Can't take my eyes off of you
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General discussion
There is ample evidence that adult substance users and addicted persons are characterized by cognitive biases for substance-related stimuli such as approach and attentional biases (Field & Cox, 2008; Stacy & Wiers, 2010). It has also been found that these cognitive biases are predictive for the strength of substance use problems, and relapse-risk (Cox et al., 2002, 2007; Marissen et al., 2006; Streeter et al., 2008). In addition, there is evidence that these cognitive biases are especially related to substance use in people characterized by a weak executive control (Farris, et al., 2010; Friese et al., 2010; Grenard et al., 2008; Houben & Wiers, 2009; Thush et al., 2008; Willem et al., 2013). However, less is known about the role of these biases and the interplay with cognitive control in adolescent substance use and in the transition from recreational to harmful use. This gap in knowledge is important to fill, as adolescent substance use is an important risk factor for the development of substance use disorders (DeWit et al., 2000; Grant et al., 2001; Lynskey et al., 2003; Winters & Lee, 2008).

This dissertation presented a series of studies on automatic and controlled cognitive processes in the context of adolescent alcohol and drug use and dependency. More specifically, the current studies were designed to examine whether (i) adolescent substance use is related to and can be explained by attentional bias toward general rewards, (ii) attentional and approach biases toward alcohol cues are related to young adolescent alcohol use, (iii) adolescents diagnosed with substance abuse or dependency are characterized by an attentional bias for substance related stimuli, and (iv) this substance-related attentional bias mediates the relationship between reward sensitivity and adolescent substance use. Furthermore, following the available evidence on the moderating role of executive controlled processes, it was investigated whether (v) the association between cognitive biases and substance use would be especially pronounced in (young) adolescents with weak executive functions. The current chapter will first summarize the outcomes of the individual studies, then connect and conceptually integrate the major findings, and conclude with suggestions for further research and clinical implications.

**MAIN FINDINGS**

*The role of reward sensitivity in adolescent substance use*

The first series of studies described in Chapter 2, 3 and 4 investigated the relationship between reward sensitivity and adolescent substance use. First of all, the study in Chapter 4 showed that adolescents who demonstrated stronger self-
reported reward sensitivity also reported heavier use of alcohol. Further, Chapter 2 provided some insight in the attentional processes of reward sensitivity. Adolescents who demonstrated a stronger engagement towards a location that predicted reward and non-punishment reported higher levels of self-reported substance use (i.e., alcohol, tobacco, cannabis). In addition, enhanced automatic attention or orienting towards places of expected non-punishment and enhanced more voluntary or maintained attention towards places of expected reward showed unique predicting value for adolescent substance use. These results suggest that the crucial substance-related attentional biases involve enhanced engagement with cues of reward and non-punishment, whereas problems with disengaging from cues of reward and non-punishment seemed less relevant for explaining adolescent substance use. In other words, when it comes to adolescent heavy substance users, attention is attracted and held more strongly to cues predicting reward compared to cues predicting frustrative nonreward, and to cues predicting nonpunishment compared to cues predicting punishment. On the one hand, a strong automatic engagement towards non-punishment relative to engagement toward punishment could reflect weak automatic fear of negative consequences (e.g., fear of getting a hang-over). On the other hand, a strong voluntary engagement towards reward could represent a heightened voluntary drive to receive rewards (e.g., attaining pleasant feelings after drug use).

The longitudinal study described in Chapter 3 showed that baseline reward biases were also predictive for substance use three years later. However, in contrast to our expectations, reward-related biases were not indicative for an increase in substance use over the next three years. Increase in adolescent substance use could thus not be explained by the strength of their earlier reward-related attentional biases. Nevertheless, the post-hoc analysis in Chapter 3 demonstrated that enhanced voluntary or maintained attention towards places of expected non-punishment was predictive for the level of illicit drug use in those adolescents who initiated the use of these drugs in between baseline and follow-up three years later. An interpretation of this finding could be that people who are striving for non-punishment (which might be avoiding pain, negative thoughts, feelings and situations) are most vulnerable for initiating illicit-drug use. This is in line with the idea that a heightened sensitivity for stimuli that signal unconditioned reward and relief from punishment might predict the development of substance (ab)use (Gray, 1970, 1982). From this perspective, high attentional sensitivity to reward-related stimuli, as indicated by a strong attentional engagement to reward and non-punishment, might be a risk factor for a fast increase after initial substance use,
whereas other factors may be more important for the further development and persistence of substance use once substance use behavior has reached a certain level.

Together, the studies described in Chapters 2, 3, and 4 provide consistent evidence for a relationship between adolescent substance use and reward sensitivity as measured by both self-report and behavioral measures. First, the studies described in these chapters all show that reward sensitivity is related to substance use in young, normative adolescents. However, reward sensitivity was not predictive for the increase in substance use over three years. Thus, reward sensitivity might especially play a role in the initiation of adolescent substance use, but not in the transition from recreational to harmful use. It is likely that adolescents whose attention is captured strongly by signals of reward or non-punishment will start using alcohol or other addictive substances. That is, when their attention is captured by the rewarding value of addictive substances, this might more or less automatically guide their behavior towards these substances (cf. Robinson & Berridge, 1993, 2000, 2003). The study described in Chapter 3 demonstrated a prospective relationship between reward-related biases and substance use three years later, and showed that those adolescents who were heavier users at baseline also were heavier users at follow-up. Therefore, (young) adolescents who show heightened attentional bias towards appetitive stimuli might be at risk for initiating substance use at a younger age and subsequently for developing substance use problems. Future research might benefit from designs developed to test the predictive role of reward sensitivity on the initiation of substance use in adolescents who have not used any alcohol and other addictive substances before. Then, it might also be relevant to test the increase in reward sensitivity and its relation with the increase in substance use (cf., Urošević et al., 2015). Further longitudinal research into substance-related cognitive biases (e.g., attentional bias, approach bias) might benefit from the inclusion of a (behavioral) measure of reward sensitivity, to increase insight in the developmental pathways of reward sensitivity and cognitive biases in the prediction of the initiation and escalation of adolescent substance use.

The role of self-reported appraisal of alcohol cues in adolescent alcohol use

The study presented in Chapter 4 showed that young adolescents who reported more positive subjective appetitive evaluations of alcohol stimuli also reported higher levels of alcohol use. Germane to this, a previous study showed increased
brain activation in alcohol abusing adolescents in response to pictures of alcohol advertisements, which was related with their frequency of drinking and urges to drink alcohol (Tapert et al., 2003). It therefore might be that alcohol cues (e.g., advertisements) that have been linked to drinking experiences might enhance escalation of drinking in adolescents. In addition, our study showed that the relation between appetitive evaluations and alcohol use was especially strong in adolescents who showed a weak executive control. This finding suggests that the positive features of alcoholic drinks may promote drinking behavior (and further escalation of drinking) especially in those adolescents who are less able to regulate their drinking behavior (i.e., those with low executive functions). Adolescents with impaired executive functions might thus be especially vulnerable for developing excessive alcohol use.

However, due to the cross-sectional nature of the study it is not possible to draw any conclusions regarding the direction of this relationship. It is therefore needed to expand the current research with longitudinal research investigating the proposed interrelationship between explicit valence and adolescent substance use, and the moderating influence of executive control. Concluding, this study showed that appetitive alcohol evaluation and adolescent alcohol use were positively related, but future longitudinal studies are required to inform about the direction of this relationship.

**The role of automatic approach tendencies and adolescent alcohol use**

One way appetitive, reward-related processes might influence adolescent substance use could be via promoting automatic approach tendencies. The study in Chapter 4 investigated whether indeed automatic approach tendencies were related to young adolescent substance use. Unexpectedly, this study did not show evidence for a positive correlation between automatic alcohol approach tendencies and alcohol use, but just the opposite. That is, those adolescents who reported higher levels of alcohol use showed a relatively strong tendency to avoid rather than to approach alcohol cues. In this study we used two measures of alcohol approach tendencies - a manikin and a joystick version – which yielded comparable results. The fact that the negative relationship between approach tendencies and alcohol use was found for both measures of approach tendencies seems to indicate that this finding was robust, and not just an artifact of the measures that were used. This finding was interpreted in the light of contextual influences; the contextual cues (i.e., school environment) may have made negative associations with drinking
alcohol more readily available, which might have activated avoidance rather than approach associations in those adolescent drinkers (cf. Roefs et al., 2006). Recent studies measuring alcohol approach bias in adolescents demonstrated a relation between alcohol approach tendencies and alcohol use in (sub)samples of young high-risk adolescents (Peeters et al., 2012), male adolescents with permissive parents (Pieters et al., 2012), and male adolescents and young adults (Willem et al., 2013). Further, a predictive role of alcohol approach tendencies for future alcohol use was found in (sub)samples of high-risk low cognitive control adolescents (Peeters et al., 2012, 2013), and adolescents with weak explicit negative expectancies (Pieters et al., 2014), but not in a group of normative adolescents (Janssen et al., 2015). This pattern of findings suggests that alcohol approach tendencies seem to be involved in adolescent alcohol use, but that the exact characteristics of adolescents for whom this concerns are still unclear. It is possible that the absence of a relation between alcohol approach tendencies and alcohol use in the current project represents the relatively low-risk nature of our sample. Related to this, a recent study failed to find evidence that baseline alcohol approach tendencies in nondrinking or light drinking young adolescents could predict drinking behavior six to 18 months later (Janssen et al., 2015). Taken together, it seems likely that alcohol approach bias plays a role in the further development of already existing risky drinking and not so much in the development of early drinking (cf., Janssen et al., 2015). To further increase insight in the role of approach tendencies in adolescent alcohol use, more longitudinal studies are needed, which investigate alcohol approach tendencies at different time points (i.e., before and after the start of alcohol use, and preferably over a long period of time) using both low-risk and high-risk samples of adolescents.

**The role of attentional bias in adolescent substance use**

Related to the role of approach tendencies in adolescent alcohol use, we were also interested in the role of attentional processes in adolescent alcohol use. In the study described in Chapter 5 we measured attentional bias for alcohol stimuli in an unselected group of adolescents. First, we expected that the relationship between reward-sensitivity and adolescent alcohol use would be mediated by alcohol attentional bias. More specifically, we expected that stronger reward sensitivity would be related to attentional bias for alcohol stimuli, which in its turn would be related to alcohol use. However, we did not find such a relationship between reward sensitivity and alcohol attentional bias in this study. With respect to the relation between attentional bias and alcohol use it was found that stronger
attentional bias for alcohol cues that were presented for a relatively long duration (1250 ms) but not for a shorter duration (500 ms), was related to adolescent alcohol use. To expand these findings, we conducted a study in a clinical sample of treatment-seeking substance-dependent adolescents to increase insight in attentional processes in substance-dependent adolescents (Chapter 6). The participants of this study were heavy users of alcohol, cannabis, amphetamine and/or GHB, and attentional biases scores for their specific primary substance were measured. In this study we found that, compared to a matched unselected group of adolescents, substance-dependent adolescents demonstrated a stronger attentional bias for substance stimuli that were presented for both a shorter (500 ms) and a longer duration (1250 ms). Thus, patients showed relatively strong engagement towards substance cues as well as a relatively strong tendency to maintain their attention to these cues. In addition, we found that a stronger maintained attention (but not stronger engagement) towards substance cues was related to problem severity. In this study we also again measured attentional bias after a 6-month period in which the substance-dependent patients received treatment of any kind and length. Consistent with the absence of a decrease in substance use and problem severity, also the attentional bias remained unaffected within this time interval.

To sum up, our results did not provide evidence to support the view that the relation between reward sensitivity and adolescent alcohol use is mediated by alcohol attentional bias. Thus, the findings did not substantiate the view that high reward sensitivity would set adolescents at risk for developing attentional bias for alcohol cues. The results did, however, provide evidence for a relationship between alcohol attentional bias and young adolescent alcohol use, but only when stimuli were presented for a relatively long duration. Further, the results of our patient study (Chapter 6) showed that substance-dependent adolescents are characterized by a bias in both the engagement and maintenance of the attention towards substance cues. These findings are in line with previous research on attentional bias for alcohol in adolescents, demonstrating alcohol attentional bias in adolescents with alcohol-dependent parents (15-20 years, as indexed with a Stroop task; Zetteler et al., 2006), and in heavy drinking adolescents (16-18 years, as indexed with a Stroop task; Field et al., 2007a), attentional bias related to alcohol use in young adolescents with an enhanced genetic risk (12-16 years, indexed with 1500 ms VPT; Pieters, et al., 2011), and a predictive role of attentional bias for adolescent alcohol use later on (12-18 years, as indexed with 1000 ms VPT, but no effects using Stroop task; Janssen et al., 2015). However, the results are dissimilar to two
other previous studies that did not find alcohol attentional bias cross-sectional related to alcohol use in normative samples of adolescents (15-21 years, as indexed with 750 ms VPT; Willem et al., 2013; 12-16 years, as indexed with 1500 ms VPT; Pieters, et al., 2014; 12-18 years, as indexed with 1000 ms VPT and Stroop task; Janssen et al., 2015). This latter study showed that baseline alcohol attentional bias was predictive for alcohol use six and 18 months later, but only in those adolescents who already had started drinking alcohol at baseline (Janssen et al., 2015).

The differences between these studies complicate direct comparison of the results. First, in some studies risk-groups of adolescents were used, compared to normative samples of adolescents in other studies. Second, it is suggested that the VPT and the Stroop task tap into different underlying components of information processing (Mogg & Bradley, 2002). The task demands differ between the Stoop task and the VPT, with the Stroop task demanding inhibiting irrelevant word meaning, and the VPT demanding scanning visual displays. Further, there is also debate about whether the Stroop interference scores reflect a fast automatic or a slower voluntary strategic process (Franken, Gootjes & van Strien, 2009; Phaf & Kan, 2007; Thomas, Johnstone & Gonsalvez, 2007). And last, the different presentation times of the VPT used in the studies described above are suggested to indicate different attentional processes (from attentional engagement to maintained attention). Zooming in on the studies that used the VPT as attentional bias measure, there is a same trend as in adult substance-related attentional bias (for review, Field & Cox, 2008). It seems that substance use behavior is especially related to a maintained attention toward substance stimuli.

Despite the use of different samples and measures in the above mentioned studies, the results seem most consistent with the view that attentional bias plays a role not so much in the early beginnings of alcohol use, but more in the maintenance and escalation of already existing excessive or risky drinking patterns. In order to further our understanding of the role of attentional bias in adolescent alcohol use, more (longitudinal) research is needed, preferably including young naïve alcohol users as well as excessive adolescent drinkers, and multiple measures of attentional bias in one study.

The study in substance abusing adolescent patients is one of the first that considered attentional bias in this specific group. One recent patient study demonstrated an attentional bias for cannabis cues in cannabis dependent adolescents using a Stroop task (Cousijn et al., in press). The study described in Chapter 6 expands the previous research by showing that substance dependent
adolescents demonstrate biases in the engagement and maintenance of attention to substance-related cues. That maintenance of attention was also associated with the severity of dependence, which shows that attention bias for substance cues goes hand in hand with substance use (problems). One way to test whether this attentional bias is causally involved in substance use (problems) would be to train the attention away from substance cues and to see whether modifying attentional bias would also have a decreasing effect on substance use (problems). Further, the finding that substance use, dependency and substance-related attentional biases were not decreased after a six-month treatment period, underscores the highly persistent condition of addiction. In this respect interventions aimed at manipulating substance-related attentional biases might also have clinical relevance as a supplement to traditional addiction treatments.

The role of executive control in adolescent substance use

Three studies investigated the role of executive control in adolescent substance use. The research did not show evidence for a moderating influence of cognitive control on the relationship between alcohol approach tendencies and adolescent alcohol use (Chapter 4). Yet there was evidence that cognitive control moderated the relation between self-reported appetitive valence and adolescent alcohol use (Chapter 4), and the relationship between alcohol attentional bias and adolescent alcohol use (Chapter 5). However, unexpectedly, we did not find a similar moderating relationship between attentional bias and cognitive control in the clinical sample of substance-dependent adolescents (Chapter 6). These findings indicate that in adolescents with weak cognitive control the extent to which they evaluate alcohol positively as well as the way they direct their attention toward alcohol (but not the way they have the tendency to approach alcohol) are predictive for their alcohol use. However, this statement is very speculative, given the still inconsistent findings of previous studies with respect to the influence of executive functions. Some studies did indeed demonstrate that the predictive validity of automatically triggered appetitive processes (i.e., attentional bias, approach bias, and associations) toward alcohol was restricted to individuals with relatively weak executive functions (Grenard et al., 2008; Houben and Wiers, 2009; Peeters et al., 2012, 2013; Thush et al., 2008), and some studies did not find such a moderating role of executive functioning on automatic processes (Pieters et al., 2012, 2014). In these studies the tasks that were used to index executive functioning were different than the ones that were used in our studies (i.e., Self Ordered Pointing Task (SOPT), Stroop task). These different tasks might tap into
different aspects of executive functions. However, the use of different tasks is not enough to explain the difference in findings. The fact is that using the SOPT and the Stroop task, some studies did find a moderating role of executive functions and some did not. The difference in findings could better be explained by the differences in population. The studies that did find a moderating role of executive functions used older adolescents (Grenard et al, 2008; Houben & Wiers, 2009; Thush et al., 2008) or at-risk adolescents who already started drinking alcohol (Peeters et al., 2012, 2013), whereas the studies that failed to find a moderating role used normative samples of adolescents (Pieters et al., 2012, 2014). The finding in our patient study that executive control did not moderate the relation between substance-related attentional bias and substance dependence is in line with recent studies in cannabis-dependent adolescents that also failed to find a moderating role of cognitive control in the relation between cannabis attentional bias and cannabis use and dependence (Cousijn et al., 2013, in press).

One interpretation of these results might be that executive functions play only a minor role in adolescents who just start to drink alcohol, but that in older or at-risk adolescents who already started to drink more alcohol those with weak executive functions are more at risk to use higher levels of alcohol. The finding that in the clinical samples such a moderating relationship did not exist is somewhat harder to explain. It could be that the role of executive control differs in alcohol and cannabis users (since our study also included mainly cannabis users), but this is somewhat hard to substantiate. It could also be that in adolescents who already use excessive amounts of a substance the automatic processes have grown so strong, that the controlled processes simply are not strong enough to control their substance use.

We further also found mixed results regarding the relationship between executive control and substance use per se. The studies described in Chapter 4 and 6 did not find such a relationship, whereas the study in Chapter 5 did find a negative relation between executive control and adolescent alcohol use. Thus, although the results of the study in Chapter 5 seem to indicate that weak executive control could be a vulnerability factor for developing substance (ab)use, the results of the studies in Chapters 4 and 6 do not further substantiate such interpretation. The differences in findings might have been partly due to the use of different measures (i.e., the RNG task in Chapter 4, and the ANT in Chapters 5 and 6), but this cannot explain all, since the ANT measure did (Chapter 5) and did not (Chapter 6) show a relation between strength of executive control and substance use. Another explanation of the differences might be related to differences between
samples of participants included in the studies. More specifically, our patient study included many cannabis-dependent adolescents, whereas the normative studies were conducted among alcohol using adolescents. Two recent studies in cannabis (ab)users also failed to find reduced executive control compared to a control group (Cousijn et al., 2013, in press). It could thus be that the role of executive control is different in alcohol users and cannabis users, or even absent in cannabis users.

Future (preferably longitudinal) research is therefore needed on this issue. It is recommended to include two executive control measures, to be able to compare the effects. Further, clinical studies in samples of adolescent patients diagnosed with different substance use disorders (to start with alcohol use dependency and cannabis use dependency) might increase insight in the automatic and controlled processes in adolescent substance dependency.

INTEGRATION OF PRESENT FINDINGS

Integrated model

In Chapter 1, a model was proposed that links the pathways that might be involved in the initiation stages of adolescent substance use and in the transition towards harmful use (Figure 1.1). Figure 7.1 presents the same model integrating the findings of the studies that are described. Most of the pathways have been tested in this dissertation, although this has been done in a largely cross-sectional manner. The pathways that are shown in this model are not intended to be exhaustive, but are meant to illustrate the variables described in this dissertation. In this model the dense lines are those relationships for which we found (at least some) supportive evidence in the studies that are part of this dissertation. The dotted lines are those relationships, which were not supported by the present studies or for which the evidence is mixed. The thin lines represent assumed relations that were not explicitly tested in this thesis.

The new aspect in this model is the inclusion of appetitive evaluation. It might be that the explicit appetitive evaluation (or rewarding value) of an addictive substance is a factor that attracts young individuals to those substances and seduces them to try it (cf. Tapert et al., 2003). One aspect that we did not include in our studies but might have been interesting to look at is whether explicit appetitive value of a substance moderates the relation between reward sensitivity and the use of this substance. It might well be that especially in those who are sensitive for reward, and striving to gain rewards, this appetitive value contributes to an individual’s motivation to use substances. It might also be that individuals who are
highly sensitive to rewards, evaluate substance cues as more appetitive. More research on this issue is therefore needed to reach more conclusive results.

Figure 7.1
Model for the interplay of approach bias and attention bias, appetitive evaluation, reward sensitivity and executive control in adolescent substance use

Note. The dark arrows represent relations that are supported by this dissertation and seem to be involved in adolescent substance (ab)use. The dotted arrows represent relations which are not or not supported by the present studies, or for which the evidence is mixed. The light arrows represent assumed relations which were not explicitly tested in this dissertation.

Theoretically, it has been suggested that both relatively controlled and relatively automatic processes are important factors in the development of adolescent alcohol (ab)use (e.g., Wiers et al., 2007). More specifically, it is proposed that strong automatic approach tendencies, and attention towards substance-related cues and weak cognitive control are predictive of subsequent adolescent substance use. The studies that were presented in this dissertation partly support this notion, and provide insights into factors that might be involved in the very early stages of adolescent substance use. The current project showed that in normative samples of adolescents appetitive (or reward-related) attentional biases are related to substance use and predictive for the initiation of substance use, but not for the increase in substance use. Further, this project showed that alcohol use was related to appetitive valence of alcohol cues, and a maintained attentional bias
for alcohol cues in weak cognitive control adolescents, but not to an approach tendency towards alcohol cues.

These findings suggest that early adolescent substance use might be driven by the appetitive (rewarding) value of these cues, which is in line with a large body of literature showing a relation between reward sensitivity and substance use (problems) (see for review, Bijttebier et al, 2009). Thus, individuals who focus their attention (automatically) on appetitive cues, who are more sensitive for reward and evaluate substance cues as more appetitive are also more likely to engage in substance use. Then, following the first experiences with substance use, and with the rewarding effects of substance use, brain systems may start to sensitize, and automatic cognitive processes (e.g., approach tendencies and attention bias) may start to develop and grow stronger (see e.g., Wiers et al., 2007, Robinson & Berridge, 1993). That reward sensitivity does not seem to play a role in this development to harmful use substantiates the suggestion that in the transition from recreational to harmful substance use other processes have become more important factors. It could therefore be that individuals who are highly reward sensitive first initiate substance use because of the expected rewarding effects, which leads to a quick increase in use. With this repeated substance use automatic cognitive biases might develop, which subsequently might lead to a further increase in substance use and a possible development of substance-related problems. The finding that in our normative samples of adolescents alcohol use was related to attentional bias in weak cognitive control adolescents only, but not to a heightened approach tendency for alcohol might indeed indicate that the development of these automatic processes has only just started. Combining these findings with recent studies investigating the role of cognitive biases in adolescent substance use indicates that the associations between cognitive biases (i.e., approach tendencies and attentional bias) and substance use in adolescence might only hold for specific subgroups (e.g., high-risk adolescents, adolescents with genetic disposition, boys with permissive parents, adolescents with explicit negative expectancies, adolescents with weak cognitive control; see for review, Wiers et al., 2015a).

Our patient study showed that attentional bias for substance cues was related to substance dependency, and that this association was unrelated to cognitive control. Further, the patient group as such was characterized by a strong attentional engagement and maintenance towards substance cues. The suggestion that attentional biases develop by repeated substance use is underscored by this finding. However, we found no supportive evidence for a moderating role of
cognitive control in the relation between attentional biases and substance use (problems). The hypothesis that especially weak cognitive control adolescents might be susceptible for developing substance use problems is thus not supported by our research.

**Attentional bias, reward sensitivity and executive control**

Figure 7.2 depicts a heuristic model representing the involvement of attentional engagement and maintained attention, reward sensitivity, and executive control in substance use and abuse. In this model the dense lines are those relationships for which we found (at least some) supportive evidence in the studies that are part of this dissertation. The dotted lines are those relationships, which were not supported by the present studies or for which the evidence is mixed. The thin lines represent assumed relations that were not explicitly tested in this thesis.

This model specifies how attentional processes might influence adolescent substance use, and the transition to substance abuse. The empirical findings support the involvement of reward sensitivity in early adolescent substance use, and are consistent with the hypothesis that adolescents with high reward sensitivity would be especially at risk for initiating in substance use. The empirical findings provide no support for the hypothesized mediating role of substance-related attentional biases in the association between general appetitive bias and adolescent substance use. However, we only were able to test this relationship using a self-report measure of reward sensitivity. It could therefore be interesting to test this hypothesized relationship using a self-report and a behavioral measure of reward sensitivity (i.e., with the latter generating reward-related attentional bias), which enables testing whether more general appetitive bias is related to substance-specific attentional bias, and/or to self-reported reward sensitivity.

Further, the hypothesized relationships between substance-related attentional biases and substance use and substance abuse were supported. We found evidence for a correlational relationship between substance-related attentional bias and substance use and dependency (Chapter 5 and 6). Specifically, we found that especially attentional bias for stimuli that were presented for a long duration (i.e., maintained attention) was related to substance use, and also to severity of dependence in adolescents diagnosed with a substance use disorder. Although we did not find a correlational relationship between engagement of attention and substance dependency, the adolescent patients were characterized by both a bias
in the engagement of attention towards substance cues and in the maintenance of the attention.

In Chapter 5 we found that impaired executive control was related to heavier alcohol use, but we did not find such a relationship in a comparable adolescent sample (Chapter 4) or in substance-dependent adolescents (Chapter 6). We also found some differential results regarding the hypothesized moderating role of executive control. That is, in Chapter 5 we found that only in adolescents with weaker executive control there was a relationship between alcohol attentional bias and alcohol use, but we did not find evidence for such a relationship in substance-dependent adolescents (Chapter 6).

Figure 7.2
Model for the interplay of attentional engagement and maintained attention, reward sensitivity and executive control in adolescent substance use and abuse

Note. The dark arrows represent relations that are supported by this dissertation and seem to be involved in adolescent substance (ab)use. The dotted arrows represent relations which are not or not supported by the present studies, or for which the evidence is mixed. The light arrows represent assumed relations which were not explicitly tested in this dissertation.
These findings shed some light on the cognitive processes that are possibly involved in substance (ab)use. Consistent with the hypothesized “vigilance-avoidance” pattern of attentional biases (Noel et al., 2006) attention might first be drawn towards, and then directed away from the substance stimulus. In adolescents who first start using substances, attention might be drawn equally strongly towards substance cues, and their use might thereafter be influenced by how long they will maintain their attention on this cue (which then will be moderated by the strength of their executive control). In substance-abusing adolescents, attention will be strongly attracted and engaged to substance stimuli, which heightens the possibility that their attention is maintained and they will start using. The actual maintenance of attention then could determine the strength of their substance abuse. Thus, the results of the current project suggest that reward-related (appetitive) bias and attentional bias are involved in the development of adolescent substance use, and provide mixed evidence for a (moderating) role of executive control. Due to the mostly cross-sectional nature of our studies we do not know the direction of these relationships. Some questions that remain to be answered are therefore: does attentional bias for substance cues precede substance use escalation, and what exactly is the role of cognitive control in the development of adolescent substance (ab)use? A longitudinal approach is therefore recommended for future research in order to shed light at these questions. Another question that arose from this dissertation is whether the roles of attentional processes and executive control are different in the development of alcohol, cannabis or illicit drug use. Research using different samples of substance abusing adolescents might provide answers to this question. Finally, research investigating the effect of attentional bias modification might reveal whether attentional biases are indeed causally involved in the development of substance use behavior.

LIMITATIONS

Some methodological considerations need to be discussed. First of all, an important limitation is the correlational nature of most of the studies that were presented in this dissertation. It is therefore not possible to draw conclusions about the causal status of relationships. Second, it should be acknowledged that the effect size of the relationships between substance use and variables that were measured behaviorally (i.e., approach tendencies, attentional bias, executive control) were very small. However, since these kinds of measures provide only rough indications of the targeted behavioral processes, small effects can still be relevant, especially given the considerable risk for negative health and societal
consequences related to substance use behavior. Next, the reliability of the attentional bias measures is subject of discussion based on findings indicating relatively low internal consistency (see Ataya et al., 2012). However, several authors (e.g., Huntjens et al., 2014) have argued that internal consistency might not be an adequate index of reliability in performance measures especially when the target stimuli (here drinks) are task-irrelevant and participants’ performance profits most from ignoring the target stimuli and to focus on the task at hand (here probe identification). Moreover, its current ability to differentiate between patients and controls, together with its stable pattern over time within the patient group seem to speak to its reliability and validity. Importantly, new algorithms are being developed to more reliably assess attentional bias (e.g., Zvielli, Bernstein & Koster, 2014). One last consideration is the use of a self-report measure for substance use. Participants might not have been entirely honest in reporting their alcohol use, because most of them had not yet reached the legal age of sixteen to use alcohol (Brener et al., 2003; note that currently in the Netherlands the legal age to drink alcohol is eighteen, but at the time of the assessments this was still sixteen). However, self-report measures of substance use have been found to be valid and reliable as long as confidentiality and anonymity is guaranteed (Del Boca & Darkes, 2003).

**CLINICAL IMPLICATIONS**

The finding that attentional bias is already involved with substance use in (young) adolescents contributes to the available literature regarding the role of alcohol attentional bias in adolescents (Field et al., 2007a; Pieters, et al., 2011; Zetteler et al., 2006). It has been suggested that by repeated use of alcohol (or drugs) related brain circuitry become sensitized, by which substance-related attentional bias will be reinforced (e.g., Wiers et al., 2007). This stresses the importance to develop interventions that are aimed at adolescent substance abusers, in order to prevent escalation of substance use problems. One way to alter attentional biases is by means of computerized Attention Bias Modification (ABM) procedures (MacLeod et al., 2002). Although initial studies in the field of anxiety yielded promising results, recent meta-analyses do not provide consistent conclusions regarding the effect of ABM on psychiatric symptoms (e.g., Beard et al., 2012; Cristea, Kok & Cuijpers, 2015; Cristea, Mogoșe, David & Cuijpers, in press; Linetzky, Pergamin-Hight, Pine & Bar-Haim, 2015), which emphasizes the need for more thorough research in this area. In the field of addiction, recent laboratory studies found that attentional bias for alcohol or smoking stimuli changed after
one ABM session, but that this change did not generalize to new pictures, and was
not related to a change in substance use symptoms (smokers: Attwood, O’Sullivan,
Leonards, Mackintosh & Munafò, 2008; Field, Munafò & Franken, 2009; McHugh,
Murray, Hearon, Calkins & Otto, 2010; drinkers: Field, Duka, Eastwood, Child,
Santarcangelo & Gayton, 2007; Schoenmakers, Wiers, Jones, Bruce & Jansen, 2007).
More recently, promising results were generated using multiple-session ABM in
(sub)clinical groups of alcohol drinkers (Fadardi & Cox, 2009; McGeary et al., 2014;
Schoenmakers et al., 2010) and smokers (Kerst & Waters, 2014; Lopes, Pires &
Bizarro, 2014). One of the major advantages of ABM is that it can be delivered via
the Internet, and that interventions can be developed with some game-like
character, which makes this kind of intervention especially suited for young
individuals. It is therefore recommended to test attentional bias modification
procedures in samples of heavy substance-using and/or substance-dependent
adolescents. If ABM would turn out to be an effective intervention for modifying
attentional bias and reducing substance use and problems, this would also provide
evidence for a causal relationship between attentional bias and the maintenance of
adolescent substance use.

Further, although the findings regarding the possible role of executive control
were mixed, it would still be recommended to test the effects of interventions
aimed at increasing executive functioning. Results of such cognitive control training
would provide insight in whether an increase in executive control would have a
decreasing effect on substance use. This would then not only provide evidence for
the efficacy of such training, but also indicate a causal relationship between
cognitive control and substance use. Preliminary results of a study using a working
memory training showed that indeed heightened working memory capacity was
associated with a decrease in alcohol intake for more than one month after the
training (Houben, Wiers & Jansen, 2011).

CONCLUSION

Together the findings of this dissertation indicate that relatively high reward
sensitivity, appetitive valence, and attentional bias, together with relatively low
executive control might help explain the early development of adolescent
substance (ab)use, whereas approach bias seems not involved in early substance
use. First, heavy substance using adolescents were characterized by a relatively
strong attentional bias towards reward, and relatively high self-reported reward
sensitivity. Second, early adolescent alcohol use was related to relatively strong
appetitive valence of alcohol stimuli and to maintained attention toward alcohol
stimuli, especially in low cognitive control adolescents. Third, casting some doubt on the relevance of impaired executive control in the development of substance abuse problems, treatment-seeking adolescents showed similar executive control abilities as non-abusing controls. Fourth, underlining the relevance of attentional processes in substance abuse problems, also treatment-seeking adolescents showed engagement and maintained attention for substance cues, whereas the strength of this latter tendency was related to the level of substance use problems. Finally, both the level of problems and the strength of maintained attention remained unaffected by 6-month conventional treatment. Perhaps, then, current addiction treatments might benefit from adding attentional bias modification interventions to treatment as usual.

To return to the major aims that were mentioned in the introductory chapter of this dissertation, it can be concluded that adolescents who are highly sensitive for rewards, evaluate substances as positive and maintain their attention toward substances strongly might be at risk for developing excessive substance use.