Can't take my eyes off of you
Ruiter, Madelon

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CHAPTER 6

Attentional bias and executive control in treatment-seeking substance-dependent adolescents: a cross-sectional and follow-up study

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Van Hemel-Ruiter, M. E., Wiers, R.W., Brook, F. G., & de Jong, P. J.
Attentional bias and executive control in treatment-seeking substance-dependent adolescents: a cross-sectional and follow-up study.
ABSTRACT

Background Research in adults shows that substance dependent individuals demonstrate attentional bias for substance-related stimuli. This study investigated the role of attentional bias in adolescents diagnosed with alcohol, cannabis, amphetamine or GHB dependency on entering therapy and six months later, and the role of executive control (EC) as a moderator of the relationship between problem severity and attentional bias.

Methods Seventy-eight substance-dependent adolescent patients (mean age = 19.5), and 64 controls (mean age = 19.0) were tested. Thirty-eight patients took part at 6-month follow-up. Attentional bias was indexed by a Visual Probe Task, EC by the Attention Network Task, problem severity by the short Alcohol (or Drug) Use Disorder Identification Test and the Severity of Dependence Questionnaire.

Results Patients demonstrated an attentional bias for substance stimuli presented for 500 ms and 1250 ms, with the latter related to severity of dependence. They showed no reduced EC, and EC did not moderate the relationship between attentional bias and dependency. Substance use, dependency, and attentional bias remained unchanged in the 6 month follow-up period.

Conclusions Substance dependent adolescents showed a stronger relatively early as well as maintained attentional bias toward substance cues. A stronger maintained attention was related to higher severity of dependence. No evidence emerged to sustain the view that EC might play an important role in adolescent substance use. The finding that follow-up attentional bias and problem severity were not decreased is consistent with the view that traditional addiction treatments may benefit from attentional bias modification procedures.
INTRODUCTION

Addiction is a serious problem worldwide, both at the individual and the societal level. Epidemiologic studies have demonstrated that the prevalence of alcohol and drug use and abuse increases with age during adolescence and peaks in young adulthood (Hibell et al., 2012; Johnston et al, 2014; SAMHSA, 2014; Van Laar et al., 2013). Therefore, it is important to increase knowledge of factors that contribute to the development of alcohol and drug use problems.

Current models of addictive behavior propose that attentional bias (AB) plays a central role in the persistence of substance (ab)use (e.g., Franken, 2003). In line with this, there is considerable evidence supporting the view that substance-related stimuli capture the attention of people who use or abuse these addictive substances (Field & Cox, 2008). The selective attention for alcohol or drug-related stimuli is assumed to activate the feeling of craving, which further promotes AB for the substance and subsequent drug-seeking behavior (Franken, 2003). Further, research has shown that substance abusers’ executive functioning is affected (e.g., Cox & Klinger, 2004; Lubman, Yücel & Pantelis, 2004; Wiers et al., 2007, but see Wiers et al., 2015a), and it has been argued that substance users with reduced Executive Control (EC) are especially susceptible to the attention-grabbing properties of substance-related stimuli (Field & Cox, 2008), because they are less able to regulate their attention (Fazio & Towles-Schwen, 1999; Wiers et al., 2007).

Thus far research on substance-related AB has focused on adult populations. Using various paradigms, these studies have demonstrated AB in non-clinical and clinical alcohol and drug users (see for review, Field & Cox, 2008; Sinclair et al., 2010). AB for substance cues has been linked to craving (see for meta-analysis, Field et al., 2009), relapse, and to the escalation of drug problems (Garland, Franken & Howard, 2012; Marhe et al., 2013; Waters et al., 2012). However, recent critical reviews demonstrate that there is inconsistent evidence regarding the predictive relationship between AB assessed in clinical settings and subsequent relapse (Christiansen et al., 2015; Field, Marhe & Franken, 2014).

For a proper appreciation of the role of AB in addictive behaviors it is important to investigate the role of AB in adolescent substance use and abuse. There are only a few studies that have examined AB for substance-related stimuli in adolescents, and all of them focused on alcohol use in nonclinical settings. These studies found evidence for an AB in heavy drinking adolescents (16-18 years: Field et al., 2007a), and high-risk adolescents (12-16 years: Pieters et al., 2011; 15-20 years: Zetteler et al., 2006), but not in unselected groups of adolescents (12-18 years: van Hemel-
The present study aimed to extend this research, by investigating substance-related AB in treatment-seeking adolescents and young adults (“youth”, 12-25 year-olds), diagnosed with a substance use dependency, and including a control group. The large majority of youth enrolling in addiction therapy are abusers of cannabis or alcohol. This applies both to the U.S. (Johnston et al, 2014; SAMHSA, 2014) as well as for Europe (EMCDDA, 2015; Van Laar et al., 2013). In the Netherlands, cocaine, amphetamine, and gamma hydroxybutyrate (GHB) are, with some distance, the next most used illicit drugs among adolescent treatment seekers. Of those, cocaine use is declining, while the use of GHB has been rising since 2007 (Wisselink et al., 2013). Previous studies about the role of substance-specific AB mainly focused on alcohol- or cannabis users, and there are some studies available that focused on cocaine or heroin users. Given the prevalence of adolescent alcohol, cannabis, amphetamine, and GHB abusers, we decided to focus on these groups for the current study.

The major aim of this study was to test whether treatment-seeking substance abusing youth diagnosed with alcohol, cannabis, amphetamine, or GHB abuse or dependency, were characterized by an AB for personally relevant substance stimuli. To index substance-specific AB we used a visual probe task (VPT) similar to the VPT designed by Field et al. (2004). To investigate the time-course of AB, different exposure durations (SOA, stimulus onset asynchrony) were used in this task. In the present study we used an SOA of 500 ms, which is found to be a robust condition demonstrating AB (e.g., Cisler & Koster, 2010, Mogg & Bradley, 1998), and is thought to reflect relative early attentional processes. We further used a longer SOA of 1250 ms, as a reflection of maintained attention, as previous studies have shown that especially biases in maintained attention are relevant in substance use problems (e.g., Field & Cox, 2008). Based on the prevalence of misuse in Dutch treatment settings, we included four categories of substance-related stimuli in the present VPT: alcohol, cannabis, amphetamine, and GHB. This enabled computing AB scores for the personally relevant substance of each participant.

Cognitive models of addiction further propose that individual differences in cognitive control will modulate the relationship between automatically triggered appetitive processes (e.g., AB) and problem severity (Field & Cox, 2008). However, there are some inconsistencies in previous research with some studies showing that indeed the predictive validity of automatically triggered appetitive processes (e.g., AB) toward alcohol was restricted to individuals with relatively weak executive
functions (Grenard et al., 2008; Houben & Wiers, 2009; Peeters et al., 2012, 2013; Thush et al., 2008; van Hemel-Ruiter et al., 2015b), and some studies that did not find such a moderating influence of executive functioning on automatic processes (Christiansen, Cole, Goudie & Field, 2012; Cousijn et al., 2013; Pieters et al., 2012; van Hemel-Ruiter et al., 2011).

The second aim of the current study was therefore to test whether treatment-seeking adolescent substance abusers are characterized by a lowered EC, and whether the relationship between substance-specific AB and problem severity is moderated by EC. To assess individual differences in EC, we used the Attention Network Task (Fan et al., 2002), as a combination of the cued reaction time (Posner, 1980) and the flanker task (Eriksen & Eriksen, 1974). This behavioral reaction time task has been developed to measure the efficiency of three attentional networks (i.e., alerting system, orienting system, and executive attention). Participants respond to a central target arrow and EC of attention is assessed from the interference effect on RT of task-irrelevant flankers (arrows which point in an incongruent direction to the central target arrow). Previous research has shown that this task is suitable for the use in young and clinical samples (Howell, Osternig, van Donkelaar, Mayr & Chou, 2013; Keehn, Lincoln, Müller & Townsend, 2010; Racer et al., 2011), and has good test-retest reliability (Fan et al., 2002; Ishigami & Klein, 2010, 2011). Recent studies using the ANT to measure executive attentional control within undergraduate samples showed that AB for alcohol stimuli was related to alcohol use only in weak EC adolescents (van Hemel-Ruiter et al., 2015b), and that there was a relationship between fear-level and heightened threat-related AB only in weak EC individuals (Hou et al., 2014; Reinholdt-Dunne et al., 2009). In addition, we investigated if substance-related AB and EC changed during therapy. There is some evidence that AB is reversed in abstinent smokers (Peuker & Bizarro, 2014), reversed or decreased in abstinent alcoholics (Noël et al., 2006; Townshend & Duka, 2001; Vollstädt-Klein et al., 2009), and decreased in treated cocaine and heroin abusers (Gardini, Caffarra & Venneri, 2009). In this study we therefore also included a follow-up assessment for the patient group, in order to investigate whether AB and EC had changed six months after entering treatment, and if so, whether this change was related to changes in problem severity.

In short, the present study was designed to investigate AB and EC in a clinical sample of substance abusing youth. Healthy peers served as a control group. According to cognitive motivational models of addiction, we hypothesized that substance abusing youth would be characterized by an AB for personally relevant substance stimuli. We expected this bias to appear at both relatively short (500 ms)
and relatively long (1250 ms) presentation times. In addition, based on the findings that people with relatively weak EC abilities are at risk for developing substance misuse and dependency (de Wit, 2009; Verdejo-García & Pérez-García, 2007), we hypothesized that youth diagnosed with substance dependency would be characterized by a relatively weak EC, compared to the control group. As a subsidiary issue, we expected that ABs would be decreased six months after entering treatment, along with substance use and problem severity. Since common therapies are aimed at increasing control over behavior (e.g., cognitive behavior therapy; see e.g., Beck, 2011), and there are indications that prolonged abstinence is beneficial for cognitive functioning (Fernandez-Serrano, Perez-Garcia & Verdejo-Garcia, 2011), we further expected that EC would increase.

**METHOD**

*Participants and Recruitment*

Participants were 78 alcohol- or drug-dependent patients (12-25 years) and 64 adolescent or young adult control participants. Youth between 12 and 25 years old who entered intake procedure at VNN Addiction Care, who were diagnosed with alcohol, cannabis, amphetamine, or GHB use disorder were eligible for this study. Patients were excluded if they were diagnosed with gambling disorder, or entered treatment for problematic gaming. Controls were healthy youth matched at group level for age, gender, and educational level with the patient group.

Patients were recruited at intake procedure of VNN Addiction Care, a large addiction care facility in the northern part of the Netherlands. The therapist leading the intake invited the patients to participate in a study about the development of substance use and abuse, which consisted of two sessions of 90 minutes each. Originally, the study also included a third assessment, which was dropped halfway through data collection, based on the large attrition between baseline and follow-up. A total of 111 patients agreed to participate in the study, of which 33 were excluded in the next step. Three were in treatment for problems other than alcohol or drug dependence (i.e., gambling), one fell out of the age-range, four moved to another residence, seventeen changed their minds about participation, and eight did not respond to our repeated attempts to contact them via the telephone. Baseline assessment started during or immediately after the intake procedure (which took three to four weeks), with follow-up assessments taking place at approximately six months after the baseline assessment. At baseline, two patients were excluded for not having a diagnosis of alcohol or drug abuse or dependence.
ATTENTIONAL BIAS AND EXECUTIVE CONTROL IN SUBSTANCE-DEPENDENT ADOLESCENTS

(i.e., their substance use did not meet criteria for dependency), one due to too many errors on the ANT at baseline (i.e., > 25%), three patients due to a VPT or ANT score that was larger than 3SD from the group mean. The final baseline patient sample therefore resulted in a total of 72 participants (48 male and 24 female; mean age = 19.7, \(SD = 2.8\); see Table 6.1 for group characteristics). Twenty patients (26.3%) reported that they had not used their primary substance over the previous month. Patients mainly received assertive community treatment, or cognitive behavioural treatment, but the exact approach and duration of treatment highly varied between patients. Medication was no standard component of treatment.

Almost half of the patients who were assessed at baseline also completed the assessment at 6-month follow-up (N = 38). A group of 28 participants did not want to participate anymore during the follow-up assessment, and we were unable to get in contact with another twelve participants. In the follow-up analysis, the data of two participants had to be removed due to too many errors on the ANT (i.e., > 25%) or an ANT score that was larger than 3SD from the group mean. Therefore, for the analysis of the longitudinal data there remained 70 participants in the study, with 32 (46%) who completed both assessments.

Control participants were recruited via schools and by word-of-mouth, for participation in a study about the development of substance use and abuse, which consisted of one session of 90 minutes. They were included for the study if they matched the patient group on the basis of age, gender, and educational level. They were allowed to be recreational users of alcohol and drugs, but were excluded from the study if they had a diagnosis of alcohol or drug dependency. Two controls had to be excluded from analysis due to a coding error (i.e., output of computer tasks were coded the same for both participants) and one due to an ANT score that was larger than 3SD from the group mean. The final control sample therefore resulted in a total of 61 participants (42 male and 19 female; mean age = 19.0, \(SD = 2.4\)).

All participants gave their written informed consent, and for under-aged participants parents gave written informed consent as well. Both patients and controls received a gift-voucher of 5 euros per session after completion. Descriptive statistics are presented in Table 6.1. The study was approved by the Medical Ethical Committee of the University Medical Centre Groningen.
### Table 6.1
Means and standard deviations of variables as a function of group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Controls</th>
<th>t or U statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, % female</td>
<td>32%</td>
<td>31%</td>
<td>2148.0</td>
</tr>
<tr>
<td>Age</td>
<td>19.69 (2.83)</td>
<td>19.00 (2.37)</td>
<td>1.52</td>
</tr>
<tr>
<td>Educational Level (a)</td>
<td>2.82 (0.79)</td>
<td>3.03 (0.58)</td>
<td>1874.5</td>
</tr>
<tr>
<td>Primary diagnosis alcohol dependence (n,%):</td>
<td>10 (14%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis cannabis dependence (n,%):</td>
<td>49 (68%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis amphetamine dependence (n,%):</td>
<td>10 (14%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis GHB dependence (n,%):</td>
<td>3 (4%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Substance use previous month (AUDIT/DUDIT):</td>
<td>5.93 (4.56)</td>
<td>1.43 (1.03)</td>
<td>8.11**</td>
</tr>
<tr>
<td>Severity of dependence (SDS):</td>
<td>5.76 (4.06)</td>
<td>0.27 (0.72)</td>
<td>11.3**</td>
</tr>
<tr>
<td>Substance AB 500 ms</td>
<td>19.00 (36.50)</td>
<td>1.60 (11.84)</td>
<td>3.82**</td>
</tr>
<tr>
<td>Substance AB 1250 ms</td>
<td>7.39 (25.33)</td>
<td>-0.19 (11.00)</td>
<td>2.30*</td>
</tr>
<tr>
<td>EC(b)</td>
<td>108.86 (40.45)</td>
<td>100.07 (32.62)</td>
<td>1.36</td>
</tr>
</tbody>
</table>

**Note.** SD = standard deviation; GHB = gamma hydroxybutyrate; AUDIT = alcohol use disorder identification test; DUDIT = drug use disorder identification test; SDS = severity of dependence scale; \(a\) educational level in categories of ‘1’ to ‘4’, where ‘1’ stands for primary education, ‘2’ for lower secondary education, ‘3’ for upper secondary education or lower tertiary education and ‘4’ for higher tertiary education; \(b\) higher score means a weaker EC; ** p < 0.01 (2-tailed); * p < 0.05 (2-tailed).

### Questionnaire measure

**Self-reported substance use.** Alcohol use was measured by a shortened version of the Alcohol Use Disorder Identification Test (AUDIT: Saunders, Aasland, Babor, de la Fuente & Grant, 1993), which included only questions about frequency and quantity of use (e.g., “At how many days in the weekend did you use alcohol in the previous month?” and “How many glasses did you consume on a drinking day?”). In the current study, the questions were formulated related to the past month. Cannabis use was measured by a shortened version of the Cannabis Use Disorder Identification Test (CUDIT: Adamson & Sellman, 2003), which consisted of three items about cannabis use in the previous month (e.g., “How many times did you use cannabis in the previous month?”). Because there were no comparable questionnaires available, we constructed a SUDIT and a GUDIT, which contained the same questions as the short CUDIT, but now related to amphetamine (speed) use and GHB use respectively. For ease of understanding we named the drug use questionnaires DUDIT. Scores could lie in between 0 and 12 and the higher the score on the AUDIT or DUDIT the higher the level of substance use. Internal reliability of these questionnaires was good to excellent, with Cronbach’s alpha ranging from 0.86 to 0.99.
**Self-reported severity of dependence.** Level of dependency was measured by the Severity of Dependence Scale (SDS: Gossop, Best, Marsden & Strang, 1997). The Severity of Dependence Scale (SDS) is a 5-item questionnaire that provides a score indicating the severity of dependence on alcohol or drugs. Each of the five items is scored on a 4-point scale (0-3). The total score for severity of dependence was calculated by the addition of the score on the five items. A higher score reflects a higher level of dependence. Reliability as indexed by internal consistency of the SDS was good to excellent with Cronbach’s alpha ranging from 0.71 to 0.92.

**Computerized Measures.**

*Substance-specific AB.* AB was measured with the Visual Probe Task (VPT: MacLeod et al., 1986). In this task we used pictures of four different categories: alcohol, cannabis, amphetamine and GHB. Each category consisted of ten different picture pairs, which were composed of a substance-related picture and a neutral picture. The neutral pictures were matched on composition and brightness. Another fourteen pairs of neutral pictures were used as practice trials at the beginning of the task, and as buffer trials in the switch between different categories of substances. All pictures were 100 mm high and 100 mm wide.

Each trial started with a fixation cross which was presented for 500 ms in the middle of the screen. Participants were told to attend to the fixation cross. Next, the cross disappeared and two pictures were presented (a substance-related and a neutral picture), each on one side of the screen, for a period of 500 or 1250 ms. After disappearance of the pictures a small arrow pointing upwards or downwards was presented at the location of either one of the pictures. Participants had to respond to the arrow by pressing the corresponding button on the response box as quickly and accurately as possible. The next trial started 500 or 1250 ms after each response. The probe was presented equally often on the right and on the left side, and was presented equally often upwards as downwards. For half of the trials the picture pairs were presented for 500 ms whereas for the other half of trials the pairs were presented for 1250 ms. The location of the neutral (and substance-related) picture was balanced across trials.

The VPT started with 16 practice trials, in which participants received feedback about their accuracy, followed by four blocks of critical trials. For each category of substance we created subsets in which the ten picture pairs were presented twice. Thus, we created a subset of 20 alcohol trials, a subset of 20 cannabis trials, a subset of 20 amphetamine trials, and a subset of 20 GHB trials. In each block those
four subsets were presented twice. Subsets were pseudo-randomly distributed, with the restriction that the same subset could not be presented in sequence, and that the same subset could not be used as a starting subset of more than one block. Each subset was preceded by 3 neutral buffer trials. Trials within the subsets were distributed pseudo-randomly, with the prescription that during the whole task each picture pair was presented evenly in 500 ms and 1250 ms, with as many probes right as left and up as down, and as many neutral pictures right as left, and that within blocks as many picture pairs were presented for 500 ms and 1250 ms, with as many probes right as left and up as down, and as many neutral pictures right as left. Response time and accuracy were recorded.

Executive Control. The Attention Network Task (ANT: Fan et al., 2002) is designed to measure the alerting, orienting, and executive function of spatial attention. Each trial started with a fixation cross which was presented for 400 ms in the middle of the screen. Participants were told to attend to the fixation cross. Next, a row of five horizontal black lines (one central arrow plus four flankers) was presented above or below the fixation cross, with arrowheads pointing left or right. The target is a left or right arrowhead at the center. The target was “flanked” on either side by two arrows in the same direction (congruent condition), the opposite direction (incongruent condition) or by two horizontal lines (neutral condition). Participants had to respond to the target by pressing the corresponding button on the response box as quickly and accurately as possible. Before appearance of the target a warning cue was presented, to signal the upcoming target. This could be one of four warning conditions: a center cue, which was presented at the center location (replacing the fixation cross), a double cue, which were two asterisks presented above and below the fixation cross, or a spatial cue which was an asterisk presented at the exact location of the upcoming target, or no cue at all.

The ANT started with 24 practice trials in which participants received feedback about their mean response time and accuracy, followed by three blocks of 96 critical trials each. Trials were presented in random order, with all types of warning cue and types of flankers presented evenly frequent, and as many target arrows left as right.
**Procedure**

Patients were tested in a quiet room at various locations of the treatment center in or near the patient’s town of residence. Controls were tested in a quiet room located in the university or schools in or near the patient’s town of residence. Measures were administered in a fixed order, and were part of a larger assessment, which further included a computerized Self-Assessment Manikin to assess valence and arousal (see van Hemel-Ruiter et al., 2011), and four questionnaires that were not part of the current study (i.e., Desire to Alcohol/Desire to Drugs Questionnaire, Sensitivity to Punishment and Sensitivity to Reward Questionnaire, Attentional Control Questionnaire, and a Motivation to Change Questionnaire). The VPT and ANT were the first computer tasks of the assessment and the questionnaires were administered after completion of the computer tasks. Computer tasks were presented on a 14 inch Acer laptop computer with a 60 Hz screen (1024 x 768 resolution) using E-prime software version 2.0 (Psychology Software Tools Inc., Pittsburg, Pennsylvania). Participants were seated 50 cm away from the screen and responses were collected with a response box.

**Data Reduction and Analysis**

VPT trials with reaction times 3SD below (probable anticipations) or above (probable distractions) the mean (baseline 4.1%, FU 4.4%), or with an incorrect response (1.3% baseline, 1.3% FU) were removed (cf., van Hemel-Ruiter et al., 2015b). We computed AB scores by subtracting the mean reaction time on substance trials from the mean reaction times on corresponding neutral trials. This resulted in AB scores for alcohol, cannabis, amphetamine and GHB. A higher AB score means a stronger AB towards substance-related pictures compared to neutral pictures.

Then, a measure of substance-specific AB was calculated in the patient group by selecting only the AB score that was related to the primary diagnosis of substance use (e.g., when the primary substance was cannabis, then the cannabis AB score was used for analysis), and in the control group by calculating a mean AB score for all four substances (i.e., AB alcohol + cannabis + amphetamine + GHB/4).

ANT trials with reaction times 3SD below (probable anticipations) or above (probable distractions) the mean (baseline 5.1%, FU 6.3%), or with an incorrect response (baseline 1.8%, FU 1.4%) were removed (van Hemel-Ruiter et al., 2015b). The EC effect was calculated by subtracting the mean RT of all congruent flanking conditions, summed across cue types, from the mean RT of incongruent flanking
conditions (see Fan et al., 2002). A higher score on this total score means a weaker EC.

Measures of substance-specific use and dependency were calculated in the patient group by selecting the alcohol or drug questionnaire (e.g., when the primary substance was amphetamine, the DUDIT, SDS-D was used for analysis) and in the control group by calculating a mean score for alcohol and drug questionnaire (e.g., AUDIT+DUDIT/2).

Because of the different frames of the research questions (i.e., one cross-sectional, one longitudinal), the study results will be reported in two parts. Part 1 will report the results of the baseline study of clients and controls. Part 2 will report the results of the longitudinal patient study (i.e., baseline and follow-up).

RESULTS

Part 1 – baseline

Group characteristics, patients and controls baseline. Independent t-tests were used to compare age, gender, educational level, substance use, and severity of dependence between the groups. As can be seen from Table 6.1, the matching of the groups on age, gender, and educational level was successful. The patient group reported higher substance use and severity of dependence than the control group.

Exploration of substance-specific AB scores. We first explored whether ABs for the various substances differed between patients and controls. We therefore made subsamples of patients based on diagnosis (alcohol, cannabis, amphetamine, or GHB dependency). Some patients were diagnosed with more than one substance use dependency. Hence, these patients were selected for more subsamples. For each of the substances, we carried out independent t-tests to examine whether patients with a dependency diagnosis differed from controls (see Table 6.2). Overall, patients showed a larger AB than controls (with the exception of GHB AB 500 ms), but this difference only reached significance for cannabis AB 500 ms and 1250 ms and amphetamine AB 500 ms. As can be seen in Table 6.2, there was an acceptable number of cannabis-dependent patients (n = 54), but the number of patients dependent on alcohol (n = 22), amphetamine (n =20), and especially GHB (n = 3) was small, which implied relatively low statistical power to find differences between patients and controls for these subgroups. Further, one sample t-tests showed that for patients diagnosed with the related substance use
dependency, cannabis AB 500 ms and 1250 ms, and amphetamine AB 500 ms were significantly larger than zero. Although not for other substances, controls showed significant cannabis AB 500 ms. This latter finding was unexpected and influenced the calculation of a mean AB score for the controls. However, the finding that cannabis-dependent patients showed a significantly larger cannabis AB than controls was taken to justify the use of a mean AB score for the control group as a reference category.

**Table 6.2**

<table>
<thead>
<tr>
<th>Substances</th>
<th>Alcohol</th>
<th>Cannabis</th>
<th>Amphetamine</th>
<th>GHB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>controls</td>
<td>patients</td>
<td>controls</td>
</tr>
<tr>
<td>n</td>
<td>n = 22</td>
<td>n = 61</td>
<td>n = 54</td>
<td>n = 61</td>
</tr>
<tr>
<td>AB 500 ms</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td></td>
<td>-3.11 (21.4)</td>
<td>-3.67 (22.8)</td>
<td>26.13 (42.9)*</td>
<td>10.23 (20.6)</td>
</tr>
<tr>
<td>AB 1250 ms</td>
<td>-0.14 (29.3)</td>
<td>-3.03 (19.6)</td>
<td>11.36 (30.7)*</td>
<td>1.29 (19.7)</td>
</tr>
</tbody>
</table>

*Note.* AB = attentional bias; SD = standard deviation; * score significantly (p < 0.05) differs between patients and controls.

**Table 6.3**

<table>
<thead>
<tr>
<th></th>
<th>Patients n = 72</th>
<th>Controls n = 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOA</td>
<td>Substance cue</td>
<td>Neutral cue</td>
</tr>
<tr>
<td></td>
<td>Mean RT (sd)</td>
<td>Mean RT (sd)</td>
</tr>
<tr>
<td>500 ms</td>
<td>574 (75)**</td>
<td>593 (82)</td>
</tr>
<tr>
<td>1250 ms</td>
<td>568 (74)*</td>
<td>575 (73)</td>
</tr>
</tbody>
</table>

*Note.* VPT = visual probe task; RT = reaction time; * RT on substance cue significantly (p < 0.05) differs from RT on neutral cue; ** RT on substance cue significantly (p < 0.01) differs from RT on neutral cue.

**AB in patients versus controls.** First, we explored whether patients and controls showed an AB by comparing the mean response time for probes that were presented on the location cued by the substance stimuli (congruent trials) to the mean response time for probes that were presented on the location cued by the neutral control stimuli (incongruent trials). For the patient group, the analysis was restricted to congruent and incongruent trials displaying pictures of their primary substance of abuse. Table 6.3 shows that for both the 500 ms and 1250 ms trials patients were significantly faster on congruent than on incongruent trials. For controls there was no overall difference in response time between congruent and incongruent trials.

In addition, patients and controls were compared on AB measures by means of a 2 (WS, SOA: 500 ms, 1250 ms) x 2 (BS, group: patient, control) mixed ANOVA.
Most important for the current context, there was a main effect of group ($F(1,131) = 14.25, p < 0.001$) indicating that patients generally demonstrated stronger AB for substance-related pictures (see Figure 6.1). Further, there was a main effect of SOA ($F(1,131) = 6.37, p = 0.01$) that was similar for both groups as evidenced by the absence of a significant interaction effect of SOA*group ($F(1,131) = 3.42, p = 0.07$). As can be seen in Table 6.3, this indicates that the AB was generally stronger for 500 ms than for 1250 ms trials. Although the interaction-effect was not significant, effect-size calculation showed that the difference between patients and controls was medium to large for the 500 ms SOA (Cohen's $d = 0.7$) and small to medium for the 1250 ms SOA (Cohen’s $d = 0.4$).

**Figure 6.1**

*Mean 500 ms and 1250 ms attentional biases for patients and controls*

![Substance-specific attentional bias graph](image)

*Note.* $* p < 0.05$ (two tailed); $** p < 0.01$ (two tailed).

Because the largest group of patients were diagnosed with cannabis dependence, we made a subsample of patients diagnosed with cannabis dependency ($n = 54$), and repeated the analyses for the cannabis-dependent group versus controls, using cannabis AB as dependent variable. The results of these analyses were comparable with the above-mentioned tests, in that patients and
controls differed in cannabis AB, and that cannabis AB was highest for active using patients ($R(2,112) = 8.59, p < 0.01$). This latter difference was significant for both cannabis AB 500 ms (mean difference between controls and active using cannabis dependent patients = 19.85, $p < 0.01$), and cannabis AB 1250 ms (mean difference between controls and active using cannabis dependent patients = 12.79, $p = 0.02$).

**AB in active using and abstinent patients.** Because some of the patients had already been abstinent during the previous month ($n = 18$), and some had not ($n = 54$), we used post-hoc comparisons of abstinent patients with controls regarding their AB scores by means of a 3 (BS, group: active using patients, abstinent patients, controls) ANOVA for 500 ms and 1250 ms separately, with Fisher’s LSD post-hoc tests. The results showed that AB differed between using patients and controls for stimuli that were presented for both 500 ms (mean difference = 19.5, $p < 0.001$), and 1250 ms (mean difference = 8.1, $p = 0.03$), but not between abstinent patients and controls (mean difference AB500ms = 11.2, $p = 0.14$; mean difference AB1250ms = 6.2, $p = 0.26$) or abstinent and using patients (mean difference AB500ms = 8.3, $p = 0.28$; mean difference AB1250ms = 1.9, $p = 0.73$). Results thus showed that substance-related AB was highest for active using patients, and lowest for controls. Post-hoc one-sample t-tests further showed that in the group of active using patients ABes significantly differed from zero (AB 500 ms: mean = 21.08, $p < 0.001$; AB 1250 ms: mean = 7.86, $p = 0.02$), whereas AB effects did not differ from zero within the group of abstinent patients.

**Executive attention in patients and controls.** A (group: patient, control) ANOVA to compare patients and controls with respect to executive attention indicated that ANT performance did not differ between patients and controls ($R(1,131) = 1.86, p = 0.18$). We post-hoc compared active using patients, abstinent patients and controls on ANT performance by means of a 3 (BS, group: active using patients, abstinent patients, controls) ANOVA. Again, the main effect of group was not significant ($R(2,130) = 1.56, p = 0.21$).

**Moderating effect of cognitive control on the relationship between substance-specific AB and problem severity.** Because of the skewed distribution, we first log10 transformed the SDS to obtain a more normal distribution. Correlational analysis showed that within the group of substance-dependent youth, severity of dependence was positively correlated with AB1250ms ($r = 0.25, p = 0.04$) but not with AB500ms ($r = 0.09, p = 0.48$) or EC ($r = -0.20, p = 0.09$). We used
a hierarchical regression analysis to investigate whether EC moderated the relation between AB1250ms and severity of dependence. In step 1 AB1250ms and EC were included and in step 2 the interaction between AB1250ms and EC. This model explained 11% ($R^2_{adj} = 0.07$, $F_{(5,71)} = 2.76$, $p = 0.05$) of the variance in severity of dependence. The results of step 1 show that AB1250ms was positively, and EC was marginally negatively associated with higher severity of dependence (see Table 6.4). However, when the interaction of AB 1250ms x EC was entered in step 2, the main effect of AB 1250 ms appeared to have no independent significant value in the prediction of problem severity. Further, contrary to the expectations, the interaction effect between AB and EC was not significantly related to severity of dependence.

Table 6.4
Moderator regression analysis in the prediction of severity of dependence (n = 72)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>T</th>
<th>p-value</th>
<th>R² Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>33.33</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attentional Bias 1250 ms</td>
<td>0.26</td>
<td>2.28</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>EC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.22</td>
<td>-1.92</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Constant)</td>
<td>32.35</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attentional Bias 1250 ms</td>
<td>0.30</td>
<td>1.08</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>EC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.21</td>
<td>-1.81</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>AB1250ms*EC</td>
<td>-0.04</td>
<td>-0.15</td>
<td>0.88</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Note. EC = Executive control; AB = attentional bias; $R^2$ final model = 0.11*; Adjusted $R^2 = 0.07$; *p = 0.05; <sup>a</sup>Higher score means weaker EC.

**Part 2**

**Group characteristics, baseline and follow-up.** Almost half of the patient participants who were assessed at baseline also completed the assessment at 6 months follow-up (N = 38). A group of 28 participants did not want to participate anymore in the follow-up assessment, and we were unable to get in contact with another twelve participants. Due to the exclusion of seven participants, we kept 70 patients in the study of whom 32 completed both assessments. Of those, 20 were still in treatment at the time of the follow-up assessment.
To test whether patients who remained in the study differed from patients who dropped out, we conducted independent t-tests on baseline measures. These analyses showed that patients who dropped out differed from patients who remained in the study on gender (i.e., 6 female/26 male in completers, 17 female/21 male in drop-outs; Mann-Whitney $U = 450, p = 0.02$), but not on age, diagnosis of primary substance, level of substance use, dependency, AB 500ms, AB1250ms, or EC at baseline. Further, although the drop-out rate was quite high, there was no reason to assume that the reason why participants dropped-out was related to research-outcome. We therefore treated the missing data as missing at random and applied multiple imputation in order to estimate the follow-up missing-data. We imputed the missing data in SPSS using $M = 40$ imputations, and to avoid bias due to missingness we used baseline variables that might be predictive for missingness at follow-up (age and gender, AB and EC variables and substance use variables) as indicators in the model (Sterne et al., 2009). We used this imputed data-set for the following analyses and report the pooled results. Paired-samples t-tests showed that neither substance use nor level of dependency were significantly decreased six months after entrance of treatment (see Table 6.5). As a check-up we repeated all following analyses for the complete cases only, and results were comparable to the results of the imputed data-set.

<table>
<thead>
<tr>
<th>Table 6.5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paired samples t-test between baseline and follow-up scores, $N = 70^a$</strong></td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Substance use previous month (AUDIT/DUDIT)</td>
</tr>
<tr>
<td>Severity of dependence (SDS)</td>
</tr>
<tr>
<td>Substance Attentional Bias 500 ms</td>
</tr>
<tr>
<td>Substance Attentional Bias 1250 ms</td>
</tr>
<tr>
<td>EC$^b$</td>
</tr>
</tbody>
</table>

Note. $^a$ Based on the imputed data-set; $^b$ Higher score means weaker EC; SD = standard deviation; EC = executive control; $^{**}p < 0.01$.

**Course of AB and executive control.** We tested whether ABs decreased between baseline and follow-up by means of paired-samples t-tests. As can be seen in Table 6.5, there was no significant difference between baseline and follow-up for the AB scores. The results further showed that EC significantly increased
from baseline to follow-up (mean increase = 21.34, \( t(110) = 3.22, p < 0.01 \)). Bivariate Pearson correlations between baseline and 6-month follow-up scores were significant for AB 500ms \( (r^2 = 0.39, p = 0.01) \) and EC \( (r^2 = 0.60, p < 0.001) \), but not for AB 1250 ms \( (r^2 = 0.09, p = 0.57) \).

**Changes in problem severity, ABs and EC.** We subsequently tested whether problem severity differences between baseline and follow-up were related to differences in ABs or EC between baseline and follow-up. We therefore calculated difference scores for both ABs, for EC, and severity of dependence. By means of a multivariate regression analysis we tested to what extent the change in severity of dependence could be predicted by change in AB and EC. This model was not significant in the explanation of change in severity of dependence \( (R^2_{\text{adj}} = 0.18, F(3,66) = 6.77, p = 0.07) \). Thus there was no convincing relationship between changes in severity of dependence and changes in AB or EC.

**DISCUSSION**

This study investigated AB and EC in a sample of treatment-seeking substance dependent youth, compared to a control group. The major results can be summarized as follows: First, substance-dependent youth showed a stronger AB for stimuli representing the primary substance of abuse than the non-abusing controls, both when presented for 500 ms and 1250 ms. Second, patients did not demonstrate a relatively low EC, compared with matched controls. Further, in the substance-dependent group, higher self-reported severity of dependence was positively related to stronger AB for stimuli that were presented for 1250 ms, and this relationship appeared independent of EC. Finally, congruent with the finding that substance dependency remained unaffected at 6-month follow-up, also AB for substance cues was similar at baseline and at follow-up six months after entering treatment. However, there was an unexpected increase in EC at 6-month follow-up.

The finding that substance-dependent youth were characterized by an AB for relevant substance stimuli is in line with previous research showing a heightened AB for substance stimuli that were presented for 500ms or longer in alcohol and drug abusers (see for review, Field & Cox, 2008), and the few adolescent studies that investigated AB for alcohol in heavy drinking and at-risk adolescents (Field et al., 2007a; Pieters et al., 2011; Zetteler et al., 2006; see for review, Wiers et al., 2015b).

The post-hoc comparison sheds some light on the course of substance-related AB, in that the highest AB was found in substance dependent youth who were
current users, and the lowest in the control group. The finding that ABs were absent in abstinent patients is in line with previous studies in abstinent alcoholics showing an absence of AB for alcohol stimuli that were presented for 500 ms or longer (Field et al., 2013; Noël et al., 2006), or even a bias away from those stimuli (Townshend & Duka, 2007; Vollstädt-Klein et al., 2009). This absence of AB for maintaining attention on substance stimuli in abstinent patients might be explained by their explicit wish to remain abstinent.

The inclusion of two stimuli presentation times demonstrated some differences between the role of early attentional processes and maintained attention in addiction. The results showed that there was a large difference between patients and controls for stimuli that were presented for 500 ms, but only a moderate difference for stimuli that were presented for 1250 ms. Interestingly, within the patient group those with stronger maintained attention reported the highest severity of dependence. The hypothesized “vigilance-avoidance” pattern of AB (see, Noël et al., 2006) might account for the relationship between AB for 1250 ms and severity of dependence. Those patients who already were abstinent or moderated their substance use (which indicates a smaller severity of dependence) might have developed a strategy in which they tried to redirect their attention away from substance stimuli, which is easier when there is more time for exerting voluntary control (i.e., 1250 ms condition). However, before making any strong conclusions, it is necessary to test the robustness of this finding by replicating this research in a larger group of substance dependent adolescent patients.

Based on previous findings that substance-abusing individuals are characterized by a lowered executive functioning (Lubman et al., 2004; de Wit, 2009; Verdejo-García & Pérez-García, 2007), we expected to find a lowered EC in the patient group compared to controls. However, we did not find such a difference in the current study. Further, in apparent contrast to previous research that found a moderating role of executive functions in the relationship of appetitive processes and alcohol use functions (Grenard et al., 2008; Houben & Wiers, 2009; Peeters et al., 2012, 2013; Thush et al., 2008; van Hemel-Ruiter et al., 2015b), the current study did not show evidence for a moderating effect of EC on the relation between AB and problem severity. However, there were also previous studies that failed to find a moderating role of executive functions on appetitive processes and substance use (Christiansen et al., 2012; Cousijn et al., 2013; Pieters et al., 2012; van Hemel-Ruiter et al., 2011). One explanation for this finding could be that the role of lowered EC plays a less critical role than often assumed. In addition, since EC is not a unitary construct, it could also be that the ANT does not index the components of
EC that are relevant for AB in substance use. However, this seems not very convincing as a previous study using the ANT to index EC did find evidence for EC moderating the relationship between AB and substance use in heavy drinking students (van Hemel-Ruiter et al., 2015b). Moreover, a series of studies in the context of internalizing symptoms similarly showed evidence for ANT performance as a moderator of the relationship between AB for threat cues and symptoms of anxiety (Hou et al., 2014; Reinholdt-Dunne et al., 2009). Another reason for the current failure to find a moderating influence of EC on the relationship between AB and substance use might be found in the characteristics of the current sample. The current study investigated AB in substance-dependent patients, whereas previous studies were mainly focused on subclinical ranges of alcohol users. To arrive at more definitive conclusions about the role of EC in adolescent substance abuse, it would be important to replicate these findings by using additional indices of EC.

The follow-up assessment of the patient group six months after entering treatment demonstrated that, contrary to expectations, AB had not systematically decreased. However, also the severity of substance dependency and substance use had not decreased. Thus the finding that overall AB remained unaffected is entirely consistent with the starting point that AB is involved in the maintenance of substance misuse. The absence of an effect of the intervention may also explain why this study failed to find a convincing relationship between the reduction in symptoms and a reduction in bias.

The finding that the enhanced AB in patients remained unaffected during the six month period after entering treatment points to the potential relevance of adding treatment components that directly address enhanced AB. Related to this, a first small clinical study showed that ABs can be decreased by means of an AB modification (ABM) training, and that this decrease in AB is related to a decreased relapse-rate in alcoholic patients (Schoenmakers et al., 2010). Further, also other forms of Cognitive Bias Modification have proven successful as add-on to regular treatment for alcoholism (Eberl et al., 2013; Wiers et al., 2011, 2013). Perhaps then conventional treatments might benefit from an add-on ABM intervention, to decrease ABs for personally relevant substance stimuli. The training of these ABs might help patients to automatically attend away from substance cues, which might be supplemental to the conventional therapies aimed at more overt behaviors that are under voluntary control. Germane to this, it has been suggested that ABM might especially be successful when combined with CBT or Motivational Enhancement Therapy (MET: Wiers et al., 2015b); two interventions that are commonly integrated in adolescent addiction treatment programs. Future studies
are therefore needed to investigate the effects of an add-on ABM to treatment as usual in adolescent substance-dependent patients.

Although substance use remained largely stable between baseline and six months after entering treatment, EC increased. One explanation could be that the EC increase reflects a learning effect (Ishigami and Klein, 2011). Further, it could be that EC was increased due to the interventions. It could also be that the EC increase reflects normal maturation of the adolescent cognitive processes. Recent research showed that especially in males attentional control continues to increase until at least age 21 (Gur et al., 2012). One way to solve this ambiguity in future research would be to use a between-groups design with half of the participants only being tested at follow-up, or, alternatively, test the control group at follow-up too.

The current study sheds some light on the role and course of substance-specific AB and EC in an adolescent substance-dependent patient group. However, there are some limitations that need attention. First of all, despite our intensive efforts to keep participants in our study, the follow-up component of the present study suffered from a substantial amount of dropout. Most of the patients were in outpatient treatment, which complicated the contact with participants and reduced opportunities to keep the patients in the study. However, we multiple imputed the data-set and completers did not differ at intake from drop-outs (except from gender). Further, results from original data analysis and imputed data analysis did not differ. Second, several authors concluded on the basis of the poor internal consistency of the visual probe task, that this task is unreliable and cannot be used as an index of individual differences in AB (see e.g., Ataya et al., 2012). However, other authors (e.g., Huntjens, Rijkeboer, Krakau & de Jong, 2014) have argued that internal consistency might not be an adequate index of reliability in performance measures especially when the target stimuli (here substance cues) 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 seem to speak to its reliability (see also Mogg, Mathews & Eysenck, 1992). Third, it is important to note that for drawing conclusions about changes in AB from the early stages of treatment to 6-months follow up, it is critical that the VPT has satisfactory test-retest reliability. In apparent conflict with this requirement, previous studies that examined the test-retest reliability of the VPT seem to converge to the conclusion that the test-retest reliability of this index of AB is relatively poor (e.g., Marks, Pike, Stoops & Rush, 2014; Schmukle, 2005; Spiegelhalder et al., 2011). However, thus far, these studies relied on non-clinical samples and showed only weak or no overall
reaction time based AB effects to begin with. Thus it remains important for future research to examine whether the test-retest reliability within clinical groups is or is not sufficient to draw meaningful conclusions about changes in AB over time. Fourth, the naturalistic setting was not only a strength but also a limitation of our study. It was impossible to direct the inclusion procedure strictly, and thus intake and therapy sometimes intertwined, and in other cases intake and therapy were weeks apart because of patient no-shows. In this way some participants already received one or more therapy sessions and some were already abstinent for a shorter or longer time, before the first assessment within this study took place. This might have influenced the results, although this also has provided some insight in the difference in substance-related AB between still using and abstinent patients. A further limitation related to the naturalistic character of this study is that the current follow-up assessment was at a time when a large number of patients were still in treatment. Although the initial design was to follow participants for a longer period of time, the actuality involved such a large dropout that we had to cancel this third assessment. Unfortunately, we were therefore not able to investigate the longer-term course of substance-specific AB during the treatment period and right after. Furthermore, by taking the AB scores for the different groups of substance abusers together, this might have washed out effects for specific sub-groups. However, the finding of an effect of this composite score also indicates that related processes are involved with dependency of different substances. But it cannot be ruled out that the results might be mainly driven by the difference in cannabis AB between patients and controls. Therefore, it is to be recommended that future studies aim at recruiting alcohol, amphetamine, and GHB using patients, to be able to test whether the relevance of AB may vary as a function of substance. Finally, it should be acknowledged that we used a fixed task order implying that the ANT was always performed after the VPT. Although previous research using a similar order did find differences in ANT performance as a function of alcohol use in early adolescents (van Hemel-Ruiter et al., 2015), it cannot be ruled out that this order may have reduced the sensitivity of the ANT to detect differences between the current patient and control groups.

Taken together, the results of the current study indicate that treatment-seeking substance-dependent youth were characterized by an AB for personally relevant substance stimuli, which was found to be both a bias in early attentional processes and in maintenance of the attention, with only the latter related to problem severity. The novel findings of demonstrating ABs in i) substance dependent youth and ii) for a variety of personally relevant substance cues (alcohol, cannabis,
amphetamine and GHB), add to the existing literature demonstrating alcohol ABs in heavy substance users, substance dependent patients and at-risk adolescents. Further, the results of this study showed no decreased EC in substance-dependent adolescent patients, and level of EC did not moderate the relationship between AB and substance dependency. Together these findings are consistent with the view that traditional addiction treatments may benefit from an additional CBM intervention aimed at decreasing substance-related AB.