Original Paper

Cognitive control in young adults with cannabis use disorder: An event-related brain potential study

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Abstract

Contemporary models of substance use disorders emphasize the role of cognitive control, which has been linked to difficulties in resisting the use of substances. In the present study, we measured two aspects of cognitive control, response inhibition (operationalized by a Go/NoGo Task) and performance monitoring (operationalized by an Eriksen Flanker Task), in a group of young cannabis-use disorder (CUD) patients and compared these functions with two control groups (i.e. a group of cigarette smokers and a group of non-smokers). We employed both behavioural and electrophysiological measures. The results indicate that CUD patients displayed reduced NoGo-P3 event-related potentials compared with non-smoking controls, but not compared with smoking controls. In addition, CUD patients were slower on Go trials than both control groups. No other between-group electrophysiological or behavioural differences were observed. These results seem to suggest that CUD patients have problems related to response inhibition, but performance monitoring seems relatively unaffected.

Keywords

Cannabis, smokers, response inhibition, performance monitoring, N2, P3, ERN, Pe

Cannabis (i.e., 9delta-tetrahydrocannabinol, a partial agonist at the cannabinoid receptor) is the most frequently used illicit drug among young adults in the Western world (Vicente et al., 2008). This is problematic, since adolescence is an important period for the continued development of cognitive functions such as cognitive control (e.g. Gogtay et al., 2004; Luna et al., 2015; Sowell et al., 2002; Tapert et al., 2007). The term 'cognitive control' refers to the higher-order mental abilities by which the flexible use of limited cognitive resources for goal-directed behaviour is optimized (Mansouri et al., 2009). Although cognitive control is a broad concept, we presently focus on two aspects of cognitive control in cannabis use disorder (CUD) patients that have repeatedly been emphasized in models explaining substance use disorders (SUDs; Diagnostic and Statistical Manual of Mental Disorders (DSM-IV): 'A maladaptive pattern of substance use with clinically significant impairment or distress'), namely response inhibition and performance monitoring (e.g. Garavan and Weierstall, 2012; Luijten et al., 2014; Luna et al., 2015).

Response inhibition has been defined as the ability to withhold a prepared response upon the appearance of new information (Nigg et al., 2006). The significance of impaired response inhibition is stressed in a number of contemporary models of SUDs; for example, Feil et al., 2010; Goldstein and Volkow, 2002; Ivanov et al., 2008; Verdejo-García et al., 2008). These models suggest that impaired response inhibition is associated with difficulties in resisting the use of a substance. For example, CUD patients may find it more difficult to decline a joint (i.e. a marijuana cigarette) when offered. This assumed relation between impaired response inhibition and substance abuse in humans has been well documented in imaging studies (see for a review Dom et al., 2005). Furthermore, other studies investigated the direct and long-term effects of substance abuse on response inhibition (see for a review Verdejo-García et al., 2008). Response inhibition in substance users is usually assessed using behavioural inhibition tasks such as the Go/NoGo Task (see for a review Luijten et al., 2014), during which participants have to inhibit well-rehearsed prepotent responses (i.e. always responding at Go trials but inhibiting response at NoGo trials). Impaired behavioural response inhibition has been found in nicotine (e.g. Luijten et al., 2011a), alcohol (e.g. Rubio et al., 2008), cocaine (e.g. Fillmore and Rush, 2002), heroin (e.g. Fu et al., 2008), and ecstasy (Roberts and Garavan, 2010) patients. Although cannabis use has been associated with several cognitive problems (Solowij et al., 2002), response inhibition of cannabis users has been studied before in only one study. In that study, response inhibition of chronic cannabis users was investigated during a Go/NoGo Task, while their blood-oxygen-level-dependent (BOLD) response was measured (Hester et al., 2009). No behavioural response inhibition deficits were observed; however, increased activity was evident in the right inferior parietal lobe, putamen and middle cingulate gyrus (Hester et al., 2009). This increase in activation was explained as a compensatory process.

With regard to the electrophysiological correlates of response inhibition in general, most studies using the Go/NoGo Task focus on two components of event-related potentials (ERPs;

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Falkenstein et al., 1999). The first component is the NoGo-N2, which is a negative wave seen approximately 200–400 ms after the NoGo stimulus with a maximum peak at frontal (Fz) and frontocentral sites (FCz; Bekker et al., 2005). A source analysis of the NoGo-N2 indicated that the neural generator is situated in medial frontal regions, presumably the anterior cingulate cortex (ACC; Bekker et al., 2005). It was originally thought that the N2 reflected a modality-specific non-motor inhibition process (Falkenstein et al., 1999), but the evidence is accumulating that the N2 represents a more general process, such as conflict monitoring (Bekker et al., 2004; Burle et al., 2004; Enriquez-Geppert et al., 2010; Nieuwenhuis et al., 2003). The second component is the NoGo-P3, which is a positive wave following the NoGo-N2. It is seen approximately 300–500 ms after stimulus onset and has a maximum peak at FCz sites (e.g. Schupp et al., 1994; Simson et al., 1977). The NoGo-P3 has been suggested to reflect inhibition (e.g. Bekker et al., 2004; Enriquez-Geppert et al., 2010; Fallgatter and Strik, 1999; Tekok-Kilic et al., 2001), although it has also been argued to be the result of conflict between different responses (e.g., Bekker et al., 2005; Smith et al., 2010). With regard to the inhibition interpretation of the P3, this component is thought to represent a later stage of the inhibition process that is closely related to the actual inhibition of the motor system in the premotor cortex (Enriquez-Geppert et al., 2010; Garavan et al., 1999). Deficits in the NoGo-N2 and NoGo-P3 have been found in other substance abuse groups, such as smokers (Luijten et al., 2011a), alcoholics (Kamarajan et al., 2005) and ecstasy users (Gamma et al., 2005), but no studies among cannabis users are known.

Performance (or error) monitoring is another aspect of the cognitive control system that is hypothesized to be affected in substance use populations. Performance monitoring is the process that allows humans to regulate their behaviour by means of self-evaluation of errors (Ullsperger and Von Cramon, 2001). Performance monitoring can be operationalized by a variety of tasks in which participants are likely to make errors. Contemporary models of addictive behaviours suggest that SUD patients are often insensitive to future negative consequences (e.g. Garavan and Stout, 2005; Lubman et al., 2004). For example, CUD adolescents may be insensitive to the aversive consequences their high may have on homework. This insensitivity is reflected in the poorer performance monitoring of SUD patients compared with controls (e.g., Franken et al., 2007; Hester et al., 2009; Schoenbaum and Setlow, 2005). Therefore, it has been hypothesized that reduced performance monitoring underlies prolonged substance abuse in the face of its adverse consequences (Forman et al., 2004; Hester et al., 2007).

With regard to the electrophysiological correlates of performance monitoring in general, most studies have focused on error-related negativity (ERN; Falkenstein et al., 1990). The ERN is a negative ERP component measured approximately 0–150 ms after an error in performance. There is increasing evidence that the ACC plays an important role in performance monitoring (Ridderinkhof et al., 2004) and may be the neural generator of the ERN (Dehaene et al., 1994; van Veen and Carter, 2002). This ERN is usually followed by a positive ERP (Pe) component, although there is some debate about the meaning of this component (Overbeek et al., 2005). The Pe component has been found to be reduced on unconscious errors compared with consciously perceived errors (Endrass et al., 2005). Therefore, it has been related to error awareness, conscious error processing and the updating of the error context (Ventouras et al., 2011). Overall, SUDs have been associated with reductions in performance monitoring (Ruchsow et al., 2005). Reduced ERNs were found in people with SUDs compared with healthy controls in studies assessing nicotine (Franken et al., 2010; Luijten and Franken, 2011b), cocaine (Franken et al., 2007), opioids (Forman et al., 2004) and cannabis (Hester et al., 2009); see Luijten et al. (2014) for a systematic review. However, two studies show an increased ERN in people with alcohol use disorder (Padilla et al., 2011; Schellekens et al., 2010). Schellekens et al. (2010) suggested that an increased ERN observed in SUDs might be associated with internalizing psychopathology, which is typically associated with an increased ERN (Hajcak et al., 2010). The only study in which performance monitoring was investigated in cannabis users (not CUD patients) showed no aberrations of the ERN (Fridberg et al., 2013). Thus, more research is needed to investigate how performance monitoring is affected in CUD patients. Since it is known that almost all CUD patients either smoke tobacco or mix tobacco with the cannabis in their cigarettes (joints), and it is known that cigarette smokers have problems with cognitive control (Luijten et al., 2011a; Luijten et al., 2011b), we adequately controlled for the use of tobacco by including a group of smokers as well as a group of non-smokers as control groups.

In the present study, several hypotheses regarding response inhibition and performance monitoring in CUD patients were investigated by means of a Go/NoGo Task and an Eriksen Flanker Task, respectively, to ease comparison with previous studies. With regard to response inhibition, we expected to find an increased percentage of errors and longer reaction times (RTs) for CUD patients compared with cigarette-smoking as well as non-smoking controls on infrequent Go trials, which would reflect inhibition problems. On an electrophysiological level, we expected to find reduced response inhibition in CUD patients compared with controls as reflected by reduced NoGo-N2 and -P3 components. With regard to performance monitoring, we expected that CUD patients would show reduced performance monitoring compared with controls as reflected by 1) an increased percentage of errors, 2) deviant post-error accuracy and/or RT response patterns, as have been found in cocaine use disorder patients (Franken et al., 2007), and 3) reduced ERN and Pe ERP components on the Eriksen Flanker Task. To the best of our knowledge, this is the first study that has investigated response inhibition and performance monitoring simultaneously in CUD patients while adequately controlling for the use of cigarette smoking.

Methods and materials

Participants

We included 37 CUD patients at two locations of a large urban addiction treatment service in Rotterdam, the Netherlands (Antes). Inclusion criteria were 1) age between 18 and 25 years, 2) presence of the DSM-IV diagnosis for CUD, clinically assessed by a physician of the treatment service, and 3) the ability to speak, read and write in Dutch at an eighth-grade literacy level. The length of time that the CUD patients had been abstinent varied from two to six weeks. The treatment service screened its patients routinely on drug use, and patients were excluded

Table 1. Demographics, substance use and behavioural inhibition variables of cannabis-dependent patients, cigarette-smoking controls and non-smoking controls.

	Cannabis dependent (*N* = 37)	Cigarette-smoking controls (*N* = 38)	Non-smoking controls (*N* = 39)	Test value	*p* value	Effect size	
Demographic variables				χ^2		Cramer's *V*	
Male (%)	83.8	65.8	69.2	3.45	.178	.18	
Low education (%)	51.4	36.8	27.5	4.68	.096	.20	
				F		η^2	*r*
Age	21.7 (2.10)	21.4 (2.5)	22.1 (2.1)	0.87	.460	.01	.12
Substance use variables							
AUDIT	8.7 (4.8)	11.0 (6.7)	6.5 (4.9)	5.53	.005	.11	.33
FTND	5.1 (1.9)	4.2 (1.8)	–	3.76	.057	.06	.24
Lifetime cannabis use[a]	186.0 (45.3)	61.0 (67.0)	–	86.77	<.001	.55	.74
Lifetime XCT use	40.5 (54.5)	51.2 (56.1)	–	0.58	.448	.01	.09
Lifetime GHB use	6.7 (12.2)	42.4 (53.4)	–	6.82	.013	.17	.40
Lifetime amphetamine use	34.2 (52.3)	43.3 (50.7)	–	0.53	.528	.01	.08
Lifetime cocaine use	23.6 (31.3)	52.3 (57.8)	–	4.27	.034	.08	.29
Lifetime magic mushroom use	7.2 (14.3)	4.8 (8.9)	–	0.27	.609	<.01	.07
BIS-11							
Motor	2.0 (0.2)	2.1 (0.3)	1.8 (0.3)	8.35	<.001	.13	.35
Non-planning	1.9 (0.4)	1.9 (0.3)	1.7 (0.2)	7.52	.008	.08	.36
Attentional	2.0 (0.5)	2.0 (0.4)	1.9 (0.3)	0.26	.693	.01	.07

Notes: Values represent means with standard deviations in brackets.

– indicates that non-smokers were not taken into account for this particular analysis because too few of them had ever used this substance, causing heterogeneous variances.

[a]For all lifetime questionnaires the scale range was 1 to 200, so for some participants this may not represent an accurate estimation of the number of times the substance was used.

AUDIT: the Alcohol Use Disorders Identification Test (Allen et al., 1997); BIS-11: the Barratt Impulsiveness Scale-II (Patton et al., 1995); FTND: the Fragerström Test for Nicotine Dependence (Heatherton et al., 1991); XCT, ecstasy, a colloquial for MDMA 3,4-Methylenedioxymethamphetamine.

from the study if they were positive on these tests. We acknowledge that we cannot completely rule out any influence of the direct effects of cannabis on cognitive control, but the chance that we included intoxicated patients is low.

As indicated above, the CUD patient group was compared with two control groups. The first was a non-smoking control group ($N = 41$): a healthy non-smoking and non-substance-using group. The second was a smoking control group ($N = 38$), since it has been shown that impaired cognitive control is associated with the use of tobacco (e.g. Luijten et al., 2011a, 2011b, 2014). Cigarette smokers smoked on average 11.1 ($SD = 5.5$) cigarettes per day. Both control groups were recruited via an advertisement on social media and the snowballing method. Table 1 shows the demographic and substance use variables of all groups.

Participants with a substance-related DSM-IV use disorder other than nicotine or cannabis were excluded. Participants with a history of head trauma or severe current psychiatric symptoms were excluded from participation. We did not exclude participants with attention deficit hyperactivity disorder (ADHD/ADD) or depression, as this would have led to a non-representative sample. In both the CUD and the cigarette-smoking control group there were four participants with ADHD/ADD. No other comorbidities were observed. In Figure 1 a participant flow chart is provided to make clear how many participants from each group were included in each step of the analyses. Participants were excluded if they scored below chance level (i.e. fewer than 50% trials correct) on either of the tasks. Further, participants were removed if their data were too noisy. On the Go/NoGo Task, participants with fewer than 20 trials were excluded. On the Eriksen Flanker Task, participants with fewer than five trials were excluded. One hundred and sixteen participants met the inclusion criteria. The questionnaires of two participants were missing, and the behavioural data on both the Go/NoGo Task and the Eriksen Flanker Task were missing for one participant. On the Go/NoGo Task, two participants scored below chance level (fewer than 50% correct trials); the data of these participants were not analysed. With regard to the EEG data, on the Go/NoGo Task four participants had data that were too noisy (fewer than 20 trials), and the data of one participant could not be retrieved due to hardware failure. On the Eriksen Flanker Task, one participant performed below chance level (less than 50% correct trials); the data of this participant were not analysed. With regard to the EEG data, on the Eriksen Flanker Task two participants had data that were too noisy (fewer than five trials), and the data of one participant could not be retrieved due to hardware failure. Participants were paid 15 euros for participating in the experiment. Testing took place according to a standardized protocol in the Erasmus Behavioural Lab of the Erasmus University Rotterdam. The Ethics Committee of the Erasmus University Medical Centre approved the study, and all procedures were conducted in accordance with the understanding and written informed consent of the participants.

Questionnaires

Barratt Impulsivity Scale 11 (BIS-11). The BIS-11 is a 30-item self-report measure of impulsivity developed by Barratt

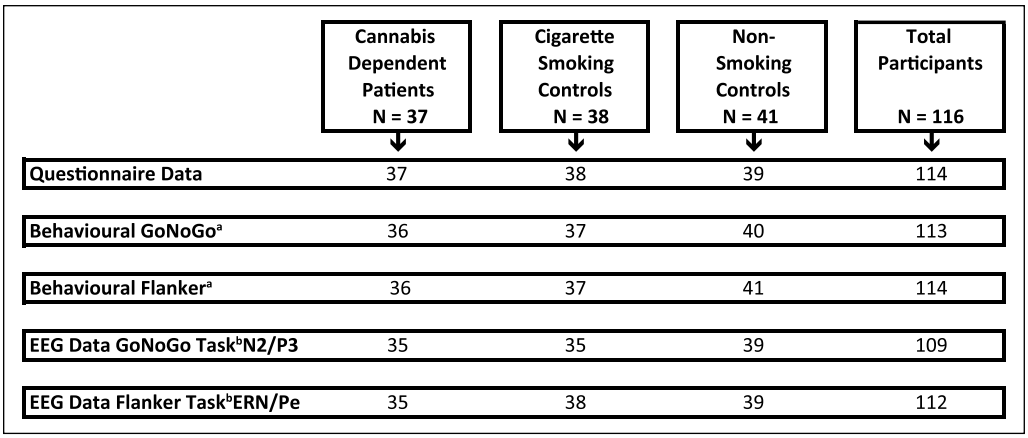

Figure 1. Valid number of participants for each part of the study.
[a]Missing scores or more than 50% errors.
[b]Missing, too noisy or too few trials.

(1959) and last revised by Patton et al. (1995). The general reliability was adequate (Cronbach's alpha (α) = .73). The test yields three second-order factors with weak to moderate reliabilities: attentional (8 items), α = .62; motor (11 items), α = .57; and non-planning impulsiveness (11 items), α = .57.

DSM-IV Substance Use Disorder Checklist. Cannabis patients were screened for CUDs according to the DSM-IV criteria, based on clinical interviews by clinicians of Antes Rotterdam.

The Alcohol Use Disorders Identification Test (AUDIT). The AUDIT (34 items) is a valid and reliable alcohol screening tool (Allen et al., 1997) and was used to screen for alcohol consumption and related risks in both patients and controls. The reliability was adequate (Cronbach's α = .83).

The Fragerström Test of Nicotine Dependence (FTND). The FTND (Heatherton et al., 1991) is a six-item screening tool for tobacco use disorders and was used to screen tobacco use disorders in both patients and controls. The reliability was adequate (Cronbach's α = .73).

Task paradigm

Go/NoGo Task. A Go/NoGo blocked design (i.e. blocks of trials intermitted by pauses) task was developed to measure response inhibition. Each of the four blocks consisted of 150 trials (i.e. 600 trials in total), and in between blocks a one-minute pause was presented. Participants were required to suppress a well-rehearsed, prepotent motor response (i.e. Go) in favour of an alternative, less frequent response (i.e. NoGo). Stimuli (i.e. vowel letters) were presented rapidly (700 ms) (e.g. Littel et al., 2012) and NoGo trials infrequently (25%). Participants were instructed to press the rightmost button of a response box with their index finger each time any vowel letter (i.e. *A, I, E, O, U*) was shown, but to withhold their response when the exact same letter was shown two times in a row (e.g. *A, A* or *E, E*). Letters were presented semi-randomly because a pilot study had indicated that it confused participants if the same letter was shown three times in a row (e.g. *E, E, E*), but each letter was presented approximately the same number of times per participant. Before each stimulus, a fixation cross (+) was shown for 300 ms. It was stressed to participants that they should respond as quickly and accurately as possible. The task was programmed with E-Prime 2.0 (Psychology Software Tools).

Eriksen Flanker Task. A modified Eriksen Flanker Task (Eriksen and Eriksen, 1974) from the study by Franken et al. (2007) was used to measure performance monitoring. Participants were randomly shown four different letter strings (*SSHSS, SSSSS, HHSHH, HHHHH*), which were all presented 100 times and divided into five different blocks. They were instructed to press the rightmost button of the response box with their right index finger if the central letter was an *H* and the leftmost button of the response box with their left index finger if the central letter was an *S*; the buttons had an *H* or *S* written next to them. Before each stimulus was presented, a fixation cross appeared for 150 ms. Then the letter string was presented for 50 ms. After a response had been made within a black screen response window with a maximum time of 1000 ms, a feedback display showed the correctness of the response (+ or −) for 500 ms. If no response was detected within the response time window, a feedback display informed the participant that the answer was not fast enough ("*Too Late!*" (in Dutch)). Response times from stimulus onset to button press on congruent (*SSSSS, HHHHH; n* = 200) and incongruent trials (*SSHSS, HHSHH; n* = 200) were recorded. It was stressed to participants that they should respond as quickly and accurately as possible. The task was programmed with E-Prime 2.0 (Psychology Software Tools).

Electroencephalographic recording and signal processing

The EEG was recorded with a Biosemi Active-Two amplifier system from 32 scalp sites (10–20 system) and two additional sites (FCz and centro-parietal) with Ag/AgCl electrodes (active electrodes) mounted on an elastic cap. Furthermore, six additional electrodes were attached to left and right mastoids, two

outer canthi of both eyes (horizontal electrooculogram), and infraorbital and supraorbital regions of the eye (vertical electrooculogram (VEOG)). All signals were digitized with a sampling rate of 512 Hz and 24-bit A/D conversion with a bandpass of 0–134 Hz. Data were further processed off-line with Brain Vision Analyzer (Brainproducts, Munich). Data were referenced off-line to computer-linked recordings from the mastoids. Off-line, EEG and EOG activity was filtered with a bandpass of 0.10–30 Hz for the Go/NoGo Task and 0.15–30 Hz for the Eriksen Flanker Task (both with phase shift-free Butterworth filters; 24 dB/octave slope). Data were segmented into epochs of 1 s (−200 ms to +800 ms with respect to response in the Go/NoGo Task). After ocular correction (Gratton et al., 1983), epochs including an EEG signal exceeding ± 75 μV were excluded from the average. The mean of the period −200 ms to 0 ms with respect to the response served as a baseline for both tasks. All ERPs were studied at a cluster of frontocentral electrodes: Fz, FCz and Cz.

Concerning the Go/NoGo Task, after baseline correction, average ERP waves were calculated for artefact-free trials at each scalp site for correct and incorrect responses separately. Segments with incorrect responses (miss for Go trials or false alarm for NoGo trials) were excluded from the EEG analyses. The N2 was defined as the mean value of the 200–300 ms time interval after stimulus onset. The P3 was defined as the mean value of the 300–500 ms time interval after stimulus onset. Participants had to have at least 20 analysable trials. The mean number of analysable Go segments was 355 and the mean number of analysable NoGo segments was 56. With regard to the Eriksen Flanker Task, after baseline correction, average ERP waves were calculated for artefact-free trials at each scalp site for correct and incorrect responses separately. The ERN was defined as the mean value in the 25–75 ms time segment after response. The Pe was defined as the mean value in the 150–250 ms time segment after response. Participants had to have at least five analysable trials. The mean number of analysable correct segments was 327 and the mean number of analysable incorrect segments was 29.

Procedure

All participants were asked to abstain from alcohol and cannabis for at least 24 hours before entering the lab and to abstain from nicotine for at least 2 hours before entering. They were told that this would be checked with a breath analyser, although breath analysers in our lab were actually not able to check whether participants had stopped smoking for such a short amount of time. On the one hand, this smoking deprivation was necessary to reduce the acute effects of nicotine on ERP amplitudes (Houlihan et al., 2001), and on the other hand, it was short because we did not want to induce withdrawal effects (Luijten et al., 2011a). After signing the informed consent, the participants filled in their demographics, the AUDIT, the FTND, drugs consumption and the BIS-11, so we were able to characterize the participants. Subsequently, the participants were seated in a comfortable EEG-chair in a light and sound-attenuated room, and electrodes were attached. For both tasks, the participants watched instructions on a screen in order to learn how the tasks worked and that they had to sit still, to make as few errors as possible, and to respond as quickly as possible. The Go/NoGo Task started with 15 practice trials. After the Go/NoGo Task had been finished, participants had a three-minute break before the instructions of the Eriksen Flanker Task appeared on the screen. The Eriksen Flanker Task started with 15 practice trials, too. After the Eriksen Flanker Task, all electrodes were removed and participants had the opportunity to be informed about the aims of the study. The total duration of the experiment was 1.5 hours per participant.

Data analysis

Repeated measurement analyses of variance (RM-ANOVA; with Greenhouse-Geisser adjusted *p*-values in case the sphericity assumption was violated) were conducted to analyse the behavioural outcomes of performance as well as the ERPs for both the Go/NoGo Task and the Eriksen Flanker Task. In all RM-ANOVAs, Group (CUD patients vs. cigarette smoking controls vs. non-smoking controls) was added as a between-subject factor. Post-hoc tests for interactions with Bonferroni corrections for multiple comparisons were performed only for interactions including the between-subject factor Group. All tests were two-tailed with a significance level of .05. Statistical information is presented in the following format: F(degrees of freedom), p, and the effect sizes are presented in eta-squared (η^2) and Pearson's r (following recommendations of Fritz et al., 2012).

With regard to the behavioural data of the Go/NoGo Task, a Group × Inhibition (Go vs. NoGo) RM-ANOVA was used to analyse both the accuracy rates and the RT data. Concerning the behavioural data of the Eriksen Flanker Task, we included the two-level within-subject factor Congruency (congruent vs. incongruent trials). A Group × Congruency RM-ANOVA was used to analyse the accuracy rates. Further, ANOVAs with Group as independent variable were conducted to analyse the percentages of overall errors, of errors following an error trial, and of missing responses. For the RT data, we used ANOVAs in order to analyse overall RT differences. In addition, three RM-ANOVAs were conducted with different two-level within-subject factors: Group × Correctness RT (correct vs. incorrect trials), Group × Post-error RT (post-error vs. post-correct trials), and Group × Congruency. Behavioural data were analysed in R (R Development Core Team, 2008).

For all ERP analyses, the three-level within-subject factor Electrode (Fz, FCz and Cz) was included. To analyse the ERPs of the Go/NoGo Task, a Group × Inhibition × Electrode RM-ANOVA was conducted. To analyse the ERPs of the Eriksen Flanker Task, we included the two-level within-subject factor Response Type (incorrect vs. correct trials). Finally, a Group × Electrode × Response Type RM-ANOVA was conducted. ERP data were analysed in SPSS (IBM Corp., 2013).

Results

Background variables

Table 1 shows all demographic and substance-use variables for the final samples included in the analyses. In comparison with the smoking control group, the CUD patient group reported lower gamma-hydroxybutyrate (GHB) and cocaine use. In comparison with the non-smoking control group, the CUD patient group reported more alcohol use and obtained higher scores on the motor and non-planning subscales of the BIS-II.

Table 2. Accuracy rates in percentages and reaction times in milliseconds on the Go-NoGo task.

	% Correct Go	% Correct NoGo	RT Go (ms)
Cannabis-dependent patients (*N* = 36)	94.7 (4.7)	61.1 (16.3)	357 (40)
Cigarette-smoking controls (*N* = 37)	96.4 (2.2)	60.7 (15.4)	335 (38)
Non-smoking controls (*N* = 40)	96.4 (3.4)	64.5 (15.2)	331 (39)

Note: Group means with standard deviations in brackets.

Table 3. Error rates on the Eriksen Flanker Task.

	Overall	Post-incorrect	Missing[a]	Congruent	Incongruent
Cannabis-dependent patients (*N* = 36)	11.1 (9.8)	13.5 (14.5)	3.4 (7.5)	7.1 (8.6)	15.0 (11.6)
Cigarette-smoking controls (*N* = 37)	11.5 (9.3)	13.5 (12.7)	1.8 (3.0)	6.5 (8.6)	16.5 (10.7)
Non-smoking controls (*N* = 41)	8.9 (7.4)	11.5 (10.5)	1.5 (1.7)	3.8 (4.1)	14.1 (11.3)

Note: Group means (SD), error rates in percentages.
[a]Missing responses were no response, too quick (<150 ms) or too slow (>1000 ms). Not all participants had missing responses; *N* was 32, 25 and 22 for CUD patients, cigarette-smoking controls and non-smoking controls, respectively.

Table 4. Reaction time measures on the Eriksen Flanker Task.

	Overall	Correct	Incorrect	Post-correct	Post-incorrect	Congruent	Incongruent
Cannabis-dependent patients (*N* = 36)	477 (53)	483 (50)	422 (69)	477 (50)	490 (81)	453 (52)	500 (58)
Cigarette-smoking controls (*N* = 37)	460 (58)	466 (56)	412 (67)	460 (58)	476 (68)	438 (55)	483 (63)
Non-smoking controls (*N* = 41)	471 (45)	475 (46)	427 (52)	471 (44)	479 (44)	444 (42)	498 (48)

Note: Group means with standard deviations in brackets; reaction times in milliseconds.

Behavioural data

Go/NoGo task. Table 2 shows the accuracy rates in percentages of the CUD patients and both controls on the Go/NoGo Task. In line with our expectations, participants were less accurate on NoGo trials than on Go trials: $F(1,110) = 549.41$, $p < .001$, $\eta^2 = .83$, $r = .91$. This indicates that the experiment provoked the intended result: participants had difficulties inhibiting their response on infrequent NoGo trials. Further, we found no overall differences in accuracy between CUD patients and the control groups: $F(2,110) = 1.12$, $p = .330$, $\eta^2 = .02$, $r = .14$. Most importantly, we also did not observe a Group × Inhibition interaction: $F(2,110) = 0.72$, $p = .488$, $\eta^2 < .01$, $r = .04$. Thus, the groups did not differ with respect to the size of the inhibition effect. Notably, however, we did observe a between-group difference on the reaction times of the Go trials: $F(2,110) = 4.92$, $p = .009$, $\eta^2 = .08$, $r = .29$. Post-hoc tests were in line with expectations; CUD patients were slower on Go trials ($M = 357.3$; $SD = 39.9$) than cigarette-smoking controls ($M = 334.6$; $SD = 37.7$), mean difference = 22.75 ($SE = 9.06$), $p = .036$, and non-smoking controls ($M = 331.4$; $SD = 38.5$), mean difference = 25.88 ($SE = 8.90$), $p = .012$.

Eriksen Flanker Task. Table 3 displays the error rates in percentages for CUD patients as well as both control groups. The groups did not differ on overall accuracy: $F(2,111) = 0.92$, $p = .402$, $\eta^2 = .02$, $r = .13$. Furthermore, we did not find differences on trials following an error: $F(2,111) = 0.34$, $p = .712$, $\eta^2 = .01$, $r = .08$. Also, we did not find between-group differences in missed responses (i.e. too quick, too late or no responses): $F(2,76) = 1.16$, $p = .318$, $\eta^2 = .03$, $r = .18$. With regard to the congruency effect, more errors were made on incongruent than on congruent trials ($F(1,111) = 229.51$, $p < .001$, $\eta^2 = .67$, $r = .82$), which shows that the task provoked the intended result. However, in contrast to our expectations, no overall group differences were observed: $F(2,111) = 0.91$, $p = .406$, $\eta^2 = .02$, $r = .13$. We did not find a Group × Congruency interaction effect, which indicates that the groups did not differ with respect to the size of the congruency effect: $F(2,111) = 1.32$, $p = .271$, $\eta^2 = .01$, $r = .09$.

Table 4 shows the mean values of the RT data for CUD patients as well as both control groups. We did not observe differences in overall RTs: $F(2,111) = 0.95$, $p = .389$, $\eta^2 = .02$, $r = .13$. With regard to the correctness of the trials, RTs were slower for correct trials than for incorrect trials: $F(2,111) = 245.82$, $p < .001$, $\eta^2 = .68$, $r = .84$. However, no overall group differences were observed: $F(2,111) = 0.70$, $p = .501$, $\eta^2 = .01$, $r = .09$. Importantly, no Group × Correctness interaction was found, indicating that the difference between correct and incorrect reaction times did not differ between the groups: $F(2,111) = 1.22$, $p = .299$, $\eta^2 = .01$, $r = .10$. With respect to post-error trials, RTs were slower for post-error trials than for post-correct trials: $F(1,111) = 12.43$, $p < .001$, $\eta^2 = .10$, $r = .32$.[a] Neither overall differences between the groups

[a]Levene's test for the Equality of Variances indicated that the assumption of homogeneity was not met for the post-incorrect reaction time trials: $F(1,111) = 6.81$, $p = .002$. However, since the variation observed was larger for the group with the smaller sample size, the estimated *F*-value is conservative rather than liberal (Field, 2009).

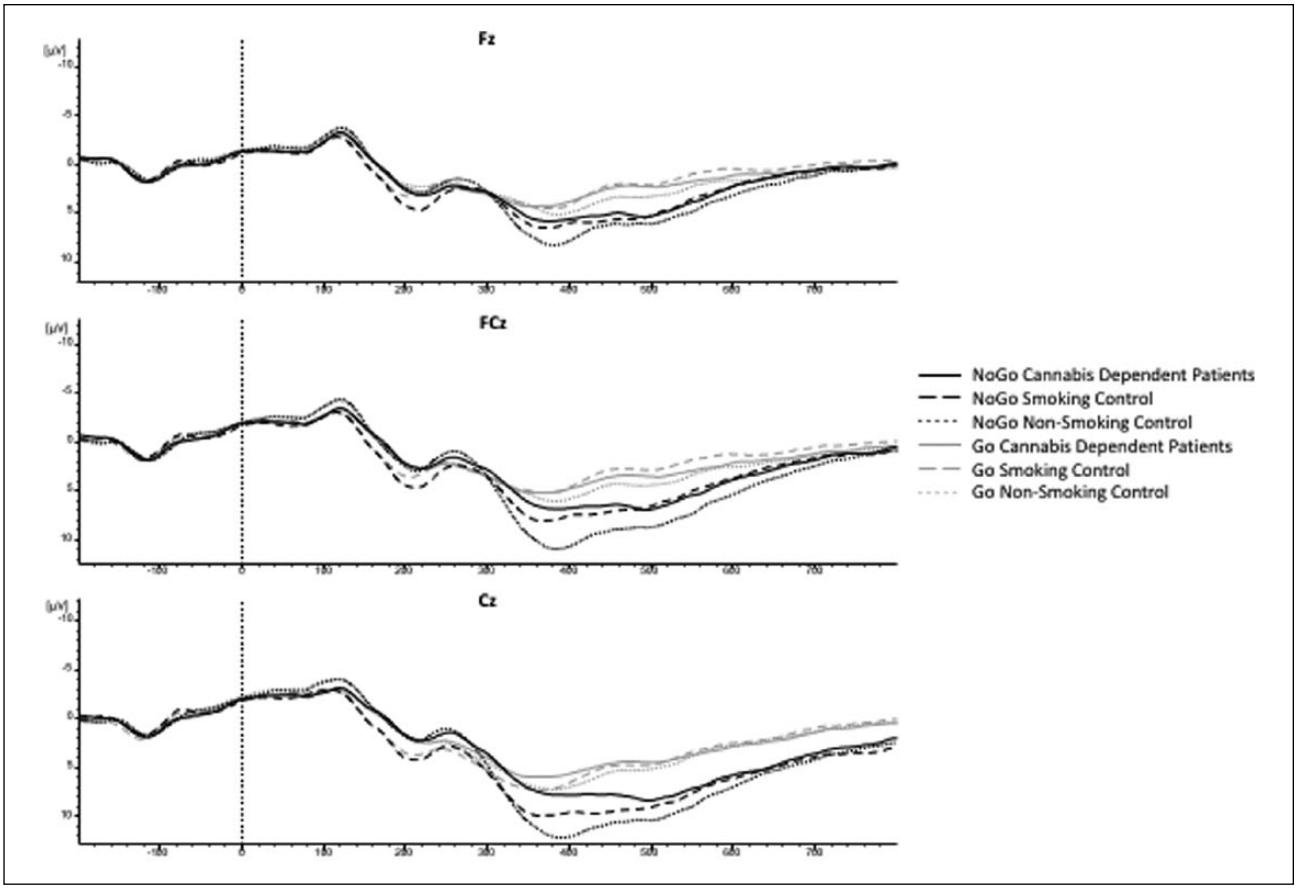

Figure 2. Grand-average stimulus-locked waveforms at Fz, FCz and Cz for correct Go and NoGo trials on the Go/NoGo Task for CUD patients, tobacco-smoking controls and healthy controls.

($F(2,111) = 0.79$, $p = .457$, $\eta^2 = .01$, $r = .11$) nor a Group × Post-error RT interaction effect ($F(2,111) = 0.40$, $p = .743$, $\eta^2 = .01$, $r = .07$) was observed. So, the difference between post-error and post-correct trials did not differ between the groups. Regarding the congruency effect, RTs were slower on incongruent than on congruent trials: $F(1,111) = 718.59$, $p < .001$, $\eta^2 = .86$, $r = .93$. However, no overall group differences were observed ($F(2,103) = 1.25$, $p = .291$, $\eta^2 = .02$, $r = .15$) and no differences were found between groups on either congruent or incongruent trials: $F(2,111) = 0.95$, $p = .390$, $\eta^2 < .02$, $r = .07$.

Event-related potentials

Go/NoGo Task

N2 amplitudes. Figure 2 shows the N2 and P3 amplitude for both CUD patients and the control groups at the frontocentral electrode cluster. Figure 3 shows the mean amplitude of the N2 for each of the frontocentral electrodes for each group. We did not find that N2 amplitudes differed between Go and NoGo trials at the frontocentral electrode cluster: $F(1,106) = 2.92$, $p = .090$, $\eta^2 = .03$, $r = .17$. This suggests that for the N2 amplitude the Go/NoGo Task may not have provoked the intended result, as it was expected that N2 amplitudes would generally be larger for NoGo than for Go trials. In addition, we did not find overall differences

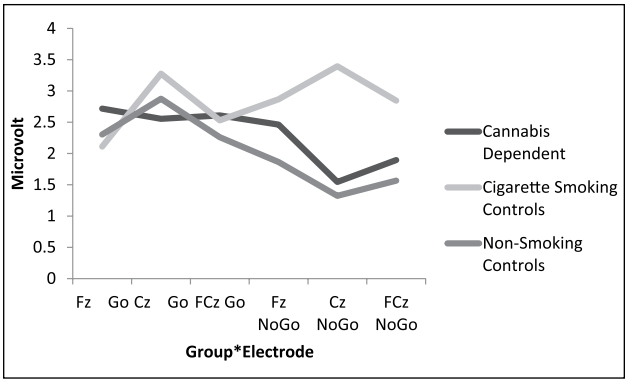

Figure 3. Mean amplitude of the N2 for each of the frontocentral electrodes for each group on the Go/NoGo Task.

between the N2 amplitudes of CUD patients and either of the controls at the frontocentral electrode cluster: $F(2,106) = 0.88$, $p = .417$, $\eta^2 = .02$, $r = .14$. We did observe a Group × Inhibition interaction effect ($F(2,106) = 3.10$, $p = .049$), although the effect was small: $\eta^2 = .06$, $r = .23$. Post-hoc tests did not reveal that N2 amplitudes were significantly reduced for CUD patients on the NoGo trials compared with either of the control groups: all p values > .177. Post-hoc tests did reveal that for the non-smoking

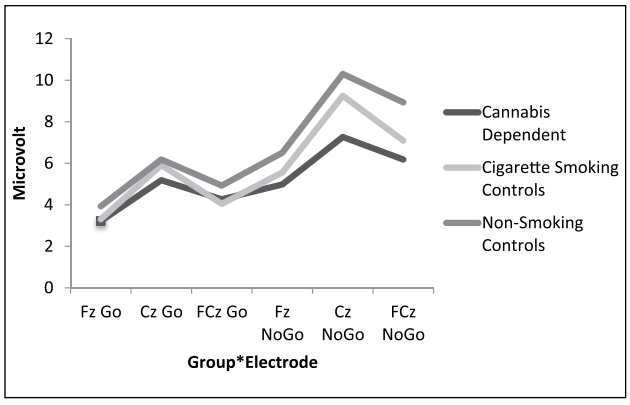

Figure 4. Mean amplitude of the P3 for each of the frontocentral electrodes for each group on the Go/NoGo task.

control group, the N2 amplitudes for the NoGo Trials were significantly reduced compared with the Go trials: mean difference = 0.90 (*SE* = 0.38), $p = .021$. This was not the case for the other groups: all p values > .101. Further, we observed a significant Electrode × Group interaction effect ($F(4,212) = 2.88$, $p = .024$), although the effect was small: $\eta^2 = .05$, $r = .22$. Post-hoc tests did not reveal that the N2 amplitudes differed between the groups on one or more of the electrodes: all p values > .187. Post-hoc tests did reveal that for the cigarette-smoking control group the N2 amplitude was somewhat larger for the Cz electrode than for the FCz electrode: mean difference = 0.65 (*SE* = 0.25), $p = .036$. This was not the case for the other groups (all p values > .451) or for a combination of electrodes within the cigarette-smoking control group (p values > .070).

P3 amplitudes. Figure 4 shows the mean amplitude of the P3 for each of the frontocentral electrodes for each group. We found that P3 amplitudes at the frontocentral electrode cluster were generally larger for NoGo trials than for Go trials: $F(1, 106) = 110.18$, $p < .001$, $\eta^2 = .51$, $r = .71$. This suggests that for the P3 amplitude, the Go/NoGo Task provoked the expected result. Again, we did not find overall differences between the P3 amplitudes of CUD patients and either of the controls at the frontocentral electrode cluster: $F(2,106) = 2.18$, $p = .118$, $\eta^2 = .04$, $r = .20$. Most importantly, we observed a Group × Inhibition interaction effect: $F(2,106) = 3.25$, $p = .043$, $\eta^2 = .06$, $r = .25$. Post-hoc tests revealed that this was due to the CUD patients having lower NoGo P3 amplitudes than non-smokers: mean difference = 2.44 (*SE* = 0.98), $p = .044$. No difference was observed between CUD patients and smokers: mean difference = 1.16 (*SE* = 0.97), $p = .744$.

We did not observe a significant Electrode × Group interaction effect: $F(4,212) = 2.40$, $p = .051$, $\eta^2 = .04$, $r = .21$, indicating that the difference in P3 amplitudes between the electrodes did not generally differ between the groups, although the effect was close to significance. Further, we observed an Electrode × Inhibition × Group interaction effect: $F(3.48, 212) = 3.66$, $p = .010$, $\eta^2 = .07$, $r = .26$. Post-hoc tests revealed that this effect was driven by CUD patients who had lower P3 amplitudes on the Cz electrode than non-smokers in the NoGo condition (*M* difference = 3.04, *SE* = 1.08, $p = .018$), while there was no significant difference between CUD patients and smokers (*M* difference = 1.98, *SE* = 1.10, $p = .220$). In addition, the three-way interaction was caused by CUD patients who had lower P3 amplitudes on the FCz electrode than non-smokers in the NoGo condition (*M* difference = 2.75, *SE* = 1.08, $p = .037$), while there was no significant difference between CUD patients and smokers (*M* difference = 0.91, *SE* = 1.10, $p = .266$).

Eriksen flanker task

ERN amplitudes. Figure 5 shows the ERN and Pe amplitudes of the CUD patients and the control groups at the frontocentral electrode cluster. In line with previous studies, we found a larger ERN amplitude for incorrect than for correct trials ($F(1,109) = 211.79$, $p < .001$, $\eta^2 < .66$, $r = .81$), indicating that the paradigm provoked the intended result. Further, we did not find overall differences between the ERN amplitudes of CUD patients and either of the control groups at the frontocentral electrode cluster: $F(2,109) = 0.03$, $p = .969$, $\eta^2 < .01$, $r = .03$. In contrast to our expectations, we did not find a Group × Response Type effect ($F(2,184.85) = 1.86$, $p = .161$, $\eta^2 = .03$, $r = .18$), which indicates that the group did not differ with respect to the size of the response type effect. Finally, we did not observe a Group × Response Type × Electrodes interaction: $F(3.39, 184.85) = 0.97$, $p = .416$, $\eta^2 = .02$, $r = .14$.

Pe amplitudes. In line with previous studies, we observed an increased Pe amplitude for incorrect compared with correct trials: $F(1,109) = 84.26$, $p < .001$, $\eta^2 = .44$, $r = .66$. Further, we did not find overall differences between the Pe amplitudes of CUD patients and either of the control groups: $F(2,109) = 0.22$, $p = .807$, $\eta^2 < .01$, $r = .03$. We also did not observe a Group × Response Type interaction ($F(2,109) = 0.39$, $p = .678$, $\eta^2 = .01$, $r = .05$), so the Pe amplitude of the groups did not differ with respect to the size of the response type effect. Finally, we did not observe a Group × Response Type × Electrodes interaction: $F(2.75,149.99) = 0.88$, $p = .446$, $\eta^2 = .02$, $r = .14$.

Discussion

The aim of our study was to identify whether CUD patients have response inhibition and performance monitoring deficits, two core features of the cognitive control system that have been emphasized in a number of contemporary models of drug addiction (e.g. Feil et al., 2010; Garavan and Stout, 2005). In line with our hypothesis, we observed a reduced P3 ERP component on the Go/NoGo Task for CUD patients compared with non-smoking controls. This finding adds to increasing evidence that marks the frontal P3 as an important electrophysiological correlate of SUDs (see for a review Luijten et al., 2014). The fact that we did not observe a difference between CUD patients and cigarette smokers highlights the urgency for future studies to more carefully control for the use of tobacco when investigating CUD patients. The reduced P3 was accompanied by longer response times on the Go trials, which can be interpreted in terms of a speed–accuracy tradeoff. Arguably, the CUD patients had to decrease the responding speed in order to avoid inhibition errors. All in all, this suggests that the response inhibition of cannabis use patients is compromised. In contrast to our expectations, we found no indications of problems in the error monitoring of cannabis use patients. We will explain the findings in more detail below.

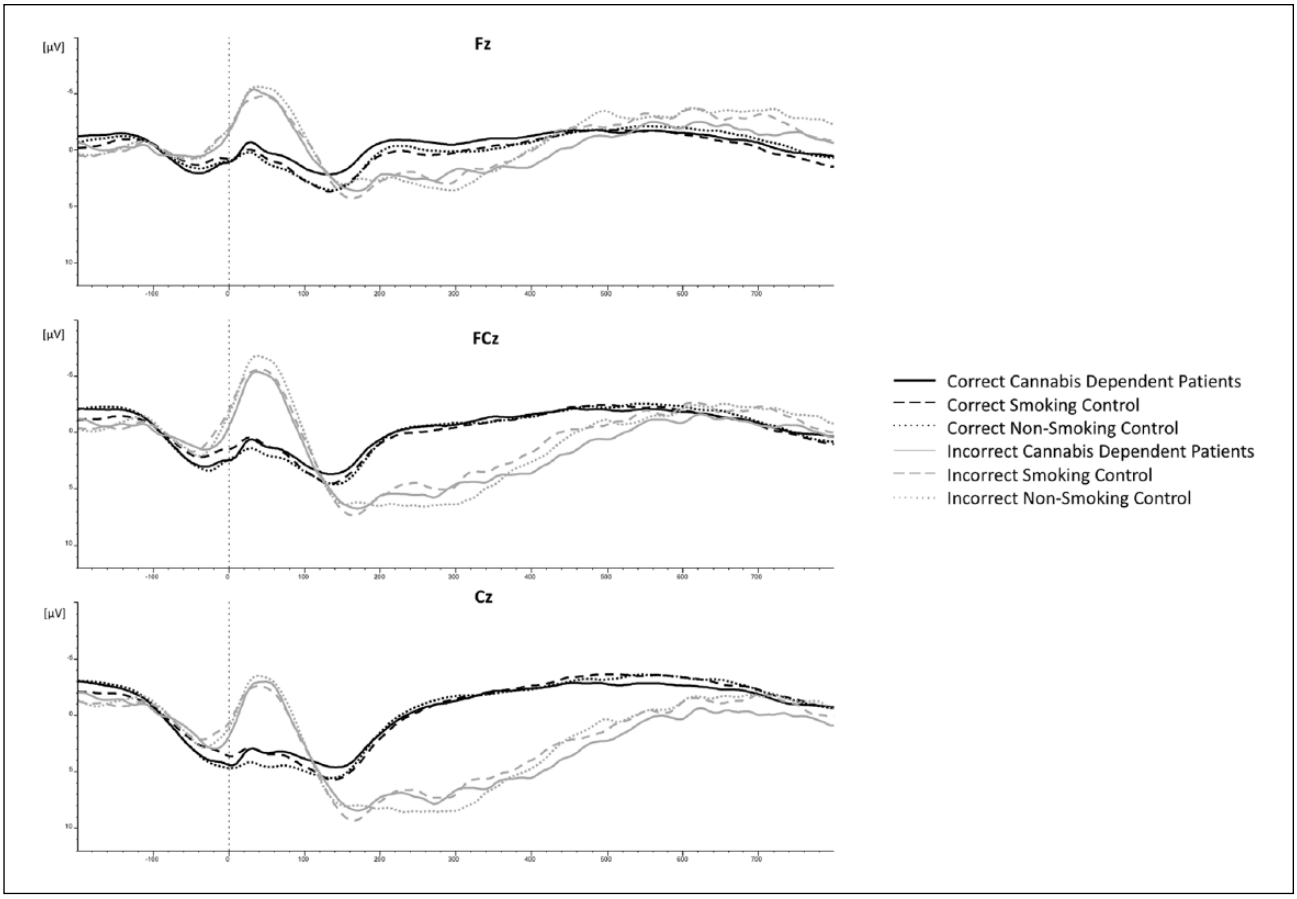

Figure 5. Grand-average response-locked waveforms at Fz, FCz and Cz of correct and incorrect trials on the Eriksen Flanker Task in CUD patients, tobacco-smoking controls and healthy controls.

Response inhibition

In contrast to the NoGo P3, we did not observe any overall differences between Go and NoGo stimuli on the N2 amplitudes, suggesting that the N2 may not be an index of response inhibition (e.g. Bekker et al., 2004; Nieuwenhuis et al., 2003; Smith et al., 2007), making interpretations with regard to response inhibition unwarranted. The results are more in line with the view that the NoGo-N2 is a non-motor inhibition process (e.g. Falkenstein et al., 2006) or reflects conflict monitoring (e.g. Nieuwenhuis et al., 2003). Importantly, we found a reduced NoGo-P3 in CUD patients as compared with non-smokers. We interpret this as meaning that CUD patients are characterized by response inhibition deficits, which extends earlier studies investigating the link between cannabis and response inhibition (e.g. Hester et al., 2009; Ramaekers et al., 2006). This interpretation is strengthened by the behavioural outcomes, which showed that cannabis-dependent patients had longer response times than both control groups on the Go trials. In our view, the CUD patients decreased the response speed in order to prevent inhibition errors (i.e. a speed–accuracy tradeoff; Wickelgren, 1977). Thus, the cannabis-dependent patients may have actively compensated for their deficits in response inhibition. Similarly, Hester et al. (2009) found CUD patients to have increased activity in the right inferior parietal lobe, putamen and middle cingulate gyrus, and they suggested that this was indicative of compensatory processes that may have masked behavioural response inhibition deficits in their study. An alternative view could be that the direct cannabis effects may have caused these slower reaction times, as response inhibition deficits can last up to six hours after ingestion (Ramaekers et al., 2006). However, as outlined below, under the limitations it is unlikely that the patients were under the influence of cannabis. In addition, this would have probably resulted in prolonged reaction times on the Eriksen Flanker Task, which we did not observe.

Another explanation could be that the NoGo-P3 is partially the electrophysiological reflection of motor impulsiveness (in the sense that lower NoGo-P3s reflect stronger motor impulsiveness) and not response inhibition per se. Our data are also in line with this view, as CUD patients as well as cigarette-smoking controls had significantly higher motor and non-planning impulsivity scores than healthy controls. This is suggestive of the idea that personality traits (i.e. impulsive personalities) may underlie reduced response inhibition (Chamberlain and Sahakian, 2007), and substances like cannabis and tobacco may be used as a form of self-medication (i.e. relaxation of impulsivity). However, we have to be cautious when drawing causal inferences, as prolonged cannabis or tobacco use may also underlie response inhibition deficits. Most likely, it is an interaction between vulnerable personality traits and the substance. Finally, in contrast to earlier

findings from our lab (e.g. Luijten et al., 2011), we did not observe differences between cigarette smokers and healthy participants. However, these results have to be interpreted with caution, as this may be due to reduced power, because we used three groups instead of the more frequently used two-group design.

Performance monitoring

With regard to performance monitoring, we did not observe any behavioural or electrophysiological differences between the groups, although we found the expected overall effects of errors on the ERN and Pe. The fact that we did not find differences in performance monitoring is in contrast to contemporary models of substance abuse disorders, which mark the importance of performance monitoring by proposing that people with SUDs are insensitive to future negative consequences (e.g. Feil et al., 2010; Garavan and Stout, 2005). This is especially striking, since CUD patients as well as cigarette-smoking participants differed significantly from non-smoking controls on nearly all measured substances as well as on impulsivity. The ERN findings are in line with the findings of Fridberg et al. (2013), who also did not observe differences in the ERN between cannabis users and controls. A consideration that could be taken into account, however, is that at the electrophysiological level cannabis use is associated with decreased performance monitoring but that this effect is masked by increased ERN and Pe amplitudes, which are known to be associated with internalizing problems (Schellekens et al., 2010). A similar line of reasoning was proposed by Schellekens et al. (2010), who found alcohol use disorder patients with anxiety problems to have increased ERNs compared with healthy controls. For future studies, it may be fruitful to include measures of anxiety when investigating performance monitoring in SUDs. Another possibility is that we failed to observe significant differences due to power problems resulting from the fact that we had three groups. Thus, the null findings regarding the performance monitoring might be the result of too low statistical power. As can be seen from the behavioural accuracy rates, the average number of errors goes in the expected direction, with healthy controls having fewer errors than CUD patients and cigarette smokers. But still, at most these differences in performance monitoring are weak, and performance and performance monitoring seem relatively unaffected.

Limitations

Some limitations of the study should be addressed. First, it is very difficult, if not impossible, to control for other substance use. In our study, CUD patients differed from controls in the usage of other substances than only cannabis. Interestingly, the cigarette-smoking controls used significantly more alcohol, GHB and cocaine than the CUD patients. This may seem to provide an explanation for an absence of differences between CUD patients and cigarette smokers, as the usage of these substances has also been related to response inhibition deficits (e.g. Luijten et al., 2014). Yet, on the other hand, it is remarkable that these poly-substance-using cigarette smokers did not significantly differ from healthy (non-substance-using) controls.

Second, CUD patients were not screened for abstinence at the time of the study. However, it is unlikely that patients had used cannabis just before they were tested: they had been told that they would be tested on being abstinent for at least 24 hours. The Antes treatment facility screens its patients routinely by urine drug screens. This leads us to the third limitation; we did not have objective quantifications (e.g. urine tests) to show the substance use of the participants, but had to rely on self-report measures. Although there may be individual differences in the accuracy of reporting, we tried to increase the reliability of their responses by stressing the anonymity of the survey (participants did not have to fill in their names anywhere). A final limitation is that we did not collect more precise data on lifetime cannabis use. In the digital questionnaire, participants could fill in their lifetime cannabis use up to a maximum of 200 times, but of course, all CUD patients used more cannabis than this in their lives. Therefore, we could not, for example, investigate the relationship between the amount of cannabis used, on the one hand, and the reduction of the ERPs or the level of impulsivity, on the other hand.

Finally, we purposefully did not counterbalance the order of the tasks. Essentially, to investigate performance monitoring, a task was needed in which errors were made. Thus, if the response inhibition task was presented first, participants would be more mentally fatigued, leading to an increase in the number of errors on the performance monitoring task. If the performance monitoring task had been presented first for half of the participants, this could have led to within-group differences in the number of errors made.

Conclusions

In conclusion, our results suggest that CUD patients have problems related to response inhibition, as is evident from their reduced P3 ERPs and prolonged reaction times. No indications were found that cannabis patients are characterized by performance monitoring problems.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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