents at risk for transitioning to heavy drinking and AUD.

1.4 THE TRAILS STUDY

All of the studies in the current thesis used the data from the first to fourth waves of TRAILS. This is a prospective cohort study conducted among Dutch pre-adolescents at age 11. The participants were recruited from five municipalities in the North of the Netherlands, covering both urban and rural areas. The selection of the sample involved two steps. First, the municipalities were requested to provide the names and addresses of all inhabitants born between 1 October 1989 and 30 September 1990 (first two municipalities) or between 1 October 1990 and 30 September 1991 (last three municipalities), which yielded 3,483 names. Subsequently, primary schools within these municipalities were approached with a request to participate. Of the 135 eligible schools, 122 (90.4%) agreed to participate, accommodating 90.3% of the adolescents. Further details about the procedure have been published elsewhere (de Winter et al., 2005; Ormel et al., 2012). Of all the subjects approached (n=3,145), 6.7% were excluded because of severe mental or physical handicap or language problems. Of the remaining 2,935 subjects, 76.0% of the adolescents and their parents agreed to participate and enrolled in the study (T1; n=2,230, mean age 11.1 years, SD=0.56, 49.2% male). In the second assessment (T2; n=2,149, mean age 13.6 years, SD=0.53, 51.2% female), 96.3% of respondents participated. The response rate on the third assessment was 81.4% (T3; n=1,816, mean age 16.3 years, SD=0.73, 52.3% female). The response rate on the fourth assessment wave was 70% (T4; n=1,596, mean age 19.2 years, SD=0.57, 46% male).

At T1, cognitive control was examined using five computerised reaction time tasks from the Amsterdam Neuropsychological Tasks (ANT) (de Sonneville, 1999), which assessed inhibition, working memory, sustained attention, and shift attention (for an overview of the measures, see the Appendix). Furthermore, behavioural control was assessed using two self-report questionnaires, the Early Adolescent Temperament Questionnaire Revised (EATQ-R; Putnam, Ellis, & Rothbart, 2001) and Youth Self Report (YSR; Achenbach, 1991; Achenbach & Rescarola, 2001), measuring high-intensity pleasure and effortful control, and attentional and externalizing problems, respectively. At T2 to T4, adolescents completed questionnaires regarding their alcohol consumption habits, such as the average amount of glasses they consumed on a regular weekend day and the frequency with which they had consumed alcohol during the last month. At T4, the ANT tasks were re-administered together with five more complex neuropsychological tasks (Rey Auditory Verbal Learning Test-Dutch version, Rey Complex Figure Test, Wechsler Adult Intelligence Scale (WAIS) III Digit Span, Verbal Fluency, and Block Design). Furthermore, behavioural control was measured again using the Youth Self Report (attentional and externalizing problems). Finally, the World Health Organization Composite International Diagnostic Interview (CIDI) version 3.0 (Kessler & Üstün, 2004) assessed AUD, differentiating between alcohol abuse and alcohol dependence.

1.5 OUTLINE OF THE THESIS

In Chapter 2, we longitudinally assessed the normal maturation of cognitive control functions and studied the effects of gender and socioeconomic status. Understanding normal cognitive development is essential for drawing conclusions on when maturation is deviant. The next three chapters address the main research question by examining the effect of alcohol use on cognitive functioning. Chapter 3 concerns the question to what extent six patterns of (heavy) drinking influence this maturation of cognitive control. In Chapter 4, the effects of these drinking patterns on more complex neuropsychological tasks are assessed. Chapter 5 focuses on adolescents with alcohol abuse and dependence. First, they are compared to their peers without a diagnosis of AUD with regard to maturation of cognitive control. Furthermore, this chapter addresses the reverse effect, by studying whether weaknesses in cognitive control predict the development of AUD. In Chapter 6, behavioural control is studied as both a precursor and outcome of both heavy drinking and AUD. It assesses whether weaknesses in behavioural control in early adolescence predict alcohol use and whether this in turn influences behavioural control in late adolescence. Finally, Chapter 7 summarises and integrates the findings of this thesis and discusses implications.

2

Executive functioning shows differential maturation from early to late adolescence. Longitudinal findings from a TRAILS study.

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ABSTRACT

Objective: Maturation of Executive Functioning (EF) is topical, especially in relation to adolescence, yet, longitudinal research covering early and late adolescence is lacking. This however, is a prerequisite for drawing conclusions on normal cognitive development, and understanding deviant maturation. The aim of this study is to longitudinally investigate six subcomponents of EF in early (mean age 11) and late adolescence (mean age 19) and to investigate the influence of sex and socioeconomic status (SES).

Method: We used data of the TRacking Adolescents' Individual Lives Survey (TRAILS). A number of 2,217 participants carried out tasks of the Amsterdam Neuropsychological Tasks (ANT), measuring *Focused Attention*, *Inhibition*, *Sustained Attention*, *Speed of Processing*, *Working Memory*, and *Shift Attention*.

Results: Linear growth models with individual varying times of observation showed significant slopes for all six measures. Sex differences were found for the majority of the measures, where boys showed more maturation. Maturation was influenced by SES for Sustained Attention and Inhibition.

Conclusion: Results show that significant maturation takes place for all the measured subcomponents over adolescence. Overall, girls show better baseline performance and smaller maturational rates, suggesting more mature skills in early adolescence. Maturation is only influenced by SES for Sustained Attention and Inhibition. Findings underline that for making statements about EF maturation in adolescence, it is essential to look at subcomponents. Furthermore, sex differences are an important factor when investing (ab)normal maturation of EF.

2.1 INTRODUCTION

Adolescence is a phase in which the important transition from childhood to adulthood takes place. One of the most prominent changes that occurs at this stage of life is the maturation in cognitive functioning (Crone, 2009). Adolescent cognitive development is a topic that receives substantial scientific and societal interest (Steinberg, 2005), driven by the question of whether the developing brain causes adolescence to be a period of advantages or of vulnerabilities for risk-taking behaviour and external influences (Crone, 2009; Spear, 2009). To gain insight in this duality and to judge the impact of risky behaviour such as substance use, it is important to have a thorough understanding of normative cognitive maturation in adolescence.

The cognitive area that shows most prominent maturation during adolescence is that of the cognitive control functions (Crone, 2009). This parallels the maturation of parietal and prefrontal cortices, the neuroanatomical regions most associated with cognitive control (Blakemore & Choudhury, 2006). During adolescence, myelination of these regions continues, increasing speed of information transmission. Furthermore, synaptic pruning takes place, resulting in optimal connections (e.g., Blakemore & Choudhury, 2006). The control functions, also called executive functioning (EF), mediate the ability to organise thoughts and behaviour in a goal-directed manner and are therefore essential for succeeding at school and work, as well as in everyday living (Jurado & Rosselli, 2007). There are different theories and models on how EF is built up. One generally accepted view is that EF consists of dissociable yet interrelated and interdependent subcomponents (Stuss & Alexander, 2000). One adaption of adult models into a developmental model of EF proposes that it consists of four components, each composed of different subcomponents: 1) *attentional control* (Selective Attention, Response Inhibition, Self-Monitoring, and Self-Regulation), 2) *information processing* (Efficiency, Fluency, and Speed of Processing), 3) *cognitive flexibility* (Working Memory, Shift Attention, and Conceptual Transfer), and 4) *goal setting* (Initiating, Planning, Problem-Solving, and Strategic Behaviour) (Anderson, 2002). Goal setting contains complex higher order processes such as planning, while attentional control, information processing, and cognitive flexibility are more basic executive functions that are hypothesised to be prerequisite for goal setting (Miyake et al., 2000). This implicates there is a certain hierarchy in EF, where more basic functions are a condition for the more complex ones. To gain more insight in the maturation of EF as a whole, an important first step is to focus on the more basic functions.

There are several comprehensive reviews available on the development of EF in children (e.g., Best & Miller, 2010; Best, Miller, & Jones, 2009; Crone, 2009; Luna, 2009), all

highlighting that EF matures significantly throughout the course of childhood. When looking at the level of distinct components, it is hypothesized that attentional control matures first, followed by information processing, cognitive flexibility, and goal setting (Anderson, 2002). More specifically, looking at differential maturation between subcomponents, it is found that simple go-no-go inhibition is among the first aspects of EF to mature (Magar, Phillips, & Hosie, 2010), while working memory (Huizinga, Dolan, & van der Molen, 2006; Magar et al., 2010), shift attention (Huizinga et al., 2006), and focused and sustained attention (Brauch Lehman, Naglieri, & Aquilino, 2010) are the last reaching full maturity, which is partly in contrast with what is found a level higher, on the level of components (Anderson, 2002).

Important methodological limitations in available research make drawing elaborate conclusions on normal development difficult. First, aforementioned reviews emphasize that research on the development of EF has disproportionally focused on children at preschool age, that is, under the age of six years, leaving out the important developmental period of adolescence. Second, the majority of studies that investigate development of EF from age 12 on focus on preadolescence only (e.g., Cragg & Nation, 2008; Davidson, Amso, Anderson, & Diamond, 2006) despite concluding that for example for cognitive flexibility, adult levels are not reached at the onset of adolescence (Davidson et al., 2006). Studies that take the entire course of adolescence into account, are generally conducted in a cross-sectional manner making use of different age cohorts (e.g., Huizinga et al., 2006). For analyses of intraindividual change, longitudinal research is necessary (Farrington, 1991).

A further limitation of existing research is that sex and socioeconomic status (SES) are generally not taken into account. As a result, information is still lacking on possible differences in adolescent EF development between girls and boys - a conceivable gap in the literature. More attention is brought upon the role of hormones on brain development. An important question concerns how and to what extent sexual differentiation is not only influenced by exposure to sex hormones in the prenatal phase, but also during adolescence. It is now hypothesised that adolescence is a second so-called organizational period in which brain function is refined and that sex hormones play a crucial role in this process (Berenbaum & Beltz, 2011). The onset of puberty in boys is generally later than in girls (Spear, 2009), and it has accordingly been proposed that females may initially exhibit better performance on EF tasks, but that males may show greater improvement in EF following the onset of puberty (Kalkut, Han, Lansing, Holdnack, & Delis, 2009), although opposite findings exist for attentional control and processing speed, where girls show greater improvement (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). Taken together, although research is scarce and results are not

consistent, the available studies suggest that there are sex differences in EF maturation while the inconsistencies in the findings serve to underpin the need for further research on this subject.

Also, SES is hypothesised to have an influence on maturation of EF. More knowledge on this gives information on to what extent SES should be taken into account when studying adolescent EF development. SES correlates positively with cognitive maturation (for a review see: Hackman & Farah, 2009) and studies indicate that SES predicts performance on a number of EF tasks (Ardila, Rosselli, Matute, & Guajardo, 2005). It has been proposed that SES has its influence largely through environmental factors (Hackman & Farah, 2009), for which EF is a particularly vulnerable domain due to its prolonged developmental trajectory. However, again, research on this association focuses predominantly on preschool aged participants.

Taken together, existing cross-sectional research proposes a significant maturation of EF during adolescence. Differential maturation is seen for various components of EF, where simple inhibition and speed of processing generally mature first. In the present study, we will investigate this in a longitudinal design, surpassing abovementioned limitations. We measure maturation of EF between early adolescence (before making the transition to high school, mean age 11 years) to late adolescence (upon entering adulthood, mean age 19 years). In addition, we want to document the effect of sex and SES. We will study the three basic EF components (Anderson, 2002) with tasks representing six subcomponents 1) *attentional control* (subcomponents Focused Attention, Inhibition, and Sustained Attention), 2) *information processing* (subcomponent Speed of Processing) and 3) *cognitive flexibility* (subcomponents Working Memory and Shift Attention). To be able to adequately interpret improvement on theses subcomponents, it is essential to use the same measures at baseline and follow-up. We therefore use straightforward tasks. An important benefit from this is that, to understand EF and especially abnormalities in EF, further insight into its elementary components is crucial. It is our aim to assess these basics and their changes over time in developing adolescence. Components might be stable or improve over time, parallel or divergent. In addition, changes might be influenced by sex and socioeconomic status.

2.2 METHODS

2.2.1 Participants

The present study uses data from the first and fourth wave of the TRacking Adolescents' Individual Lives Survey (TRAILS). TRAILS is a prospective cohort study conducted among

Dutch preadolescents at age 11 (De Winter et al., 2005; Ormel et al., 2012). The participants were recruited from five municipalities in the North of the Netherlands, covering both urban and rural areas. Selection of the sample involved two steps. First, the municipalities were requested to provide the names and addresses of all inhabitants born between 1 October 1989 and 30 September 1990 (first two municipalities) or between 1 October 1990 and 30 September 1991 (last three municipalities), which yielded 3,483 names. Subsequently, primary education schools within these municipalities were approached with a request to participate. Of the 135 eligible schools, 122 (90.4%) agreed to participate, accommodating 90.3% of the adolescents. Further details about the procedure have been published elsewhere (de Winter et al., 2005). Of all the subjects approached (n=3,145), 6.7% were excluded because of severe mental or physical handicap or language problems. Of the remaining 2,935, 76.0% of the adolescents and their parents agreed to participate and were enrolled in the study at baseline (n=2,230, mean age 11.1 years, SD=0.56, 49.2% male). On the fourth assessment (follow-up) wave (n=1,596, mean age 19.2 years, SD=0.57, 46% male), the response rate was 70%). Exclusion criteria were being enrolled in special education at follow-up (n=2), self-reported mental disability at follow-up (n=2), and self-reported multiple neurological tumours (n=1). Regarding attrition from baseline to follow-up, respondents who dropped out were significantly more often boys (56% of dropped out sample, $\chi^2(1)=19.3$, $p<.001$), had a lower SES (44% of the lowest class dropped out, vs. 29% of the middle and 16% of highest class, $\chi^2(2)=107.8$, $p<.001$). Furthermore, dropped out respondents were significantly older at baseline (11.5 years vs. 11.3 years, $t(2212)=4.71$, $p<.001$) and also showed worse performance on baseline Sustained Attention (1.89 s versus 1.70 s, $t(1086)=4.23$, $p<.001$).

2.2.2 Procedure

On the first assessment, most adolescents were measured in a group setting at their school or in designated testing centres by trained undergraduate psychology students (for more information, also see Brunnekreef et al., 2007). Participants who were unable to attend these assessments were tested at home. On the fourth assessment, the majority of adolescents were no longer in secondary education and were therefore tested individually by trained professional interviewers at home (24%) or a nearby community centre. The confidentiality of the study was emphasised. Verbal task instructions were given before each task emphasising both speed and accuracy of performance. To ensure that the adolescents understood these instructions, a small number of practice trials were performed prior to task assessment. In a workshop, interviewers were trained by researchers from the study in how to administer

the computerized tasks. The workshop was followed by practice administrations on several test cases, which were monitored. The observations and the quality of the collected practice data were evaluated to decide whether these trainees administered the tests correctly and according to the written protocol. Trainees who passed the quality-control phase were allowed to administer the tests and measurements in the TRAILS sample. Test administrations were monitored at random throughout the data collection period. Interviewers who did not pass these quality checks were suspended and prior test administrations were removed from the dataset (n=10).

At baseline, completion time for the ANT was approximately 70 minutes (short breaks included). At follow-up, time to complete the tasks took the respondents approximately 40 minutes on average. The study was approved by the Dutch Central Committee on Research Involving Human Subjects. Parents' and adolescents' written informed consent was obtained.

2.2.3 Measures

2.2.3.1 Executive Functioning

Executive Functioning was operationalised into the three components 1) *attentional control*, 2) *information processing*, and 3) *cognitive flexibility* with six according subcomponents: Focused Attention, Inhibition and Sustained Attention (representing *attentional control*), Speed of Processing (representing *information processing*), and Working Memory and Shift Attention (representing *cognitive flexibility*). We examined the subcomponents using five computerised tasks from the Amsterdam Neuropsychological Tasks (ANT) (De Sonneville, 1999). The use of computerised tasks guarantees standardised assessment while working with reaction times allows detection of subtle improvements in performance. The main outcome parameter was speed (reaction time: mean RT in milliseconds, except for Sustained Attention where RT was measured in seconds). The ANT has proven to be a sensitive and valid tool in nonreferred samples (De Sonneville et al., 2002; De Sonneville, 2005; Stins et al., 2005), as well as in referred samples of various clinical domains (Altink et al., 2009; Huijbregts et al., 2003; Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009; Van Rijn, Aleman, De Sonneville, & Swaab, 2009). The ANT has previously been used in the TRAILS sample at T1 (baseline) to examine information-processing speed in relation to internalising and externalising problem behaviour (Brunnekreef et al., 2007).

Output measures were a) Focused Attention (from *Feature Identification*), b) Inhibition (of prepotent responses) (from *Shifting Attentional Set – visual*), c) Sustained

Attention (from *Sustained Attention – dots*), d) Speed of Processing (from *Baseline Speed*), e) Working Memory (from *Memory Search – letters*), and f) Shift Attention (from *Shifting Attentional Set – visual*). See the Appendix for a summary of the tasks used and a thorough overview of the cognitive function indices (description/operationalisation) that were used in the analyses. Please note that all components except Speed of Processing and Sustained Attention were calculated by subtracting the RT of a relatively easy task from a more difficult version of that task. This leads us to assume that the basic speed of information processing does not influence Focused Attention, Working Memory, Inhibition and Shift Attention. Intercorrelations between measures at baseline in on average .16 (range .07 to .40) and at follow-up .17 (range .02 to .40).

2.2.3.2 Socioeconomic status

The TRAILS database contains various variables for SES: income level, educational level of the father and the mother, and occupational level of both parents (occupational level was based on the *International Standard Classification for Occupations*; Ganzeboom & Treiman, 1996). These five variables were standardized and combined into one scale with an internal consistency of .84. The scale captures 61.2% of the variance in the five items. Missing values (e.g., when there is only one parent in the family) did not affect the association of this scale with other variables (for more information see: Veenstra et al., (2005)). The standardized values were divided into three groups, of low (lowest quartile, i.e., lowest score to -0.6589), middle (middle two quartiles; -0.6589 to 0.5719), and high (highest quartile; 0.5719 to highest score) SES.

2.2.4 Data analyses

To examine maturation from baseline to follow-up we conducted linear growth models using the software package Mplus, version 7.11 (Muthén, L.K., & Muthén, B.O., 1998–2010). We conducted different models for the six subcomponents. Because the time between baseline and follow-up varied significantly between participants (between 6.5 and 9.5 years), we used a model where individually varying times of observation could be estimated. In order to interpret intercepts in a meaningful way, we calculated individual times of observation at both baseline and follow-up as the deviation from mean age at baseline (i.e., 11.4 years), because without this, intercepts are extrapolated to 0 years. We now interpreted intercepts as mean estimated performance at age 11.4 years. MPlus uses Full Integration Maximum Likelihood (FIML) to estimate a model in which some of the variables have missing data.

RTs were analysed in seconds, because using milliseconds resulted in numeric problems in Mplus.

For our first research question, that is, whether significant maturation takes place from early to late adolescence, we estimated a slope and intercept for the six subcomponents of the ANT and evaluated whether slopes differed from zero. For the second research question, i.e., whether maturation is influenced by sex and SES, we added a grouping variable to investigate differences in slope and intercept between the groups. In the first step, Mplus estimated both parameters freely. In the next step, because we were most interested in maturation, we constrained the slope and compared model fit with the original model. If constraining the slope led to a significant change in the model fit, we subsequently estimated the slope freely but now constrained the intercept. Again, we compared model fit to evaluate if the intercept could be constrained. However, if constraining the slope did not result in a difference in model fit, we subsequently estimated the model with both a constrained slope and constrained intercept. This way, we investigated whether slope, intercept or both were different between boys and girls and between SES groups. For reasons of power due to large sample size, a p-value <.01 was considered to be significant, to reduce the chance of Type I error.

2.3 RESULTS

Because there were no stringent exclusion criteria, we identified respondents who had self-reported conditions such as dyslexia, ADHD, autism spectrum disorders, and/or had clinical scores on depression and anxiety scales. These were 360 respondents, with prevalence scores being in line with those in the general population. To investigate whether including these respondents in our sample changed the results, which would have indicated that more stringent exclusion criteria would have been necessary, we conducted our analyses with and without this group. Findings did not differ between these two sets of analyses, and therefore, respondents with self-reported conditions were left in the sample.[1]

2.3.1 Rank order stability

Stability of measurements over a period of up to eight years were indicated by modest to moderate correlations between the same measures at baseline and follow-up, for five of the subcomponents. Only for Focused Attention, correlation was smaller albeit significant (see Table 2.1).

1 Data not published, available by first author on request.

2.3.2 Change over time of EF

Mean RTs at baseline and follow-up as well the decline in RT in percentage are depicted in Table 2.1. Model fit (AIC, BIC and Maximum Likelihood Estimation) and intercepts and slopes for the six growth models are depicted in Table 2.2. All slopes are negative and significant at a level of $p<.001$, meaning a significant decline in RT over time, which indicates a performance improvement from baseline to follow-up for all of the subcomponents. We thereby confirm our hypotheses that maturation is visible for all EF subcomponents from early to late adolescence.

2.3.3 Sex differences

Next, we specified two different models for boys and girls and compared model fit when constraining intercepts and slopes. Results are depicted in Table 2.3. For Focused Attention (FOA), constraining both the intercept and slope did not result in a change in the model fit, meaning that both performance at baseline and improvement between baseline and follow-up are the same for boys and girls. For Shift Attention (SHA), constraining the slope did not change model fit, but additionally constraining the intercept did. This resulted in two models where girls had a larger intercept, and therefore less optimal performance at baseline, but slopes were the same for both sexes. For Inhibition (INH), Sustained Attention (SUA), Working Memory (WM), and Speed of Processing (SoP) constraining either the intercept or slope changed the model fit. This resulted in separate models for boys and girls, each with their own intercepts and slopes. For Inhibition, Sustained Attention, and Working Memory, girls had a smaller intercept and thus showed a better performance at

Table 2.1 Descriptive statistics for the six EF subcomponents

Subcomponents	R baseline – follow-up	RT baseline (*SD*)	RT follow-up (*SD*)	Decline in RT (%)
Focused Attention	.09	482 (336)	239 (202)	50
Inhibition	.32	197 (156)	168 (144)	14
Sustained Attention[a]	.55	1.76 (0.92)	0.89 (0.44)	49
Speed of Processing	.46	309 (39)	236 (22)	23
Working Memory	.47	477 (267)	237 (148)	50
Shift Attention	.30	558 (220)	338 (144)	40

a: reaction time in seconds.

Table 2.2 Model fit and intercept and slopes for the six EF subcomponents

Subcomponents	AIC	BIC	Maximum Loglikelihood	Intercept (*SE*) (ms)	Slope (*SE*) (ms)
Focused Attention	884.68	924.61	-435.72	480 (7.09)	-31 (1.08)***
Inhibition	-3736.24	-3696.31	1872.20	197 (3.28)	-3.5 (0.53)***
Sustained Attention[a]	7346.76	7386.69	-3656.88	1.75 (0.20)	-0.11 (0.002)***
Speed of Processing	35936.89	35976.78	-17956.58	308 (0.83)	-9.21 (0.11)***
Working Memory	-1473.29	-1433.36	743.73	476 (5.68)	-30 (0.68)***
Shift Attention	-2187.65	-2147.74	1101.37	556 (4.66)	-28 (0.66)***

a: reaction time in seconds; ***: $p<.001$.

baseline. Girls also had smaller slopes, indicating less improvement between baseline and follow-up. Most remarkable, for Inhibition, girls' slope was not significantly different from zero, indicating no change in performance between baseline and follow-up, where boys did improve. For Speed of Processing, the pattern was reversed, with a smaller intercept and smaller slope for boys.

2.3.4 Socioeconomic status

For each of the six measures, we specified different models for the three SES groups, constrained slopes and intercepts and evaluated model fit. Results are depicted in Table 2.4. For Focused Attention, there were no differences between the SES groups. For Speed of Processing and Working Memory, there were only differences regarding the intercept, where the lower SES groups had the highest intercepts. Slopes were equal across the groups for these measures, meaning that the lower SES groups perform generally less optimal than the high SES group, but rate of maturation is the same for all SES groups. For Sustained Attention and Inhibition, there were differences regarding both intercept and slope. For Sustained attention, lower SES meant higher intercepts and larger slopes. This indicates that lower SES groups perform less that the higher SES groups but show more maturation into late adolescence. For Inhibition, the high SES group had the smallest intercept and the largest slope, indicating a better performance at baseline and more maturation for the high SES group.

Table 2.3 Model fit, intercept, and slopes for the six EF subcomponents per sex

Subcomponents	Constraints	AIC	BIC	Maximum Loglikelihood	χ^2 difference test	Intercept (SE) of final model	Slope (SE) of final model
FOA	None	882.42	962.28	-427.21	-		
	S	881.16	955.31	-427.58	$\chi^2(1)=0.74$, $p=.38$		
	I+S	880.58	949.02	-428.28	$\chi^2(1)=2.16$, $p=.14$	480 (7.09)	-31 (1.08)***
INH	None	-3754.58	-3674.73	1891.29	-	Girls: 187 (4.36)	-1.2 (0.07)
						Boys: 208 (4.92)	-6.1 (0.77)***
	S	-3735.23	-3661.09	1880.62	$\chi^2(1)=21.34$, $p<.001$		
	I	-3747.16	-3673.01	1886.58	$\chi^2(1)=9.42$, $p=.002$		
SUA[a]	None	7244.80	7324.65	-3608.40	-	Girls: 1.65 (0.03)	-0.10 (0.001)***
						Boys: 1.85 (0.03)	-0.12 (0.001)***
	S	7265.64	7339.79	-3619.82	$\chi^2(1)=22.84$, $p<.001$		
	I	7269.95	7344.10	-3621.98	$\chi^2(1)=27.16$, $p<.001$		
SoP	None	35883.96	35963.74	-17927.98	-	Girls: 311 (1.23)	-9.49 (0.16)***
						Boys: 306 (1.10)	-8.86 (0.14)***
	S	35892.23	35966.31	-17933.12	$\chi^2(1)=10.27$, $p=.001$		
	I	35892.20	35966.28	-17933.10	$\chi^2(1)=10.24$, $p=.001$		
WM	None	-1556.91	-1477.064	792.45	-	Girls: 438 (7.18)	-27 (0.91)***
						Boys: 515 (8.65)	-33 (1.02)***
	S	-1539.98	-1465.840	782.99	$\chi^2(1)=18.93$, $p<.001$		
	I	-1512.73	-1438.593	769.37	$\chi^2(1)=46,17$, $p<.001$		
SHA	None	-2266.87	-2187.06	1147.43	-		
	S	-2265.31	-2191.21	1145.65	$\chi^2(1)=3.56$, $p=.06$	Girls: 576 (5.76)	-28 (0.001)***
						Boys: 536 (5.56)	
	S+I	2226.69	-2158.29	1125.35	$\chi^2(2)=40.62$, $p<.001$		

a: reaction time in seconds; ***: $p<.001$.

Table 2.4 Model fit, intercept, and slopes for the six EF subcomponents per SES group

Subcomponents	Constraints	AIC	BIC	Maximum Loglikelihood	χ^2 difference test	Intercept (SE) of final model	Slope (SE) of final model
FOA	None	809.339	928.729	-383.67	-		
	S	805.822	913.841	-383.91	$\chi^2(1)=0.48$, $p=.49$		
	I+S	813.118	909.767	-389.56	$\chi^2(2)=0.22$, $p=.64$	480 (7.09)	-31 (1.08)***
INH	None	13443.98	13563.36	-6700.99	-	Low: 214 (0.76)	-2.9 (0.13)***
						Middle: 193 (0.45)	-2.2 (0.08)***
						High: 190 (0.63)	-5.6 (0.09)***
	S	13448.98	13556.99	-6705.49	$\chi^2(1)=9.60$, $p=.002$		
	I	13447.03	13555.04	-6704.51	$\chi^2(1)=9.04$, $p=.003$		
SUA[a]	None	6970.715	7090.105	-3464.358	-	Low: 1.98 (.05)	-0.12 (0.001)***
						Middle: 1.75 (.03)	-0.11 (0.003)***
						High: 1.51 (.03)	-0.09 (0.003)***
	S	7002.859	7110.879	-3482.429	$\chi^2(1)=36.14$, $p<.001$		
	I	7041.102	7149.121	-3501.551	$\chi^2(1)=74.39$, $p<.001$		
SoP	None	35241.058	35360.332	-17599.53	-		
	S	35241.321	35349.236	-17601.66	$\chi^2(1)=4.26$, $p=.04$	Low: 311 (1.54)	
						Middle: 308 (0.99)	-9.12 (0.11)***
						High: 305 (0.41)	
	I+S	35260.277	35356.832	-17613.14	$\chi^2(1)=22.96$, $p<.001$		
WM	None	-1556.906	-1477.064	797.927	-		
	S	-1539.979	-1465.840	795.480	$\chi^2(1)=4.89$, $p=.03$	Low: 497 (9.18)	
						Middle: 473 (6.69)	-29 (6.82)***
						High: 447 (7.80)	
	S+I	-1512.732	-1438.593	782.330	$\chi^2(1)=31.20$, $p<.001$		
SHA	None	14889.77	15009.08	-7423.89	-		
	S	14887.24	14995.19	-7424.62	$\chi^2(1)=0.54$, $p=.46$	Low: 564 (8.83)	
						Middle: 560 (5.71)	-28 (0.67)***
						High: 542 (7.19)	
	S+I	14891.08	14987.67	-7428.54	$\chi^2(1)=7.84$, $p=.005$		

a: reaction time in seconds; ***: $p<.001$.

2.4 DISCUSSION

The aim of the present study was to investigate maturation of EF in early and late adolescence in a longitudinal design. We were interested in differential maturation between six subcomponents of EF and the influence of sex and SES. An indication of the reliability of the subcomponents in a longitudinal design was investigated by looking at their rank-order stability and we found an acceptable significant correlation for five of the subcomponents. This suggest that even though individuals demonstrate maturation on a sub-component, their position relative to others shows modest to moderate stability over a period as long as eight years, an indicator that the tasks measured the same capacity in both early and late adolescence. For the three measured EF components *attentional control*, *speed of processing*, and *cognitive flexibility* we found significant improvement in performance between early and late adolescence, confirming maturation of EF over adolescence. This was the case for all of the subcomponents. When looking at sex differences, we found differences for all measures, except Focused Attention. For Working Memory and Sustained Attention, we found boys underperforming in early adolescence, but showing larger performance improvement through late adolescence. For Inhibition, boys again performed less optimal at baseline. Girls however, did not improve significantly over adolescence. For Shift Attention, boys outperformed girls in early adolescence, but performance improvement until late adolescence was equal between the sexes. For Speed of Processing, boys also outperformed girls at baseline, but showed less improvement over the course of adolescence. Regarding the influence of SES, we found differences for Working Memory, Speed of Processing, Sustained Attention, and Inhibition. For the first two measures, the higher SES groups performed best at baseline, but interestingly, maturation was similar for the three groups. For Sustained Attention, higher SES groups again performed better at baseline but also improved less; an indication of catching up behaviour of the lower SES groups. For Inhibition, the high SES group showed best performance at baseline and the largest slope, indicating a benefit that is not only maintained but also magnified through adolescence.

2.4.1 Measuring maturation of EF in adolescence

Maturation of EF during adolescence is assumed to mirror biological development, as it has been shown that neural association tracks needed for complex control tasks mature into young adulthood (Lebel & Beaulieu, 2011). On a functional level this has indeed been concluded based on convergent evidence from cross-sectional research (e.g., Brauch Lehman

et al., 2010; Huizinga et al., 2006) which was confirmed in our longitudinal study. We interpreted smaller slopes as reflecting a higher level of maturation already before onset of the study. First, looking at 1) *attentional control*, we found Inhibition to demonstrate smallest change rates and therefore might be the first sub-component to reach mature levels. This is in accordance with the theoretical assumption that inhibition is a prerequisite process for other EF abilities (Best et al., 2009), for example, shifting attention to the next stimulus or task requires intact inhibition of the ongoing process. Our finding is consistent with a study in which no significant improvement was found on a task measuring inhibition between ages 11 and 17 (Magar et al., 2010). It is, however, in contrast with other findings of inhibition improvement until the age of 21 on one (out of three) inhibition tasks tested (Huizinga et al., 2006). These contradicting findings can be interpreted by differences in task characteristics; in the latter study an adaptation of the Stroop Task, which relies on cognitive interference and not simple inhibition thus requiring more mental processing, was used. We, on the other hand, used a simple task measuring the inhibition of prepotent responses, which is a more basal form of inhibition. The contradictive results can reflect a methodological bias and underline the relevance of using basic tasks for measuring EF maturation. For the other subcomponents of *attentional control*, being Sustained and Focused Attention, we found larger maturational rates than for Inhibition, which is in contrast with the suggestion that the entire component *attentional control* matures first (Anderson, 2002). However, other studies that looked at subcomponents have also found that focused and sustained attention reach mature levels at a relatively late moment in adolescence (Brauch Lehman et al., 2010). An explanation for this contradiction can be found in the suggestion that subcomponents are related but still dissociable. Looking on the level of components makes differences in maturational rates between subcomponents indistinguishable, stressing the importance of investigating the subcomponents. Second, it was hypothesised that 2) *information processing* would be next to reach mature levels (Anderson, 2002). We found change rates for Speed of Processing to be second smallest after Inhibition, confirming this hypothesis. However, general speed of information processing does mature after age 11, which might play a confounding role in interpreting performance increases on other measures. It should therefore be taken into account when using RT tasks in developmental studies, as observed increases in performance might reflect actual maturation of the depicted sub-component or (also) increases in general speed of processing. It is advisable to consider this when designing a study, as has been suggested before (Kail & Salthouse, 1994). In the current study this was circumvented by using RT differences between two versions of the same task as outcome

measures, which makes it unlikely for general processing speed to confound the specific EF sub-component investigated. Finally, the component 3) *cognitive flexibility*, Working Memory and Shift Attention, showed largest change rates and therefore most maturation over the course of adolescence, consistent with previous findings on a functional level (Anderson, 2002), as well as on the level of subcomponents (Huizinga et al., 2006; Magar et al., 2010).

Our findings are consistent with previous findings from cross-sectional research and give insight in intra-individual maturation of EF over adolescence. A challenge in longitudinal designs is task selection. We showed that it is possible to measure EF maturation from early to late adolescence making use of the same computer-aided reaction time tasks at both time points. Tasks were sensitive enough to measure improvement in the reaction times over the course of adolescence. Furthermore, rank-order stabilities between both time points were modest to moderate, with the exception of Focused Attention. The latter proved to be a difficult task, as represented by large absolute RTs on its subconditions. The complexity of the tasks could have forced participants to rely more on cognitive strategies, that might have been different ones in early than in late adolescence, thereby compromising task stability. Hence, caution must be taken when interpreting the results from this measure. The fact that the test-retest correlations were modest to moderate is of interest. They are generally very comparable with or higher than other RT measures of neurocognitive functioning, over even smaller time intervals (Fernie et al., 2013) and comparable to longitudinal rank-order stability of personality measures, which are assumed to reflect very stable measures (Roberts & DelVecchio, 2000). We interpret our test-retest correlations as illustrative for substantial stability of the individual test scores over even a period of eight years in which considerable brain development takes place. Therefore, we conclude that this paradigm is feasible and provides valuable information in a longitudinal design. In general, our research provides knowledge on normal maturation of cognitive function and can thereby serve as a frame of reference for further research.

2.4.2 Influence of sex and SES on EF

Research indicates that there are sex differences in adolescent brain development, where males reach peak volumes generally later than females. It is unclear, however, how this translates to differences in neurocognitive capacities. The influence of sex differences have not always been a focus of research in studying maturation of EF and findings so far have been ambiguous. Some studies found girls to show more improvement during adolescence for attentional control and processing speed (Anderson, 2002), where others found the

opposite pattern for shift attention (Kalkut et al., 2009). The present study showed larger slopes for boys for Working Memory and Sustained Attention, indicating more maturation after the onset of adolescence. For Inhibition, larger slopes were seen for boys too, but more importantly, girls did not show improvement over time on this task. We interpreted this as the girls already having reached mature levels of Inhibition at the onset of adolescence. On the other hand, boys did show better performance on Shift Attention in early adolescence, with equal slopes for boys and girls. This indicates a weaker performance of girls on this task that is maintained throughout adolescence. For Speed of Processing, girls lack behind in early adolescence, and their larger slopes could reflect catching up over the course of adolescence. In sum, for most measures, boys seem to mature more than girls, although their general speed of processing appeared to be more developed than that of girls in early adolescence. As maturation is influenced by sex for all subcomponents except Focused Attention, we stress the importance of taking sex into account when assessing EF maturation.

For SES, discordant findings are most clear in Sustained Attention and Inhibition in our study, where other studies have found differences for a larger variety of tasks (Ardila et al., 2005; Mezzacappa, 2004). An explanation could be that some of the studies are conducted in countries generally less prosperous than the Netherlands, where differences between lower and higher socioeconomic status are more pronounced. Furthermore, differences between public and private school are virtually nonexistent in the Netherlands. Therefore, our results are not systematically influenced by differences in quality of education between different SES groups. It should be noted, however, that the TRAILS study is possibly biased toward generally higher SES, as 25% of invited participants at baseline were nonresponders with a slight overrepresentation of lower SES individuals (Ormel et al., 2012). Because our division in SES groups is data driven, the difference between the categories might reflect an underestimation of the population differences. We found the high SES group to outperform lower SES groups in early adolescence and only reducing the gap during adolescence for Sustained Attention. For Inhibition, we found a benefit of the higher SES groups over the lower SES groups, that was not only maintained but even magnified over time, possibly adding up to the vulnerability of the lower SES groups. For the other measures, there were differences in baseline performance between the different SES groups. where amount of maturation was comparable. This indicates that the influence of SES on neurocognition might mainly be confounding in cross-sectional assessments and not directly when looking at maturation.

2.4.3 Strengths and limitations

To our knowledge, this is the first study to longitudinally investigate EF in a large population-based sample covering early and late adolescence. Moreover, due to the large sample size, it was possible to make reliable comparisons between the maturation of boys and girls and different SES groups over time. We used the same tasks at both time points, amplifying the possibility of interpreting developmental change. Tasks were straightforward, yet sensitive to subtle improvements in performance due to the use of RTs. We found modest to moderate rank-order stability, important for the use of these measures for investigating maturation of EF in adolescence.

Regarding limitations, we did not assess the aspect of goal setting behaviour. Even though this is an important and interesting aspect of EF, there are problems regarding its feasibility in longitudinal investigations. In particular, strategic behaviour and problem-solving skills are difficult to measure using the same task for both younger and older individuals. The other components of EF are thought to be prerequisite for goal setting, and our aim was to gain more insight in these more basic components. Although this can be seen as a reductionist approach, it has important benefits. When looking at dynamic functions, it is valuable to assess this in a step-by-step manner, starting with the basal elements. Our finding that differential maturation is visible for all of these elements from early to late adolescence can serve as a frame of reference to further longitudinally investigate the maturation of goal setting.

A second limitation of this study is the fact that EF was measured at two points in time. This means that it is not possible to investigate the trajectories of EF maturation, that is, whether or not maturation is linear, and investigating the occurrence of developmental spurts and the age at which the specific skills plateau and reach their adult levels. On the other hand, additional measurements with resulting smaller test-retest intervals also increase the likelihood of practice effects. To properly judge the vulnerability of tasks for repeated testing, an assessment of practice effects is required. What minimizes the likelihood of this unwanted effect, is the fact that our measurements were an average of eight years apart, making a test-retest effect unlikely (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Furthermore, our test-retest intervals were variable from 6.5 to 9.5 years. Varying test-retest intervals among participants might decrease the impact of practice effects because in this case, there is no perfect correlation between increase in age and increase in test experience (Salthouse, 2010).

Our study is unique in the repeated measurement of EF across this important developmental period. Our study provides insight in the capabilities of adolescents entering

young adulthood, making the transition to an independent life and full societal participation. Nevertheless, maturation proceeds well into the early twenties (e.g., Tau & Peterson, (2009). and we do not implicate our follow-up measurement to be the endpoint of development.

A third limitation regards to working with a large longitudinal cohort sample. Despite apparent benefits, this comes with some negative aspects as well. Attrition is a well-known problem in longitudinal studies, and attrition is often nonrandom. In our study, dropped-out respondents were more often boys and of lower SES, a phenomenon that is seen more often (e.g., Bjertness et al., 2010). Although this might have influenced our results, we generally observed the largest slopes for boys and low SES participants. Therefore, bias due to attrition had possibly led to an underestimation of maturational rates and not to an overestimation. Logistical difficulties also arise in standardizing test-retest intervals and testing locations. In our sample, test-retest intervals varied substantially. We used this in our advance by applying a time based model. Regarding testing locations, at baseline all respondents were tested in their schools. At follow-up we aimed to test as many respondents as possible on location (community houses, test rooms within the research centre), but approximately a quarter of our sample was tested at their homes. Interviewers were instructed to minimize distraction and arrange a suitable testing location. Respondents tested at home did not perform differently from the respondents who were tested at external locations.[2]

Finally, we aimed to gain insight in maturation of EF in a general representative population as opposed to abnormal development within specific populations or conditions. For this reason we included only those children who fitted primary education without having mental disabilities which implies an expectation to develop an independent and full participation in society. Hereby we exclude children with known medical conditions, developmental and neurological disorders, or psychiatric conditions interfering with normal daily life within the regular schooling system. Possible bias from minor psychological neurological or medical conditions are treated as representative within the normal ranges of development.

2.4.4 Conclusion and implications

Looking at maturation of EF in adolescence in a longitudinal design, we found significant maturation for all subcomponents measured. This maturation is not only differentiated in maturational rates between subcomponents but also in to what extent they are influenced

2 Data not published, available by first author on request.

by SES and more importantly, sex. Therefore, general statements on maturation of EF are unwarranted and zooming into its subcomponents is essential. The use of basic tasks is beneficial from this view point, as more difficult tasks often rely on more than one subcomponent. Although differences in performance were found for different SES groups, SES did not prove to play a large role in maturation of EF for the majority of subcomponents. As sex showed to be influencing maturational rates for various subcomponents, it is an important factor to take into consideration when assessing what is normal maturation of EF and what is deviant. In sum, this study provides a frame of reference for future studies on EF and maturation in adolescence.

3

Adolescent heavy drinking does not affect basic neurocognitive maturation: Longitudinal findings from the TRAILS study.

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ABSTRACT

Background: Excessive alcohol use is assumed to affect neurocognitive maturation in adolescence. However, most existing studies that have tested this hypothesis are seriously flawed due to the use of selective groups and/or cross-sectional designs, which limits our ability to draw firm conclusions. This longitudinal study investigated whether patterns of alcohol use affect neurocognitive maturation in adolescence. Additionally, gender was tested as a possible moderator.

Methods: We used data from the Tracking Adolescents' Individual Lives Survey (TRAILS), which comprises a cohort of 2,230 Dutch adolescents. Neurocognitive maturation was measured at ages 11 and 19 by assessing the standardised improvement on each of four basic neurocognitive functions (i.e., inhibition, working memory, and shift- and sustained attention). Participants were assigned to one of six (heavy) drinking groups (i.e., non-drinkers, light drinkers, infrequent heavy drinkers, increased heavy drinkers, decreased heavy drinkers, and chronic heavy drinkers). We conducted linear regression analyses, and adjusted for relevant confounders.

Results: The six drinking groups did not reveal significant differences on maturation. E.g., neurocognitive maturation of chronic heavy drinkers in comparison to non-drinkers; inhibition: *B*=-0.14, 95% CI [-0.41 to 0.14], working memory: *B*=-0.03, 95% CI [-0.26 to 0.21], shift attention: *B*=0.13, 95% CI [-0.17 to 0.41], sustained attention: *B*=0.12, 95% CI [-0.60 to 0.36]. Furthermore, gender did not show to be a significant moderator.

Conclusions: Four years of weekly heavy drinking (i.e., chronic heavy drinkers) did not result in measurable impairments in four basic neurocognitive functions. Thus, regular heavy drinking in adolescence does not seem to affect these basic behavioural measures of neurocognitive functioning.

3.1 INTRODUCTION

In adolescence, significant increases in alcohol consumption are usually found, with prevalence rates of last month alcohol use rising from 16.1% at age 12 to 84.8% at age 16 in Dutch adolescents (Verdurmen et al., 2012). Alcohol drinking in adolescence has been associated with several negative consequences. In particular, the neurotoxic effects of alcohol are assumed to be harmful because the developing adolescent brain may be particularly vulnerable to the adverse effects of alcohol (Clark, Thatcher, & Tapert, 2008). However, the findings from empirical studies that tried to assess these effects so far remain inconclusive due to a number of methodological pitfalls.

Most studies that compared alcohol abusing adolescents with non-abusing adolescents on a broad range of neurocognitive functions, such as language and general intelligence (Moss, Kirisci, Gordon, & Tarter, 1994), attention and intelligence (Tarter, Mezzich, Hsieh, & Parks, 1995), learning, memory, and visuospatial functioning (Brown, Tapert, Granholm, & Delis, 2000), are not convincing in their conclusions because they were cross-sectional in nature. As a result these studies neglected the reverse effect of neurocognitive impairments on heavy alcohol use (Tapert, Baratta, Abrantes, & Brown, 2002; Tarter et al., 2003). Furthermore, they were conducted among adolescents diagnosed with Alcohol Use Disorder (AUD), which limits the generalisability of the findings because this specific group has behavioural problems associated with controlling their behaviour (according to DSM-IV-criteria (American Psychiatric Association, 2000)) and often psychiatric comorbidity (Hermens et al., 2013). This furthermore corroborates problems in assessing causal relations. In contrast, population studies have shown almost no significant differences between excessive drinkers and controls on neurocognitive functioning (Schweinsburg, McQueeny, Nagel, Eyler, & Tapert, 2010; Squeglia, Schweinsburg, Pulido, & Tapert, 2011) However, these population studies are again limited by cross-sectional designs and small sample sizes. Also, definitions of excessive or heavy drinking are not consistent across the studies.

To the best of our knowledge, only three small scale studies (n=75 and n=40) have analysed the effects of alcohol use on neurocognitive maturation in adolescence using a longitudinal design with pre- and post-measurements of neurocognitive functioning in a general population (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009; Squeglia et al., 2012; Wetherill, Squeglia, Yang, & Tapert, 2013). The results of these studies do not support the damaging effects of alcohol use in adolescence either. One study found differences between heavy drinkers (average drinks per month: 9.9 for girls and 6.1 for boys) and controls on only one out of seven neurocognitive tasks, and this difference was significant for girls

only (Squeglia et al., 2009). Two other studies (Squeglia et al., 2012; Wetherill et al., 2013) showed increased brain activation with fMRI measurements (but not in all hypothesised brain areas) in adolescents who transitioned to heavy drinking (drinks per drinking day: 4.2 and 6.1 respectively), while no differences between drinkers and non-drinkers were found on task performance. Thus, empirical research on the effects of heavy alcohol use on neurocognitive maturation does not result in undisputed findings and calls for large scale population studies on this subject.

The aim of the present study was to investigate whether adolescent alcohol use affects maturation of basic neurocognitive functions in a large population-based sample. We conducted a pre-exposure measure of neurocognitive functioning at age 11 and follow-up measurement at emerging adulthood (age 19). Furthermore, since girls are supposedly more vulnerable due to differences in neuromaturation, hormonal fluctuations, and alcohol metabolism (Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007), gender was considered as a possible moderator. Executive functioning (EF), defined as the ability to guide and direct behaviour (Jurado & Rosselli, 2007), is hypothesised to develop specifically during adolescence (Crone, 2009). As a result it is assumed particularly vulnerable to the effects of alcohol. We therefore used four measures of EF: inhibition, working memory, sustained attention, and shift attention, as our main outcome in this study. We used computerised tasks to assess basics forms of these functions, which allowed us to use the same tasks in both early and late adolescence, and compare maturation of task performance between adolescents with different drinking habits.

3.2 METHODS

3.2.1 Study design

The present study used data from the first, second (for descriptive statistics only), third, and fourth wave of the TRacking Adolescents' Individual Lives Survey (TRAILS). This is a prospective cohort study of Dutch pre-adolescents at age 11. The target sample involved children living in the North of the Netherlands, covering urban and rural areas (for details on the procedure see: De Winter et al., 2005; Ormel et al., 2012). Seventy-six percent of eligible adolescents and their parents agreed to participate and were enrolled in the study at baseline (T1) (n=2,230, mean age 11.1 years, SD=0.56, 49.2% male). At the third (T3) wave (n=1,816, mean age 16.3 years, SD=0.70, 47.7% male), the response rate was 81.4%.

At the fourth (T4) wave (*n*=1,596, mean age 19.2 years, *SD*=0.57, 46% male), the response rate was 70%.

3.2.2 Procedure

On the first assessment, trained undergraduate psychology students administered neuropsychological test in adolescents' schools or designated testing centres (for more information, see Brunnekreef et al., 2007). Participants who were unable to attend these assessments were tested at home. On the first to third assessments, adolescents completed self-report questionnaires in groups in school, supervised by an assistant. Their parents also completed a written questionnaire. On the fourth assessment, most adolescents were no longer in secondary education. Therefore, trained professional interviewers conducted the neuropsychological test battery individually at participants' homes or in a nearby community centre (for more information, see Boelema et al., 2014). Parents and their children were asked to fill out a computerised questionnaire (or, per request, a paper-and-pencil questionnaire). The Dutch Central Committee on Research Involving Human Subjects approved the study. Parents and adolescents' written informed consent was obtained. The confidentiality of the study was emphasised.

3.2.3 Measures

3.2.3.1 Alcohol use

Descriptive statistics. A number of measures were added to compare the drinking groups on alcohol-related behaviour. At T1, adolescents were asked: "How often have you been drinking alcohol (for example, a bottle of beer or a glass of wine)?" up until that time point, on a 5-point scale ranging from 0 to 7 times or more. Furthermore, at T2-T4 adolescents were asked how many times they had been drunk in the last 12 months. We dichotomised these answers into never and once or more.

At T2-T4, adolescents were furthermore asked to report their average drinking habits between the previous data collection wave and the present. They were asked four questions: "On how many week(end) days do you normally drink alcohol" and "On an average week(end) day on which you drink alcohol, how much alcohol (glasses, cans, bottles) do you drink?" By multiplying and adding the answers, average weekly quantity of alcohol use can be computed. A Dutch standard drink contains 10 grams of alcohol.

Drinking groups. For constructing drinking groups, we used the average amount of glasses on a weekend day (since previous measurement wave), since weekend quantity of alcohol use has been shown to be a useful and specific measure of alcohol use at this age (Weingardt et al., 1998). In order to select respondents who were regular heavy drinkers, we furthermore used the question "On how many occasions in the last month have you had an alcoholic beverage to drink?" Since legal age for buying alcohol in the Netherlands was 16 years at time of the data collection, we used data from T3 and T4 to determine group assignment.

We first identified a group of non-drinkers who indicated that they did not consume alcohol on a regular weekend day. For the respondents who consumed alcohol, we set the cut off score for heavy drinking at 6 glasses on a weekend day for boys and 5 glasses for girls (Koning, van den Eijnden, Verdurmen, Engels, & Vollebergh, 2013). We furthermore distinguished between frequent (last month prevalence ≥ 4 times heavy drinking) and non-frequent heavy drinking. This resulted in participants being labelled as non-drinkers, not heavy drinkers, infrequent heavy drinkers (i.e., less than weekly), or heavy drinkers (weekly) at both T3 and T4. Finally, these categorizations per time point were combined into longitudinal drinking groups. Participants were divided into six groups: Non-drinker, light drinker, infrequent heavy drinker, increasing heavy drinker, decreasing heavy drinker, and chronic heavy drinker (for descriptive statistics, see Table 3.1).

3.2.3.2 Neurocognitive functioning

Baseline neurocognitive functioning was examined at T1, using three computerised reaction time tasks from the Amsterdam Neuropsychological Tasks (ANT) (De Sonneville, 1999). The ANT has proven to be a sensitive and valid tool in non-referred samples (Brunnekreef et al., 2007; De Sonneville et al., 2002; Stins et al., 2005), as well as in referred samples of various clinical domains (Altink et al., 2009; Huijbregts et al., 2003; Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009; Van Rijn, Aleman, De Sonneville, & Swaab, 2009). We assessed four basic neurocognitive functions: inhibition, working memory, shift attention, and sustained attention, since they have sufficient longitudinal stability (Boelema et al., 2014) and the functions are theoretically hypothesised to be associated with alcohol deficits (Tarter et al., 1995). The ANT has shown to be applicable for longitudinally assessing these basic neurocognitive functions in an adolescent population (Boelema et al., 2014). In the Appendix a description of the tasks used is provided.

The use of computerised tasks guarantees standardised assessment while working with reaction times allows detection of subtle improvements in performance. Working memory,

inhibition, and shift attention were calculated by subtracting the performance time of a baseline version from a more difficult version of the task. Performance results reflecting more than 50% errors were coded as missing and imputed because they were assumed to reflect either misunderstood instructions or false computer settings, undermining the validity of the testing. In accordance with previous research on neurocognitive maturation (Squeglia et al., 2009), we calculated change scores for each of the four neurocognitive functions by computing z-scores for the T1 and T4 measures and subsequently subtracting these scores from each other (T1-T4). The neurocognitive measures have been used in other studies within the TRAILS-project (Boelema et al., 2014).

3.2.3.3 Measurement of covariates

In accordance with previous studies (Squeglia et al., 2009), age at T1, SES, paternal and maternal alcohol use, delinquent behaviour at age 11, and smoking and cannabis use at age 16 and 19 were included as covariates if they significantly correlated with the outcomes measure (p<.05) (see Table 3.2). *SES* was assessed using income level, educational level, and occupational level of both parents (occupational level was based on the *International Standard Classification for Occupations* Ganzeboom & Treiman, 1996). These five variables were standardised and combined into one scale with an internal consistency of .84 (for more information, see Veenstra et al., 2005). *Paternal and maternal alcohol use* was assessed at T1 by asking the parent who filled out the questionnaire how much alcohol (s)he drinks per week on average and how much his or her partner drinks. *Delinquent behaviour* was measured at T1 Youth Self Report (YSR) (Achenbach, 1991; Achenbach & Rescarola, 2001), consisting of 15 items (α=.71). *Smoking* was also measured at both T3 and T4 by asking: "How many times have you smoked cigarettes during the last month?" *Cannabis use* was assessed at T3 and T4 by asking: "How many times have you used weed (marihuana) or hash during the last year?".

3.2.4 Data analyses

Multiple data sets in SPSS 20, using fully conditional specification (MCMC) with Predictive Mean Matching because there were missing values due to attrition on both predictors and outcome measures (Van Buuren, 2007). This approach generated five datasets and one pooled dataset (Van Buuren, 2007).

The six drinking groups were validated by comparing them on alcohol related behaviour, such as prevalence of last year drunkenness and drinking in early adolescence. For variables measuring prevalence, Pearson χ^2 with standardised residuals was used to identify observed

Table 3.1 Descriptive statistics of the six drinking groups

	Non-drinkers	Light drinkers	Infrequent heavy drinkers	Increased heavy drinkers	Decreased heavy drinkers	Chronic heavy drinkers
Drinking behaviour (ages 16;19)	ND;ND	ND;DNHD DNHD;ND DNHD;DNHD	ND/DNHD;IHD IHD;ND/DNHD IHD;IHD	ND;HD, DNHD;HD IHD;HD	HD;ND HD;DNHD HD;IHD	HD/HD
N	85	873	272	514	250	232
% male	34	48	39	58	47	54
Age at baseline	11.3[a]	11.4[a]	11.4[a]	11.4[a]	11.4[a]	11.4[a]
Parent SES at baseline	-0.09[a]	-0.01[a]	-0.15[a]	0.01[a]	-0.18[a]	-0.08[a]
Maternal alcohol use	2.5(3.7)[a]	3.3(4.1)[ab]	3.0(4.0)[ab]	3.7(4.4)[bc]	3.7(4.4)[bc]	4.5(5.1)[c]
Paternal alcohol use	4.4(5.0)[a]	5.1(5.3)[ab]	5.1(5.3)[ab]	6.2(5.6)[bc]	6.0(5.8)[bc]	6.7(5.9)[c]
Delinquent behaviour age 11	0.19(0.18)[a]	0.21(0.15)[ab]	0.22(0.16)[ab*]	0.24(0.17)[abc]	0.26(0.18)[bc]	0.28(0.22)[c]
Prevalence last year cannabis use age 16 (%)	7[-]	33[-]	42	45	62[+]	70[+]
Prevalence last year cannabis use age 19 (%)	2[-]	40[-]	44	61[+]	58	67[+]
Prevalence daily smoking at age 16 (%)	10[-]	16[-]	29	27	44[+]	48[+]
Prevalence daily smoking at age 19 (%)	8[-]	21	29	40[+]	42[+]	56[+]
Prevalence of haven drunk >1 glass age 11 (%)	5[†]	12[-]	15	19	21	23[+]
Prevalence last year drunkenness age 13 (%)	9[-]	20[-]	26	28	35[+]	36[+]
Prevalence last year drunkenness age 16 (%)	14[-]	55[-]	74	77	94[+]	98[+]
Prevalence last year drunkenness age 19 (%)	22[-]	74[-]	88	98[+]	82	97[+]
N glasses per week age 13 (*SD*)	1.0(3.1)[a]	1.1(3.2)[a]	1.4(3.1)[a]	1.5(3.2)[b]	3.1(5.6)[b]	3.1(5.0)[b]
N glasses per week age 16 (*SD*)	0.1(0.1)[a]	3.1(2.5)[a]	5.8(4.5)[b]	5.8(4.8)[b]	12.9(6.5)[c**]	14.2(7.1)[c**]
N glasses per week age 19 (*SD*)	0.4(2.0)[a]	4.8(3.5)[b***]	7.2(5.0)[c]	14.0(7.5)[d****]	6.6(5.3)[c***]	15.8(8.2)[e****]

	Non-drinkers	Light drinkers	Infrequent heavy drinkers	Increased heavy drinkers	Decreased heavy drinkers	Chronic heavy drinkers
Inhibition *M* (*SD*) age 11 in ms	198 (141)	197(157)	190(170)	197(156)	202(140)	199(148)
Working Memory *M* (*SD*) age 11 in ms	443 (268)	479(270)	475(277)	473(256)	480(272)	487(268)
Sustained Attention *M* (*SD*) age 11 in sec	1.79(1.05)	1.76(0.94)	1.69(0.85)	1.74(0.92)	1.83(0.93)	1.78(0.89)
Shift Attention *M* (*SD*) age 11 in ms	586(245)	559(219)	544(201)	544(210)	556(210)	570(219)
Inhibition *M* (*SD*) age 19 in ms	162(141)	173(142)	172(201)	174(142)	196(151)	189(148)
Working Memory *M* (*SD*) age 19 in ms	243(175)	240(150)	245(146)	235(143)	257(157)	260(155)
Sustained Attention *M* (*SD*) age 19 in sec	0.97(0.51)	0.93(0.44)	0.92(0.42)	0.92(0.49)	0.97(0.47)	0.95(0.41)
Shift Attention *M* (*SD*) age 19 in ms	359(132)	334(131)	332(120)	339(134)	351(169)	350(143)
Inhibition standardised change score	0.11(1.09)	0.03(1.17)	-0.01(1.17)	0.02(1.19)	-0.10(1.17)	-0.07(1.13)
Working Memory standardised change score	-0.12(1.23)	0.03(1.03)	-0.01(1.06)	0.04(1.03)	-0.08(1.03)	-0.08(1.02)
Sustained Attention standardised change score	-0.05(0.87)	0.02(0.95)	-0.04(0.85)	0.01(1.11)	-0.01(0.92)	-0.01(0.93)
Shift Attention standardised change score	0.00(1.26)	0.06(1.14)	0.00(1.04)	-0.05(1.19)	-0.08(1.31)	-0.01(1.32)

ND = non-drinking, DNHD = drinking, not heavy drinking, IHD = infrequent heavy drinking, HD = heavy drinking.
+ or - signs mean Pearson-Chi-Square Test is significant. + means cell count is higher than expected, - means cell count is lower than expected (based on significant standardised residuals for all imputed datasets). †: cell count was lower than 5.
Different superscript letters refer to significant differences ($p<.05$) in mean scores between groups: if two group scores are labelled with the same letter, the scores of these groups do not differ. If two scores are labelled with different letters, these scores differ.
*: in two of the five imputed datasets, there was a significant difference between increasers and other heavy drinking groups.
**: in one of the five imputed datasets, there was a significant difference between decreasers and chronic heavy drinkers.
***: in one of the five imputed datasets, there was no significant difference between light drinkers and decreasers.
****: in two of the imputed datasets, there was no significant difference between increasers and chronic heavy drinkers.

Table 3.2 Bivariate correlations among the covariates and neurocognitive maturation (T1-T4)

Controlling variable	Δ Inhibition	Δ Working Memory	Δ Shift Attention	Δ Sustained Attention
T1 performance	.59*	.52*	.59*	.49*
Age at T1	-.04	-.08*	-.08*	-.07*
SES	.05	.02	.04	-.01
Maternal alcohol use	.01	.01	.02	-.01
Paternal alcohol use	.05	-.02	.05	-.02
Delinquency scores	.03	-.01	.01	-.01
T3 last year cannabis use	-.01	-.02	-.01	-.05
T4 last year cannabis use	.01	.00	-.02	-.03
T3 last month smoking	.00	.03	-.09*	-.04
T4 last month smoking	-.06*	-.04	-.09*	-.08*

*: correlation is significant (p<.05). These variables were controlled for in the regression analyses.

counts that were significantly different (p<.05) from expected counts. For continuous variables, MANOVAs with post-hoc tests were used. In both cases, the five datasets were analysed separately, as pooled analyses are unavailable for these tests.

To examine the influence of drinking groups on neurocognitive maturation, we conducted bivariate and multivariate linear regression analyses. Standardised change scores were entered as the dependent variables and the dummy variables of drinking groups as predictors (non-drinkers served as the reference group). First, we conducted four separate linear regression analyses without covariates. In the second model, we conducted multivariate linear regression analyses adjusting for controlling variables. Main effects of drinking groups and drinking patters*gender interaction were entered in separate blocks and interpreted accordingly. To reduce Type 1 error, we set α at <.01.

3.3 RESULTS

3.3.1 Descriptive statistics for the drinking groups

Descriptive statistics are depicted in Table 3.1. There were no differences between the groups for baseline neurocognitive functioning, SES, and age. Pearson χ^2 yielded significant differences between groups for prevalence rates of other substance use, drinking in early adolescence, and drunkenness. Non-drinkers and light drinkers scored lower than expected

on all variables while the chronic drinkers scored higher on all variables. A MANOVA indicated significant differences between groups on all continuous measures (p<.001). Parental alcohol use and delinquency scores in pre-adolescence are largest in the regular heavy drinking groups. Also, those who later would be classified as regular heavy drinkers drank significantly more at age 13 than the future non regular heavy drinkers. Chronic heavy drinkers, as to be expected, drank most, with an average weekly consumption finally exceeding 14 glasses. Taken together, the results indicated significant differences between the drinking groups on all measures of alcohol related behaviour, validating our identification of the six drinking patterns. The patterns become more differentiated as the adolescents get older.

Table 3.3 Standardised maturation in EF (T1-T4) predicted by drinking groups (T3-T4) without controlling for covariates

	B	95% CI of *B*	β
Δ Inhibition (T1-T4)			
Light drinkers (ref=non-drinkers)	-0.08	-0.35 to 0.18	-.04
Infrequent (ref=non-drinkers)	-0.12	-0.42 to 0.18	-.03
Increasing (ref=non-drinkers)	-0.09	-0.37 to 0.19	-.03
Decreasing (ref=non-drinkers)	-0.22	-0.56 to 0.13	-.06
Chronic (ref=non-drinkers)	-0.18	-0.51 to 0.14	-.05
Δ Working Memory (T1-T4)			
Light drinkers (ref=non-drinkers)	0.15	-0.08 to 0.39	.07
Infrequent (ref=non-drinkers)	0.11	-0.15 to 0.37	.03
Increasing (ref=non-drinkers)	0.17	-0.08 to 0.42	.07
Decreasing (ref=non-drinkers)	0.04	-0.23 to 0.31	.01
Chronic (ref=non-drinkers)	0.04	-0.28 to 0.32	.01
Δ Shift Attention (T1-T4)			
Light drinkers (ref=non-drinkers)	0.06	-0.22 to 0.33	.02
Infrequent (ref=non-drinkers)	0.00	-0.29 to 0.29	.00
Increasing (ref=non-drinkers)	-0.05	-0.34 to 0.23	-.02
Decreasing (ref=non-drinkers)	-0.08	-0.39 to 0.23	-.02
Chronic (ref=non-drinkers)	-0.01	-0.33 to 0.31	-.00
Δ Sustained Attention (T1-T4)			
Light drinkers (ref=non-drinkers)	0.07	-0.15 to 0.29	.04
Infrequent (ref=non-drinkers)	0.01	-0.23 to 0.26	.01
Increasing (ref=non-drinkers)	0.06	-0.17 to 0.29	.03
Decreasing (ref=non-drinkers)	0.04	-0.21 to 0.30	.01
Chronic (ref=non-drinkers)	0.04	-0.23 to 0.30	.01

: significant at p<.01; *: significant at p<.001.

3.3.2 The influence of drinking groups on neurocognitive maturation

Raw scores of baseline (T1) and follow-up (T4) neurocognitive functioning and standardised change scores are depicted in Table 3.1. The results of the bivariate linear regression analyses are depicted in Table 3.3. Drinking group did not significantly predict neurocognitive maturation from age 11 to age 19 for any of the four measures.

The results of the multivariate linear regression analyses are depicted in Table 3.4. In step 1, T1 baseline performance, gender, and other covariates (see Table 3.2) were added. For all neurocognitive measures, baseline performance significantly predicted neurocognitive maturation, with a higher initial score predicting more maturation. So a worse performance at baseline predicted more maturation, which is to be expected since a less optimal performance leaves more room for improvement. Gender differences were significant for inhibition and shift attention, with boys showing more improvement on these tasks. In step 2, we added drinking groups as dummy variables, with non-drinkers as reference group. This did not significantly improve model fit for any of the measures, and none of the dummy variables predicted neurocognitive maturation compared to the non-drinkers. In step 3, we added drinking group*gender interaction variable. Again, this did not improve model fit and thus, gender did not moderate the effects of drinking groups on neurocognitive maturation.

Table 3.4 Standardised maturation of EF (T1-T4) predicted by drinking groups (T3-T4) controlling for covariates

		B	95% CI of *B*	β
Δ Inhibition (T1-T4)				
Step 1	T1 Inhibition	4.36***	4.09 to 4.64	.57
	Gender	0.17**	0.08 to 0.26	.05
Step 2	Light drinkers (ref=non-drinkers)	-0.08	-0.29 to 0.14	-.03
	Infrequent (ref=non-drinkers)	-0.06	-0.30 to 0.18	-.02
	Increasing (ref=non-drinkers)	-0.07	-0.29 to 0.16	-.03
	Decreasing (ref=non-drinkers)	-0.19	-0.48 to 0.09	-.05
	Chronic (ref=non-drinkers)	-0.14	-0.41 to 0.14	-.04
Step 3	Light drinkers (ref=non-drinkers) * gender	-0.09	-0.54 to 0.36	-.03
	Infrequent (ref=non-drinkers) * gender	-0.13	-0.63 to 0.37	-.02
	Increasing (ref=non-drinkers) * gender	-0.09	-0.56 to 0.38	-.03
	Decreasing (ref=non-drinkers) * gender	-0.10	-0.43 to 0.62	.02
	Chronic (ref=non-drinkers) * gender	-0.05	-0.46 to 0.56	.01
R^2=.35 for Step 1, ΔR^2=.002 for Step 2 (n.s), ΔR^2=.001 for Step 3 (n.s)				

Table 3.4 continues on next page

		B	95% CI of *B*	β
Δ Working Memory (T1-T4)				
Step 1	T1 Working Memory	2.02***	1.86 to 2.19	.52
	Gender	-0.05	-0.13 to 0.04	-.02
Step 2	Light drinkers (ref=non-drinkers)	0.10	-0.11 to 0.30	.04
	Infrequent (ref=non-drinkers)	0.05	-0.17 to 0.27	.02
	Increasing (ref=non-drinkers)	0.12	-0.09 to 0.33	.05
	Decreasing (ref=non-drinkers)	-0.02	-0.25 to 0.21	-.07
	Chronic (ref=non-drinkers)	-0.03	-0.26 to 0.21	-.01
Step 3	Light drinkers (ref=non-drinkers) * gender	-0.42	-0.84 to 0.00	-.16
	Infrequent (ref=non-drinkers) * gender	-0.41	-0.86 to 0.05	-.08
	Increasing (ref=non-drinkers) * gender	-0.41	-0.84 to 0.02	-.13
	Decreasing (ref=non-drinkers) * gender	-0.35	-0.81 to 0.11	-.08
	Chronic (ref=non-drinkers) * gender	-0.33	-0.82 to 0.16	-.07
R^2=27 for Step 1, ΔR^2=.003 for Step 2 (n.s), ΔR^2=.002 for Step 3 (n.s)				
Δ Shift Attention (T1-T4)				
Step 1	T1 Shift Attention	3.27***	3.06 to 3.48	.59
	Gender	0.26***	0.17 to 0.34	.11
Step 2	Light drinkers (ref=non-drinkers)	0.15	-0.07 to 0.37	.06
	Infrequent (ref=non-drinkers)	0.19	-0.04 to 0.43	.05
	Increasing (ref=non-drinkers)	0.11	-0.12 to 0.32	.04
	Decreasing (ref=non-drinkers)	0.10	-0.15 to 0.34	.03
	Chronic (ref=non-drinkers)	0.13	-0.17 to 0.41	.03
Step 3	Light drinkers (ref=non-drinkers) * gender	0.22	-0.23 to 0.67	.07
	Infrequent (ref=non-drinkers) * gender	0.09	-0.44 to 0.61	.02
	Increasing (ref=non-drinkers) * gender	0.17	-0.30 to 0.65	.04
	Decreasing (ref=non-drinkers) * gender	0.51	-0.03 to 1.06	.09
	Chronic (ref=non-drinkers) * gender	0.40	-0.13 to 0.94	.06
R^2=.37 for Step 1, ΔR^2=.002 for Step 2 (n.s), ΔR^2=.004 for Step 3 (n.s)				
Δ Sustained Attention (T1-T4)				
Step 1	T1 Sustained Attention	0.52***	0.48 to 0.56	.49
	Gender	0.03	-0.04 to 0.11	.02
Step 2	Light drinkers (ref=non-drinkers)	0.13	-0.06 to 0.32	.07
	Infrequent (ref=non-drinkers)	0.14	-0.08 to 0.35	.05
	Increasing (ref=non-drinkers)	0.18	-0.02 to 0.39	.08
	Decreasing (ref=non-drinkers)	0.14	-0.11 to 0.38	.05
	Chronic (ref=non-drinkers)	0.19	-0.04 to 0.43	.06
Step 3	Light drinkers (ref=non-drinkers) * gender	-0.18	-0.58 to 0.22	-.07
	Infrequent (ref=non-drinkers) * gender	-0.19	-0.65 to 0.27	-.04
	Increasing (ref=non-drinkers) * gender	-0.11	-0.52 to 0.31	-.04
	Decreasing (ref=non-drinkers) * gender	-0.17	-0.63 to 0.28	-.04
	Chronic (ref=non-drinkers) * gender	-0.12	-0.60 to 0.36	-.03
R^2= .25 for Step 1, ΔR^2=.001 for Step 2 (n.s), ΔR^2=.001 for Step 3 (n.s)				

: significant at $p<.01$; *: significant at $p<.001$.

3.3.3 Additional analyses

We conducted three additional analyses. First, we were interested if the use of a continuous measure of alcohol consumption resulted in different outcomes. Therefore, we conducted separate linear regression analyses where the average number of glasses per week at T3, at T4, and the sum of these two measures as predictors. This did not result in significant findings (p>.01). Second, we tested whether the findings changed when drinking groups were formed according to the definition of heavy drinking by the National Institute on Alcohol Abuse and Alcoholism (i.e., >3/4 glasses daily and >7/14 glasses weekly for women and men respectively) (NIAAA, "Drinking levels defined", 2013). The analysis did not yield significant results (p>.01). Third, non-drinkers may consist of a non-normative group of adolescents; therefore, we also examined whether the findings changed when we used light drinkers or infrequent heavy drinkers as reference group instead of non-drinkers. The results were not significant (p>.05).[1]

3.4 DISCUSSION

Our longitudinal study did not show any measurable effect of groups of alcohol use on neurocognitive maturation, contrary to the hypothesis that the developing adolescent brain is particularly vulnerable to neurocognitive aversive effects of alcohol (e.g., Clark et al., 2008). The present study clearly found expected maturation on all the neurocognitive tests that we used (inhibition, working memory, and sustained and shift attention) (Boelema et al., 2014), hereby measuring neurocognitive functioning over a time span of eight years, i.e., with a pre-exposure measure and after four years of (heavy) alcohol consumption. However, we did not find an effect on any of the measures of any of the drinking groups, not even in the heaviest drinking group (i.e., drinking every weekend and drinking an average of 15 glasses of alcohol each week) for a period of at least four years in adolescence. Gender did not moderate the effect of drinking groups on neurocognitive maturation, which is in contrast to the previous findings that girls are assumed more vulnerable to the toxic effects of alcohol than are boys (Caldwell et al., 2005; Squeglia et al., 2011).

Our findings are thus in sharp contrast with the common assumption that alcohol leads to measurable changes in adolescents neurocognitive functioning, although they appear to be in line with the results from the few existing longitudinal studies in adolescents in the

1 Data not presented, available by first author on request.

general population that did not find neurocognitive deficits at a behavioural level in heavy drinkers for the vast majority of tasks. This implies that statements on how alcohol affects the adolescent brain apparently suffer from an overgeneralisation of research in clinical groups and an over-interpretation of cross-sectional research. On the positive side, the effect of alcohol on the developing brain does not appear to affect the basic neurocognitive functioning in an irreversible and devastating way. Thus, despite the obvious acute effects of alcohol as a toxic substance on the adolescent brain (being drunk, being unable to reason while being intoxicated, having hangovers and headaches), it may seem to be flexible enough to cope with these effects of alcohol at least at the level of behavioural development and neuropsychological maturation. That is not to say that the damaging effects of alcohol can be neglected *as such*, as heavy alcohol use in adolescents is associated with a large number of other well-established risks, such as developing an AUD, driving under influence, and engaging in risky behaviour, including violence and fighting while being intoxicated (Hingson & Zha, 2009). Furthermore, our results do not rule out the possibility of irreversible effects of alcohol in the long run, either after continuation of heavy drinking of a longer period of time, or the possibility that adolescent heavy drinking might set the stage for deficits in neurocognitive functioning that would manifest at some point later in life.

3.4.1 Strengths and limitations

Our approach has several strengths and limitations. Strengths are the large population sample and the longitudinal design. To the best of our knowledge, this study was the first to assess the effects of heavy drinking on neurocognitive functioning in a longitudinal population cohort of adolescents, covering about eight years, which is longer than in any of the other previous studies. We controlled for several significant covariates that correlated with our dependent variable. We conducted our study in the Netherlands, where legal drinking age is much younger than for example in the United States and alcohol consumption in adolescence is very common, optimising the chances for finding the effects of heavy drinking on neurocognitive maturation.

The first limitation concerns the basic tasks used to measure Executive Functioning. We measured the behavioural consequences of heavy and regular alcohol use with straightforward reaction time tasks, which measure the basics of Executive Functioning. This does not entail any knowledge on whether the underlying neuro-anatomy is affected and to what extent. For example, equal task performance in heavy drinkers and controls can still be accompanied by differences in neural activation while performing this task (Squeglia

et al., 2011). It is unclear what these differences represent, but they suggest that alterations in neural processing do not necessarily appear at a behavioural level (Squeglia et al., 2012). In addition, the possibility exists that more complex neuropsychological tasks might have been more sensitive in picking up such alterations. However, an important advantage of starting with the basics was that it allowed using exactly the same tasks at both age 11 and 19, which is a requirement for finding longitudinal change. More complex and strategy-based tasks usually have more stringent age restrictions, and tasks that are both feasible for early adolescents yet still challenging in late adolescence are difficult to find (Best & Miller, 2010). Furthermore, using straightforward tasks circumvents the problem of 'task impurity'. Since more complex tasks are assumed to rely on multiple cognitive processes and their integration (Jurado & Rosselli, 2007; Squeglia et al., 2009; Tsuchida & Fellows, 2013), it is difficult to identify processes that are responsible for a suboptimal performance (Best, Miller, & Jones, 2009). The reaction time tasks we used were not designed to detect deficits, but are able to detect differences between groups on the level of performance. Our findings indicate no performance differences between drinking adolescents and abstaining peers on basic functions, making deficits in these skills unlikely.

The second limitation could be that drinking groups were constructed manually using self-reported measures of alcohol use, although this is common in longitudinal research on adolescent alcohol use (Squeglia et al., 2009; Squeglia et al., 2012). Self-report questionnaires have proved to be reliable for assessing alcohol use in adolescence (Koning, Harakeh, Engels, & Vollebergh, 2010). In addition, our drinking groups showed good and consistent differentiation on validating measures, with chronic drinkers scoring highest on all alcohol-related behaviours and revealing a heavy drinking pattern at two consecutive waves, which cover at least four years of regular heavy drinking. We are therefore confident that we have adequately identified the most risky drinkers.

The final limitation in longitudinal designs is that attrition may have biased the findings, with most at-risk participants dropping out, resulting in an underestimation of effects and possible loss of power. However, using multiple imputation, missing data on alcohol use and neurocognition were imputed based on a wide variety of associated variables. This technique improves validity of datasets with missing data (Blankers, Koeter, & Schippers, 2010). Therefore, in our study, attrition bias is unlikely to explain the absence of significant results.

3.4.2 Conclusion

We did not find the effects of adolescent alcohol use on neurocognitive maturation in adolescence. Four years of weekly heavy drinking did not result in deviancies in behavioural performance on a variety of straightforward neurocognitive tasks. However, these finding should not be seen as reassuring about adolescent alcohol use as there are numerous other risks related to heavy drinking, such as, developing an alcohol use disorder, driving under influence, and engaging in risky behaviour that include violence and fighting while being intoxicated (Hingson & Zha, 2009). Consideration of these risks calls for continuous prevention efforts targeting heavy alcohol use in adolescents.

4

Differences in visuospatial problem-solving between drinking and non-drinking adolescents. Longitudinal findings from the TRAILS study.

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ABSTRACT

Background: The aim of the present longitudinal study was to investigate the relationship between heavy drinking and neurocognitive functioning in adolescence. We assessed whether alcohol use was associated with (1) cognitive deficits, and (2) visuospatial problem-solving.

Methods: We used the data from the TRacking Adolescents' Individual Lives Survey (TRAILS) study (n=1,596). Six groups of drinkers, ranging from non-drinkers to chronic drinkers, were identified based on individuals' drinking behaviour at ages 16 and 19. We measured neurocognitive functioning at age 19. Indicators of cognitive deficits were assessed with the Rey Auditory Verbal Learning Test-Dutch version, Rey Complex Figure Test, Wechsler Adult Intelligence Scale (WAIS) III Digit Span, and Verbal Fluency. Problem-solving was assessed using WAIS-III Block Design. Linear regression analyses were conducted, adjusting for basic neurocognitive functioning at age 11 (measured with the Amsterdam Neuropsychological Tasks) and covariates (e.g., gender, cannabis use and delinquent behaviour).

Results: (1) No differences on tests assessing cognitive deficits were found between drinkers and non-drinkers. (2) Regarding problem-solving, non-drinkers outperformed other drinking groups, even the light drinkers. Post-hoc analyses did not show differences between light drinkers and other categories of drinkers on Block Design.

Conclusions: Drinkers showed less optimal visuospatial problem-solving skills compared to non-drinkers but the absence of a dose-response relationship between alcohol use and problem-solving skills suggests that alcohol may not account for this difference.

4.1 INTRODUCTION

Alcohol use is common in adolescence, with monthly prevalence rates as high as 77% for Dutch 16 year-olds (Verdurmen et al., 2012). Adolescent alcohol use raises various widespread concerns on serious injuries, impaired judgement, and brain development problems, which have been reflected, for example, in communications by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA; "Special populations", 2013), and policies on underage alcohol use such as the recent increase from 16 to 18 years for the legal age for buying alcohol in the Netherlands. These concerns are supported by the assumption that the adolescent brain is particularly vulnerable to the adverse effects of alcohol (Clark, Thatcher, & Tapert, 2008; Spear, 2011; Steinberg, 2005) as result of significant maturation of both brain structure (Giedd et al., 1999) and functions (e.g., Boelema et al., 2014; Crone, 2009), presumably under the influence of sex hormones (Berenbaum & Beltz, 2011). This proposed vulnerability is particularly relevant at this age, since adolescence is a phase in which societal demands related to the transition to young adulthood, such as going to college, leaving the parental home and being financially independent, increase. Essential for success in everyday living is the ability to organise thoughts and behaviour in a goal-directed manner, which relies on intact cognitive control functions (Jurado & Rosselli, 2007). If the maturation of such functions is specifically vulnerable to the effects of alcohol, this is a reason to be particularly worried about adolescent alcohol use.

However, most studies in this field have been conducted in clinical groups (i.e., adolescents with Alcohol Use Disorder) and with cross-sectional designs hampering generalising to a societal level or drawing inferences on the causality of cognitive dysfunction (Brown et al., 2000; Hanson et al., 2011; Moss et al., 1994; Tarter et al., 1995). The latter because it is not only presumed that alcohol has an effect on neurocognitive functioning, but also that neurocognitive functioning influences the behaviour with respect to alcohol use. This holds especially for neurocognitive control functions, such as inhibition, attention, and working memory (Grenard et al., 2008; Tapert, Baratta, Abrantes, & Brown, 2002; Tarter et al., 2003). Longitudinal designs with pre- and post-exposure measures of neurocognitive functioning can overcome this problem.

To the best of our knowledge, only three studies have investigated the effects of alcohol use on maturation of neurocognitive functioning in a longitudinal design (Squeglia et al., 2009; Squeglia et al., 2012; Wetherill, Squeglia, Yang, & Tapert, 2013). One study (n=75) found differences between heavy drinkers (average drinks per month: 9.9 for girls and 6.1 for boys) and controls on one out of four neurocognitive domains, and even more specifically

this difference was found for girls only (Squeglia et al., 2009). Two other studies (*n*=40) showed increased brain activation with fMRI measurements (but not in all hypothesized brain areas) in adolescents who transitioned to heavy drinking (drinks per drinking day: 4.2 and 6.1 respectively), while no differences between drinkers and non-drinkers were found on task performance (Squeglia et al., 2012; Wetherill, Squeglia, Yang, & Tapert, 2013).

In a recent longitudinal study in 2,230 adolescents (Boelema et al., submitted for publication) we found no significant effects of four years of weekly heavy drinking on tasks measuring basic neurocognitive control functioning (i.e., inhibition, working memory, sustained, and shift attention). One explanation for this finding is that these merely basic cognitive control functions are not specifically sensitive to the effects of alcohol. Notwithstanding the fact that they are prerequisite for neurocognitive skills that are more complex (Miyake et al., 2000), adequate performance in daily life requires more than intact basic skills. At a neuro-anatomical level, alcohol use in adolescence is assumed to influence maturational myelination and pruning (Moss, 2008), two processes involved in facilitating synaptic connections between different brain areas essential for the transfer of information throughout the brain (Luna et al., 2001). More complex classical neuropsychological tasks relying on multiple integrated cognitive processes might better relate to control function likely to be involved in daily life (Jurado & Rosselli, 2007; Squeglia et al., 2009; Tsuchida & Fellows, 2013).

Therefore, in task selection, a point of concern is the fact that classical neuropsychological tasks are generally designed to investigate deficits in neurocognitive functioning that would be suggestive of brain dysfunction and not evaluate performance level per se. However, adolescent alcohol use might (initially) cause more subtle neural alterations, which do not directly exceed the threshold of deficits (Boelema et al., submitted for publication; Squeglia et al., 2012). When using such tasks to assess differences between groups in normative populations, such differences might not be severe enough to be picked up by indicators of cognitive deficits. Therefore, it is useful to also investigate performance on more dynamic cognitive tasks, based on the combination of both task difficulty and speed of processing, in order to learn more about the level of functioning that can be achieved. Such a task would encompass various cognitive domains and its complexity would make it more sensitive to the effects of alcohol. This general fluid ability is reflected in tasks assessing logical reasoning or problem-solving.

In the present longitudinal study, we investigated the relations between alcohol use and two types of tasks, assessing indicators of *cognitive deficits* and *visuospatial problem-solving*

skills, in late adolescence in a large late adolescent sample. We included neuropsychological tasks that cover various functional domains and rely on the collaboration and integration of cognitive functions. Our aim was twofold. First, we investigated cognitive performance of alcohol consuming adolescents on tasks designed to assess deficits. We used well-known and robust international standard tasks, such as the Rey Auditory Verbal Learning Test (Rey & Osterrieth, 1993; Shin, Park, Park, Seol, & Kwon, 2006) and subtests from the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997). We hypothesised that alcohol use negatively predicted performance on these tasks. Second, we investigated whether and to what extent drinking patterns are associated with differences in visuospatial problem-solving and logical reasoning, as measured with WAIS-III Block Design. Again, we expected drinking patterns to be negatively related to these capacities. We controlled for basic cognitive control functions of inhibition, attention, and working memory, which we measured before drinking onset to avoid the possibility that pre-existing difference in these functions might bias the findings. By using longitudinal drinking patterns, we assessed a dose-response relationship between neurocognitive functioning and alcohol, where we expected more severe drinkers to show a less optimal performance.

4.2 MATERIALS AND METHODS

4.2.1 Study design

The present study used the data from the first, second (for descriptive statistics only), third, and fourth waves of the TRacking Adolescents' Individual Lives Survey (TRAILS). This is a prospective cohort study of Dutch pre-adolescents at age. The target sample involved children living in the North of the Netherlands, covering urban and rural areas (For details on the procedure see: De Winter et al., 2005; Ormel et al., 2012). Seventy-six percent of eligible adolescents and their parents agreed to participate and were enrolled in the study at baseline (n=2,230, mean age 11.1 years, SD=0.56, 49.2% male). On the third (T3) assessment (n=1,816, mean age 16.3 years, SD=0.70, 47.7% male), the response rate was 81.4%. On the fourth (T4) assessment (n=1,596, mean age 19.2 years, SD=0.57, 46% male), the response rate was 70%.

4.2.2 Procedure

On the first assessment, trained undergraduate psychology students administered neuropsychological test in adolescents' schools or designated testing centres (for more information, see Brunnekreef et al., 2007). Participants who were unable to attend these assessments were tested at home. On the first to third assessments, adolescents completed self-report questionnaires in groups in school, supervised by an assistant. Their parents also completed a written questionnaire. On the fourth assessment, most adolescents were no longer in secondary education. Therefore, trained professional interviewers administered the neuropsychological test battery individually at participants' homes or at a nearby community centre (for more information, see Boelema et al., 2014). Parents and their children were asked to fill out a computerised questionnaire (or, per request, a paper-and-pencil questionnaire). The Dutch Central Committee on Research Involving Human Subjects approved the study. Parents and adolescents' written informed consent was obtained. The confidentiality of the study was emphasised.

4.2.3 Measures

4.2.3.1 Alcohol use

Descriptive statistics. At T1, adolescents were asked: "How often have you been drinking alcohol (for example, a bottle of beer or a glass of wine)?" up until that time point, on a 5-point scale ranging from 0 to 7 times or more. We dichotomised these answers into 'never or once' and 'twice or more'. At T2-T4, adolescents were asked to report their average drinking habits between the previous data collection wave and the present. They were asked four questions: "On how many week(end) days do you normally drink alcohol" and "On an average week(end) day on which you drink alcohol, how much alcohol (glasses, cans, bottles) do you drink?" By multiplying and adding the answers, average weekly quantity of alcohol use can be computed. A Dutch standard drink contains 10 grams of alcohol. Furthermore, at T2-T4 adolescents were asked how many times they had been drunk in the last 12 months. We dichotomised these answers into never and once or more. These measures of alcohol use were used as descriptive statistics.

Drinking groups. For constructing drinking groups, we used the average amount of glasses on a weekend day (since previous measurement wave), since weekend quantity of alcohol use has been shown to be a useful and specific measure of alcohol use at this age (Weingardt et al., 1998). In order to select respondents that were regular heavy drinkers, we

furthermore used the question "On how many occasions in the last month have you had an alcoholic beverage to drink?" Since legal age for buying alcohol in the Netherlands was 16 years at time of the data collection, we used data from T3 and T4 to determine group assignment.

We first identified a group of non-drinkers who indicated that they did not consume alcohol on a regular weekend day. For the respondents who consumed alcohol, we set the cut off score for heavy drinking at 6 glasses on a weekend day for boys and 5 glasses for girls (Koning, van den Eijnden, Verdurmen, Engels, & Vollebergh, 2013). We furthermore distinguished between frequent (last month prevalence ≥ 4 times heavy drinking) and non-frequent heavy drinking. This resulted in participants being labelled as non-drinkers, not heavy drinkers, infrequent heavy drinkers (i.e., less than weekly), or heavy drinkers (weekly) at both T3 and T4. Finally, these categorizations per time point were combined into longitudinal drinking patterns. Participants were divided into six groups: Non-drinker, light drinker, infrequent heavy drinker, increasing heavy drinker, decreasing heavy drinker, and chronic heavy drinker (for descriptive characteristics, see Table 4.1). The measures to construct drinking groups have been used in other studies within the TRAILS-project (Boelema et al., re-submitted for publication).

4.2.3.2 Neurocognitive functioning

Neurocognitive outcome measures. At T4, The neuropsychological test battery assessed consolidation, retention, and retrieval of information, as well as adequate functioning of attention and working memory, which are prerequisite functions. The assessment battery included a subtest of the WAIS-III (Digit Span) (Wechsler, 1997), the Rey Verbal Learning Test (RVLT) (Rey, 1958; Van Der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005), the Complex Figure of Rey (CFR) (Rey & Osterrieth, 1993; Shin, Park, Park, Seol, & Kwon, 2006), and the Word Fluency Task (Harrison, Buxton, Husain, & Wise, 2000). Another subtest of the WAIS-III (Block Design) was used to assess visuospatial problem-solving. For an overview of tests used, see Table 4.2.

Baseline neurocognitive functioning. At T1, three computerised reaction time tasks from the Amsterdam Neuropsychological Tasks program (ANT) were administered (De Sonneville, 1999). The ANT is a sensitive and valid tool in non-referred (De Sonneville et al., 2002; Stins et al., 2005) as well as in clinical samples (Altink et al., 2009; Huijbregts et al., 2003; Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009; Van Rijn, Aleman, De Sonneville, & Swaab, 2009). We assessed four basic neurocognitive functions: Inhibition

Table 4.1 Descriptive statistics of the six drinking groups

	Non-drinkers	Light drinkers	Infrequent heavy drinkers	Increased heavy drinkers	Decreased heavy drinkers	Chronic heavy drinkers
Drinking behaviour (ages 16;19)	ND;ND	ND;DNHD DNHD;ND DNHD;DNHD	ND/DNHD;IHD IHD;ND/DNHD IHD;IHD	ND;HD, DNHD;HD IHD;HD	HD;ND HD;DNHD HD; IHD	HD/HD
N	85	873	272	514	250	232
% male	34	48	39	58	47	54
Age at baseline	11.3[a]	11.4[a]	11.4[a]	11.4[a]	11.4[a]	11.4[a]
Parent SES at baseline	-0.09[a]	-0.01[a]	-0.15[a]	0.01[a]	-0.18[a]	-0.08[a]
Maternal alcohol use	2.5(3.7)[a]	3.3(4.1)[ab]	3.0(4.0)[ab]	3.7(4.4)[bc]	3.7(4.4)[bc]	4.5(5.1)[c]
Paternal alcohol use	4.4(5.0)[a]	5.1(5.3)[ab]	5.1(5.3)[ab]	6.2(5.6)[bc]	6.0(5.8)[bc]	6.7(5.9)[c]
Delinquent behaviour age 11	0.19(0.18)[a]	0.21(0.15)[ab]	0.22(0.16)[ab*]	0.24(0.17)[abc]	0.26(0.18)[bc]	0.28(0.22)[c]
Prevalence last year cannabis use age 16 (%)	7[-]	33[-]	42	45	62[+]	70[+]
Prevalence last year cannabis use age 19 (%)	2[-]	40[-]	44	61[+]	58	67[+]
Prevalence daily smoking at age 16 (%)	10[-]	16[-]	29	27	44[+]	48[+]
Prevalence daily smoking at age 19 (%)	8[-]	21	29	40[+]	42[+]	56[+]
Prevalence of haven drunk >1 glass age 11 (%)	5[†]	12[-]	15	19	21	23[+]
Prevalence last year drunkenness age 13 (%)	9[-]	20[-]	26	28	35[+]	36[+]
Prevalence last year drunkenness age 16 (%)	14[-]	55[-]	74	77	94[+]	98[+]
Prevalence last year drunkenness age 19 (%)	22[-]	74[-]	88	98[+]	82	97[+]
N glasses per week age 13 (*SD*)	1.0(3.1)[a]	1.1(3.2)[a]	1.4(3.1)[a]	1.5(3.2)[b]	3.1(5.6)[b]	3.1(5.0)[b]
N glasses per week age 16 (*SD*)	0.1(0.1)[a]	3.1(2.5)[a]	5.8(4.5)[b]	5.8(4.8)[b]	12.9(6.5)[c**]	14.2(7.1)[c**]
N glasses per week age 19 (*SD*)	0.4(2.0)[a]	4.8(3.5)[b***]	7.2(5.0)[c]	14.0(7.5)[d****]	6.6(5.3)[c***]	15.8(8.2)[e****]

	Non-drinkers	Light drinkers	Infrequent heavy drinkers	Increased heavy drinkers	Decreased heavy drinkers	Chronic heavy drinkers
Inhibition *M* (*SD*) age 11 in ms	198 (141)	197(157)	190(170)	197(156)	202(140)	199(148)
Working Memory *M* (*SD*) age 11 in ms	443 (268)	479(270)	475(277)	473(256)	480(272)	487(268)
Sustained Attention *M* (*SD*) age 11 in sec	1.79(1.05)	1.76(0.94)	1.69(0.85)	1.74(0.92)	1.83(0.93)	1.78(0.89)
Shift Attention *M* (*SD*) age 11 in ms	586(245)	559(219)	544(201)	544(210)	556(210)	570(219)
Inhibition *M* (*SD*) age 19 in ms	162(141)	173(142)	172(201)	174(142)	196(151)	189(148)
Working Memory *M* (*SD*) age 19 in ms	243(175)	240(150)	245(146)	235(143)	257(157)	260(155)
Sustained Attention *M* (*SD*) age 19 in sec	0.97(0.51)	0.93(0.44)	0.92(0.42)	0.92(0.49)	0.97(0.47)	0.95(0.41)
Shift Attention *M* (*SD*) age 19 in ms	359(132)	334(131)	332(120)	339(134)	351(169)	350(143)
Inhibition standardised change score	0.11(1.09)	0.03(1.17)	-0.01(1.17)	0.02(1.19)	-0.10(1.17)	-0.07(1.13)
Working Memory standardised change score	-0.12(1.23)	0.03(1.03)	-0.01(1.06)	0.04(1.03)	-0.08(1.03)	-0.08(1.02)
Sustained Attention standardised change score	-0.05(0.87)	0.02(0.95)	-0.04(0.85)	0.01(1.11)	-0.01(0.92)	-0.01(0.93)
Shift Attention standardised change score	0.00(1.26)	0.06(1.14)	0.00(1.04)	-0.05(1.19)	-0.08(1.31)	-0.01(1.32)

ND = non-drinking, DNHD = drinking, not heavy drinking, IHD = infrequent heavy drinking, HD = heavy drinking.
+ or - signs mean Pearson-Chi-Square Test is significant. + means cell count is higher than expected, - means cell count is lower than expected (based on significant standardised residuals for all imputed datasets). †: cell count was lower than 5.
Different superscript letters refer to significant differences ($p<.05$) in mean scores between groups: if two group scores are labelled with the same letter, the scores of these groups do not differ. If two scores are labelled with different letters, these scores differ.
*: in two of the five imputed datasets, there was a significant difference between increasers and other heavy drinking groups.
**: in one of the five imputed datasets, there was a significant difference between decreasers and chronic heavy drinkers.
***: in one of the five imputed datasets, there was no significant difference between light drinkers and decreasers.
****: in two of the imputed datasets, there was no significant difference between increasers and chronic heavy drinkers.

Table 4.2 Description of the neuropsychological tasks (T4)

Measure	Aimed at testing
WAIS-III	
Digit Span Forwards	Attention span
Digit Span Backwards	Working memory span
Rey Verbal Learning Test	
RVLT Short Term	Learning and consolidation of verbal material
RVLT Long Term	Retrieval of verbal material
RVLT Recognition	Recognition of verbal material
Complex Figure of Rey	
CFR Copy	Visuoconstruction
CFR Long term	Visual memory and incidental learning
Word Fluency	
Phonological Fluency	Concept generation
Semantic Fluency	Semantic memory
WAIS-III	
Block Design	Visuospatial problem-solving and logical reasoning

(of prepotent responses), Working Memory speed, Shift Attention, and Sustained Attention, since they have sufficient longitudinal stability (Boelema et al., 2014), and are theoretically hypothesised to be associated with alcohol deficits (Tarter et al., 1995). The ANT has shown to be applicable for longitudinally assessing these basic neurocognitive functions in an adolescent population (as studied in the TRAILS-project, Boelema et al., 2014). The Appendix describes the tasks used and provides an overview of the operationalization of neurocognitive functions it measures.

4.2.3.3 Measurement of covariates

In accordance with previous studies (Squeglia et al., 2009), age at T1, SES, educational level, paternal and maternal alcohol use, delinquent behaviour at age 11, and smoking and cannabis use at age 16 and 19 were included as covariates if they significantly correlated with the outcomes measure ($p<.05$) (See Table 4.3). *SES* was assessed using income level, educational level, and occupational level of both parents (occupational level was based on the *International Standard Classification for Occupations* (Ganzeboom & Treiman, 1996). These five variables were standardised and combined into one scale with an internal consistency of .84 (for more information, see Veenstra et al., 2005). *Educational level* was classified using the coding system for secondary education (Verhage, 1964), where the level of achieved

Table 4.3 Bivariate correlations among the covariates and neurocognitive functioning (T4)

Covariate	Digit Span forward	Digit Span backward	RVLT short term	RVLT long term	RVLT recog-nition	CFR copy	CFR recall	Phono-logical Fluency	Semantic Fluency	Block design
T1 Inhibition	-.03	-.12*	-.08*	-.08*	-.03	-.07*	-.11*	-.04	-.10*	-.21*
T1 Working Memory	-.13*	-.17*	-.18*	-.17*	-.13*	-.11*	-.07*	-.14*	-.11*	-.12*
T1 Sustained Attention	-.21*	-.21*	-.21*	-.16*	-.19*	-.22*	-.11*	-.20*	-.15*	-.27*
T1 Shift Attention	-.08*	-.10*	-.06*	-.02	.002	-.08*	-.07*	-.09*	-.04	-.13*
Age at T1	-.07*	-.04	-.06*	-.01	.03	-.03*	-.01	-.02	-.02	-.04
SES	.19*	.23*	.20*	.13*	-.13*	.18*	.21*	.29*	.25*	.30*
Educational level	.26*	.30*	.31*	.23*	-.19*	.28*	.22*	-.31*	.26*	.37*
Maternal alcohol use	.10*	.11*	.09*	.04	-.06*	.09*	.09*	.14*	.09*	.15*
Paternal alcohol use	.07*	.04	.08*	.02	.03	.09*	.06*	.14*	.09*	.12*
Delinquency scores	.03	-.03	-.06*	-.05	-.04	-.04	.00	.02	.04	-.03
T3 last year cannabis use	-.02	-.06*	-.11*	-.09*	.08*	-.07*	-.05*	.00	.03	-.08*
T4 last year cannabis use	.04	-.03	-.11*	-.09*	-.07	-.02	-.05	.02	-.03	-.05
T3 last month smoking	-.07*	-.08*	-.16*	-.10*	-.05	-.11*	-.12*	-.13*	-.12*	-.22*
T4 last month smoking	-.06*	-.08*	-.15*	-.11*	.04	-.11*	-.13*	.12*	.12*	-.19*

*: correlation is significant ($p<.05$). These variables were controlled for in the regression analyses.

education is divided into seven categories. *Paternal and maternal alcohol use* was assessed at T1 by asking the parent who filled out the questionnaire how much alcohol (s)he drinks per week on average and how much his or her partner drinks. *Delinquent behaviour* was measured at T1 Youth Self Report (YSR) (Achenbach, 1991; Achenbach & Rescarola, 2001), consisting of 15 items (α=.71). *Smoking* was also measured at both T3 and T4 by asking: "How many times have you smoked cigarettes during the last month?" *Cannabis use* was assessed at T3 and T4 by asking: "How many times have you used weed (marihuana) or hash during the last year?"

4.2.4 Data analyses

Because there were missing values due to attrition on both predictors and outcome measures, we imputed multiple data sets in SPSS 20, using fully conditional specification (MCMC) with Predictive Mean Matching (Van Buuren, 2007). This approach generated five datasets and one pooled dataset (Van Buuren, 2007). In the original database, drop-out on neurocognitive tests at T4 did not significantly differ across the drinking groups (p>.01).

The six drinking patterns were validated by comparing them on alcohol related behaviour, such as prevalence of last year drunkenness and drinking in early adolescence. For variables measuring prevalence, Pearson χ^2 with standardised residuals was used to identify observed counts that were significantly different (p<.05) from expected counts. For continuous variables, MANOVA with post-hoc tests was used. In both cases, the five datasets were analysed separately, as pooled analyses are unavailable for these tests.

To investigate the influence of drinking patterns on neurocognitive functioning, we conducted bivariate and multivariate linear regression analyses. Performance on tasks assessing cognitive deficits and problem-solving scores were the dependent variables and dummy variables of drinking patterns predictors (non-drinkers served as the reference group). The baseline scores (T1) of the ANT tasks were added as indicators of pre-exposure functioning. First, we conducted ten separate linear regression analyses without covariates. Second, we conducted multivariate linear regression analyses for each of the nine cognitive deficit scores and for problem-solving and adjusted for gender (in all analyses) and other covariates. All these variables were entered in the first block. In the second block, the drinking patterns were included as dummies. To reduce Type 1 error, we set α at <.01.

4.3 RESULTS

4.3.1 Descriptive statistics for the drinking groups

Descriptive statistics are depicted in Table 4.1. There were no differences between the groups for baseline neurocognitive functioning, SES, and age. Pearson χ^2 yielded significant differences between groups for prevalence rates of other substance use, drinking in early adolescence, and drunkenness. Non-drinkers and light drinkers scored lower than expected on all variables while the chronic drinkers scored higher on all variables. A MANOVA indicated significant differences between groups on all continuous measures (p<.001). Parental alcohol use and delinquency scores in pre-adolescence were largest in the regular heavy drinking groups. Also, those would later would be classified as regular heavy drinkers drank significantly more at age 13 than the future non regular heavy drinking. Chronic drinkers, as to be expected, drank most, with an average weekly consumption finally exceeding 14 glasses. Taken together, the results indicated significant differences between the drinking groups on all measures of alcohol related behaviour, validating our identification of the six drinking patterns. The patterns become more differentiated as the adolescents get older.

4.3.2 Indicators of cognitive deficits

Scores for the population as a whole were comparable with regard to mean and standard deviation to norm scores for all tasks (data not presented). Regression analyses without covariates yielded no significant differences between drinkers and controls for the nine measures of cognitive deficits. Additionally, no significant results were found in the regression analyses for any of the measures after adding covariates (see Table 4.4).

4.3.3 Visuospatial problem-solving skills

Regression analyses without covariates showed that being a member of the drinking groups significantly predicted worse performance on problem-solving task compared to non-drinkers, with an exception of light drinkers who did not differ from non-drinkers in performance. When adjusting for covariates, being a member of all five drinking groups, in contrast to non-drinkers, predicted a lower score. Noteworthy is that both sustained attention at T1 (*B*:-2.08, *SE B*:0.38; 95%CI [-2.83 to -1.33], p<.001) and especially inhibition at T1 (*B*:-14.52, *SE B*: 2.30; 95%CI [-19.15 to -9.90], p<.001) were important predictors of

Table 4.4 Neurocognitive functioning (T4) predicted by drinking groups (T3-T4) and basic neurocognitive functioning (T1) controlling for covariates. A higher score means better performance

Indicators of cognitive deficits		*B*	95% Confidence Interval (CI) of *B*	β
Digit span forward				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	0.18	-0.07 to 0.43	.08
	Infrequent (ref=non-drinkers)	0.12	-0.18 to 0.41	.03
	Increasing (ref=non-drinkers)	0.22	-0.03 to 0.48	.09
	Decreasing (ref=non-drinkers)	0.06	-0.22 to 0.35	.02
	Chronic (ref=non-drinkers)	0.26	-0.01 to 0.54	.07
Plus covariates	Light drinkers (ref=non-drinkers)	0.13	-0.11 to 0.37	.06
	Infrequent (ref=non-drinkers)	0.14	-0.16 to 0.44	.04
	Increasing (ref=non-drinkers)	0.17	-0.08 to 0.43	.07
	Decreasing (ref=non-drinkers)	0.07	-0.22 to 0.37	.02
	Chronic (ref=non-drinkers)	0.24	-0.04 to 0.52	.07
R^2=.11 for Block 1. ΔR^2=.002 for Block 2 (n.s).				
Digit span backward				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	0.06	-0.21 to 0.34	.02
	Infrequent (ref=non-drinkers)	-0.07	-0.39 to 0.24	-.02
	Increasing (ref=non-drinkers)	0.05	-0.26 to 0.36	.02
	Decreasing (ref=non-drinkers)	-0.08	-0.39 to 0.23	-.02
	Chronic (ref=non-drinkers)	-0.06	-0.39 to 0.26	-.02
Plus covariates	Light drinkers (ref=non-drinkers)	0.00	-0.27 to 0.27	.00
	Infrequent (ref=non-drinkers)	-0.05	-0.35 to 0.26	-.01
	Increasing (ref=non-drinkers)	-0.00	-0.30 to 0.29	.00
	Decreasing (ref=non-drinkers)	-0.06	-0.36 to 0.25	-.02
	Chronic (ref=non-drinkers)	-0.08	-0.43 to 0.27	-.02
R^2=.13 for Block 1, ΔR^2=.001 for Block 2 (n.s).				
RVLT short term				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	-0.08	-2.14 to 1.97	-.01
	Infrequent (ref=non-drinkers)	-0.20	-2.36 to 1.97	-.01
	Increasing (ref=non-drinkers)	-0.99	-3.09 to 1.10	-.05
	Decreasing (ref=non-drinkers)	-0.91	-3.20 to 1.39	-.03
	Chronic (ref=non-drinkers)	-1.17	-3.47 to 1.14	-.04
Plus covariates	Light drinkers (ref=non-drinkers)	-0.09	-0.69 to 0.51	-.02
	Infrequent (ref=non-drinkers)	-0.25	-0.91 to 0.40	-.03
	Increasing (ref=non-drinkers)	-0.24	-0.90 to 0.43	-.04
	Decreasing (ref=non-drinkers)	0.01	-0.68 to 0.69	.00
	Chronic (ref=non-drinkers)	-0.10	-0.79 to 0.58	-.01
R^2=.11 for Block 1. ΔR^2=.001 for Block 2 (n.s).				

Table 4.4 continues on next page

		B	95% CI of *B*	β
RVLT long term				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	-0.20	-0.82 to 0.42	-.04
	Infrequent (ref=non-drinkers)	-0.46	-1.13 to 0.21	-.06
	Increasing (ref=non-drinkers)	-0.54	-1.20 to 0.13	-.08
	Decreasing (ref=non-drinkers)	-0.34	-1.03 to 0.36	-.04
	Chronic (ref=non-drinkers)	-0.51	-1.21 to 0.18	-.06
Plus covariates	Light drinkers (ref=non-drinkers)	-0.11	-0.72 to 0.50	-.02
	Infrequent (ref=non-drinkers)	-0.28	-0.93 to 0.38	-.04
	Increasing (ref=non-drinkers)	-0.26	-0.91 to 0.40	-.04
	Decreasing (ref=non-drinkers)	-0.02	-0.70 to 0.66	-.00
	Chronic (ref=non-drinkers)	-0.13	-0.81 to 0.55	-.02
R^2=.11 for Block 1, ΔR^2=.003 for Block 2 (n.s).				
RVLT recognition				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	-0.06	-0.32 to 0.20	-.03
	Infrequent (ref=non-drinkers)	-0.02	-0.29 to 0.26	-.01
	Increasing (ref=non-drinkers)	-0.15	-0.40 to 0.11	-.06
	Decreasing (ref=non-drinkers)	-0.15	-0.44 to 0.15	-.04
	Chronic (ref=non-drinkers)	-0.03	-0.34 to 0.23	-.02
Plus covariates	Light drinkers (ref=non-drinkers)	-0.04	-0.30 to 0.21	-.02
	Infrequent (ref=non-drinkers)	0.04	-0.23 to 0.31	.01
	Increasing (ref=non-drinkers)	-0.09	-0.35 to 0.18	-.03
	Decreasing (ref=non-drinkers)	-0.05	-0.35 to 0.24	-.01
	Chronic (ref=non-drinkers)	0.05	-0.24 to 0.33	.01
R^2=.07 for Block 1, ΔR^2=.002 for Block 2 (n.s).				
CFR copy				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	-0.16	-0.88 to 0.55	-.02
	Infrequent (ref=non-drinkers)	-0.24	-1.03 to 0.65	-.03
	Increasing (ref=non-drinkers)	-0.26	-1.00 to 0.47	-.03
	Decreasing (ref=non-drinkers)	-0.15	-0.93 to 0.64	-.01
	Chronic (ref=non-drinkers)	-0.68	-1.53 to 0.17	-.06
Plus covariates	Light drinkers (ref=non-drinkers)	-0.20	-0.90 to 0.51	-.03
	Infrequent (ref=non-drinkers)	-0.09	-0.85 to 0.68	.00
	Increasing (ref=non-drinkers)	-0.21	-0.94 to 0.52	-.02
	Decreasing (ref=non-drinkers)	0.08	-0.71 to 0.87	.00
	Chronic (ref=non-drinkers)	-0.49	-1.34 to 0.37	-.04
R^2=.11 for Block 1, ΔR^2=.002 for Block 2 (n.s).				
CFR recall				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	0.06	-1.24 to 1.36	.01
	Infrequent (ref=non-drinkers)	-0.91	-2.39 to 0.57	-.05
	Increasing (ref=non-drinkers)	-0.44	-1.90 to 1.02	-.03
	Decreasing (ref=non-drinkers)	-0.29	-1.97 to 1.34	-.02
	Chronic (ref=non-drinkers)	-0.51	-2.08 to 1.06	-.03

Table 4.4 continues on next page

Table 4.4 *Continued*

Indicators of cognitive deficits		*B*	95% Confidence Interval (CI) of *B*	β
Plus covariates	Light drinkers (ref=non-drinkers)	0.04	-1.24 to 1.31	.00
	Infrequent (ref=non-drinkers)	-0.52	-1.93 to 0.89	-.03
	Increasing (ref=non-drinkers)	-0.25	-1.63 to 1.14	-.02
	Decreasing (ref=non-drinkers)	0.31	-1.49 to 2.10	.02
	Chronic (ref=non-drinkers)	0.03	-1.55 to 1.61	.00
R^2=.08 for Block 1, ΔR^2=.002 for Step 2 (n.s).				
Phonological fluency				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	0.92	-0.83 to 2.66	.06
	Infrequent (ref=non-drinkers)	-0.20	-2.00 to 1.60	.01
	Increasing (ref=non-drinkers)	0.71	-1.10 to 2.53	.04
	Decreasing (ref=non-drinkers)	-0.11	-2.04 to 1.82	-.01
	Chronic (ref=non-drinkers)	0.73	-1.12 to 2.56	.03
Plus covariates	Light drinkers (ref=non-drinkers)	0.54	-1.13 to 2.20	.04
	Infrequent (ref=non-drinkers)	0.10	-1.60 to 1.80	.00
	Increasing (ref=non-drinkers)	0.35	-1.38 to 2.08	.02
	Decreasing (ref=non-drinkers)	0.24	-1.64 to 2.12	.01
	Chronic (ref=non-drinkers)	0.73	-1.13 to 2.60	.03
R^2=.15 for Block 1, ΔR^2=.001 for Block 2 (n.s).				
Semantic fluency				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	-0.41	-2.41 to 1.60	-.02
	Infrequent (ref=non-drinkers)	-1.31	-3.40 to 0.78	-.05
	Increasing (ref=non-drinkers)	-0.19	-2.19 to 1.80	-.01
	Decreasing (ref=non-drinkers)	-1.96	-3.16 to 1.23	-.04
	Chronic (ref=non-drinkers)	-1.13	-3.30 to 1.04	-.04
Plus covariates	Light drinkers (ref=non-drinkers)	-0.58	-2.50 to 1.34	-.03
	Infrequent (ref=non-drinkers)	-0.84	-2.86 to 1.18	-.03
	Increasing (ref=non-drinkers)	-0.14	-2.12 to 1.83	-.01
	Decreasing (ref=non-drinkers)	-0.29	-2.40 to 1.83	-.01
	Chronic (ref=non-drinkers)	-0.65	-2.91 to 1.61	-.02
R^2=.11 for Block 1, ΔR^2=.001 for Block 2 (n.s).				
Visuospatial problem-solving				
Block design				
With pre-exposure functioning	Light drinkers (ref=non-drinkers)	-4.03	-7.52 to -0.96	-.14
	Infrequent (ref=non-drinkers)	-6.61**	-10.87 to -3.59	-.15
	Increasing (ref=non-drinkers)	-4.87**	-8.34 to -1.41	-.13
	Decreasing (ref=non-drinkers)	-6.99**	-10.71 to -3.08	-.14
	Chronic (ref=non-drinkers)	-6.26**	-10.27 to -2.43	-.13

Table 4.4 continues on next page

		B	95% CI of *B*	β
Plus covariates	Light drinkers (ref=non-drinkers)	-4.98**	-8.05 to -1.91	-.16
	Infrequent (ref=non-drinkers)	-5.96**	-9.35 to -2.58	-.13
	Increasing (ref=non-drinkers)	-5.34**	-8.54 to -2.14	-.15
	Decreasing (ref=non-drinkers)	-5.17**	-8.70 to -1.65	-.11
	Chronic (ref=non-drinkers)	-5.32**	-9.12 to -1.53	-.11
R^2=.23 for Block 1, ΔR^2=.005 for Block 2 (p=.018).				

**: p<.01; ***: p<.001.
See Table 4.3 for relevant covariates.

Table 4.5 Neurocognitive functioning (T4) predicted by drinking groups (T3-T4) and basic neurocognitive functioning (T1) controlling for covariates. (Reference group are light drinkers)

Block design		*B*	95% CI of *B*	β
With pre-exposure functioning	Non-drinkers (ref=light drinkers)	0.92	-0.83 to 2.66	.05
	Infrequent (ref=light drinkers)	-0.20	-1.99 to 1.60	-.06
	Increasing (ref=light drinkers)	0.71	-1.10 to 2.53	-.02
	Decreasing (ref=light drinkers)	-0.11	-2.04 to 1.82	-.06
	Chronic (ref=light drinkers)	-0.73	-1.11 to 2.56	-.05
Plus covariates	Non-drinkers (ref=light drinkers)	4.99**	1.91 to 8.05	.06
	Infrequent (ref=light drinkers)	-0.98	-3.07 to 1.10	-.02
	Increasing (ref=light drinkers)	-0.36	-2.06 to 1.34	-.01
	Decreasing (ref=light drinkers)	-0.19	-2.24 to 1.85	.00
	Chronic (ref=light drinkers)	-0.34	-2.79 to 2.11	-.01
R^2=.229 for Block 1, ΔR^2=·005 for Block 2 (n.s)				

**: p<.01; ***: p<.001.

problem-solving, where lower performance on these tasks predicted lower Block Design scores eight years later. This stresses the importance of controlling for baseline performance.

In addition, to investigate differences between drinking groups with an aim to determine whether more severe drinking patterns lead to worse performance on Block Design, post-hoc analyses were conducted, with light drinkers being used as a control group. (Results are depicted in Table 4.5). In analyses both without covariates well as with covariates, none of the drinking groups performed significantly differently from the light drinkers.

For all measures, interaction effects with gender were assessed, which did not yield significant results.[1]

1 Data not presented, available by first author on request.

4.4 DISCUSSION

The aim of the present longitudinal study was twofold. First, we investigated if adolescent drinking patterns from middle to late adolescence were longitudinally related to cognitive deficits in late adolescence, as assessed with nine measures that require the collaboration and integration of different cognitive skills. Second, we aimed to determine whether these drinking patterns were related to less optimal performance on a task assessing visuospatial problem-solving and logical reasoning. No significant differences were found between the heavy drinkers and controls on the tasks assessing deficits. Regarding the second aim, being a member of any of the drinking groups predicted less optimal problem-solving as compared to non-drinkers.

4.4.1 Indicators of cognitive deficits

Our first hypothesis, proposing that tasks measuring integrative functions would be sensitive to the effects of alcohol, was not supported. This suggests that heavy drinking, not even over a period of four years, does not result in measurable cognitive underperformance from early to late adolescence. This is in contrast with the previous longitudinal study using some of the same tasks (Squeglia et al., 2009). An explanation could be a difference in the scope of the studies; we assessed neurocognitive and alcohol use from early to late adolescence on a population level, instead of focusing on a smaller and specific sample over a smaller time frame. This might have prevented small, transitory effects from emerging. Furthermore, there are differences in the design: we did not calculate change scores between baseline and follow-up, but instead controlled for basic cognitive control functions.

Our results show that despite the obvious acute effects of alcohol (being drunk, being unable to reason while being intoxicated, having hangovers and headaches), the adolescent brain seems to be able to cope with these effects of alcohol in terms of behavioural development and neurocognitive maturation. This does not implicate that the negative effects of alcohol can be neglected *as such*, as heavy alcohol use in adolescents is associated with a large number of other well-established risks, such as driving under influence and engaging in risky behaviour, including violence and fighting (Hingson & Zha, 2009). Also, the absence of measurable differences in cognitive functioning does not preclude that the underlying neuro-anatomy is affected. For example, equal task performance in heavy drinkers and controls can still be accompanied by differences in

neural activation while carrying out the task (Squeglia et al., 2011). It is unclear what these differences represent, but they indicate that alterations in neural processing are not always reflected in behavioural outcomes (Squeglia et al., 2012). Furthermore, it could be that neuropsychological tasks aimed at measuring cognitive deficits, are just not taxing enough to discern changes as a result of alcohol use. For this reason, we also administered tests of problem-solving.

4.4.2 Visuospatial problem-solving skills

We found that non-drinkers outperformed drinking adolescents irrespective of the specific patterns of drinking. A dose-response relationship with neurocognitive performance could be expected, reflected in differences between the drinking groups. However, this was not found, questioning if alcohol intake itself can account for performance differences between non-drinkers and drinkers.

Given the above, an explanation in terms of a *behavioural component* in relation to alcohol related behaviour as opposed to an explanation in terms of alcohol itself emerges. In other words, a latent behavioural factor could account for both an above average performance on the problem-solving task and for the decision to abstain from alcohol. Despite the apparent negative outcomes related to adolescent substance use, engagement in such rule-breaking behaviour could be seen as normative and adaptive in adolescence (Moffitt, 1993). This is reflected in prevalence rates; almost 90% of Dutch 16-year-olds drinks on a regular basis (Verdurmen et al., 2012). Specific characteristics of adolescent non-drinkers have been investigated. For example, a curvilinear relationship between substance use and psychological well-being has been proposed; heavy users were characterised as being alienated and having problems in inhibition while abstainers were characterised as anxious, over-controlling, and having poorer social skills (Shedler & Block, 1990). The above-mentioned characteristics could also be related to the performance on the problem-solving task. The task is designed to 'push the limits' of healthy respondents instead of diagnosing deficits in brain damaged individuals, which is also reflected in the fact that time pressure is a factor in this task. On a more speculative account, one can imagine that these assumed (over)controlling characteristics of non-drinkers enhances performance on the problem-solving task while at the same time, this controlling characteristic is responsible for keeping them from going out and drinking alcohol in the presence of their peers. More research on the specific characteristic of non-drinkers is encouraged.

Our findings indicate that non-drinkers may not be most suitable reference group, at least not as the single reference group. Discriminating the various drinking patterns made clear that we need to look further to behavioural components in alcohol-related problems and not only focus on the harmful effects of the alcohol intake itself. Since most studies so far have compared alcohol behaviour rather dichotomous, that is heavy drinkers compared to (almost) abstaining controls, it is likely that this false attribution has been made before. Our findings stress the importance of not only investigating the effects of heavy drinking, but also testing the effects of different *amounts* of alcohol by using one or more groups of intermediate drinkers. To the best of our knowledge, this has not been done before.

4.4.3 Strengths and limitations

Our results should be interpreted in the light of several strengths and limitations. Strengths are the large population sample and the longitudinal design, covering a follow-up time frame of eight years. We conducted our study in the Netherlands, where the legal drinking age is lower compared to, for example, the United States and where alcohol consumption in adolescence is very common. We did not only investigate whether alcohol resulted in difference on indicators of cognitive deficits, but also whether alcohol was related to a less optimal problem-solving skills.

One limitation is that we did not administer the same tasks in early and late adolescence. An important reason for this is that more complex, integrative neurocognitive tasks have relatively stringent age restrictions; thus, the majority of tasks that are suitable for late adolescents are not applicable to 11-year-olds. To address the issue of the proposed dual relationship between neurocognitive functioning and adolescent substance use (e.g., Tarter, Kirisci, Reynolds, & Mezzich, 2006), we controlled for relevant neurocognitive functions in early adolescence, i.e., attention, inhibition, and working memory. These functions are theoretically related to future substance use (Grenard et al., 2008; Tapert et al., 2002; Tarter et al., 2006), and were found to be significant predictors of all neurocognitive functions in our regression analyses (data not presented). This approach therefore represents an adequate way of enhancing the possibility to draw conclusions on causality. The neurocognitive tasks we used are standardised tasks. They have proved to be sensitive also to subtle impairments in cognitive functioning and to be able to, for instance, discriminate between patients with Mild Traumatic Brain Injury and healthy controls (Lebowitz & Vanderploeg, 2005). This indicates that the absence of significant results is unlikely to be attributable to the insensitivity of the test to differentiate between individuals.

The second limitation is that attrition in longitudinal designs may have biased the findings. If a larger proportion of participants who are most at-risk drop out, the effects may be underestimated, leading to possible loss of power. We used multiple imputation to deal with this problem, replacing the missing data on alcohol use and neurocognition with the data of associated variables, improving the validity in datasets with missing data (Blankers, Koeter, & Schippers, 2010).

A final limitation could be our outcome measure of choice. It has been suggested that other measures, such as post-drinking symptoms may also adequately mark the extent of heavy drinking (e.g., Squeglia et al., 2009). We chose amount of glasses per occasion as a more objective measure. These drinking patterns were constructed manually using self-reported measures of alcohol use instead of using data-driven methods. However, this is common in longitudinal research on adolescent alcohol use (Squeglia et al., 2009; Squeglia et al., 2012). Self-report questionnaires have proved to be reliable for assessing alcohol use in adolescence (Koning, Harakeh, Engels, & Vollebergh, 2010). Looking at the average amount of alcohol that our chronic drinkers consume (14 to 16 glasses on a weekly basis), as well as prevalence of drunkenness (97% have been drunk during the last year) this group represents the heavy drinking adolescent that our society worries about most. Therefore, we believe that the absence of an effect cannot be attributed to a misidentification of most at-risk drinkers, but rather indicates that heavy drinkers do not show large cognitive deficits on a behavioural level.

4.4.4 Conclusion

In sum, results show no differences with respect to indicators of cognitive deficits between alcohol drinking adolescents and their abstaining peers, not even after four years of weekly heavy drinking, on a broad set of neurocognitive tasks that require collaboration and integration of cognitive skills. This implies pitfalls in research on the effects of alcohol on the adolescent brain are overgeneralisation of research in clinical groups and over-interpretation of cross-sectional research. Differences between non-drinkers and drinking adolescents have however been found for problem-solving, and it is likely that these differences can be attributed to psychosocial differences between abstaining and alcohol consuming adolescents, rather than the amount of alcohol consumed. This emphasises the importance of comparing different drinking groups instead of comparing only heavy drinkers and controls in this type of research. Furthermore, we strongly encourage more research on the specific (neurocognitive) characteristics of abstaining adolescents.

5

Executive functioning before and after onset of Alcohol Use Disorder in adolescence. A TRAILS study.

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ABSTRACT

Background: The aim of the present study was to investigate whether executive functioning (EF) in early adolescence predicted alcohol use disorder (AUD) in late adolescence and whether adolescents with AUD differed in maturation of EF from controls without a diagnosis.

Methods: We used the data from the Tracking Adolescents' Individual Lives Survey (TRAILS), a cohort of 2,230 Dutch adolescents. Working memory, inhibition, and attention were measured at ages 11 and 19. At age 19, lifetime DSM-IV diagnoses were determined, resulting in a control group (n=1,111) and AUD groups, i.e., alcohol abusers (n=348) and alcohol dependents (n=51). Regression analyses assessed whether EF at age 11 predicted the transition to AUD in late adolescence and whether AUD affected maturation of EF from age 11 to 19.

Results: EF in early adolescence did not predict AUD in late adolescence. A significant interaction effect emerged between gender and alcohol dependence for shift attention (β=.12, SE=0.36), with girls showing smaller maturational rates. This effect remained significant after controlling for alcohol intake (ages 16 and 19) and comorbid psychiatric disorders.

Conclusions: Our results do not replicate the finding that EF is a significant predictor of later AUD. Furthermore, for the majority of tasks, adolescents with AUD did not differ in EF maturation. Alcohol dependent girls show less maturation of shift attention. This is independent of the quantity of alcohol intake, which could suggest that non-normative maturation of EF is associated with the behavioural components of AUD.

5.1 INTRODUCTION

Adolescent alcohol use has raised specific concerns because the maturing brain and associated cognitive functions may be particularly vulnerable to the aversive effects of alcohol (Clark, Thatcher, & Tapert, 2008; Spear, 2011; Steinberg, 2005). The cognitive control functions show most prominent maturation during adolescence (Crone, 2009). Cognitive control, also called Executive Functioning (EF), encompasses various functions , such as attention, inhibition, and working memory (Anderson, 2002). Disturbances in the maturation of EF as a result of external influences, such as alcohol use, would be extremely concerning, since the functions are essential for succeeding in school and everyday life, which is highly important in this specific stage of life (Jurado & Rosselli, 2007).

Among adolescent drinkers, those who meet the criteria for an Alcohol Use Disorder (AUD) are of particular concern. DSM-IV-TR criteria for AUD consist of behavioural problems associated with using alcohol, such as the impossibility to inhibit the urge to drink even if one is aware of the fact that (more) drinking is harmful. Alcohol abuse and alcohol dependence are diagnostically different, as dependence is associated with tolerance and/or withdrawal symptoms (Clark, 2004). Adolescents with AUD form a considerable group (i.e., approximately 12% of 17-18 year-olds abuse alcohol and 3% exhibit dependence (Swendsen et al., 2012)). Prevalence rates of AUD in adolescence appear to be increasing (Merikangas et al., 2010), and presumably most cases of adult AUD have their onset in adolescence (Swendsen et al., 2012). Monitoring this group is important, since AUD can become chronic and cause both personal and societal burden.

Less optimal neurocognitive functions have been found in adolescents diagnosed with AUD (e.g., Brown et al., 2000; Sher, Martin, Wood, & Rutledge, 1997). However, most research in this field is cross-sectional, which limits causal inferences. Indeed, neurocognitive deficits found in adolescents with AUD have been interpreted as being a consequence of the disorder or as being pre-existing, preceding the abuse (Peeters, Vollebergh, Wiers, & Field, 2014). Therefore, longitudinal studies investigating this bidirectional relationship are essential. To the best of our knowledge, only one study followed up on adolescents diagnosed with AUD. It suggests that prolonged alcohol use is related to less optimal neurocognitive functioning compared to controls and that EF, specifically attention, is one domain that is being affected (Hanson, Medina, Padula, Tapert, & Brown, 2011; Tapert & Brown, 1999; Tapert, Granholm, Leedy, & Brown, 2002). However, the results should be interpreted with caution, due to a lack of a pre-exposure baseline measurement of cognitive functioning. There are indications that weaknesses in EF, specifically in inhibition, predict later substance use

(Norman et al., 2011; Squeglia, Nguyen-Louie, & Tapert, 2014; Wetherill, Squeglia, Yang, & Tapert, 2013). However, this applies to non-clinical drinking adolescents, and it is unclear whether these mechanisms are the same for AUD. Despite indications for a bidirectional relationship between EF and AUD, there is a need for stronger evidence.

A large prospective cohort would be an optimal design for such a study, as baseline measures of EF can be administered before AUD develops. The second advantage is a natural distribution of covariates, which is not the case when using matched controls. Considering possible covariates enhances our understanding of the relation between AUD and EF. First, the quantity of alcohol intake is not explicitly formulated in the diagnostic criteria for AUD; thus, average alcohol intake of adolescents without AUD might be comparable to alcohol intake of adolescents with AUD. Defining the quantity of alcohol intake could enhance understanding of the predictive effect of EF on AUD and the influence of AUD on maturation of EF. The second covariate concerns psychiatric comorbidity, for the effect of AUD on EF. Both in- and externalizing disorders, such as anxiety and depression, Conduct Disorder (CD), and Attention Deficit Hyperactivity Disorder (ADHD) are highly prevalent in adolescents with AUD (Roberts, Roberts, & Xing, 2007; Rohde, Lewinsohn, & Seeley, 1996). Comorbidity might be a specific risk factor possibly because these comorbid disorders are in themselves associated with neurological and cognitive disturbances (Airaksinen, Larsson, & Forsell, 2005; Hammar & Ardal, 2009; Marchetta, Hurks, De Sonneville, Krabbendam, & Jolles, 2008; Sergeant, Geurts, & Oosterlaan, 2002). Therefore, comorbid disorders could obscure or explain the effect of AUD on the maturation of EF, and should therefore be considered. Third, gender differences can play a role, since the prevalence rates of AUD in males are higher compared to females (Keyes, Martins, Blanco, & Hasin, 2010; Swendsen et al., 2012), and boys generally show larger neurocognitive maturational rates, indicating a prolonged maturational trajectory (Boelema et al., 2014).

In view of the above discussion, the aim of the present longitudinal study was to investigate the relationship between EF and alcohol abuse and alcohol dependence in a population-based sample while accounting for important covariates (i.e., quantity of alcohol intake, comorbidity, and gender). EF measures were inhibition, working memory, and attention, since previous studies have indicated that these variables are risk factors for the development of AUD and that they are sensitive to the possible negative consequences of the disorder. First, we investigated whether EF in early adolescence could be identified as a risk factor for AUD. Second, we investigated whether adolescents with AUD showed a different maturation of EF from early to late adolescence compared to their peers without

AUD. We carried out our analyses with and without controlling for the quantity of alcohol intake and psychiatric comorbidity and assessed interaction effects with gender.

5.2 METHODS

5.2.1 Study design

The present study used data from the first, third, and fourth wave of the TRacking Adolescents' Individual Lives Survey (TRAILS). This is a prospective cohort study of Dutch 11-years old pre-adolescents (De Winter et al., 2005; Ormel et al., 2012). The target sample comprised children living in urban and rural areas of the Northern Netherlands. Seventy-six percent of eligible adolescents and their parents agreed to participate and were enrolled in the study at baseline (*n*=2,230, mean age 11.1 years, *SD*=0.56, 49.2% male). On the third (T3) assessment (*n*=1,816, mean age 16.3 years, *SD*=0.70, 47.7% male), the response rate was 81.4%. On the fourth (T4) assessment (*n*=1,596, mean age 19.2 years, *SD*=0.57, 46% male), the response rate was 70%.

5.2.2 Procedure

During the first assessment (T1), tests assessing EF were administered to adolescents in their schools or in designated testing centres by trained undergraduate psychology students (for more information, also see Brunnekreef et al., 2007). Participants who were unable to attend these assessments were tested at home. At T1 and T3, adolescents also completed the self-report questionnaires in groups in their schools under the supervision of a TRAILS assistant. The parents also completed a written questionnaire. During the fourth assessment (T4), trained professional interviewers administered the EF tests and clinical interview individually at home or at a nearby community centre (for more information, see (Boelema et al., 2014). Respondents were asked not to use alcohol in the 24 hours prior to the test administration. Parents and their children were asked to fill out a computerised questionnaire (or, per their request, using a paper-and-pencil questionnaire).

The Dutch Central Committee on Research Involving Human Subjects approved the study. Parents and adolescents' written informed consent was obtained. The confidentiality of the study was emphasised.

5.2.3 Measures

5.2.3.1 Descriptive statistics

A number of measures were added to compare adolescents with AUD and controls on alcohol-related behaviour and substance use. At T1, adolescents were asked: "How often have you been drinking alcohol (for example, a bottle of beer or a glass of wine)?" up until that time point, on a 5-point scale ranging from 0 to 7 times or more. Furthermore, at T3 and T4 adolescents were asked how many times they had been drunk in the last 12 months. At T4, adolescents were asked how often they had used other substances, being cannabis, amphetamines, cocaine, heroin, and psilocybin mushroom in their lives. We dichotomised all answers into never and once or more.

5.2.3.2 Alcohol Use Disorder

At T4, the World Health Organization Composite International Diagnostic Interview (CIDI) version 3.0 (Kessler & Üstün, 2004) was used to assess AUD. This is a structured diagnostic interview assessing current and lifetime DSM-IV mental disorders. It has been shown to have good reliability and validity (Andrews & Peters, 1998; Kessler & Üstün, 2004). We identified participants who had met the criteria for *alcohol abuse* or *alcohol dependence* at some point in their lives. These categories are mutually exclusive. Participants reported the age of onset of their alcohol problems retrospectively, ranging from 10 to 20 years for abuse and from 15 to 20 years for dependence. Since two alcohol-abusing participants reported having the disorder before the baseline measure of EF, these participants were removed from the analyses, resulting in 348 participants with alcohol abuse and 51 with alcohol dependence. The adolescents with no diagnoses of alcohol abuse or dependence were used as a reference group (n=1,183).

5.2.3.3 Executive functioning

At T1 and T4, EF was examined using three computerised reaction time tasks from the Amsterdam Neuropsychological Tasks (ANT) (De Sonneville, 1999). We assessed inhibition, working memory, shift attention, and sustained attention. These functions have sufficient longitudinal stability and they can be longitudinally assessed with the ANT in an adolescent population (Boelema et al., 2014). The Appendix gives a description of the tasks used and an overview of the operationalisation of functions. Using computerised tasks guarantees standardised assessment while working with reaction times allows detection of subtle improvements in performance. Performance results with more than 50% errors were coded

as missing because they were assumed to reflect either misunderstood instructions or false computer settings, undermining the validity of the testing. For maturation from early to late adolescence, we calculated change scores for each of the four functions by computing z-scores for the T1 and T4 measures and subsequently subtracting these scores from each other (T1-T4). The neurocognitive measures have been used in other studies within the TRAILS-project (Boelema et al., 2014).

5.2.3.4 Covariates of interest

Psychiatric comorbidity. At T4, psychiatric comorbidity was assessed at age 19 using the CIDI, differentiating between five categories of comorbidity according to life time DSM-IV diagnoses: externalizing problems (CD or Oppositional Deviant Disorder (ODD)), substance use problems (drug abuse or drug dependence), affective disorders (bipolar disorder type I and II, major depressive disorder), anxiety disorders (generalised anxiety disorder, panic disorder, social phobia, and agoraphobia), and ADHD.

Quantity of alcohol intake. Alcohol consumption was measured at T3 and T4 using two questions: "On how many days during the weekend do you drink alcohol?" and "On an average weekend day on which you drink alcohol, how many glasses do you drink?" Weekend quantity of alcohol use has been shown to be a useful and specific measure of alcohol use at this age (Weingardt et al., 1998). Average quantity of alcohol intake was calculated by multiplying the number of weekend days and average number of glasses. A Dutch standard drink contains 10 grams of alcohol.

5.2.3.5 Control variables

We added control variables in accordance with previous studies (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009; Tarter et al., 2003). When investigating EF as a predictor of AUD, *gender* and *socioeconomic status* (SES) were used as control variables. For the effect of AUD on EF maturation, control variables were included if they significantly correlated with the outcome measures ($p<.05$) (See Table 5.1 for possible control variables and correlations). When investigating maturation of EF, *baseline scores* (T1) of the corresponding task were considered with respect to regression to the mean since in change scores, the initial performance influences the amount of change (Squeglia et al., 2009).

Table 5.1 Bivariate correlations among the controlling variables and EF maturation (T1-T4)

Controlling variable	Δ Working Memory (T1-T4)	Δ Inhibition (T1-T4)	Δ Sustained Attention (T1-T4)	Δ Shift Attention (T1-T4)
T1 performance	.52*	.59*	.49*	.60*
Age (T1)	-.08*	-.05	-.07*	-.09*
SES (T1)	.00	.03	-.04	.03
Maternal alcohol use (T1)	.00	-.05	-.03	.01
Paternal alcohol use (T1)	-.02	.00	-.03	.04
Delinquency scores (T1)	.01	.01	-.01	-.01
Last year cannabis use (T3)	-.01	-.01	-.04	.01
T4 last year cannabis use (T4)	-.01	.01	-.04	-.02
Last month smoking (T3)	-.04	-.08*	-.02	-.09*
Last month smoking (T4)	-.04	-.06*	-.05	-.08*

*: correlation is significant (p<.05). These variables were controlled for in the regression analyses.

5.2.4 Data analyses

5.2.4.1 EF predicting development of AUD

Multinomial logistic hierarchical regression analyses were conducted to determine the extent to which EF at age 11 predicted the transition to alcohol abuse or dependence in late adolescence. First we conducted bivariate analyses with T1 EF scores as predictors. Next, three multivariate models were conducted with control variables and quantity of alcohol intake. In Model 1, gender and SES were entered as predictors. In Model 2, EF scores were added. In Model 3, quantity of alcohol intake was added as a covariate of interest.

5.2.4.2 Effects of AUD on EF maturation

In Model 1, four bivariate linear regression analyses were conducted with standardised EF maturation as a dependent variable and AUD as a predictor by using diagnoses as dummy variables. Adolescents without an AUD diagnosis were used as the reference group. In Model 2, we conducted multivariate linear regression analyses adjusted to account for control variables. The main effects of AUD and AUD*gender interactions were entered in separate blocks and interpreted accordingly. The quantity of weekly alcohol consumption, comorbid psychiatric diagnoses, and both covariates together were added in Model 3 through 5, respectively. We set α <.01 to control for multiple comparisons and because of our large sample size.

5.3 RESULTS

For group size, gender distribution, and descriptive statistics, see Table 5.2.

Table 5.2 Descriptive statistics of adolescents without and with a diagnosis AUD

	No AUD diagnosis (T4)	Life time Alcohol Abuse (T4)	Life time Alcohol Dependence (T4)
N	1,183	348	51
% male	40^{-}	65^{+}	53
T1 Age	11.3 (0.6)^{a}	11.3 (0.6)^{a}	11.4 (0.6)^{a}
T1 Parent SES (age 11)	0.1 (0.8)^{a}	0.1 (0.8)^{a}	0.3 (0.7)^{a}
T1 Prevalence of haven drunk >1 glass (%) (age 11)	12^{-}	22^{+}	20^{+}
T3 Prevalence last year drunkenness (%) (age 16)	53^{-}	77^{+}	92^{+}
T4 Prevalence last year drunkenness (%) (age 19)	73^{-}	91^{+}	98^{+}
T4 Prevalence life time cannabis use (%) (age 19)	42^{-}	75^{+}	88^{+}
T4 Prevalence life time amphetamine use (%) (age 19)	5^{-}	16^{+}	47^{+}
T4 Prevalence life time cocaine use (%) (age 19)	3^{-}	13^{+}	37^{+}
T4 Prevalence life time heroin use (%) (age 19)	0.3	0.3	2^{+}
T4 Prevalence life time psilocybin mushroom use (%) (age 19)	3^{-}	11^{+}	20^{+}
T3 *N* glasses per week age (T3)	4.7 (5.6)^{a}	8.5 (7.6)^{b}	9.8 (6.8)^{b}
Male	5.4 (6.2)^{a}	9.0 (8.2)^{b}	12.0 (7.1)^{b}
Female	4.3 (5.1)^{a}	7.6 (5.6)^{b}	7.8 (6.4)^{b}
T4 *N* glasses per week age (age 19)	6.7 (6.1)^{a}	12.1 (7.6)^{b}	16.1 (10.1)^{c}
Male	8.7 (7.0)^{a}	12.6 (7.7)^{b}	19.6 (9.0)^{c}
Female	5.3 (5.0)^{a}	11.2 (7.4)^{b}	12.5 (8.9)^{b}
T4 Prevalence externalizing problems (%) (age 19)	10^{-}	23^{+}	33^{+}
Male	12^{-}	22^{+}	41^{+}
Female	8^{-}	25^{+}	25^{+}
T4 Prevalence other drug problems (%) (age 19)	6^{-}	31^{+}	45^{+}
Male	9^{-}	34^{+}	37^{+}
Female	4^{-}	27^{+}	54^{+}
T4 Prevalence affective disorders (%) (age 19)	16	17	41^{+}
Male	10	11	37^{+}
Female	20	29	46^{+}
T4 Prevalence AD(H)D (%) (age 19)	3^{-}	6^{+}	14^{+}
Male	2	9^{+}	8^{+}
Female	4	5	19^{+}
T4 Prevalence anxiety disorders (%) (age 19)	16	14	28^{+}
Male	12	10	30^{+}
Female	18	21	25^{+}

+ or - signs means Pearson-Chi-Square Test is significant. + means cell count is higher than expected, - means cell count is lower than expected (based on significant standardised residuals). Different superscript letters refer to significant differences (p<.05) of mean scores between groups: if two group scores are labelled with the same letter, the scores of these groups do not differ. If two scores are labelled with different letters, these scores differ.

5.3.1 EF predicting development of AUD

The results of the logistic regression analyses are depicted in Table 5.3. The bivariate analyses showed sustained attention being a significant predictor of alcohol abuse, where larger scores (i.e., a less optimal performance) at T1 increased the risk of having an AUD in late adolescence. Multivariate Model 1 showed an effect of gender, indicating that boys have a higher chance of being diagnosed with alcohol abuse. No effects of SES were found. Model 2 showed that none of the EF measures in early adolescence were significant predictors of AUD diagnosis in late adolescence when accounting for gender and SES. Model 3 also

Table 5.3 Risk of having a diagnosis alcohol abuse or dependence (T4) predicted by baseline EF (T1) and alcohol use (T3 and T4)

	Life time alcohol abuse vs. no AUD (T4)		Life time alcohol dependence vs. no AUD (T4)	
	OR	95% CI	OR	95% CI
Bivariate				
T1 Inhibition in sec (age 11)	1.31	0.61 to 2.82	1.53	0.27 to 8.63
T1 Working Memory in sec (age 11)	1.32	0.85 to 2.06	0.63	0.20 to 1.99
T1 Sustained attention in sec (age 11)	1.25**	1.07 to 1.38	1.12	0.75 to 1.43
T1 Shift Attention in sec (age 11)	0.79	0.44 to 1.41	0.57	0.17 to 2.63
Multivariate Model 1				
Gender (ref=male)	0.37***	0.29 to 0.47	0.57	0.33 to 1.02
T1 SES (age 11)	1.07	0.91 to 1.25	1.35	0.93 to 1.97
R^2=.04 (Cox&Snell); .06 (Nagelkerke). Model $\chi^2(4)=68.74$ ($p<.001$)				
Multivariate Model 2				
T1 Inhibition in sec (age 11)	1.10	0.48 to 2.55	1.93	0.30 to 12.52
T1 Working Memory in sec (age 11)	0.92	0.55 to 1.55	0.51	0.14 to 1.82
T1 Sustained attention in sec (age 11)	1.16	0.99 to 1.36	1.16	0.81 to 1.67
T1 Shift Attention in sec (age 11)	0.76	0.40 to 1.42	0.65	0.15 to 2.89
R^2=.05 (Cox&Snell); .06 (Nagelkerke). Model $\chi^2(12)=72.23$ ($p<.001$)				
Multivariate Model 3				
T1 Inhibition in sec (age 11)	1.28	0.50 to 3.00	3.90	0.56 to 27,15
T1 Working Memory in sec (age 11)	0.76	0.41 to 1.38	0.60	0.14 to 2.29
T1 Sustained attention in sec (age 11)	1.15	0.95 to 1.38	0.93	0.60 to 1.46
T1 Shift Attention in sec (age 11)	0.70	0.34 to 1.45	0.87	0.17 to 4.42
T3 Number of glasses per week (age 13)	1.05**	1.01 to 1.09	1.05	0.97 to 1.13
T3 Number of glasses per week (age 16)	1.08***	1.06 to 1.11	1.12**	1.07 to 1.16
R^2=.10 (Cox&Snell); .14 (Nagelkerke). Model $\chi^2(16)=143.64$ ($p<.001$)				

OR: Odd's Ratio; CI: Confidence Interval. *: $p<.05$; **: $p<.01$; ***: $p<.001$.

showed that alcohol intake at age 13 and 16 predicted alcohol abuse in late adolescence, and alcohol intake at age 16 significantly predicted alcohol dependence at age 19.

5.3.2 Effects of AUD on EF maturation

Model 1 bivariate linear regression analyses did not yield significant differences among abusers, dependents, and controls in EF maturation (See Table 5.4). In Model 2, with controlling variables, a significant interaction effect of dependence*gender emerged for shift attention. It was found that for girls, being labelled as dependent predicted smaller maturation compared to the control group. In Model 3, this interaction effect remained significant after adding quantity of weekly alcohol consumption. This was the same in Model 4 (controlling for comorbid disorders) and Model 5 (controlling for comorbid disorders and quantity of alcohol consumption). In sum, these results indicate that alcohol dependent girls showed a relative stagnation in maturation of shift attention compared to controls without a diagnosis, independent of quantity of weekly alcohol consumption and comorbid psychiatric disorders.

An trend towards significance of inhibition ($p<.05$) emerged for the abusers, with abusing adolescents showing more maturation than adolescents without a diagnosis in all four multivariate models.

5.4 DISCUSSION

The aim of the present paper was to investigate longitudinally the relationship between adolescent EF (i.e., working memory, inhibition, sustained and shift attention) and AUD (alcohol abuse and dependence) in a population-based sample while considering the quantity of alcohol consumption, comorbid psychiatric disorders, and gender. We did not find evidence that weaknesses in EF measures in early adolescence were risk factors for alcohol abuse or dependence in late adolescence. Furthermore, we did not find differences in EF maturation between adolescents with and without AUD for most of analyses. For shift attention on the other hand, there was a significant interaction effect with gender consistently over the models, with dependent girls showing smaller maturational rates compared to girls without a diagnosis. This effect could not be explained by the quantity of alcohol consumption and comorbid psychiatric disorders, as it remained significant after controlling for these variables.

Contrary to our findings, previous studies have identified EF as a risk factor for the development of AUD. However, this only applied to response inhibition (and not attention

Table 5.4 Standardised maturation in EF, predicted by AUD diagnosis, without and with controlling for weekly alcohol intake and comorbid psychiatric diagnoses at 19

	Δ Working Memory (T1-T4)			Δ Inhibition (T1-T4)			Δ Sustained Attention (T1-T4)			Δ Shift Attention (T1-T4)		
	B	95% CI of *B*	β	*B*	95% CI of *B*	β	*B*	95% CI of *B*	β	*B*	95% CI of *B*	β
Model 1 Bivariate												
T4 Abusers (ref=no AUD) (age 19)	-0.04	-0.16 to 0.09	-.01	0.13	-0.00 to 0.25	.04	0.04	-0.08 to 0.16	.02	-0.01	-0.14 to 0.12	-.00
T4 Dependents (ref=no AUD) (age 19)	-0.03	-0.31 to 0.24	-.01	-0.12	-0.17 to 0.40	.02	0.00	-0.27 to 0.27	.00	-0.23	-0.52 to 0.07	-.03
Model 2 Contr+AUD												
T4 Abusers (ref=no AUD) (age 19)	-0.03	-0.15 to 0.10	-.01	0.17*	0.01 to 0.33	.06	0.05	-0.07 to 0.17	.02	-0.02	-0.18 to 0.15	-.01
T4 Dependents (ref=no AUD) (age 19)	-0.03	-0.30 to 0.25	-.00	0.20	-0.15 to 0.56	.03	0.12	-0.15 to 0.39	.02	-0.38*	-0.75 to -0.00	-.05
T4 Abusers*gender (ref=no AUD) (age 19)	0.03	-0.22 to 0.28	.01	-0.11	-0.42 to 0.20	-.03	-0.06	-0.30 to 0.18	-.02	-0.06	-0.38 to 0.26	-.02
T4 Dependents*gender (ref=no AUD) (age 19)	-0.09	-0.67 to 0.44	-.02	0.19	-0.51 to 0.89	.02	0.04	-0.51 to 0.58	.01	1.08**	0.36 to 1.80	.12
Model 3 Contr+AUD + QF												
T4 Abusers (ref=no AUD) (age 19)	-0.03	-0.17 to 0.11	-.01	0.17*	0.00 to 0.34	.06	0.03	-0.11 to 0.16	.01	-0.02	-0.19 to 0.15	-.01
T4 Dependents (ref=no AUD) (age 19)	-0.00	-0.30 to 0.29	.00	0.19	-0.19 to 0.56	.03	0.13	-0.16 to 0.42	.02	-0.38	-0.77 to 0.00	-.06
T4 Abusers*gender (ref=no AUD) (age 19)	-0.06	-0.32 to 0.20	-.02	-0.09	-0.41 to 0.23	-.03	-0.10	-0.39 to 0.16	-.03	-0.05	-0.38 to 0.27	-.01
T4 Dependents*gender (ref=no AUD) (age 19)	-0.11	-0.69 to 0.46	-.02	0.19	-0.52 to 0.91	.02	-0.03	-0.52 to 0.59	.00	1.09**	0.37 to 1.82	.12

	Δ Working Memory (T1-T4)			Δ Inhibition (T1-T4)			Δ Sustained Attention (T1-T4)			Δ Shift Attention (T1-T4)		
	B	95% CI of *B*	β	*B*	95% CI of *B*	β	*B*	95% CI of *B*	β	*B*	95% CI of *B*	β
Model 4 Contr+AUD + Com												
T4 Abusers (ref=no AUD) (age 19)	0.03	-0.10 to 0.16	.01	0.18*	0.01 to 0.34	.06	0.06	-0.07 to 0.18	.02	0.00	-0.17 to 0.17	.00
T4 Dependents (ref=no AUD) (age 19)	0.07	-0.21 to 0.36	.01	0.22	-0.15 to 0.58	.03	0.13	-0.15 to 0.41	.02	-0.31	-0.69 to 0.07	-.04
T4 Abusers*gender (ref=no AUD) (age 19)	0.00	-0.25 to 0.25	.00	-0.12	-0.43 to 0.20	-.03	-0.06	-0.30 to 0.19	-.02	-0.08	-0.40 to 0.24	-.02
T4 Dependents*gender (ref=no AUD) (age 19)	-0.10	-0.66 to 0.47	-.01	0.27	-0.53 to 0.87	.02	0.01	-0.54 to 0.56	.00	1.08**	0.36 to 1.81	.12
Model 5 Contr+AUD + QF + Com												
T4 Abusers (ref=no AUD) (age 19)	0.01	-0.13 to 0.15	.00	0.18*	0.00 to 0.35	.06	0.03	-0.10 to 0.17	.01	-0.00	-0.17 to 0.18	-.00
T4 Dependents (ref=no AUD) (age 19)	0.06	-0.24 to 0.36	.01	0.19	-0.19 to 0.57	.03	0.14	-0.15 to 0.43	.03	-0.32	-0.71 to 0.08	-.05
T4 Abusers*gender (ref=no AUD) (age 19)	0.10	-0.36 to 0.16	-.03	-0.09	-0.41 to 0.23	-.03	-0.10	-0.35 to 0.16	-.03	-0.07	-0.39 to 0.25	-.02
T4 Dependents*gender (ref=no AUD) (age 19)	-0.08	-0.78 to 0.49	-.01	0.16	-0.56 to 0.88	.02	0.02	-0.54 to 0.58	.00	1.10**	0.36 to 1.82	.12

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

Contr: control variable (See Table 5.2); QF= quantity of weekly alcohol intake at T3 and T4 (ages 13 and 16); Com: psychiatric comorbidity at T4 (age 19).

and working memory) with a modest predictive power (Nigg et al., 2006). Our findings support the suggestion that not the cognitive component of EF in isolation puts adolescents at risk for developing substance use disorders, but rather that this vulnerability is associated with a combination of impaired inhibition, impaired behavioural control, and emotion regulation problems (Chapman, Tarter, Kirisci, & Cornelius, 2007; Tarter, Kirisci, Habeych, Reynolds, & Vanyukov, 2004; Tarter, Kirisci, Reynolds, & Mezzich, 2006). A risk profile for AUD can therefore be best identified by a combination of affective, cognitive, and behavioural factors.

In other studies differences between adolescents with AUD and controls were absent at baseline (Hanson et al., 2011; Tapert & Brown, 1999; Tapert et al., 2002), but visible at follow-up. This indicates that AUD may lead to measurable EF impairments but only after prolonged exposure and only in persistent alcohol abusers or dependents. In contrast to previous research, we investigated AUD instead of a broader Substance Use Disorder (which generally means involvement in alcohol and at least one other substance). Polysubstance users might display more severe patterns of use and substance interaction effects are not completely understood (Tapert et al., 2002). Another explanation for the difference in the findings could be that in our study, we looked at basic forms of EF with reaction time tasks, which could be relatively robust in terms of the effects of AUD. For example, equal task performance in adolescents with AUD and controls can still be accompanied by differences in neural activation while carrying out a task (Caldwell et al., 2005), which could mean that a greater brain activation is required in some regions to compensate for areas of decreased activation to achieve adequate performance (Tapert et al., 2004). Despite adequate task performance, there could still be differences between adolescents with AUD and controls.

Dependent girls showed significantly less maturation in shift attention. This function has previously been found to be sensitive to impairments associated with AUD and to correlate negatively with withdrawal symptoms (Tapert & Brown, 1999; Tapert et al., 2002). This can explain why we found differences specifically for alcohol dependence, since this group is defined by the presence of withdrawal symptoms. Gender differences have been found in (cross-sectional) research before (Medina et al., 2008; Tapert et al., 2001). Theoretically, gender differences can be explained by the so-called gender paradox, which states that in disorders that have an unequal gender ratio, the gender with the lower prevalence tends to be more affected by the risk factors associated with that disorder (Taylor & Ounsted, 1972). Alcohol dependence is less prevalent in females (Keyes et al., 2010), suggesting that girls who meet the criteria for alcohol dependence differ more in risk factors from non-dependent peers than do dependent boys.

The interaction effect of shift attention was robust over the different models, indicating that quantity of alcohol intake did not influence the effect. It is surprising that differences in EF functioning in AUD are unrelated to higher levels of alcohol use. This indicates that instead of heightened levels of alcohol use, the mere presence of the disorder has a small influence on EF maturation. One explanation is that a psychiatric disorder can have a negative influence on neurocognitive maturation. Support for this hypothesis comes from pathological gambling, which has symptoms similar to substance use disorders, and it can be theoretically classified as a behavioural addiction (Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2006; Potenza, 2006; Potenza, 2008). Similar impairments in EF have been found among pathological gamblers and adults with AUD (Goudriaan et al., 2006). Although the direction of this relationship is unclear, it has been suggested that pathological gambling can induce changes in developmental trajectories of EF by altering the brain's reward system (Betancourt et al., 2012; Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005). This could be the case for AUD as well. Second, the weaker performance of dependent girls may not be an expression of disturbed maturation, but rather a temporarily impaired performance. Alcohol dependence is an impairing condition associated with a high level of co-occurring problems that can cause psychosocial stress. Such stress has been found to disrupt prefrontal processing, as reflected in a diminished ability for attentional shifting, a process that is reversible when the stressors disappear (Liston, McEwen, & Casey, 2009). Further longitudinal research with more EF measurements that would contribute to our understanding of the persistence of attentional problems is encouraged.

5.4.1 Strengths and limitations

This study must be seen in the light of several strengths and limitations. The strengths are a large population sample and the longitudinal design. We conducted baseline measurements before the onset of AUD and follow-up measurements of neurocognitive functioning to investigate the bidirectional relationship between AUD and neurocognitive functioning in a single design.

The first limitation concerns the basic tasks that were used to measure neurocognitive functioning. An important drawback is that they might not be sensitive enough to pick up subtle alterations in performance. However, an important advantage of measuring basic EF is that it allows using exactly the same tasks in early and late adolescence, which is a requirement for detecting longitudinal change. More complex and strategy-based tasks usually have

more stringent age restrictions, and tasks that are both suitable for early adolescents yet still challenging in late adolescence are difficult to find (Best & Miller, 2010).

A second limitation could be that, despite the large sample size and representative prevalence rates, the number of adolescents with alcohol dependence was still relatively small, especially when investigating the interaction effects. This may have resulted in a loss of power. However, our respondents were still young, with a mean age of 19 years and prevalence of dependence at this age is still relatively small in the population (Swendsen et al., 2012). Furthermore, previous studies tended to use relatively small sample sizes as well.

Finally, we conducted a relatively large number of analyses, increasing the likelihood of Type 1 error. However, we controlled for multiple comparisons by setting a stringent significance level. Still, a significant interaction effect of drinking group by gender was consistently found for the four models that were tested, decreasing the likelihood of coincidental findings.

5.4.2 Conclusion

Youth who develop an AUD during adolescence could not be identified by weaknesses in EF in early adolescence. Differences in EF maturation between adolescent with AUD and controls without a diagnosis where small and task dependent. Furthermore, the effects seemed to depend on the type of AUD, providing evidence for a conceptual distinction between alcohol abuse and dependence. Our results appear to be independent of the quantity of alcohol intake, a possible indication that they are associated with the disorder AUD or co-occurring psychosocial factors. The concerning results were found only for dependent girls, a small group reflecting about 2% of our sample. Without trivializing the seriousness of adolescent AUD, with a younger age of onset of AUD being associated with persistency of the disorder (Grant et al., 2012; Lopez-Quintero et al., 2011), and the direct effects of alcohol intake, such as driving under influence and engaging in risky behaviour that includes violence and fighting while being intoxicated (Hingson & Zha, 2009), the findings for shift attention are the result of focusing closely on a specific risk group. Traditionally, deficits in adolescents with AUD have been attributed to their alcohol use, and these results are often generalised to non-problematic drinking populations. Our findings plead against this attribution and generalization.

6

Behavioural control as a determinant and outcome of adolescent (problematic) drinking. A TRAILS study.

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ABSTRACT

Background: The aim of the study was to investigate whether behavioural control in early adolescence predicted heavy drinking and Alcohol Use Disorder (AUD) in late adolescence. Furthermore, we investigated the extent to which behavioural control was affected by alcohol use and its interaction with gender.

Methods: This study is part of the Tracking Adolescents Individual Lives Survey (TRAILS), a Dutch prospective cohort study (*n*=2,230). Self-reports of behavioural control (high-intensity pleasure (HIP), effortful control (EC), attentional and externalizing problems) at age 11 were used to predict membership of six groups of alcohol (mis)use at age 19 with logistic regression analyses. Multivariate linear regression analyses were used to predict attentional and externalizing problems from alcohol (mis)use in late adolescence.

Results: *Heavy drinking* was found to be predicted by heightened HIP and lower EC, *abuse* by heightened HIP, lower EC, and more externalizing problems, and *dependence* by heightened HIP and externalizing problems, compared to light drinking. Regarding the effects of drinking on behavioural control, *heavy drinking* prospectively led to attentional problems only in females (β=-.10). *Alcohol abuse* predicted more externalizing problems (β=.10) and attentional problems in females (β=-.14). *Alcohol dependence* predicted more attentional (β=-.07) and externalizing problems (β=.18).

Conclusions: Our results indicated associations among behavioural control, heavy drinking, and AUD, with externalizing problems being uniquely associated with AUD. Furthermore, we found that alcohol (mis)use affected these risk factors, particularly in females, which might indicate a vicious circle.

6.1 INTRODUCTION

Alcohol use in adolescence is highly prevalent, with 93% of Dutch adolescents having consumed alcohol at age 18 (Verdurmen et al., 2012). Some adolescent alcohol users become heavy weekly drinkers or even develop an Alcohol Use Disorder (AUD, i.e., alcohol abuse of alcohol dependence) over the course of adolescence. Heavy alcohol use has raised considerable concerns regarding serious injuries, impaired judgement, and brain development problems, as expressed in communications by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA, "Special populations", 2013). Furthermore, prevalence rates of AUD in adolescence (in the USA) appear to be increasing (Merikangas et al., 2010), and presumably, most cases of adult AUD have their onset in adolescence (Swendsen et al., 2012). Hence, it is crucial to identify young people who are likely to engage in alcohol (mis)use – heavy drinking or AUD – in the future to develop effective prevention programs.

Earlier research has clearly confirmed that intrapersonal characteristics related to behavioural control are important predictors of heavy drinking trajectories and other substance use. This encompasses the full spectrum going from personality characteristics, such as sensation seeking and (lack of) effortful control (Creemers et al., 2009; Willem, Bijttebier, & Claes, 2010; Wong et al., 2006) to more problematic behavioural syndromes such as attentional problems (Groenman et al., 2013; Wilens et al., 2011; Zulauf, Sprich, Safren, & Wilens, 2014), and externalizing problem behaviours (Fergusson, Horwood, & Ridder, 2007; Fite, Colder, Lochman, & Wells, 2008; Monshouwer et al., 2012; White, Xie, Thompson, Loeber, & Stouthamer-Loeber, 2001; Wills et al., 2001; Wills, McNamara, Vaccaro, & Hirky, 1996). Theoretically, these characteristics are all related to (lack of) self-regulation, and they are best seen as manifestations of the same underlying dimension, from personality characteristics, which reflect dispositional traits belonging to the diversity of personality in the normal population that may nonetheless predispose towards risk behaviours to more extreme manifestations of under-regulation in high risk populations (Lahey, 2004). Although these characteristics are identified as predictors of heavy alcohol use in adolescence, several issues in this relationship need to be inspected more in depth.

First, the effect of alcohol (mis)use on behavioural control has not been investigated extensively, possibly because characteristics such as behavioural control have long been viewed as a fixed and stable traits not influenced by environmental factors (e.g., Kilpatrick, Sutker, & Smith, 1976; Zuckerman, 1979). However, more recent studies have indicated that intrapersonal characteristics are a dynamic part of human developmental processes

(Crawford, Pentz, Chou, Li, & Dwyer, 2003). Genetic influences contribute to intrapersonal characteristics, but generally with less than 50%, leaving room for environmental factors to shape behavioural control as well (Iervolino et al., 2002). It has been suggested that neurobiological changes, as a direct or chronic effect of substance use, can influence intrapersonal characteristics (Stautz & Cooper, 2013), which could decrease behavioural control. Furthermore, alcohol use is prospectively associated with externalizing problem behaviour such as violent offenses and deviant behaviour, possibly through the disinhibiting characteristics of alcohol (Boden, Fergusson, & Horwood, 2012; Wells, Horwood, & Fergusson, 2004). If risk factors for problematic drinking are in turn affected by alcohol, this can lead to a cascade where it becomes increasingly hard for an individual to disengage from the problematic behaviour. A study that considers behavioural control as a predictor and an outcome of adolescent alcohol use in one design can help disentangle this bidirectional relationship.

Second, most studies consider either non-clinical risky drinking, such as heavy weekly drinking, or clinical drinking such as AUD. DSM-IV-TR criteria for AUD list behavioural problems associated with using alcohol, such as the impossibility to inhibit the urge to drink even when one is aware of the fact that (more) drinking is harmful. Within AUD, alcohol abuse and alcohol dependence are diagnostically different categories, as dependence is associated with tolerance and/or withdrawal symptoms. The quantity of alcohol intake is not explicitly formulated in the diagnostic criteria for AUD; thus, average alcohol intake of adolescents without AUD might be comparable to alcohol intake of adolescents with AUD. Comparing the outcomes and predictors of both heavy drinking and AUD might help us identify specific risk profiles and contribute to our understanding of why some adolescents develop behavioural problems associated with alcohol use while others do not, despite drinking heavily.

Finally, gender differences in the way alcohol influences behavioural control need to be considered, since alcohol influences males and females differently. Some studies indicate that girls are more vulnerable to the aversive effects of alcohol (Caldwell et al., 2005; National Institutes of Health, 2000; Squeglia, Schweinsburg, Pulido, & Tapert, 2011), supposedly due to differences in neuromaturation, hormonal fluctuations, and alcohol metabolism (Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007). On the other hand, onset of puberty is generally later in boys (Spear, 2009) and boys' cognitive control tends to show larger maturational rates (Boelema et al., 2014), possibly making development of self-control abilities more vulnerable to external influences.

In the light of the above discussion, we investigated whether a) behavioural control (i.e., high-intensity pleasure (HIP), effortful control (EC), attentional problems, and externalizing problems) in early adolescence predicted heavy drinking and AUD in late adolescence. Furthermore, we investigated whether b) heavy drinking and AUD predicted deviances in problem behaviour in late adolescence compared to controls and how this interacted with gender.

6.2 METHODS

6.2.1 Study design

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study of Dutch pre-adolescents at age 11 (De Winter et al., 2005; Ormel et al., 2012). The target sample involved children living in the North of the Netherlands, covering urban and rural areas. Seventy-six percent of eligible adolescents and their parents agreed to participate and were enrolled in the study at baseline (T1; *n*=2,230, mean age 11.1 years, *SD*=0.56, 49.2% male). On the second assessment (T2; *n*=2,149, mean age 13.6 years, *SD*=0.53, 51.2% female), 96.3% of respondents participated. On the third assessment (T3; *n*=1,816, mean age 16.3 years, *SD*=0.73, 52.3% female), the response rate was 81.4%. On the fourth assessment wave (T4: *n*=1,596, mean age 19.2 years, *SD*=0.57, 46% male), the response rate was 70% for the questionnaires assessment and 71.0% for the psychiatric interview.

6.2.2 Procedure

On the first to the third assessment, adolescents completed self-report questionnaires on behavioural control and drinking behaviour in groups in school, supervised by a research assistant. The parents also completed a written questionnaire. On the fourth assessment, parents and their children were asked to fill out a computerised questionnaire (or, per request, a paper-and-pencil questionnaire). Additionally, trained professional interviewers conducted a clinical interview individually at home or at a nearby community centre. The Dutch Central Committee on Research Involving Human Subjects approved the study. Parents and adolescents' written informed consent was obtained. The confidentiality of the study was emphasised.

6.2.3 Measures

6.2.3.1 Alcohol use

Descriptive statistics. A number of measures were added to compare adolescents with AUD and controls on alcohol-related behaviour and substance use. At T1, adolescents were asked: "How often have you been drinking alcohol (for example, a bottle of beer or a glass of wine)?" up until that time point, on a 5-point scale ranging from 0 to 7 times or more. Furthermore, at T2, T3, and T4 adolescents were asked how many times they had been drunk in the last 12 months. We dichotomised all answers into never and once or more.

At T2-T4, adolescents were asked to report their average drinking habits between the last data collection wave and the present. They were asked four questions: "On how many week(end) days do you normally drink alcohol?" and "On an average week(end) day on which you drink alcohol, how much alcohol (glasses, cans, bottles) do you drink?" Average weekly quantity of alcohol use can be computed by multiplying and adding the answers. A Dutch standard drink contains 10 grams of alcohol.

Alcohol (mis)use. We used a stepwise, bottom-down procedure to identify six groups of drinkers. First, AUD was assessed at T4 using the World Health Organization Composite International Diagnostic Interview (CIDI) version 3.0 (Kessler & Üstün, 2004). The CIDI is a structured diagnostic interview assessing current and lifetime DSM-IV mental disorders, and it has been shown to have good reliability and validity (Andrews & Peters, 1998; Kessler & Üstün, 2004). Of 1,584 participants, CIDI-data for the AUD items were complete. Of those 1,584 participants, 72 had missing data on the alcohol use questionnaires (either T2, T3, or T4) so that their data could not be used. For the remaining 1,612 participants, we started by identifying participants who had met the criteria for *alcohol dependence* (*n*=51) at some point in their lives. In the next step, we classified *alcohol abuse*. These two categories are mutually exclusive and hierarchical, and adolescents meeting the criteria of both abuse and dependence were classified as being alcohol dependent. Participants retrospectively reported the age of onset of their alcohol problems. For abuse, this ranged from 10 to 20 years, and for dependence from 15 to 20. Since two alcohol-abusing participants reported that they developed the disorder before the baseline measure of personality, these participants were removed from the analyses, resulting in 348 alcohol abusers. In the remaining group (participants without AUD), we first identified *heavy drinkers* (n=392). Participants were considered heavy drinkers if they drank more than 6 glasses on a weekend day for boys and 5 glasses for girls (Koning, van den Eijnden, Verdurmen, Engels, & Vollebergh, 2013) and did so on a frequent basis (last month prevalence ≥ 4 times heavy drinking) at T2, and/or T3, and/or T4. Next, *infrequent*

heavy drinkers (*n*=149) were those respondents who indicated drinking 5-6 glasses or more on a regular weekend day, but with last month prevalence <4 at T2, and/or T3, and/or T4. The remaining group, *light drinkers* (*n*=504) therefore consumed less than 5-6 glasses at all of data collection points. A small group of participants were *non-drinkers* (*n*=66) who did not drink alcohol on a regular weekend day on any measurement points. The reference group were light drinkers, since the group of non-drinkers was very small and we did not find them to be an optimal reference group (Boelema et al., re-submitted for publication). See Figure 6.1 for a graphical representation. The measures to construct drinking groups have been used before within the TRAILS-project (Boelema et al., re-submitted for publication[a], Boelema et al., re-submitted for publication[b], Boelema et al., re-submitted for publication[c]).

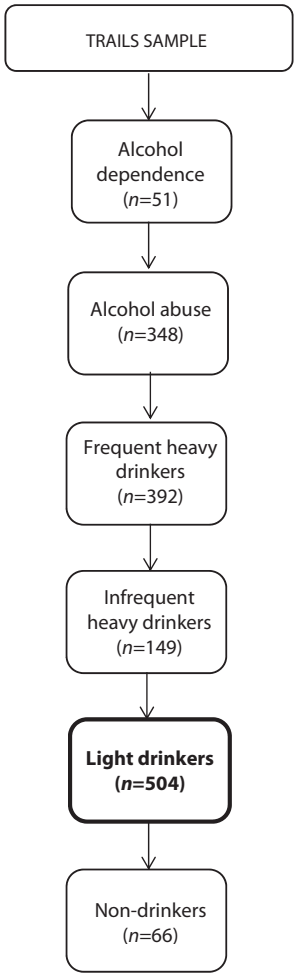

Figure 6.1 Graphical representation of classifying participants into groups of alcohol (mis)use.

6.2.3.2 Behavioural control

At T1, HIP and EC were assessed using the Dutch child and parent version of the Early Adolescent Temperament Questionnaire-Revised (EATQ-R) (Putnam, Ellis, & Rothbart, 2001). *High-intensity pleasure* consisted of 3 items (α=0.64) and *effortful control* comprised 11 items (α=0.69). Items were measured on a five-point scale (hardly ever true to almost always true), and the mean scores were calculated for each scale.

Attentional problems and externalizing problems were assessed using the Youth Self Report (YSR) (Achenbach, 1991; Achenbach & Rescarola, 2001). *Attention problems* comprised 9 items (α=0.64) and the broadband scale *externalizing problems* comprised 30 items (α=0.85). Items were measured on a three-point scale (not at all (0), sometimes (1) almost clearly or often (2)), and the mean scores were calculated for each scale.

At T4, adolescents were older than 18 years and therefore completed the adult version of the YSR (Adult Self Report (ASR)) (Achenbach & Rescarola, 2001), containing the scales *Attention problems* (15 items, α=0.84) and *externalizing problems* (27 items, α=0.88). The EATQ-R was not examined at this measurement wave. For correlations between the measures, see Table 6.1.

6.2.3.3 Covariates

When investigating behavioural control as a predictor of alcohol (mis)use, gender and socioeconomic status (SES) (see Veenstra, Lindenberg, Oldehinkel, De Winter, & Ormel, 2006) were added as covariates. For the effects of alcohol (mis)use on behavioural control in late adolescence, age at T1, SES, parental alcohol use at T1, and smoking and cannabis use at T3 and T4 were included as covariates in the model if they correlated significantly with the outcome measures ($p<.05$). This was the case for smoking and cannabis use (T3/T4) for all outcome measures, and additionally paternal alcohol use for EC (all positively correlated).

Table 6.1 Bivariate correlations among measures of behavioural control at age 11 (below diagonal) and age 19 (above diagonal)

	High-intensity pleasure	Effortful control	Attentional problems	Externalizing problems
High-intensity pleasure	-	N/A	N/A	N/A
Effortful control	.08***	-	N/A	N/A
Attentional problems	-.03	-.51***	-	.80[a]
Externalizing problems	.11***	-.41***	.59***	-

a: correlation between the measures at age 19 (T4).
*: significant at $p<.05$; **: significant at $p<.01$; ***: significant at $p<.001$.

6.2.4 Data analyses

6.2.4.1 Descriptive statistics

To compare groups on descriptive measures, for continuous variables, MANOVAs with post-hoc tests were used. For variables measuring prevalence, Pearson χ^2 with standardised residuals was used to identify observed counts that were significantly different ($p<.05$) from expected counts.

6.2.4.2 Behavioural control as predictor of alcohol (mis)use

Multinomial logistic hierarchical regression analyses were conducted to determine the extent to which behavioural control at age 11 predicted alcohol (mis)use in late adolescence. Light drinkers were the reference group. First, we tested the predictive power of each of the measures in separate models. Next, we included all behavioural control characteristics and covariates in one model per outcome measure to assess the independent predictive power of the different predictor variables.

6.2.4.3 Behavioural control as outcome of alcohol (mis)use

To investigate the influence of adolescent drinking on behavioural control in late adolescence, multivariate linear regression analyses were conducted. Attentional and externalizing problems were the dependent variables and alcohol (mis)use was used as a predictor by using drinking groups as dummy variables, with light drinkers being the reference group. In the analysis, we adjusted for attentional or externalizing problems at T1 and for covariates. The main effects of alcohol (mis)use and interactions with gender were entered in separate blocks and interpreted accordingly.

6.3 RESULTS

6.3.1 Descriptive statistics

Table 6.2 shows the descriptive statistics. There were no differences in age and SES at baseline between light drinkers and other drinking groups. As to be expected, higher prevalence of other substance use and drunkenness were found among heavy drinkers and adolescents with AUD. Alcohol consumption was significantly higher in these groups than in light drinkers.

Table 6.2 Descriptive statistics of the six drinking patterns and alcohol abuse and dependence

	Non-drinker	Light drinkers	Infrequent heavy drinkers	Heavy drinkers	Alcohol abuse	Alcohol dependence
N	66	504	149	392	348	51
Age at baseline *M* (*SD*)	11.3 (0.49)^{a}	11.3 (0.57)^{a}	11.3 (0.54)^{a}	11.3 (0.56)^{a}	11.4 (0.58)^{a}	11.4 (0.58)^{a}
% male	36	39^{-}	31^{-}	46	65^{+}	53
SES at baseline *M* (*SD*)	0.01 (0.77)^{ab}	0.10 (0.76)^{ab}	-0.05 (0.81)^{b}	0.11 (0.73)^{ab}	0.11 (0.80)^{ab}	0.25(0.75)^{b}
Maternal alcohol use *M* (*SD*)	2.8 (1.2)^{a}	2.7 (1.2)^{abc}	2.6 (1.2)^{a}	2.9 (1.3)^{abc}	3.0 (1.4)^{bc}	3.2 (1.2)^{c}
Paternal alcohol use *M* (*SD*)	3.1 (1.4)^{a}	3.3 (1.2)^{ab}	3.2 (1.3)^{ab}	3.6 (1.2)^{bc}	3.6 (1.2)^{bc}	3.8 (1.3)^{c}
Last year cannabis use age 16 (%)	2^{-}	10^{-}	28	34	38^{+}	65^{+}
Last year cannabis use age 19 (%)	2^{-}	13^{-}	24	37^{+}	55^{+}	73^{+}
Daily smoking age 16 (%)	0^{-}	9^{-}	25	33^{+}	37^{+}	46^{+}
Daily smoking age 19 (%)	3^{-}	20^{-}	26^{-}	43^{+}	47^{+}	56^{+}
Haven drunk >1 glass age 11 (%)	3^{-}	8^{-}	16	18	22^{+}	20
Last year drunkenness age 13 (%)	2^{-}	8^{-}	20	22	28^{+}	39^{+}
Last year drunkenness age 16 (%)	3^{-}	15^{-}	32	50^{+}	51^{+}	70^{+}
Last year drunkenness age 19 (%)	12^{-}	63^{-}	84	91^{+}	91^{+}	98
N glasses per week age 13 *M* (*SD*)	0.1 (0.3)^{a}	0.6 (1.7)^{b}	1.3 (2.9)^{bc}	1.9 (3.4)^{bc}	1.9 (4.8)^{c}	2.1 (3.9)^{c}
N glasses per week age 16 *M* (*SD*)	0.0 (0.0)^{a}	2.6 (2.8)^{b}	5.3 (4.4)^{c}	8.3 (7.5)^{d}	8.5 (7.5)^{d}	9.8 (6.7)^{d}
N glasses per week age 19 *M* (*SD*)	0.1 (0.4)^{a}	4.2 (3.9)^{b}	6.7 (3.8)^{c}	11.3 (7.0)^{d}	12.1 (7.6)^{d}	16.1 (10.0)^{e}
Self-report age 11						
High-intensity pleasure *M* (*SD*)	2.82 (1.11)^{a}	2.98 (1.05)^{ab}	3.12 (0.94)^{abc}	3.27 (1.06)^{bc}	3.38 (0.91)^{bc}	3.48 (0.91)^{c}
Effortful control *M* (*SD*)	3.70 (0.50)^{a}	3.67 (0.54)^{ab}	3.58 (0.54)^{ab}	3.56 (0.54)^{ab}	3.50 (0.54)^{ab}	3.49 (0.56)^{c}
Attentional problems *M* (*SD*)	0.51 (0.31)^{a}	0.45 (0.29)^{a}	0.47 (0.30)^{a}	0.48 (0.29)^{a}	0.50 (0.31)^{a}	0.64 (0.27)^{b}
Externalizing problems *M* (*SD*)	0.23 (0.19)^{a}	0.25 (0.18)^{a}	0.26 (0.17)^{ab}	0.28 (0.20)^{ab}	0.33 (0.21)^{b}	0.44 (0.25)^{c}
Self-report age 19						
Attentional problems *M* (*SD*)	0.46 (0.31)^{ab}	0.41 (0.31)^{ab}	0.38 (0.27)^{a}	0.44 (0.30)^{ab}	0.51 (0.32)^{b}	0.64 (0.32)^{c}
Externalizing problems *M* (*SD*)	0.19 (0.21)^{ab}	0.13 (0.16)^{a}	0.17 (0.18)^{a}	0.25 (0.21)^{ab}	0.31 (0.25)^{b}	0.50 (0.27)^{b}

+ or - signs mean Pearson-Chi-Square Test is significant. + means cell count is higher than expected, - means cell count is lower than expected. Different superscript letters refer to significant differences ($p<.05$) in mean scores between groups: if two group scores are labelled with the same letter, the scores of these groups do not differ. If two scores are labelled with different letters, these scores differ.

6.3.2 Behavioural control as predictor of alcohol (mis)use

Multinomial logistic regression analyses were conducted to predict drinking group membership by behavioural control in early adolescence, while controlling for gender and SES. Regarding bivariate associations, heightened levels of HIP were predictive of frequent heavy drinking (OR=1.35, $p<.001$, CI=1.18-1.54), alcohol abuse (OR=1.48, $p<.001$, CI=1.28-1.70), and alcohol dependence (OR=1.62, $p<.01$, CI=1.19-2.20). Higher EC was found to be a protective factor for frequent heavy drinking (OR=0.67, $p<.01$, CI=0.52-0.86), alcohol abuse (OR=0.52, $p<.001$, CI=0.40-0.68), and alcohol dependence (OR=0.50, $p<.05$, CI=0.28-0.90). More attentional problems were a strong risk factor of alcohol dependence (OR=7.26, $p<.001$, CI=2.81-18.75). Finally, more externalizing problems were found among frequent heavy drinkers (OR=2.29, $p<.05$, CI=1.09-4.80), alcohol abusers (OR=8.06, $p<.001$, CI=3.84-16.94), and alcohol dependents (OR=51.20, $p<.001$, CI=13.81-189.81).

The results of the multivariate model are depicted in Table 6.3. Attentional problems were found to predict non-drinking. Both heightened levels of HIP and lower levels of EC predicted frequent heavy drinking in late adolescence. Significant predictors of alcohol abuse were heightened HIP, lower levels of EC, and more externalizing problems. Finally, heightened HIP and more externalizing problems were significant predictors of alcohol dependence.

6.3.3 Behavioural control as outcome of alcohol (mis)use

Linear regression analyses were conducted for each alcohol group to predict attentional problems and externalizing problems in late adolescence while controlling for these measures in early adolescence and covariates (see Table 6.4). T1 measures were significant and strong predictors of the same measures at T4. We found a significant main effect of alcohol dependence on *attentional problems*, with alcohol dependent adolescents reporting more attentional problems in late adolescence, above and beyond their reported attentional problems in early adolescence. Furthermore, the results revealed two significant group*gender interaction effects for frequent heavy drinking and alcohol abuse. Females reported more attentional problems (heavy drinkers: mean=0.63; abusers=mean: 0.71; controls=mean: 0.59 (based on regression coefficients)) compared to males (heavy drinkers: mean=0.53; vs. abusers: mean=0.57; controls: mean=0.59). For *externalizing problems*, the results revealed significant main effects for alcohol abuse and dependence, with higher levels of externalizing problems reported by these groups.

Table 6.3 Risk of alcohol (mis)use (T4) predicted by behavioural control (T1) in a multivariate model

	Non-drinkers vs. light drinkers (T2-T4)		Infrequent heavy drinkers vs. light drinkers (T2-T4)		Heavy drinkers vs. light drinkers (T2-T4)		Abusers vs. light drinkers (T2-T4)		Dependents vs. light drinkers (T2-T4)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Self-report (T1)										
Gender (ref=male)	0.83	0.16 to 1.49	1.60*	1.02 to 2.50	0.81	0.60 to 1.10	0.47***	0.34 to 0.65	0.75	0.34 to 1.48
SES	0.81	0.56 to 1.18	0.79	0.61 to 1.03	0.90	0.74 to 1.10	0.94	0.77 to 1.16	1.34	0.85 to 2.11
High-intensity pleasure	0.89	0.68 to 1.18	1.20	0.98 to 1.47	1.35***	1.16 to 1.56	1.47***	1.25 to 1.72	1.57**	1.12 to 2.20
Effortful control	1.55	0.82 to 2.97	0.76	0.48 to 1.21	0.56***	0.40 to 0.79	0.52***	0.36 to 0.75	1.01	0.47 to 2.19
Attentional problems	4.47*	1.29 to 15.45	0.96	0.38 to 4.62	0.69	0.36 to 3.84	0.53	0.26 to 1.09	2.39	0.56 to 10.18
Externalizing problems	0.16	0.02 to 1.39	1.10	0.29 to 5.26	1.44	0.54 to 4.01	3.83***	1.42 to 10.33	25.46***	4.35 to 148.95
R^2=.12 (Cox&Snell); .13 (Nagelkerke). Model $\chi^2(30)$=166.89, p<.001										

*: significant at p<.05; **: significant at p<.01; ***: significant at p<.001.

Table 6.4 Behavioural control (T4) predicted alcohol (mis)use (T2-T4), controlling for behavioural control at baseline (T1) and covariates

		B	β	95% CI of *B*
Attentional problems age 19 (self-report)				
Multivariate	Gender (ref=female)	-0.04*	-.06	-0.08 to -0.01
	T1 attentional problems	0.30***	.28	0.24 to 0.36
	Non-drinkers (ref=light drinkers)	0.04	.03	-0.04 to 0.13
	Infrequent heavy drinkers (ref=light drinkers)	-0.03	-.03	-0.10 to 0.03
	Frequent heavy drinkers (ref=light drinkers)	-0.00	-.00	-0.05 to 0.04
	Alcohol abuse (ref=light drinkers)	0.05	.06	-0.01 to 0.10
	Alcohol dependence (ref=light drinkers)	0.13*	.07	0.02 to 0.24
	Non-drinkers (ref=light drinkers)* gender	0.10	.04	-0.08 to 0.27
	Infrequent heavy drinkers (ref=light drinkers)* gender	-0.03	-.02	-0.16 to 0.10
	Frequent heavy drinkers (ref=light drinkers)* gender	-0.10*	-.10	-0.19 to -0.01
	Alcohol abuse (ref=light drinkers)* gender	-0.14**	-.14	-0.24 to -0.04
	Alcohol dependence (ref=light drinkers)* gender	-0.10	-.04	-0.32 to 0.11
R^2=.13 for Step 1. ΔR^2=.01 for Step 2 (p<.05). ΔR^2=.005 for Step 3 (p<.05)				
Externalizing problems age 19 (self-report)				
Multivariate	Gender (ref=female)	-0.03*	-.07	-0.05 to -0.00
	T1 externalizing problems	0.27***	.25	0.21 to 0.33
	Non-drinkers (ref=light drinkers)	0.17	.05	-0.02 to 0.37
	Infrequent heavy drinkers (ref=light drinkers)	-0.02	.03	-0.06 to 0.02
	Frequent heavy drinkers (ref=light drinkers)	0.01	-.08	-0.02 to 0.04
	Alcohol abuse (ref=light drinkers)	0.05**	.10	0.02 to 0.09
	Alcohol dependence (ref=light drinkers)	0.24***	.18	0.16 to 0.31
	Non-drinkers (ref=light drinkers)* gender	0.18	.03	-0.22 to 0.58
	Infrequent heavy drinkers (ref=light drinkers)* gender	-0.03	-.02	-0.11 to 0.06
	Frequent heavy drinkers (ref=light drinkers)* gender	0.04	-.06	0.10 to 0.02
	Alcohol abuse (ref=light drinkers)* gender	-0.05	-.07	-0.11 to 0.02
	Alcohol dependence (ref=light drinkers)* gender	-0.11	-.06	-0.26 to 0.04
R^2=.19 for Step 1. ΔR^2=.03 for Step 2 (p<.001). ΔR^2=.003 for Step 3 (n.s)				

*: significant at p<.05; **: significant at p<.01; ***: significant at p<.001.

6.4 DISCUSSION

The aim of the present study was to investigate the bidirectional relationship between behavioural control and alcohol (mis)use in adolescence in a prospective population cohort. Our results clearly confirmed the importance of intrapersonal characteristics related to behavioural (under)control for patterns of alcohol (mis)use and furthermore confirmed the bidirectional nature of this relationship. Personality characteristics, such as high intensity

pleasure and lack of effortful control in early adolescence, contributed to the likelihood of heavy drinking in late adolescence while more problematic behavioural syndromes, such as externalizing problems, contributed only to higher prevalence of alcohol use disorder and not to heavy drinking as is more common within adolescence. The level of attentional problems did not contribute to the risk for engaging in alcohol (mis)use. Conversely, AUD – most notably alcohol dependence – appeared to influence these problem behaviours confirming a mutually reinforcing mechanism in the more extreme end of the underlying dimension of (lack of) behavioural control.

6.4.1 Behavioural control as predictor of alcohol (mis)use

Our findings are in line with previous studies that have found heightened HIP (Teichman, Barnea, & Ravav, 1989; Willem et al., 2010), lower levels of EC (Wills et al., 2001; Wills & Dishion, 2004), and more externalizing problems (Fergusson et al., 2007; Loeber, Stouthamer-Loeber, & Raskin White, 1999) as predictors of later alcohol (mis)use. In contrast with the finding that attentional problems predicted alcohol (mis)use (Groenman et al., 2013; Wilens et al., 2011; Zulauf et al., 2014), we found no effect of attentional problems in a multivariate model, although it was a bivariate predictor of alcohol dependence. This is in line with the finding that attentional problems were largely unrelated to substance use after controlling for conduct problems (Fergusson et al., 2007). Interestingly, we found that attentional problems predicted non-drinking. Attentional problems have been found to be negatively related to alcohol use before, although the mechanism behind this is still unclear (Fergusson et al., 2007). This finding supports the suggestion that non-drinkers might not be the optimal choice for the (single) reference group.

By considering both personality and externalizing problems as predictors and heavy drinking and AUD as outcomes in one model, we found them to be uniquely interrelated. Adopting the viewpoint of a spectrum model of personality, problematic behaviour can be seen as an extreme set of healthy characteristics that potentially lead to pathologies (Lahey, 2004; Tackett, 2006). Indeed, more extreme personality characteristics have been prospectively related to problematic behaviour (Van den Akker, 2013). In our study, we found that normative personality characteristics were more likely to predict frequent alcohol use and AUD, whereas externalizing problems were more likely to predict only AUD, indicating that the tendency to cross boundaries and engage in rule-breaking behaviour is already visible in early adolescence. Our results are consistent with previous studies, which found that a greater number of conduct symptoms and externalizing problems are likely to characterise

risky patterns of substance use (i.e., early onset) rather than less risky patterns among late onset groups (Flory, Lynam, Milich, Leukefeld, & Clayton, 2004; Monshouwer et al., 2012).

6.4.2 Behavioural control as outcome of alcohol (mis)use

Frequent heavy drinking and AUD are suggested to have an effect on attentional and externalizing problems in late adolescence. Adolescents with AUD have shown less optimal performance on neuropsychological tasks measuring attention (Tapert & Brown, 1999; Tapert, Granholm, Leedy, & Brown, 2002). An explanation could be that alcohol induces neurobiological changes resulting in attentional problems (Stautz & Cooper, 2013). However, longitudinal evidence for this hypothesis is scarce, and we found this effect to be small and gender specific (Boelema et al., submitted for publication). Another explanation could be that problematic drinking, again especially AUD, is an impairing condition that is associated with psychosocial stress. Such stress has been found to disrupt prefrontal cortex processing, which can lead to attentional problems (Liston, McEwen, & Casey, 2009).

Previous studies have found alcohol use to be prospectively associated with violent offences (Boden et al., 2012; Wells et al., 2004). Alcohol use could increase maladaptive behaviour (de Wit, 2009) and enhance the likelihood of involvement in impulsive criminal offences (Fergusson, Lynskey, & Horwood, 1996). Particularly AUD could cause individuals to be exposed to a social environment where deviant behaviour such as substance use, aggression, and delinquency are more normative and accepted. For example, affiliations with deviant peers have found to be associated with both alcohol misuse and juvenile offending (Fergusson et al., 1996). The fact that alcohol (mis)use influences those psychosocial characteristics that are risk factors for the same behaviour, is disturbing, since a cascade effect could occur, where it becomes increasingly difficult to disengage from the behaviour.

When looking at gender differences, we found that attentional problems affected female heavy drinkers and abusers more than they did their male counterparts. This is in line with the suggestion that females are more sensitive to the effects of alcohol due to differences in body weight and alcohol metabolism (Medina et al., 2007). Furthermore, alcohol abuse is less common among females. The so-called gender paradox states that in disorders that have an unequal gender ratio, the gender with the lower prevalence tends to be more affected by the risk factors associated with that disorder (Taylor & Ounsted, 1972). This suggests that girls who meet the criteria for alcohol abuse differ from non-abusing peers more than boys do.

6.4.3 Strengths and limitations

This study must be interpreted in the light of its strengths and limitations. Strengths include the large population-based cohort and the longitudinal design. This study is unique in investigating both heavy drinking and AUD as well as the full spectrum of behavioural control as predictors and outcomes in one design, which allowed us to study the interrelation between these measures.

A limitation is that behavioural control was measured in late adolescence making use of problem behaviour where HIP and EC were not assessed. The reason for this was a practical one, as the EATQ-R was not re-administered in late adolescence. It can be argued that the effects of alcohol (mis)use on behavioural control are most pronounced on the more extreme end of the behaviour spectrum, i.e., in problem behaviour. On the other hand, it would have been interesting to see whether alcohol (mis)use has an influence on HIP and EC as well, since this could also contribute to the difficulty to disengage from alcohol consumption. Future research should study this relation.

The second limitation is that despite the large sample size and representative prevalence rates, the number of adolescents with alcohol dependence was still relatively small, especially when investigating the interaction effects. This could have resulted in a loss of power. However, our respondents were still young, with the mean age of 19 years, and prevalence of alcohol dependence at this age is still relatively small in the population (Swendsen et al., 2012).

6.4.4 Conclusions

Our findings indicate that (non-clinical) heavy drinking and clinical drinking are characterised by distinct profiles of behavioural (under)control in early adolescence. It is suggested that heavy drinking and AUD are two distinct groups with respect to risk factors and adverse outcomes. Regular heavy drinkers appear to have an urge to seek thrills and experience exciting things, and they appear to be less efficient in controlling their behaviour. In addition to that, adolescents with alcohol abuse and dependence appear to have a tendency to engage in rule-breaking behaviour and deviate from societal norms early in their lives. When looking at the effects of alcohol (mis)use, we found that heavy drinking and AUD influence more extreme risk factors, which could result in a vicious circle, where it is increasingly difficult to disengage from alcohol (mis)use.

7
General discussion

The overall aim of the current thesis was to investigate the effect of alcohol use in adolescence on neurocognitive functioning in a longitudinal design. We wanted to know whether adolescents who engage in heavy drinking or are diagnosed with alcohol use disorder (AUD) were at risk for an abnormal maturation of neurocognitive functioning compared to non-drinkers. Furthermore, we investigated whether a diminished neurobehavioural control capacity was a risk factor for engaging in heavy drinking or developing an AUD. All studies in this thesis are based on the Tracking Adolescents' Individual Lives Survey (TRAILS), a prospective cohort study, which started in 2000 among 2,230 10- to 11-year-olds (de Winter et al., 2005; Ormel et al., 2012). This chapter reviews and integrates the main findings from the thesis. Furthermore, methodological reflections and implications for prevention and future research are provided.

7.1 SUMMARY OF THE MAIN FINDINGS

7.1.1 Maturation of cognitive control

To draw conclusions about deviant cognitive maturation, it is essential to understand normal cognitive development. During adolescence, particularly cognitive control functions (also called executive functioning; EF) are hypothesised to mature significantly (Crone, 2009). This is assumed to parallel the maturation of parietal and prefrontal cortices, the neuroanatomical regions most associated with cognitive control (Blakemore & Choudhury, 2006). Although existing cross-sectional research indeed proposes a significant maturation of EF during adolescence (Brauch Lehman, Naglieri, & Aquilino, 2010; Huizinga, Dolan, & van der Molen, 2006; Magar, Phillips, & Hosie, 2010), longitudinal studies are scarce. In *Chapter 2*, we therefore investigated the maturation of six subcomponents of EF (focused attention, inhibition, sustained attention, speed of processing, working memory, and shift attention) as well as differences with respect to gender and socioeconomic status (SES). The results illustrated that, as expected, significant maturation over the course of adolescence takes place for all subcomponents. Furthermore, gender differences in rates of maturation between the subcomponents emerged, with boys showing greater improvement in working memory, sustained attention, and inhibition, and girls showing greater improvements on speed of processing. Larger improvements in performance where interpreted as a prolonged maturational trajectory. SES appears to influence maturation only moderately and only with respect to sustained attention and inhibition. That is, middle and high SES

adolescents outperformed their peers from low SES families. For focused attention and speed of processing, there was not enough variance in the data; therefore, these measures were not considered in the following chapters.

7.1.2 Effects of alcohol use on cognitive and behavioural control

With this knowledge about normal maturation, the next step was to assess in a longitudinal design whether adolescent heavy drinking influences these maturational trajectories. In *Chapter 3*, six groups of drinking patterns were construed, ranging from non-drinkers to chronic heavy drinkers – adolescents who have been drinking 5-6 glasses or more on a single occasion every weekend for the last four years. Weekend quantity of alcohol use has been shown to be a useful and specific measure of alcohol use at this age (Weingardt et al., 1998), and the cut-off we used is comparable to previous research (Koning, van den Eijnden, Verdurmen, Engels, & Vollebergh, 2013). Because we had pre-exposure and follow-up measures of cognitive functioning, we were able to compare the six drinking groups on maturation of cognitive control drawing causal conclusions. In contrast to the hypothesis, the results indicated no significant differences between any of these drinking patterns and non-drinkers on either working memory, inhibition, sustained attention, and shift attention, not even in the heaviest drinking group (i.e., drinking every weekend and drinking an average of 15 glasses of alcohol each week). Gender did not moderate the effect of drinking patterns on neurocognitive maturation. This is in contrast to the previous findings, which indicated that girls are assumed more vulnerable to the toxic effects of alcohol compared to boys (Caldwell et al., 2005; Squeglia et al., 2011).

One explanation for this finding is that we measured merely basic cognitive control functions. Although these functions are prerequisite for neurocognitive skills that are more complex (Miyake et al., 2000), the integration of basic skills into more complex functions is essential for adequate performance in daily life. At a neuro-anatomical level, maturational myelination and pruning are two processes involved in facilitating synaptic connections between different brain areas that essential for the transfer of information throughout the brain (Luna et al., 2001). Alcohol use in is assumed to influence these processes (Moss, 2008), and more complex classical neuropsychological tasks relying on multiple integrated cognitive processes might more sensitive to pick up the effects of such alterations. In *Chapter 4*, we assessed differences between the drinking groups on such tasks. Again, we found no differences between heavy drinkers and controls on nine tasks assessing neurocognitive deficits in verbal memory, visuoconstruction and visual memory, concept generation, and

semantic memory. A point of concern in task selection is that classical neuropsychological tasks are generally designed to investigate deficits in neurocognitive functioning that would be suggestive of brain dysfunction and that these tasks thus do not evaluate performance levels per se. Adolescent alcohol use might (initially) cause more subtle neural alterations, which do not directly exceed the threshold of deficits. Therefore, it is useful to also investigate performance on more dynamic cognitive tasks based on the combination of both task difficulty and processing speed in order to learn more about the optimal level of functioning that can be achieved. Only on the performance-based task, Block Design, which assesses visuospatial problem-solving under time pressure, we found that non-drinkers outperformed all of the drinking groups, whereas no differences emerged between all the other drinking groups. The absence of a dose-response relationship indicates that the explanation for the difference in problem-solving skills between non-drinkers and alcohol-consuming adolescents does not rely on the quantity of alcohol intake. An explanation might be that abstaining adolescents are a non-normative group with specific psychosocial characteristics, for example, strong behavioural control (Moffitt, 1993; Shedler & Block, 1990). One can speculate that these assumed '(over)controlling' characteristics of non-drinkers enhance the performance on the problem-solving task while at the same time, this controlling characteristic may be responsible for keeping them from going out and engage in group related drinking in the presence of their peers. These findings also indicate that caution should be taken when non-drinkers are the only reference group in research on the effects of alcohol, as this group might be non-normative.

Our data suggest that heavy drinking does not have a large influence on neurocognitive functioning. One could hypothesise that heavy drinkers do not represent the group that is most at-risk for aversive outcomes of alcohol use regarding neurocognitive maturation. Pathological behaviour towards alcohol might better account for the risks associated with alcohol use. Adolescents with AUD might form a high-risk group, and studying this group more in depth increases our understanding of the effect of alcohol-related behaviour on cognitive control. In *Chapter 5*, we therefore focused on adolescents with AUD, i.e., a lifetime diagnosis of either alcohol abuse or alcohol dependence. A diagnosis of AUD is relatively independent of the quantity of alcohol intake, and the amount of glasses consumed by these groups can be very different. Furthermore, comorbid psychiatric disorders, such as ADHD, anxiety, depression, substance use disorder, and externalizing problems, which can in turn influence neurocognitive functioning, are highly prevalent among these adolescents. We therefore controlled for weekly quantity of alcohol intake and comorbid psychiatric

disorders. Again, we found no significant differences in neurocognitive maturation of inhibition, working memory, sustained attention, and shift attention between these groups and controls without a diagnosis. An exception was shift attention, where girls with alcohol dependence showed less maturation, but differences were small. Attentional functioning has been found to be affected in adolescents with AUD before (Tapert & Brown, 1999; Tapert, Granholm, Leedy, & Brown, 2002). This interaction effect of shift attention with gender did not change when controlling for the quantity of weekly alcohol intake and comorbid disorders, indicating that neither higher levels of alcohol consumption nor higher rates of comorbid disorders can explain this stagnation in shift attention in alcohol dependent girls. It is surprising that differences in cognitive functioning in AUD are unrelated to the quantity of alcohol use. This indicates that instead of heightened levels of alcohol use, the mere presence of the disorder may have a (small) influence on the maturation of cognitive control. It is unclear whether the weaker performance of alcohol dependent girls is an expression of disturbed maturation, or rather a (temporarily) diminished performance. Alcohol dependence is an impairing condition associated with a high level of co-occurring problems that can cause psychosocial stress. Such stress has been found to disrupt prefrontal related cognitive processing, as reflected in a weakened ability of attentional shifting, a process that was found to be reversible when the stressors disappeared (Liston, McEwen, & Casey, 2009). If this were indeed the case, the treatment of alcohol dependence would decrease attentional problems.

Adequate functioning in everyday life does not rely solely on intact cognitive functioning but requires sufficient behavioural control as well. It is largely unknown whether and the extent to which adolescent alcohol use affects these capacities in the long term. It could be hypothesised that behavioural control, which encompasses more complex skills and is present also in social situations, may be influenced by alcohol use more clearly than neurocognitive functioning assessed in a laboratory setting. In *Chapter 6*, we therefore investigated the effects of both heavy drinking and AUD on behavioural control using questionnaires measuring attentional and externalizing problems. Female heavy drinkers, female alcohol abusers, and alcohol dependents experienced significantly more attentional problems, compared to light drinkers. Furthermore, alcohol abusers and alcohol dependents experienced more externalizing problem behaviour. This suggests that alcohol use can results in problem behaviour related to self-regulation, and that these negative outcomes are most clear for adolescents with AUD and females appear to be most vulnerable.

7.1.3 Cognitive and behavioural control capacity as a risk factor for alcohol use

A reciprocal relationship between neurocognitive functioning and alcohol use has been proposed, as weaknesses in inhibition, attention, or working memory might be risk factors for engaging in problematic alcohol use (Grenard et al., 2008; Kirisci, Tarter, Reynolds, & Vanyukov, 2006; Tapert et al., 2002; Tarter et al., 2003). In *Chapter 5*, we therefore assessed whether neurocognitive functioning in early adolescence predicted AUD in adolescence. No evidence was found for the hypothesised effect, the best predictor of adolescent AUD was found to be alcohol use in early and middle adolescence.

In line with what is described above, measures of behavioural control might be more sensitive tools when assessing risk factors for engaging in problematic behaviour. In *Chapter 6*, intrapersonal characteristics measured in early adolescence, which tap onto behavioural control, encompassing the full spectrum going from the personality characteristics sensation seeking and (lack of) effortful control to more the problematic behavioural syndromes of attentional and externalizing problems, were found to be prospectively related to heavy drinking and AUD. These were all found to be significant predictors of heavy drinking and AUD, in line with previous research (Creemers et al., 2009; Fergusson, Horwood, & Ridder, 2007; Fite, Colder, Lochman, & Wells, 2008; Groenman et al., 2013; Monshouwer et al., 2012; White, Xie, Thompson, Loeber, & Stouthamer-Loeber, 2001; Wilens et al., 2011; Willem et al., 2010; Wills et al., 2001; Wills, McNamara, Vaccaro, & Hirky, 1996; Wong et al., 2006; Zulauf, Sprich, Safren, & Wilens, 2014). By considering both personality and externalizing problems as predictors and heavy drinking and AUD as outcomes in one model, we found them to be uniquely interrelated. The normative personality traits, that is, high-intensity pleasure and effortful control, were found to be risk factors for later frequent heavy alcohol use and AUD while externalizing problems were indicative exclusively of AUD. These findings stress that caution should be taken when interpreting findings from cross-sectional studies, since weaknesses in (behavioural) control capacity are likely to precede risky drinking.

7.2 EXPLANATIONS AND IMPLICATIONS

When addressing our main research question, we found no compelling evidence for the effects of alcohol use in adolescence on cognitive functioning. These findings are in sharp contrast with concerns expressed by, for example, the National Institute of Alcohol and Alcoholism (NIAAA) about the dangers of alcohol for the developing brain. It is commonly

accepted in both science and society that alcohol use is specifically harmful for the adolescent brain and cognitive functioning. Yet, we found no strong evidence of a causal relationship. Three hypotheses developed to explain this discrepancy are discussed below and implications for future research are given. First, the findings from previous research on which the existing hypotheses and concerns are based might have been overinterpreted and overgeneralised. Second, the suitability and sensitivity of neurocognitive outcome measures for investigating the effects of alcohol use should be considered. Finally, it could be more fitting not to perceive the adolescent brain only as highly vulnerable, but also as plastic and flexible.

7.2.1 Explanation I: Overinterpretation and overgeneralisation of research

Since the ideal randomised trial to study the effects of alcohol on neurocognitive maturation is clearly unacceptable for ethical reasons, more indirect designs have to be used. Longitudinal studies with neurocognitive pre- and post-measurements are the best option. Such studies, however, have not been available until recently (Squeglia et al., 2009; Squeglia et al., 2012; Whetherill et al., 2013; for a discussion of those studies, see Explanation II, page 124) and therefore concerns and hypotheses regarding the effects of alcohol on adolescent neurocognitive functioning are usually based on cross-sectional studies, often conducted with individuals with AUD, or animal studies.

7.2.1.1 (Cross-sectional) studies in humans

As stated in the introduction of this thesis, the first studies on the effects of alcohol on neurocognition have been conducted in adolescents with AUD (Brown et al., 2000; Moss et al., 1994; Tarter et al., 1995) presumably because this is a well-defined group often with severe patterns of alcohol use. Although one study conducted follow-up measurements on adolescents with AUD (Tapert & Brown, 1999; Tapert et al., 2002), most previous studies were cross-sectional in the sense that there were no baseline measures of neurocognitive functioning before the onset of drinking. Although these pioneering studies are important, they have two clear limitations: they utilized cross-sectional designs and studied pathological groups, that is, adolescents with AUD.

Cross-sectional designs hamper the possibility to draw causal conclusions, as it is unclear whether deficits found in heavy drinkers or adolescents with AUD are a result of their alcohol use or might have been pre-existent. Indeed, impairments in cognitive control functions, such as inhibition, attention, and working memory have been prospectively related to alcohol use (Grenard et al., 2008; Tapert et al., 2002; Tarter et al., 2003). Although the

current thesis did not replicate this finding (Chapter 5), we found that behavioural under-control is a strong risk factor for AUD (Chapter 6). Since there is evidence for risk factors related to cognitive and behavioural control in future alcohol users, caution should be taken when interpreting findings from cross-sectional studies, as it is unclear whether reported differences between groups are actually caused by the alcohol use.

Furthermore, findings that apply to adolescents with AUD are often generalised to all (heavy) drinking adolescents. As stated above, AUD is a psychiatric disorder in which alcohol use and alcohol-related behaviour are intertwined. It is therefore not clear whether differences between adolescents with AUD and controls are the result of the alcohol intake or of the psychiatric disorder. The findings from this thesis indicate that adolescents with AUD indeed form a group that is different from heavy drinkers with respect to risk factors and adverse outcomes (Chapter 6) and that the effect of their disorder on the maturation of attention is independent of the quantity of alcohol intake (Chapter 5).

Taken together, the findings from this thesis therefore underline the caution that should be taken when interpreting the findings from studies that have cross-sectional design and/or are conducted with adolescents with AUD.

7.2.1.2 Animal studies

Findings from animal studies are often used as support that findings from cross-sectional studies should indeed be interpreted in favour of effects being caused by alcohol. The evident benefit of animal studies is the possibility for administering alcohol to randomly chosen individuals. They have, however, several limitations as well.

A recent review of animal studies on the effects of substance abuse on adolescent development indicated that most studies have focused on brain structure, neurophysiology, and neurochemistry (Gulley & Juraska, 2013), reporting loss of neurons in various brain areas, differences in neural activation, and an effect of alcohol on the body's stress response system. On the other hand, studies on cognitive-behavioural effects are relatively scarce and a large proportion of available studies have assessed the direct effects of alcohol intoxication, i.e., how cognition is impaired when animals are under the influence of alcohol. Some studies that investigated the long term effects of alcohol consumption suggested that adolescent rats exposed to alcohol are more impulsive and less anxious, which are characteristics that might result in less optimal decision-making (Gilpin, Karanikas, & Richardson, 2012; Nasrallah, Yang, & Bernstein, 2009). In contrast, one study did not find differences between alcohol-exposed and control rats on measures of attention, impulsivity, or cognitive flexibility

(Semenova, 2012). Nevertheless, long-term differences between rats that consumed alcohol and controls on memory and learning have been found (Pascual, Blanco, Cauli, Miñarro, & Guerri, 2007; Schulteis, Archer, Tapert, & Frank, 2008).

Next to obvious restrictions regarding the generalizability of the rat brain and the timing and course of adolescence to humans, other important factors to consider are the frequency and quantity of alcohol consumption. Methods for alcohol administrations differ greatly between studies. In general, rats often receive alcohol multiple times a week or even daily while the majority of (Dutch) human adolescents drink approximately twice a week or less, and drinking during weekdays is rather uncommon (Verdurmen et al., 2012). Alcohol administration in rats occurs for several weeks in a row, which means that animals are being intoxicated with alcohol on a regular basis over the entire adolescent period, which only lasts two to four weeks in rats (Gulley & Juraska, 2013). Most human adolescents do not start weekly drinking until age 16, being already in mid adolescence (Verdurmen et al., 2012). Quantity of alcohol intake in above mentioned studies ranged from 2.0 g/kg (Gilpin et al., 2012) to as much as 11.4 g/kg (Nasrallah et al., 2009) per drinking occasion, which is comparable to 12 to 68 glasses for humans (for an individual of 60 kilos and a standard drink with 10 gram of alcohol per glass). This clearly exceeds human adolescent drinking, since even the lowest amount of alcohol administered to the animals per occasion (the equivalent of 12 glasses) is consumed by less than a third of (Dutch) human adolescents (Verdurmen et al., 2012). In some studies, blood alcohol levels of rats were 2 to 3.5 per mille three times a week (Schulteis et al., 2008), exceeding the legal limit in the Netherlands four to seven times. In another study, rats received a 20%-ethanol-solution as the only source of liquid for eight weeks (Farr, Scherrer, Banks, Flood, & Morley, 2005), which is an extremely unrealistic situation even for high-risk adolescents. These issues strongly question the ecological validity of findings from animal studies. Although supporting the suggestion for the neurotoxic potential of extreme quantities of alcohol on the (developing) mammal brain, the extent to which lower amounts of alcohol intake cause this harm is not yet understood.

Taken together, critical reflections of cross-sectional studies in human and animal studies indicate that when methodological considerations should have been made and caution should have been taken in interpreting the findings and generalizing them to the majority of adolescents and their drinking habits, this is not what happened when the results from the abovementioned studies came out. This is both understandable and sensible, as one can never be cautious enough when it comes to protecting future generations from possible harm. The problem is, however, that taking caution is not the same in science and

in prevention policy. In science, one should be careful interpreting an effect as univocally negative when other interpretations might also be valid. In prevention policy, on the other hand, one should be careful neglecting an effect that could have negative outcomes, even though other interpretations might be valid as well. This difference in fundamental tenets can cause friction and misunderstandings between scientists and prevention workers.

An issue that should be considered here is the phenomenon of publication bias. There is a persistent tendency to publish significant results more (and presumably more easy) than null findings, which has the potential to do serious harm to not only the accuracy of knowledge within a field but also scientific integrity. First, it is a responsibility of researchers to publish the results of well-conducted and meaningful studies, irrespective of their outcomes. On the other hand, editors of journals should judge papers based on their research questions and methodology, not on whether the null hypothesis is accepted or rejected and have the courage to publish papers that contradict current lines of thought.

7.2.2 Explanation II: Importance of outcome measures

It is important to bear in mind that the effects of alcohol on the human brain and concurring cognitive functioning can be measured almost exclusively (except for post-mortem research) indirectly by either making use of neuropsychological tasks or fMRI measurements. This means that the effects and their interpretation depend greatly on the sensitivity of the outcome measure of choice, as direct damage is not assessed.

7.2.2.1 Neuropsychological tests

In this thesis, we studied behavioural expressions of possible brain damage or alterations on neuropsychological tasks and questionnaires. We touched upon the issue of outcome measure-dependent effects by taking into account basic computerised tasks of cognitive control (Chapter 3), complex neuropsychological tasks (Chapter 4), and measures of behavioural control (Chapter 6). Although no convincing damaging effect of alcohol use has been demonstrated on neither of these measures, our findings illustrate that different outcome measures generate different interpretations of the effects of alcohol on cognitive functioning and behavioural control.

It is important to bear in mind that the neuropsychological tests used to assess the effects of alcohol use were initially designed to assist in and add information to the diagnosis of brain pathology. They are based on cognitive constructs and not on performance that can be reached. Recently, they have been used increasingly to answer questions about

individuals' everyday cognitive skills and ability to succeed in academia (Chaytor & Schmitter-Edgecombe, 2003). This is a different approach and use of testing, but the tests themselves have not changed accordingly. The focus of these tests is how well they can discriminate between brain-injured and normal individuals and controls rather than how well they capture the full normal variation in levels of adequate everyday functioning (Chaytor & Schmitter-Edgecombe, 2003). This suggests that a non-deviant performance can still be accompanied by differences in cognitive functioning within the normal range of functioning. Such differences could be assessed using performance-based tasks. Findings from the present thesis indicate that a basic form of such tasks can be used in an adolescent population, but the fact that they do not tap onto multiple cognitive domains could hamper their applicability for differentiating between heavy drinkers and controls.

The results from the present thesis suggest that any possible brain damage in heavy drinkers or adolescents with AUD because of their alcohol use is not such that is being picked up by either basic or more complex neurocognitive tasks. These findings do not differ largely from the results of the only other longitudinal study that used neuropsychological tasks, which indicated no differences between heavy drinkers and controls on nine out of ten tasks (Squeglia et al., 2009). A suggestion for future research is to develop neuropsychological tasks that are performance-based and encompass multiple cognitive domains, while being suitable for younger and older adolescents. Ecologically valid instruments, possibly supported by questionnaires, could be used to gain insight into the impact of cognitive capacities in everyday life.

7.2.2.2 fMRI measurements

There are two longitudinal studies that conducted fMRI-measurements during visual working memory (Squeglia et al., 2011) and inhibition tasks (Wetherill et al., 2013). Although they measured different constructs, the findings are comparable; participants who made the transition to heavy drinking in adolescence showed more Blood Oxygen Level Dependent (BOLD)-activation compared to controls during task performance. Importantly, the performance levels between heavy drinkers and controls were the same (Squeglia et al., 2011). This provides important information, indicating that there might be different brain activation patterns, suggestive of alcohol-induced differences, that are not expressed in task performance.

However, there is no straight forward answer to what these differences in BOLD-activation represent: is more activation harmful or beneficial? It is assumed that the answer

to this questions depends on the age of the participant. In early adolescence, more activation is thought to be normative and less activation has been interpreted as hypoactivation representing less adequate abilities. In late adolescence, less activation is interpreted as normative as it is more efficient, and more activation is thought to reflect the recruitment of more neural networks in order to maintain adequate performance (Wetherill et al., 2013). This interpretation is in line with the assumed typical maturation of neural networks, which suggests that less activation is normative as individuals grow older since it reflects pruning of brain connections and more efficient recruitment of brain areas (Luna, Padmanabhan, & O'Hearn, 2010). However, there are questions left unanswered. It is unclear at what moment in adolescence less activation becomes normative and whether this is related to chronological age or rather pubertal timing. Furthermore, it is uncertain whether differences in neural activation will become expressed at a behavioural level as heavy drinking continues, or whether abnormal activation patterns will (eventually) interfere with everyday living. Future research could aim at using a wide variety of outcome measures, such as cognitive tests, questionnaires, and neuro-imaging measures, that might increase understanding of the discrepancies between behavioural and imaging measures and the predictive power of imaging results for behavioural outcomes.

7.2.3 Explanation III: Vulnerability or plasticity?

The interest in studying the effects of alcohol on the adolescent brain partly relies on the assumption that the maturing brain is particularly vulnerable to external influences. Support for this assumption comes, for example, from Foetal Alcohol Spectrum Disorders (FASD), which has indicated that prenatal exposure to maternal alcohol use can do extensive harm to the foetal brain, that clearly undergoes significant development (Guerri, Bazinet, & Riley, 2009). Since puberty has been viewed as the second organizational period in human brain development (Berenbaum & Beltz, 2011), it is understandable that the adolescent brain has been hypothesised to be vulnerable to the effects of alcohol.

On the other hand, traditionally, the developing brain has often been viewed as plastic, as children have been found to be more resilient after traumatic brain injury compared to adults, with lesions not always resulting in functional deficits (Aram & Ekelman, 1986; Teuber & Rudel, 1962). This perspective has been nuanced with findings that this particularly applies to mild injuries and has found to be dependent upon severity of injury and age at which the lesion occurred (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005). Regarding alcohol-induced impairments in unborn children, less than half of the children

of alcoholic mothers displayed foetal alcohol syndrome (Little, VanBeveren, & Gilstrap, 1998). The effects of alcohol on the foetal brain is presumably influenced by factors such as dose of alcohol, exposure pattern, timing of the exposure in relation to brain development, maternal nutrition, maternal age, genetic factors of mother and foetus, other drug use, and socioeconomic status (Guerri et al., 2009). This finding indicates that alcohol-induced impairments in the developing brain are not a given fact that always occurs nor that lesions in the developing brain always result in functional impairments.

Similarly, the differences in BOLD activation patterns between heavy drinkers and controls mentioned above, have also been explained as the flexibility of the brain to appeal other brain areas or neural paths, to compensate for possible impairments in the obvious brain regions (Squeglia et al., 2012). It is unknown whether and when this flexibility will ever become insufficient or whether the brain will ever pay the price for its ability to regenerate. Some impairments might be too large to overcome and alterations in brain functioning might eventually be the beginning of a developmental trajectory that will lead to adverse outcomes.

A parallel debate on adolescence as a period of strength or vulnerability is ongoing in social psychology. Two influential, opposing, theories on adolescent risk-taking behaviour are Moffitt's theory of adolescence-limited antisocial behaviour (Moffitt, 1993) and Jessor and Jessor's problem behaviour theory (Jessor & Jessor, 1977). The former states that adolescent substance use is a reflection of a normative process, with norm-breaking behaviour being part of healthy adolescent development. The latter theory declares that adolescent substance use is problematic and an expression of an underlying larger cluster of problems, such as aggression and delinquency. The findings of the current thesis can be interpreted in the light of both these theories. Without trivializing its apparent risks, one can view heavy drinking as a normative behaviour that subsides for the majority of individuals when they make the transition into adulthood. Personality characteristics that reflect behavioural undercontrol but are within the healthy range predict this behaviour, as shown in Chapter 6 of this thesis. Adolescent AUD, on the other hand, is classified as a psychiatric disorder that often persists into adulthood (Grant et al., 2012; Lopez-Quintero et al., 2011). This was found to be most strongly related to an early expression of socially unaccepted behaviour, providing support for an underlying syndrome of problematic behaviour. Furthermore, we found that particularly AUD is associated with negative outcomes, such as impairments in attention and increased externalizing problem behaviour.

Taken together, there are reasons to assume that adolescence is a period of great vulnerability but also great resilience (Dahl, 2004). The actual harm of external influences,

such as alcohol use, on the developing brain is not yet understood. If we draw a parallel to FASD, such harm is presumably dependent on numerous factors, such as the magnitude and duration of the external force, timing in relation to brain development, genetically predisposed vulnerability, and protective factors such as premorbid functioning, nutrition, and general physical health. It is not clear when and how much alcohol is needed to exceed the threshold with which the individual brain can cope. From the viewpoint of prevention, it therefore is advisable to limit the amount of alcohol that adolescents consume as much as possible.

Three possible explanations were formulated to aid to our understanding of why the present thesis found no large effects of alcohol use on adolescent neurocognitive functioning. There is likely a considerable overlap between the mechanisms and processes described by the three explanations. The reciprocal relationship between alcohol use and cognitive and behavioural control is complex, and longitudinal studies are time-consuming and costly. We are still far from completely understanding what patterns of brain activation actually mean in real life nor do we know when adolescent resilience shifts towards adolescent vulnerability. On the other hand, the tentative findings of the effects of alcohol on young people growing up, combined with the steady increase in alcohol consumption of adolescents, have caused a shock wave in the scientific community, prevention, and society, which possibly has led us not to exercise the amount of caution that this delicate and complex matter requires.

7.3 METHODOLOGICAL REFLECTIONS

This thesis was the first to assess the reciprocal relationship between heavy drinking and AUD on the one hand and cognitive and behavioural control on the other hand longitudinally in a population-based cohort of adolescents, covering the complete range of adolescence. We conducted our study in the Netherlands, where the legal drinking age, at the time of conducting the study, was much younger than for example in the United States and alcohol consumption in adolescence is very common, optimising the chances for finding the effects of heavy drinking. We measured both cognitive and behavioural aspects of control functions as both outcomes and predictors of alcohol use and considered both heavy drinking and problematic drinking. The studies in this thesis were also limited in some respects that need to be considered when interpreting the results.

First, in Chapters 3 and 5, we used computerised tasks to study neurocognitive maturation. As stated above, this is a proxy for studying whether the underlying neuro-

anatomy is affected and to what extent. An important advantage of starting with the basics was that it allowed us to use exactly the same tasks at both age 11 and 19, which is a requirement for finding longitudinal change. More complex and strategy-based tasks usually have more stringent age restrictions, and tasks that are both feasible for early adolescents yet still challenging in late adolescence are difficult to find (Best & Miller, 2010). Furthermore, using straightforward tasks circumvents the problem of 'task impurity'. Since more complex tasks are assumed to rely on multiple cognitive processes and their integration (Jurado & Rosselli, 2007; Squeglia et al., 2009; Tsuchida & Fellows, 2013), it is difficult to identify processes that may be responsible for a suboptimal performance (Best, Miller, & Jones, 2009). The reaction time tasks we used were not designed to detect deficits, but were able to detect differences between groups at the level of performance. In Chapter 4, we used more complex neuropsychological tasks, but we did not collect baseline pre-exposure data. To address the proposed dual relationship between neurocognitive functioning and adolescent substance use (e.g., Tarter, Kirisci, Reynolds, & Mezzich, 2006), we controlled for relevant neurocognitive functions in early adolescence.

The second limitation could be that drinking groups (Chapter 3 and 4) were constructed manually using self-reported measures of alcohol use, although this is common in longitudinal research on adolescent alcohol use (Squeglia et al., 2009; Squeglia et al., 2012). Self-report questionnaires have proved to be reliable for assessing alcohol use in adolescence (Koning, Harakeh, Engels, & Vollebergh, 2010). In addition, our drinking groups showed good and consistent differentiation on validating measures, with chronic drinkers scoring highest on all alcohol-related behaviours, revealing a heavy drinking pattern at two consecutive waves, which covers at least four years of regular heavy drinking. We are therefore confident that we have adequately identified the most risky drinkers. However, future longitudinal research could aim at using measures of binge drinking, since this is hypothesised to be particularly harmful (Ehlers & Criado, 2010), or post-drinking symptoms, as they have found to be associated with less optimal neurocognitive functioning (Squeglia et al., 2009).

The final limitation of longitudinal designs is that attrition may bias the findings, with most at-risk participants dropping out, resulting in an underestimation of the effects and possible loss of power. However, when possible, we used multiple imputation to impute missing data on alcohol use and neurocognition based on a wide variety of associated variables. This technique improves the validity of datasets with missing data (Blankers, Koeter, & Schippers, 2010). Therefore, in our study, attrition bias is unlikely to explain the absence of significant results. This technique was not applied in the chapters that considered

AUD, as the data in this case were missing for the entire clinical interview, which left us with too little information to impute missing data.

7.4 PROTECTING ADOLESCENTS – IMPLICATIONS FOR PREVENTION

It is essential to stress that absence of evidence is not the same as evidence of absence. This means that although neurocognitive functioning was not found to be measurably impaired by alcohol use, this should not be a reason to stop discouraging adolescent alcohol use.

First, these findings tell us nothing about the long-term effects of alcohol use or drinking. Although we measured alcohol use over four years and neurocognitive maturation over eight years, cognitive functioning will continue to develop for more years to come. It could be the case that small alterations in brain functioning that are not measurable at a behavioural level will still disrupt future development. This has been found to be the case in children with traumatic brain injury who displayed delayed brain pathologies (Eslinger, Grattan, Damasio, & Damasio, 1992; Giedd et al., 1999). Furthermore, in line with Moffitt's (1993) theory of life course persistent antisocial behaviour, it could be that adolescents who continue heavy drinking into adulthood are most at risk for negative outcomes, such as externalizing problem behaviour. Since early onset of drinking is an important predictor of persistent alcohol use (Hill, White, Chung, Hawkins, & Catalano, 2000), postponing the age of onset could be fruitful.

Second, as discussed above in "Explanation II" (page 124) heavy drinkers and controls have found to differ in brain activation patterns. Although we should practice caution when scientifically interpreting these findings, they indicate there may be differences between heavy drinkers and controls in how the brain responds to cognitive tasks. Since it is not clear what these differences represent and whether and how they will ever invade actual behaviour, it is best to minimize the differences by limiting alcohol use.

Third, the reason for wanting to specifically prevent adolescent drinking is not necessarily that adolescents would be more vulnerable to the effects of alcohol. A very plausible reason is that adolescents are not always capable of making adequate decisions. Risky decision-making increases during adolescence and is most pronounced when emotions are at stake or when in contact with peers (Blakemore & Robbins, 2012), which is often the case in decision-making regarding alcohol use. Adolescents therefore need adult guidance and set boundaries to acquire appropriate decision-making skills.

Finally, due to the amount of societal interest in and attention given to the brain and neurocognitive research, we seem to forget that the negative consequences of (adolescent) alcohol use are much more encompassing than only those that apply to maturation of neurocognitive functioning. The acute risk of being under the influence of alcohol is of major concern. For instance, alcohol use generally decreases the likelihood of using a condom (Rehm, Shield, Joharchi, & Shuper, 2012), and alcohol abusers have been found to use condoms less consistently and they are more likely to have sexually transmitted diseases, amongst others HIV (Tapert, Aarons, Sedlar, & Brown, 2001). Recent alcohol use in adolescence has been associated with suicide attempts (Woods et al., 1997). Up to a fifth of adolescents who were admitted to the emergency department with traumatic injuries were under the influence of alcohol (Meropol, Moscati, Lillis, Ballow, & Janicke, 1995). More specifically, alcohol is involved in 50% of adolescent traumatic brain injury (Hicks, Morris Jr, Bass, Holcomb III, & Neblett, 1990). Adolescents who are heavy drinkers at a younger age are at a higher risk for having an alcohol-related injury (Hingson, Heeren, Jamanka, & Howland, 2000). A major concern of alcohol use is driving under the influence, which is less relevant for the Dutch adolescent population because the legal driving age is 18 years. However, alcohol is involved in 30% of bicycles accidents, the most important means of transportation of Dutch youth (Reurings, 2010). A Dutch study found that 85% of the perpetrators of violence in the party scene were under the influence of frequently very large amounts of alcohol (Bieleman, Maarsingh, & Meijer, 1998). Furthermore, there are long-term health risks. Alcohol abusers report significantly more health problems, such as weight loss, eczema, episodes of loss of consciousness, and headaches. In addition, liver injuries are found in this group (Arria, Dohey, Mezzich, Bukstein, & Van Thiel, 1995). Chronic heavy drinkers were found to be overweight and have high blood pressure (Oesterle et al., 2004). Early drinkers report significantly more academic problems (Ellickson, Tucker, & Klein, 2003). Finally, these risk are intensified by the fact that an early onset of alcohol use is a risk factor for developing alcohol related problems, specifically, 40% of adolescents who drink before the age of 14 will develop alcohol dependence later in life (Grant & Dawson, 1997), which was illustrated in this thesis with the finding that alcohol use in middle adolescence is an important predictor of AUD in late adolescence.

In sum, there are multiple reasons why the results of the present thesis are not contradicting the policy that prohibits the sale of alcohol to and possession of alcohol by under aged individuals. It is, however, important that information available to the public is accurate and complete, and claims that are not based on compelling evidence should be

avoided. The present thesis indicated that the risks of adolescent alcohol apply specifically to adolescents with AUD, a small but considerable group at an increased risk for negative outcomes. The results indicated that this group could be identified based on specific risk factors in early adolescence, of which externalizing problems were the most pronounced. This information could be used for targeted interventions.

7.5 CONCLUSION

The aim of the present thesis was to investigate the effects of alcohol use in adolescence on neurocognitive functioning. The results of this thesis indicate that although neurocognitive functioning matures over the course of adolescence, heavy drinkers and alcohol abusers may not be at risk for a deviant maturation of such functions. Only in the small and specific group of female alcohol dependents less maturation of shift attention was found. It is important to note that this seems unaffected by the amount of alcohol they consume. On top of that, this distinct maturational pattern may not reflect permanent irreversible damage. Nevertheless, heavy drinking and more pronounced AUD are prospectively related to increases in problematic behaviour reflecting diminished behavioural control. Such behavioural 'undercontrol' can also be a risk factor for adverse outcomes while basic neurocognitive functions are intact. This leads to two important implications. First, even when the cognitive 'hardware' for being able to control and direct behaviour is intact, actual behavioural control can be suboptimal, leading to adverse outcomes such as heavy drinking and AUD. Second, alcohol (mis)use can influence behavioural control, possibly opening the door to a vicious effect where risk behaviour intensifies risk factors.

To conclude, no compelling evidence for vast cognitive deficits as a result of alcohol use was found, and findings from this thesis indicate that the effects of alcohol on the developing brain might more subtle than has been assumed thus far. It is important to keep bearing this in mind when approaching the subject rather than assuming that the effects of alcohol use on adolescent neurocognitive functioning are well-established. More research is needed to understand which influence alcohol has on the developing brain and how this could affect functioning in daily life.

Summary

It has been suggested that the adolescent brain is particularly vulnerable to the neurotoxic effects of alcohol because significant maturation of brain structure and corresponding cognitive control function takes place over the course of adolescence. However, research on this subject has remained inconclusive thus far due to numerous methodological pitfalls. Therefore, there is a need for a large longitudinal study on the precursors and outcomes of alcohol use related to cognitive and behavioural control. The main aim of the present thesis was to longitudinally investigate the effect of alcohol use in adolescence on cognitive functioning. To address this research question adequately, we first studied normal maturation of cognitive control. Next, answering the main research question, we assessed whether deviances from this normal maturation where found among heavy drinkers and adolescents with alcohol use disorder (AUD). Furthermore, we assessed cognitive and behavioural control as precursors of alcohol use in order to identify adolescents at risk for transitioning to heavy drinking and AUD.

All of the studies in the current thesis used the data from the first to fourth wave of the TRacking Adolescents' Individual Lives Survey (TRAILS). This prospective cohort study started in 2000 among 2,230 Dutch pre-adolescents aged 11 years. At T2, the response rate was 96% (*n*=2,149). At T3 and T4, 1,816 and 1,596 respondents participated again, respectively. At T1 and T4, cognitive control was examined using the Amsterdam Neuropsychological Tasks (ANT) and five more complex neuropsychological tasks were added at T4. Behavioural control was assessed using two self-report questionnaires, the Early Adolescent Temperament Questionnaire Revised (EATQ-R) and the Youth Self Report (YSR). At T2 to T4, adolescents completed questionnaires regarding their alcohol consumption habits, such as the average amount of glasses they consumed on a regular weekend day and the frequency with which they had consumed alcohol during the last month. At T4, the World Health Organization Composite International Diagnostic Interview (CIDI) was used to assess AUD, differentiating between alcohol abuse and alcohol dependence.

Maturation of cognitive control

In *Chapter 2*, the maturation of cognitive control was examined. Significant maturation over the course of adolescence took place for all measured subcomponents (focused attention, inhibition, sustained attention, speed of processing, working memory, and shift attention). We found gender differences in the maturation of cognitive control, with boys showing larger maturational rates for working memory, sustained attention, and inhibition. Socioeconomic status had a moderate influence on maturation of cognitive control. Focused attention and speed of processing were not considered in the next chapters.

Effects of alcohol use on maturation of neurocognitive functioning

Next, in *Chapter 3*, we investigated whether patterns of heavy drinking influenced maturation of neurocognitive functioning. We construed six drinking groups (non-drinkers, light drinkers, infrequent heavy drinkers, increasing heavy drinkers, decreasing heavy drinkers, and chronic heavy drinkers) and compared them on maturation of inhibition, working memory, sustained attention, and shift attention. We found no differences between the groups, indicating that even weekly drinking of an average of 15 glasses of alcohol over four years did not influence the maturation of cognitive control functions.

In order to test the hypothesis that there were some alcohol-induced deficits that were not as such that they could be picked up by computerised tasks of cognitive control, in *Chapter 4*, we compared the drinking groups on more complex cognitive tasks. We studied differences between the six groups on tasks measuring verbal memory, visuoconstruction and visual memory, concept generation, semantic memory, and visuospatial problem-solving. We found differences on the latter function only, as measured with the Block Design task, between the non-drinkers and any of the drinking groups. There were no differences between light drinkers and the heavy drinking groups, indicating the absence of a dose-response relationship between alcohol and problem-solving skills. It is suggested that non-drinkers are a specific group and that caution should be taken when using this group as the only reference group. The findings from these two chapters indicate that heavy drinkers do not form a group that is directly at risk for developing deficits in neurocognitive functioning.

To investigate whether there is a certain group that is more at-risk, in *Chapter 5*, we studied adolescents with AUD, both alcohol abuse and alcohol dependence, and compared their performance on the ANT to controls without a diagnosis. We found that girls with alcohol dependence performed less optimally compared to controls on shift attention. No effects were found for other tasks. This effect remained significant after controlling for the quantity of alcohol intake and comorbid psychiatric disorders.

In *Chapter 6*, the effects of heavy drinking and AUD on measures of behavioural control were studied. Significantly more attentional problems were found for female heavy drinkers, female alcohol abusers, and alcohol dependents compared to light drinkers. Furthermore, alcohol abusers and alcohol dependents displayed more externalizing problem behaviour.

Cognitive and behavioural control capacity as a risk factor for alcohol use

It is hypothesised that weaknesses in cognitive control functions predict later alcohol use, which we studied in *Chapter 5*. No evidence was found for the hypothesised effect. The best predictor of adolescent AUD was found to be alcohol use in early and middle adolescence. In *Chapter 6*, intrapersonal characteristics measured in early adolescence that tap onto behavioural control were prospectively related to heavy drinking and AUD. These were all found to be significant predictors of alcohol (mis)use, in line with previous research. The normative personality traits, specifically high-intensity pleasure and effortful control were found to be risk factors for later frequent heavy alcohol use and AUD, while externalizing problems were indicative exclusively of AUD.

The present thesis is the first large longitudinal study on the effects of alcohol use in adolescence on cognitive functioning. It contributes to more insight into the complex reciprocal relationship between adolescent alcohol use with cognitive and behavioural control while simultaneously underlining the fact that much more research is necessary. Heavy drinkers and alcohol abusers may not be at risk for a deviant maturation of such functions. Only the small and specific group of female alcohol dependents showed a distinct maturation of shift attention, but it is unclear whether this distinct maturational pattern reflects permanent irreversible damage. Nevertheless, heavy drinking and, more pronounced, AUD is prospectively related to increases in problematic behaviour reflecting diminished behavioural control. This implicates that even when the cognitive 'hardware' for being able to control and direct behaviour is intact, that is, cognitive control functions, actual behavioural control can be suboptimal, leading to adverse outcomes, such as heavy drinking and AUD. No evidence for vast cognitive deficits as a result of alcohol use was found, and findings from this thesis indicate that the effects of alcohol on the developing brain might more subtle than has been assumed thus far. More research is needed to understand what influence alcohol has on the developing brain and how this would affect functioning in daily life.

Samenvatting

Het is een heersende gedachte dat het adolescente brein specifiek kwetsbaar is voor de neurotoxische effecten van alcohol, omdat er tijdens de adolescentie significante rijping van hersenstructuren en de daarbij behorende cognitieve functies plaatsvindt. Er kunnen echter geen eenduidige conclusies getrokken worden uit bestaand onderzoek door een aantal methodologische problemen. Er bestond daarom behoefte aan een grote longitudinale studie naar de voorlopers en gevolgen van alcoholgebruik met betrekking tot cognitieve en gedragscontrole. Het hoofddoel van dit proefscrift was het effect van alcoholgebruik in de adolecentie op het cognitief functioneren te onderzoeken in een longitudinaal design. Om deze onderzoeksvraag te kunnen beantwoorden, hebben we eerst de normale rijping van cognitieve controle onderzocht. Vervolgens, bij het beantwoorden van de hoofdonderzoeksvraag, is gekeken of deze rijping afwijkend verliep voor zware drinkers en jongeren met alcoholproblematiek (jongeren die voldeden aan de criteria voor een diagnose alcoholmisbruik of -afhankelijkheid). Tot slot zijn maten van cognitieve en gedragscontrole als voorspellers van later alcoholgebruik onderzocht, om zo jongeren die de stap maken naar zwaar drinken of alcoholproblematiek vroegtijdig te kunnen identificeren.

Alle onderzoeken in deze thesis maken gebruik van data van de eerste tot en met vierde meetronde van de Tracking Adolescents' Individual Lives Survey (TRAILS). Dit is een prospectieve cohortstudie, gestart in 2000 onder 2.230 Nederlandse preadolescenten van 11 jaar oud. Op T2 deed 96% van de jongeren weer mee (n=2.149). Op T3 en T4 participeerden respectievelijk 1.816 en 1.596 respondenten. Op T1 en T4 werd cognitieve controle gemeten met behulp van de Amsterdam Neuropsychological Tasks (ANT), waaraan op T4 vijf complexere neuropsychologische taken werden toegevoegd. Gedragscontrole werd gemeten met twee zelfrapportagevragenlijsten, the Early Adolescent Temperament Questionnaire Revised (EATQ-R) en de Youth Self Report (YSR). Van T2 tot T4 vulden respondenten eveneens vragenlijsten in over hun alcoholgebruik, met vragen over bijvoorbeeld het gemiddeld aantal glazen dat ze consumeerden op een weekenddag en de frequentie van alcoholgebruik gedurende de afgelopen maand. Op T4 werd het World Health Organization Composite International Diagnostic Interview (CIDI) afgenomen om alcoholproblematiek in kaart te brengen, waarbij onderscheid werd gemaakt tussen de DSM-IV-diagnoses alcoholmisbruik en -afhankelijkheid.

De rijping van cognitieve controle

In hoofdstuk 2 werd de rijping van cognitieve controle onderzocht met behulp van de ANT. Significante rijping tussen de vroege en late adolescentie vond plaats voor alle

gemeten subcomponenten (te weten gerichte aandacht, inhibitie, volgehouden aandacht, verwerkingssnelheid, werkgeheugen en verdeelde aandacht). We vonden sekseverschillen, waarbij voor jongens een grotere mate van rijping werd gevonden voor werkgeheugen, verdeelde aandacht en inhibitie. Sociaal-economische status had een beperkte invloed op de rijping van cognitieve controle. In de volgende hoofdstukken werden gerichte aandacht en verwerkingssnelheid buiten beschouwing gelaten.

Effecten van alcoholgebruik op de rijping van cognitieve controle

Vervolgens werd in hoofdstuk 3 onderzocht of patronen van zwaar drinken invloed hadden op de rijping van cognitieve controle. We stelden zes groepen samen op basis van het drinkgedrag (niet-drinkers, lichte drinkers, infrequent zware drinkers, stijgers, dalers en chronisch zware drinkers) en vergeleken hun rijping van inhibitie, werkgeheugen en volgehouden en verdeelde aandacht. We vonden geen verschillen tussen de groepen, wat suggereert dat zelfs het wekelijks drinken van gemiddelde 15 glazen alcohol gedurende een periode van vier jaar geen invloed heeft op de rijping van cognitieve controlefuncties.

Om de hypothese te toetsen dat er wel alcohol-geïnduceerde schade was, maar dat deze niet van dien aard was dat zij kon worden opgepikt door gecomputeriseerde cognitieve taken, richtten we ons in hoofdstuk 4 op meer complexe cognitieve taken. We bestudeerden dezelfde zes groepen op taken die de volgende functies in kaart brachten: verbaal geheugen, visuoconstructie en visueel geheugen, het genereren van concepten, semantisch geheugen en visuospatieel probleemoplossen. We vonden uitsluitend effecten voor de laatstgenoemde functie, gemeten met behulp van de taak Blokpatronen, waarbij er verschillen waren tussen de niet-drinkers en elk van de groepen die alcohol gebruikten. Er waren geen verschillen tussen de lichte en zware drinkers, wat duidt op de afwezigheid van een dosisresponsrelatie tussen alcoholgebruik en het probleemoplossend vermogen. Dit kan betekenen dat niet-drinkers een specifieke groep vormen en dat voorzichtigheid is geboden bij het interpreteren van de resultaten wanneer zij de (enige) controlegroep vormen.

Op basis van de bevindingen van deze twee hoofdstukken kunnen we veronderstellen dat zware drinkers geen groep vormen met een verhoogd risico op het ontwikkelen van afwijkingen in het cognitief functioneren. Om te onderzoeken of er een groep is die meer risico loopt, hebben we in hoofdstuk 5 adolescenten met alcoholmisbruik en -afhankelijkheid onderzocht, waarbij hun prestatie op de ANT is vergeleken met een controlegroep zonder diagnose. De resultaten laten zien dat meisjes met een diagnose alcoholafhankelijkheid slechter presteren dan de controlegroep op verdeelde aandacht. Er werden geen effecten

gevonden op de andere taken. Dit effect bleek significant na controle voor kwantiteit van alcoholinname en comorbide psychiatrische problematiek, wat suggereert dat deze verminderde prestatie niet samenhangt met de hoeveelheid alcohol die gedronken wordt.

In hoofdstuk 6 is het effect van zwaar drinken en alcoholproblematiek op maten van gedragscontrole bestudeerd. Er werden significant meer aandachtproblemen gerapporteerd door meisjes die zwaar dronken, meisjes met een diagnose alcoholmisbruik en jongeren met een alcoholafhankelijkheid (in vergelijking met de lichte drinkers). Jongeren met alcoholmisbruik en -afhankelijkheid lieten tevens meer externaliserend probleemgedrag zien.

Cognitieve en gedragscontrolende vaardigheden als risicofactor voor alcoholgebruik

Eerder onderzoek veronderstelt dat verminderde cognitieve controlevaardigheden voorspellers zijn van later alcoholgebruik, wat we bestudeerden in hoofdstuk 5. Er werd geen bewijs gevonden voor het voorgestelde effect. De beste voorspeller voor alcoholproblematiek in de late adolescentie bleek de hoeveelheid alcoholgebruik in de vroege en mid-adolescentie. In hoofdstuk 6 werden vervolgens intrapersoonlijke kenmerken prospectief gerelateerd aan zwaar drinken en alcoholproblematiek. Het betrof hier kenmerken die gerelateerd zijn aan gedragscontrole en die gemeten werden in de vroege adolescentie. Deze bleken alle significante voorspellers van later gebruik en misbruik van alcohol, wat in overeenstemming is met voorafgaand onderzoek. Meer normatieve persoonlijkheidskenmerken zoals *high-intensity pleasure* (verhoogd) en *effortful control* (verlaagd) bleken risicofactoren voor later frequent zwaar drinken en alcoholproblematiek, terwijl externaliserend probleemgedrag uitsluitend alcoholproblematiek voorspelde.

Het huidige proefschrift is de eerste omvangrijke longitudinale studie naar de effecten van alcoholgebruik in de adolescentie op het cognitief functioneren. Het draagt bij aan het begrip van de complexe wederkerige relatie tussen alcoholgebruik en cognitieve en gedragscontrole, terwijl het tegelijkertijd benadrukt dat er nog veel meer onderzoek nodig is. Zware drinkers en jongeren die alcohol misbruiken lijken geen verhoogd risico te lopen op een afwijkende ontwikkeling van het cognitieve functioneren. Alleen de kleine en specifieke groep van alcoholafhankelijke meisjes laat een afwijkende rijping van de verdeelde aandacht zien, maar het is onduidelijk of dit een momentopname is of dat er sprake is van blijvende schade. Aan de andere kant blijkt zwaar drinken en, meer uitgesproken, alcoholmisbruik prospectief gerelateerd te zijn aan probleemgedrag dat een uiting is van verminderde gedragsmatige

controle. Dit betekent dat, hoewel de cognitieve 'hardware' om het gedrag te sturen en te richten intact is – de cognitieve controlefuncties – het daadwerkelijke gedrag toch suboptimaal kan zijn en dat dit kan leiden tot negatieve uitkomsten, zoals zwaar drinken en alcoholproblematiek. Omdat er geen bewijs is gevonden voor omvangrijke schade als gevolg van alcoholgebruik, vormen de bevindingen in dit proefschrift een aanwijzing dat de effecten van alcohol op het zich ontwikkelende brein mogelijk subtieler zijn dat tot dusver werd aangenomen. Er is meer onderzoek nodig om te begrijpen wat alcohol teweeg brengt in het rijpende brein en hoe zich dit zal uiten in het dagelijks functioneren.

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Appendix

An overview of the six subcomponents measured with the Amsterdam Neuropsychological Tasks

Task (in order of assessment)	Subcom-ponent	Description (answer device: buttons on computer mouse)	Operationalisation
Baseline Speed	Speed of Processing	Simple reaction time. The task consists of two parts – for the left and right index finger – starting with the non-dominant index finger in the first part and the dominant index finger in the second part. Each part consists of 32 trials. On the computer screen, a cross is depicted which changes, at unexpected moments, into a square. When the participant sees the square s/he has to directly press the mouse button with the index finger. Cognition is limited to the detection of the mere presence of the signal.	The ability to detect and respond to a stimulus (simple reaction time). A higher score indicates a slower reaction time.
Feature Identification	Focused Attention	The recognition of abstract visuo-spatial patterns. The target pattern is a 3x3 matrix pattern which is ordered in a specific manner with three red and six white compartments and is shown during the instructions. Afterwards, four matrix patterns are depicted simultaneously each time, and the participant has to indicate whether the target pattern is among them by pressing the mouse button with the dominant index finger ('yes') or non-dominant index finger ('no'). Distracters vary in degree of similarity with target pattern. When similarity is high, controlled processing is required. When similarity is low, automatic processing suffices. The task consists of 80 trials, half of which consist of the target, and half of both target as non-target trials consist of similar distracters, the other half dissimilar.	Operationalised as the difference in reaction time on similar non-target and similar target trials. A higher score indicates less optimal focused attention
Sustained Attention – dots	Sustained Attention	The discrimination of patterns. The participant is shown 600 pictures with 3, 4 or 5 dots (200 trials of each type of stimulus). The target signal is the one with the 4 dots, and the participant has to indicate whether this target signal is shown in the picture, by pressing the mouse button with the dominant index finger ('yes') or non-dominant index finger ('no'). The participant hears a sound when s/he makes a mistake. Primary sustained attention index is fluctuation in tempo.	Reflects the ability to maintain a stable performance over a prolonged period. Measured as within-subject SD per set of 50 trials, reflecting fluctuation in tempo. A higher fluctuation in tempo indicates low scores on sustained attention.

Task (in order of assessment)	Subcomponent	Description (answer device: buttons on computer mouse)	Operationalisation
Memory Search – letters	Working Memory	Recognition of target letters. The task comprises three parts and in each part pictures with four letters are depicted. In the first part, consisting of 40 trials, participants have to indicate whether the letter 'k' is present in the picture by pressing the mouse button with the either dominant index finger ('yes') or non-dominant index finger ('no'). In the second part, consisting of 72 trials, participants have to indicate whether both letters 'k' and 'r' are present in the picture. In the third part, consisting of 96 trials, they have to indicate whether all three letters ('k', 'r' and 's') are shown in the picture. Half of the trials in each part contain a target. This task provides index for memory search capacity (deterioration in speed as a function of memory load).	The ability to maintain and compare increasing informational load in working memory (WM) was evaluated as the difference in RT between Part 3 (high working memory load) and Part 1 (low working memory load). A higher score indicates a poorer working memory capacity.
Shifting Attentional Set – visual	Inhibition	A square jumping randomly left/right on a horizontal bar (containing 10 grey squares). The task consists of three parts. In the first part, one of the ten squares is green and jumping randomly left/right on the horizontal bar. If the green square jumps left, the participant has to press the left mouse button and the right mouse button if it jumps right (fixed compatible stimulus-response (SR) mapping condition) (40 trials). In the second part, one of the ten squares is red and jumping randomly left/right on the horizontal bar. If the red square jumps left, the participant has to press the right mouse button and vice versa (fixed incompatible SR-mapping condition requiring inhibition of prepotent responses) (40 trials). The third part is a combination of the first and second part. The square will randomly jump right/left and will turn green/red. When the square is green after the jump, the participant has to press the button in the same direction while if the square becomes red after the jump the participant has to press the opposite button (random SR-mapping condition, requiring mental flexibility – set shifting) (80 trials).	The ability to inhibit an inappropriate, habitual response tendency. Inhibition was analysed by subtracting RT to (compatible) responses in Part 1 from (incompatible) responses in Part 2). A higher score indicates low (slow) inhibition of prepotent responses.
	Shift Attention		The ability to switch between two competing and unpredictable response sets. Inhibition was analysed subtracting RT to (compatible) responses in Part 1 from compatible responses in Part 3. A higher score indicates less Shift Attention.

About the author

CURRICULUM VITAE

Sarai Boelema (1982) behaalde haar doctoraaldiploma aan de Universiteit Utrecht in 2006, met als afstudeerrichting biologische en neuropsychologie. In haar afstudeerjaar heeft ze praktijkstage gelopen bij de afdeling Medische Psychologie van het Meander Medisch Centrum te Amersfoort, waar ze haar basisaantekening psychodiagnostiek behaalde. Voor haar afstudeerscriptie ontwierp en valideerde ze een vragenlijst om individuele verschillen in geurgerichtheid in kaart te brengen. Na haar afstuderen werkte zij als basispsycholoog in het Meander MC en als docent aan de opleiding Psychologie van de Universiteit Utrecht. In 2008 begon zij met haar promotieonderzoek aan diezelfde universiteit. De eerste twee jaar van dit project werkte zij in Groningen, waar ze de verzameling van de neuropsychologische data coördineerde voor de TRAILS studie. Vanaf oktober 2014 zal zij werkzaam zijn als neuropsycholoog in het Universitair Medisch Centrum Utrecht.

SCIENTIFIC PUBLICATIONS (PUBLISHED OR IN PRESS)

In this thesis

Boelema, S. R., Harakeh, Z., Ormel, J., Hartman, C. A., Vollebergh, W. A., & van Zandvoort, M. J. (2014). Executive functioning shows differential maturation from early to late adolescence: Longitudinal findings from a TRAILS study. *Neuropsychology*, *28*(2), 177-187.

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Boelema, S. R., Harakeh, Z., van Zandvoort, M. J. E., Reijneveld, S. A., Verhulst, F. C., Ormel, J., & Vollebergh, W. A. M. (re-submitted for publication). Differences in visuospatial problem-solving between drinking and non-drinking adolescents. Longitudinal findings from the TRAILS study.

Boelema, S. R., Harakeh, Z., van Zandvoort, M. J. E., Reijneveld, S. A., Verhulst, F. C., Ormel, J., & Vollebergh, W. A. M. (submitted for publication). Executive functioning before and after onset of Alcohol Use Disorder in adolescent. A TRAILS study.

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