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

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ABSTRACT

Background: Research in adults shows that substance dependent individuals demonstrate attentional bias (AB) for substance-related stimuli. This study investigated the role of AB 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 AB.
Methods: Seventy-eight young substance-dependent (SD) patients (mean age = 19.5), and 64 healthy controls (HC; mean age = 19.0) were tested. Thirty-eight SD patients took part at 6-month follow-up (FU). AB 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: SD patients demonstrated an AB for substance stimuli presented for 500 ms and 1250 ms, with the latter related to severity of dependence. There was a nonsignificant tendency indicating that EC was higher in HC than SD participants, but EC did not moderate the relationship between AB and dependency. Substance use, dependency, EC and AB remained unchanged in the 6 month FU period.
Conclusions: Young SD patients showed a stronger relatively early as well as maintained AB toward substance cues. A stronger maintained attention was related to higher severity of dependence. Further, there were some indications that EC might play a role in adolescent substance use. The finding that at FU AB and problem severity were not decreased, and EC was not increased underlines the persistent character of addiction.

1. 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., 2014). 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; Wiers et al., 2007, 2013). In line with this, there is considerable evidence supporting the view that substance-related stimuli capture the attention of individuals who (ab) use these addictive substances (Field and 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 and Klinger, 2004; Lubman et al., 2004; Wiers et al., 2007; but see Boelema et al., 2015; Wiers et al., 2015), 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 and Cox, 2008), because they are less able to regulate their attention (Fazio and 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 demon-

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strated AB in non-clinical and clinical alcohol and drug users (see for review, Field and 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 et al., 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 et al., 2014).

For a proper appreciation of the role of AB in the development of addictive behaviors, it is important to investigate the role of AB in the early stages of substance (ab) use. There are only a few studies that have examined AB for substance-related stimuli in younger age groups, 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., 2007), 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-Ruiter et al., 2015; 15–21 years Willem et al., 2013; see for review: Wiers et al., 2015). However, a recent longitudinal study in a normative sample of young adolescents showed that alcohol AB predicted adolescent alcohol use later on (12–18 years: Janssen et al., 2015). Only one study investigated the role of attentional bias in relatively young (adolescent/early adult) cannabis users, demonstrating an AB for cannabis cues in heavy users, which was strongest in cannabis dependent individuals (18–30 years: Cousijn et al., 2013).

The present study aimed to extend this research, by investigating substance-related AB in adolescents and young adult ("young", 12–25 year-olds) substance-dependent (SD) patients. The large majority of youth enrolling in addiction therapy are abusers of cannabis or alcohol. This applies both to the U.S. (SAMHSA, 2014; Johnston et al., 2014) as well as for Europe (EMCDDA, 2015; van Laar et al., 2014). Given the relatively high prevalence of adolescent alcohol, cannabis, amphetamine, and GHB abusers in The Netherlands (Wisselink et al., 2013), we decided to focus on these groups for the current study.

The major aim of this study was to test if young SD patients diagnosed with alcohol, cannabis, amphetamine, or GHB abuse or dependency are 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 and Koster, 2010; Mogg and 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 and Cox, 2008).

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 and 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 and Wiers, 2009; Peeters et al., 2012, 2013; Thush et al., 2008; van Hemel-Ruiter et al., 2015), and some studies that did not find such a moderating influence of executive functioning on automatic processes (Christiansen et al., 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 young SD patients are characterized by a relatively weak 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). Recent studies using the ANT to measure EC within undergraduate samples showed that AB for alcohol stimuli was related to alcohol use only in weak EC adolescents (van Hemel-Ruiter et al., 2015), 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).

The last aim of this study was to investigate whether substance-related AB and EC change during therapy. There is some evidence that AB is reversed in abstinent smokers (Peuker and Bizarro, 2014), reversed or decreased in abstinent alcoholics (Noël et al., 2006; Townshend and Duka, 2007; Vollstädt-Klein et al., 2009), and decreased in treated cocaine and heroin abusers (Gardini et al., 2009). In this study we therefore also included a follow-up assessment for the SD group, 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 young SD patients. Healthy peers served as a control group (HC). Based on cognitive motivational models of addiction, we hypothesized that SD patients 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 individuals with relatively weak EC abilities are at risk for developing substance misuse and dependency (de Wit, 2009; Verdejo-García and Pérez-García, 2007), we hypothesized that the SD group would be characterized by a relatively weak EC, compared to the HC 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 et al., 2011), we further expected that EC would increase.

2. Method

2.1. Participants and recruitment

Participants were 78 alcohol- or drug-dependent young patients (12–25 years) and 64 young healthy controls. 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. HCs were matched at group level for age, gender, and educational level with the SD group.

SD 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 them to participate in a study about the development of substance use and abuse, which consisted of two sessions of 90 min 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 (FU). The participation of both SD and HC group throughout the study is demonstrated in Fig. 1. The final baseline patient sample resulted in a total of 72 SD patients (48 male and 24 female; mean age = 19.7, SD = 2.8; see Table 1 for group characteristics). Twenty SD patients (26.3%) reported that they had not used their primary substance over the previous month. SD patients mainly received assertive community treatment, or

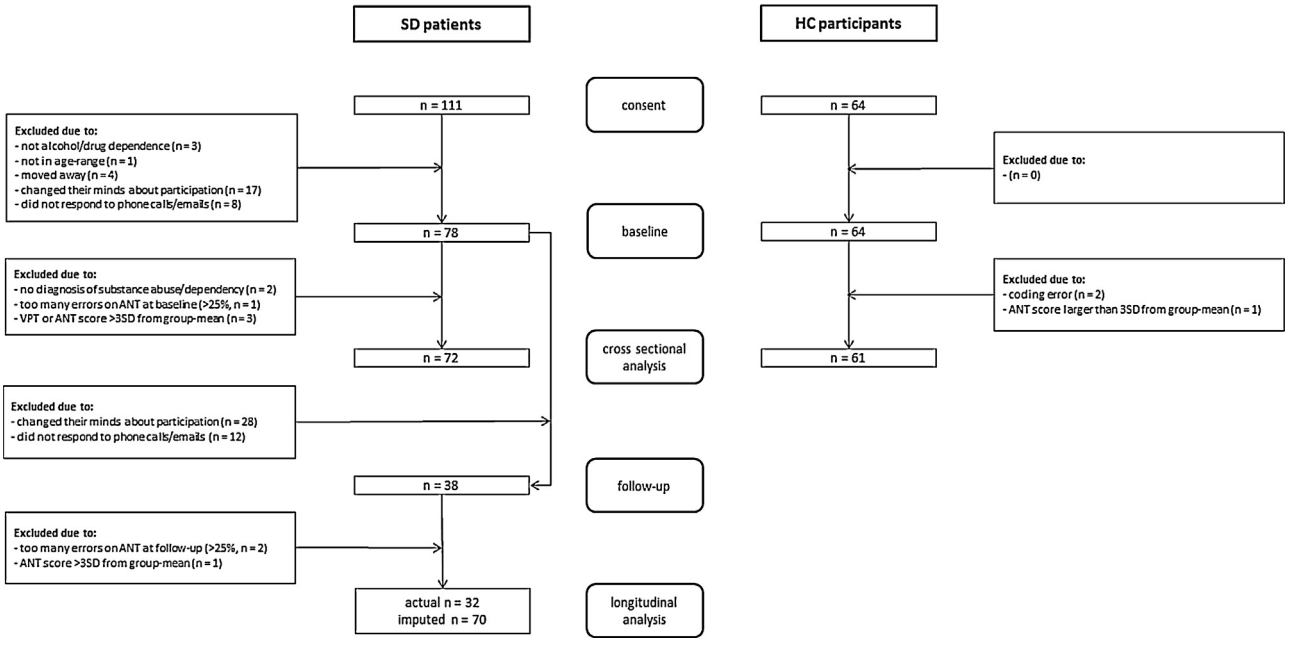

Fig. 1. Flow-chart of the number of initially consenting SD patients and HCs and the inclusion/exclusion process for both baseline and follow-up assessment.

Table 1
Means and standard deviations of variables as a function of group.

Variable	Patients $n = 72$ Mean (SD)	Controls $n = 61$ Mean (SD)	T-statistics/Mann–Whitney U
Gender, % female	32%	31%	2148.0
Age	19.69 (2.83)	19.00 (2.37)	1.52
Educational level[a]	2.82 (0.79)	3.03 (0.58)	1874.5
Primary diagnosis alcohol dependence (*n*, %)	10 (14%)	–	
Primary diagnosis cannabis dependence (*n*, %)	49 (68%)	–	
Primary diagnosis amphetamine dependence (*n*, %)	10 (14%)	–	
Primary diagnosis GHB dependence (*n*, %)	3 (4%)	–	
Substance use previous month (AUDIT/DUDIT)	5.93 (4.56)	1.43 (1.03)	8.11**
Severity of dependence (SDS)	5.76 (4.06)	0.27 (0.72)	11.3**
Substance AB 500 ms	19.00 (36.50)	1.60 (11.84)	3.82**
Substance AB 1250 ms	7.39 (25.33)	−0.19 (11.00)	2.30*
EC[b]	0.20 (0.09)	0.17 (0.08)	1.92

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 '1–4', 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).

cognitive behavioral treatment, but the exact approach and duration of treatment highly varied between patients. Medication was no standard component of treatment. For the analysis of the longitudinal data there remained 70 SD patients in the study, with 32 (46%) who completed both assessments (see Fig. 1).

HCs 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 min. 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. As can be seen in Fig. 1, the final HC sample 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 SD and HC participants received a gift-voucher of 5 euros per session after completion. Descriptive statistics are presented in Table 1. The study was approved by the Medical Ethical Committee of the University Medical Centre Groningen.

2.2. Questionnaire measures

2.2.1. Self-reported substance use. Alcohol use was measured by a shortened version of the alcohol use disorder identification test (AUDIT: Saunders et al., 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 and 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. Inter-

nal reliability of these questionnaires was good to excellent, with Cronbach's alpha ranging from 0.86 to 0.99.

2.2.2. Self-reported severity of dependence. Level of dependency was measured by the severity of dependence scale (SDS: Gossop et al., 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.

2.3. Computerized measures

2.3.1. 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.

2.3.2. Executive control. The attention network task (ANT; Fan et al., 2002) was 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.

2.4. Procedure

SD patients were tested in a quiet room at various locations of the treatment center in or near the patient's town of residence. HCs 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 in. Acer laptop computer with a 60 Hz screen (1024 × 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.

2.5. Data reduction and analysis

VPT trials with reaction times (RT) 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., 2015). We computed AB scores by subtracting the mean RT on substance trials from the mean RT 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 RTs 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., 2015). The EC effect was calculated by subtract-

Table 2
Attentional bias scores for patients diagnosed with alcohol, cannabis, amphetamine or GHB dependency.

	Alcohol		Cannabis		Amphetamine		GHB	
	Patients $n=22$	Controls $n=61$	Patients $n=54$	Controls $n=61$	Patients $n=20$	Controls $n=61$	Patients $n=3$	Controls $n=61$
AB	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
500 ms	−3.11 (21.39)	−3.67 (22.81)	26.13 (42.94)[a]	10.23 (20.57)[a]	12.06 (34.32)[a]	−1.63 (23.15)	−2.59 (36.83)	1.48 (19.41)
1250 ms	−0.14 (29.34)	−3.03 (19.57)	11.36 (30.73)[a]	1.29 (19.68)	4.52 (26.52)	−2.25 (22.08)	7.52 (5.86)	3.22 (30.02)

Note: AB = attentional bias.
[a] Score significantly ($p<0.05$) differs from zero.

ing the mean RT of congruent no-cue conditions from the mean RT of incongruent no-cue conditions and by subsequently dividing this score by the mean RT of incongruent no-cue conditions (see Wang et al., 2014). A higher score on this total score means a *weaker* EC.

Measures of substance-specific use and dependency were calculated for the SD 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 for the HC 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 FU).

3. Results

3.1. Part 1—baseline

3.1.1. Demographics. For both groups, age, gender, educational level, substance use, and severity of dependence are displayed in Table 1. As can be seen from Table 1, both groups were very similar apart from substance use and dependency.

3.1.2. Exploration of substance-specific AB scores. We first made subsamples of SD patients based on diagnosis (alcohol, cannabis, amphetamine, or GHB dependency) and explored whether ABs for the various substances differed between patients and controls. Patients who were diagnosed with more than one substance use dependency were selected for more subsamples. For each of the substances, we performed independent t-tests to examine group differences (see Table 2). Overall, SD patients showed larger AB than HCs (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. There was an acceptable number of cannabis-dependent patients ($n=54$), but the numbers of patients dependent on alcohol ($n=22$), amphetamine ($n=20$), and especially GHB ($n=3$) were 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-dependency, cannabis AB 500 ms and 1250 ms, and amphetamine AB 500 ms were significantly larger than zero. Although not for other substances, HCs showed significant cannabis AB 500 ms. This latter finding was unexpected and influenced the calculation of a mean AB score for the HCs. However, the finding that cannabis-dependent patients showed a significantly larger cannabis AB than HCs was taken to justify the use of a mean AB score for the control group as a reference category.

3.1.3. AB in SD versus HC group. First, we performed one-sample t-tests to explore whether SD patients and HCs showed a substance AB by comparing the mean RT for probes that were presented on the location cued by the substance stimuli (congruent trials) to the mean RT for probes that were presented on the location cued by the neutral control stimuli (incongruent trials). For the SD group, the analysis was restricted to trials displaying pictures of their primary substance of abuse. For both 500 and 1250 ms SD patients were significantly faster on congruent than on incongruent trials, but for HCs there was no overall difference (Table 3).

Table 3
Mean VPT reaction times for primary substance cues and neutral cues.

	Patients $n=72$		Controls $n=61$	
SOA	Substance cue Mean RT (SD)	Neutral cue Mean RT (SD)	Substance cue Mean RT (SD)	Neutral cue Mean RT (SD)
500 ms	574 (75)**	593 (82)	568 (83)	569 (82)
1250 ms	568 (74)*	575 (73)	558 (83)	557 (82)

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.

A 2 (WS, SOA: 500 ms, 1250 ms) × 2 (BS, group: SD, HC) mixed ANOVA showed that there was a main effect of group ($F(1,131)=14.25$, $p<0.001$) indicating that SD patients generally demonstrated stronger AB for substance-related pictures. 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 ($F(1,131)=3.42$, $p=0.07$). This indicates that the AB was generally stronger for 500 ms than for 1250 ms trials (see Table 3). Although the interaction-effect was not significant, effect-size calculation showed that the difference between the SD and HC group was medium to large for the 500 ms SOA (Cohen's $d=0.64$) and small to medium for the 1250 ms SOA (Cohen's $d=0.39$).

3.1.4. EC in SD and HC group. A (group: SD, HC) ANOVA indicated that there was a nonsignificant tendency indicating that EC was higher in HC than SD participants ($F(1,131)=3.67$, $p=0.06$). Effect-size calculations showed that the difference between the SD and HC group was small to medium (Cohen's $d=0.33$).

3.1.5. Moderating effect of EC 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 SD group, severity of dependence was positively correlated with AB1250 ms ($r=0.25$, $p=0.04$) but not with AB500 ms ($r=0.09$, $p=0.48$) or EC ($r=-0.20$, $p=0.09$). We used a hierarchical regression analysis to investigate whether EC moderated the relation between AB1250 ms and severity of dependence. In step 1 AB1250 ms and EC were included and in step 2 the interaction between AB1250 ms and EC. This model explained 11% (R^2 adj = 0.07, $F(3,71)=1.64$, $p=0.19$) of the variance in severity of dependence. The results showed that AB1250 ms was positively associated with higher severity of dependence (see Table 4). However, contrary to the expectations, EC and

Table 4
Moderator regression analysis in the prediction of severity of dependence ($n = 72$).

Variable		Beta	t	R^2 change
Step 1				
	(Constant)		89.70**	
	Attentional bias 1250 ms	0.26	2.18*	
	EC[a]	−0.07	−0.62	0.07
Step 2				
	(Constant)		88.14**	
	Attentional Bias 1250 ms	0.26	2.17*	
	EC[a]	−0.07	−0.62	
	AB1250 ms × EC	0.04	0.37	0.00

Note: EC = executive control; AB = attentional bias.
R^2 final model = 0.11*; Adjusted R^2 = 0.07; * $p = 0.05$.
[a] Higher score means weaker EC.

the AB1250 ms × EC interaction were not significantly related to severity of dependence.

3.2. Part 2

3.2.1. Group characteristics, baseline and FU. A total of 38 SD patients also completed the assessment at 6-month FU. The flowchart in Fig. 1 shows that we kept 70 SD patients in the study of whom 32 completed both assessments. Of those, 20 were still in treatment at the time of the FU assessment.

To test whether SD patients who remained in the study differed from SD patients who dropped out, we conducted independent t-tests on baseline measures. These analyses showed that completers differed from drop-outs 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, educational level, diagnosis of primary substance, level of substance use, dependency, AB 500 ms, AB1250 ms, 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 FU missing-data as a state-of-the-art method for dealing with missing data (e.g., Jeličić et al., 2010). 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 FU (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 5).

3.2.2. Course of AB and EC. Paired-samples t-tests showed that there was no significant difference between baseline and FU regarding AB and EC (see Table 5). Bivariate Pearson correlations between baseline and FU scores were significant for AB 500 ms ($r^2 = 0.40$, $p = 0.01$) and EC ($r^2 = 0.60$, $p < 0.001$), but not for AB 1250 ms ($r^2 = 0.11$, $p = 0.51$).

3.2.3. Changes in problem severity, ABs and EC. We subsequently tested whether problem severity differences between baseline and FU were related to differences in ABs or EC between baseline and FU. We therefore calculated difference scores for ABs, 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 adj = 0.24, $F(3,66) = 11.30$, $p = 0.08$). Thus there was no convincing relationship between changes in severity of dependence and changes in AB or EC.

4. Discussion

This study investigated AB and EC in a sample of young SD patients, compared to a HC group. The major results can be summarized as follows: first, SD patients showed a stronger AB for stimuli representing the primary substance of abuse than the HCs, both when presented for 500 ms and 1250 ms. Second, there was a non-significant tendency suggesting that EC was higher in HC than SD participants (small to medium effect size). Further, in the SD 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, unexpectedly, but congruent with the finding that substance dependency remained unaffected at 6-month FU, also AB for substance cues and EC did not change between baseline and FU six months after entering treatment.

The finding that young SD patients 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 500 ms or longer in alcohol and drug abusers (see for review, Field and Cox, 2008), and the few adolescent studies that investigated AB for alcohol in heavy drinking and at-risk adolescents (Field et al., 2007; Pieters et al., 2011; Zetteler et al., 2006; see for review, Wiers et al., 2015).

We included two stimulus presentation times to examine the relevance of relatively early attentional processes and maintained attention in addiction. The results showed that there was a large difference between SD patients and HCs for stimuli that were presented for 500 ms, but only a moderate difference for stimuli that were presented for 1250 ms. Interestingly, within the SD 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 SD 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 young SD patients.

The results of the current study also demonstrated a nonsignificant tendency indicating that EC was lower in SD participants than in HCs. This in accordance with previous studies that demonstrated lowered executive functioning in substance-abusing individuals (Lubman et al., 2004; de Wit, 2009; Verdejo-García and Pérez-García, 2007). However, the current study did not show evidence for a moderating effect of EC on the relation between AB and problem severity. This finding differs from previous studies that did find a moderating role of executive functions on appetitive processes and substance use (Grenard et al., 2008; Houben and Wiers, 2009; Peeters et al., 2012, 2013; Thush et al., 2008; van Hemel-Ruiter et al., 2015), but is in correspondence with other studies that also failed to find such a moderating role (Christiansen et al., 2012; Cousijn et al., 2013; Pieters et al., 2012; van Hemel-Ruiter et al., 2011). Thus although it seems that SD patients are characterized by a relatively weak EC, there is no consistent evidence for a moderating role of EC on the relation between AB and substance abuse. One 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 SD patients, whereas previous

Table 5
Paired samples *t*-test between baseline and follow-up scores, $N = 70$[a].

Variable	Baseline Mean (SD)	Follow-up Mean (SD)	T-statistics
Substance use previous month (AUDIT/DUDIT)	5.79 (4.55)	5.42 (5.26)	0.36
Severity of dependence (SDS)	5.63 (4.01)	4.89 (5.44)	0.83
Substance attentional bias 500 ms	19.31 (36.96)	11.72 (37.46)	1.03
Substance attentional bias 1250 ms	7.31 (25.64)	11.34 (44.10)	−0.35
EC[b]	0.20 (0.09)	0.18 (0.10)	1.34

Note: EC = executive control.
[a] Based on the imputed data-set.
[b] Higher score means weaker EC.

studies were mainly focused on subclinical ranges of alcohol users. Further, this study did not find an AB in the alcohol dependent, GHB dependent, or amphetamine dependent (1250 ms condition) groups, which might have contributed to the negative finding. To arrive at more definitive conclusions about the role of EC in adolescent substance abuse, it would be important to replicate these findings in different samples of substance (ab) using adolescents.

The FU assessment of the SD group six months after entering treatment demonstrated that, contrary to expectations, AB was not systematically decreased, and EC was not increased. However, also the severity of substance dependency and substance use was not significantly reduced at FU. Thus the finding that overall AB and EC remained unaffected is entirely consistent with the starting point that AB and EC are 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, a reduction in biases, and an increase in EC.

The current study sheds some light on the role and course of substance-specific AB and EC in young SD patients. However, there are some limitations that need to be considered. First of all, despite our intensive efforts to keep participants in our study, the FU component of the present study suffered from a substantial amount of dropout. Most of the SD patients were in outpatient treatment, which complicated the contact with them and reduced opportunities to keep them in the study. However, we performed multiple imputations on the data-set and completers did not differ at intake from drop-outs (except from gender). 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 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 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 SD patients and HCs seem to speak to its reliability (see also Mogg et al., 1992).

Third, it is important to note that for drawing conclusions about changes in AB from the early stages of treatment to 6-months FU, 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 et al., 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 SD patients 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 FU assessment was at a time when a large number of patients were still in treatment. Although the initial design was to follow patients 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 SD patients 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 SD patients and HCs. 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 SD and HC group.

Taken together, the current results indicated that young SD patients 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, (ii) for personally relevant substance cues (cannabis, amphetamine), add to the existing literature demonstrating substance-related ABs in heavy substance users, substance dependent patients, and at-risk adolescents. Moreover, this study did find some preliminary evidence that EC was relatively low in SD patients, but the level of EC did not moderate the relationship between AB and substance dependency.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Contributors

All authors contributed to the design of the study. The first author took the lead in data collection and statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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