Dose-dependent effects of cannabis on the neural correlates of error monitoring in frequent cannabis users

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Abstract

Cannabis has been suggested to impair the capacity to recognize discrepancies between expected and executed actions. However, there is a lack of conclusive evidence regarding the acute impact of cannabis on the neural correlates of error monitoring. In order to contribute to the available knowledge, we used a randomized, double-blind, between-groups design to investigate the impact of administration of a low (5.5 mg THC) or high (22 mg THC) dose of vaporized cannabis vs. placebo on the amplitudes of the error-related negativity (ERN) and error positivity (Pe) in the context of the Flanker task, in a group of frequent cannabis users (required to use cannabis minimally 4 times a week, for at least 2 years). Subjects in the high dose group ($n=18$) demonstrated a significantly diminished ERN in comparison to the placebo condition ($n=19$), whereas a reduced Pe amplitude was observed in both the high and low dose ($n=18$) conditions, as compared to placebo. The results suggest that a high dose of cannabis may affect the neural correlates of both the conscious (late), as well as the initial automatic processes involved in error monitoring, while a low dose of cannabis might impact only the conscious (late) processing of errors.
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1. Introduction

Cannabis sativa is a plant which contains over 70 active constituents named cannabinoids (Schoedel and Harrison,

2012). Delta-9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid present in the plant, has been found to evoke most of the subjective effects of marijuana (Grotenhermen, 2003). Around 20% of young people worldwide abuse the psychoactive effects of THC and other cannabinoids through regular use of the cannabis plant (Moore et al., 2007). This makes it important to understand whether and how cannabis intoxication affects human information processing. In the present study, we investigated the impact of cannabis on the monitoring of action errors, that is, on the recognition of discrepancies between expected and executed actions. To date, only one study has addressed the acute effects of cannabis on error monitoring (Spronk et al., 2011), while three other studies have considered the after-effects of chronic cannabis use (Hester et al., 2009; Harding et al., 2012; Fridberg et al., 2013). The present study aimed to contribute to the available knowledge by means of a between-subjects, double-blind, placebo-controlled design that compared the effects of two different doses of THC, in the form of herbal cannabis, on event-related potentials (ERPs) in a population of frequent cannabis users.

The monitoring of errors is an important element of cognitive control. It contributes to the fine-tuning of top-down control over information processing by signaling insufficient degrees of control to goal-related control systems (Botvinick et al., 2001). Interestingly for our purposes, the monitoring of errors can be assessed by means of electroencephalography (EEG). Specifically, a negative deflection can be noticed in the event-related potential (ERP) at around 50-100 ms after a person commits an error in a task—the so-called error-related negativity (Ne: Falkenstein et al., 1990; ERN: Gehring et al., 1993). The ERN has been established as a valid measure of error monitoring (Holroyd and Coles, 2002; Yeung et al., 2004; Ullsperger et al., 2014) and imaging research has identified the anterior cingulate cortex (ACC) as the most likely brain area responsible for generating the potential (Herrmann et al., 2004; Stemmer et al., 2004; Debener et al., 2005).

The ACC, aside of being an important relay station for cognitive control processes, is also a brain region that integrates cognitive and emotional information (Bush et al., 2000; Botvinick et al., 2001; Paus, 2001; Shackman et al., 2011). In line with that, it has been proposed that its activity is directly related to that of the mesencephalic dopamine system, by which the error signal is conveyed to the ACC (Holroyd and Coles, 2002). Considering the neural effects of THC, the connection between error monitoring and DA seems to be especially interesting. Application of THC has been identified to indirectly stimulate DA production in the striatum (Bossong et al., 2009; Kuepper et al., 2013). Moreover, research indicates that chronic THC administration can result in long-term dopaminergic hypoactivity, particularly if the onset of cannabis use is at an early age (Hoffman et al., 2003; Urban et al., 2012; Bloomfield et al., 2014). Consequently, since error monitoring is assumed to depend on phasic changes in the tonic activity of the mesencephalic dopaminergic system (Holroyd and Coles, 2002), it seems likely that cannabis has an effect on this process.

In line with this dopamine account of the ERN, the only up-to-date study investigating the impact of acute administration of THC on error monitoring showed a reduced ERN in response to this cannabinoid (16 mg in total), compared to placebo (Spronk et al., 2011). Moreover, cannabis has been identified to alter the neural correlates of error monitoring in the long-term. Specifically, an ERP study showed an increased amplitude of the error positivity (Pe; i.e. a positive component which can be observed in the time interval between 200 and 500 ms after an erroneous response; Falkenstein et al., 2000) in a group of chronic cannabis users, compared to non-users (Fridberg et al., 2013). Although the Pe has not been studied as well as the ERN (Fridberg et al., 2013), evidence suggests that it represents a later stage of error processing, independent of the ERN (Falkenstein et al., 2000), and is linked to the conscious awareness of errors (Nieuwenhuis et al., 2001; Murphy et al., 2012). In case of neuroimaging research, a decreased blood-oxygen level dependent (BOLD) signal to errors has been observed in the ACC and right insula of regular cannabis users, as compared to non-user controls (Hester et al., 2009). Furthermore, heightened demand for cognitive control has been associated with increased connectivity between the prefrontal (PFC) and occipitoparietal cortex (OP) in the brains of chronic users (Harding et al., 2012). Accordingly, the combined results of the different studies suggest that chronic cannabis use leads to both impaired error monitoring in these individuals, as well as to possible development of a mechanism to compensate for the deterioration of the process of identification of errors in information processing. Specifically, compared to non-user controls, cannabis users recruit additional cortical activity in areas associated with cognitive control, or other brain regions not associated with this process (Tapert et al., 2007; Hester et al., 2009). In case of the acute effects of cannabis, based on the single study by Spronk et al. (2011), it can be assumed that error monitoring is impaired as a result of administration of THC.

Due to the scarcity of the data on this topic, it would be especially interesting to take into account different factors which can modulate the effect of administering THC on error monitoring. One such factor is the link between chronic and acute cannabis use. Specifically, the history of cannabis use of an individual has been shown to modulate the effects of cannabis intoxication. Chronic cannabis users smoking cannabis cigarettes (joints; containing maximally 39 mg of THC) have been shown to demonstrate no accuracy deficiencies on a number of tasks tapping into different cognitive functions (Hart et al., 2001) and, in particular, on episodic and working memory tests (Hart et al., 2010). In addition, compared to infrequent users, chronic users did not display any behavioral impairments on tasks evaluating tracking error and divided attention (Ramaekers et al., 2009) or changes in an ERP indicative of early attentional processes (Theunissen et al., 2012), following smoking of a cannabis joint (with 500 μg/kg body weight THC). Conversely, inhibitory control has been identified to be equally diminished among both chronic and occasional users due to cannabis administration (Ramaekers et al., 2009). In summary, it makes sense to assume that this specific cannabinoid tolerance of regular users is not limited to particular cognitive functions, but extends to the development of a compensatory mechanism for deficiencies in cognitive control (Harding et al., 2012; Fridberg et al., 2013). However,

Table 1 Demographic and substance use data for each experimental condition.

	Placebo	5.5 mg THC	22 mg THC	Significance level
N (Male: Female)	19 (18: 1)	18 (17: 1)	18 (14: 4)	n.s.
Age	21.3 (2.3)	21.1 (2.1)	22.3 (2.3)	n.s.
IQ test score	8 (2.5)	7.3 (2.7)	7.1 (2.5)	n.s.
Monthly cannabis use	42.1 (30.6)	51.3 (52.6)	40 (29)	n.s.
Years of cannabis exposure	5.8 (3.1)	4.8 (1.9)	6.3 (2.2)	n.s.
Monthly alcohol use	26.5 (18.1)	23.7 (19.8)	21 (15.4)	n.s.
Years of alcohol exposure	5.5 (2.6)	4.8 (2.5)	7.2 (2.5)	$p = 0.026$
Monthly nicotine use	207.3 (204.2)	121.3 (140)	160.8 (194.3)	n.s.
Years of nicotine exposure	4.5 (3.7)	3.5 (4.2)	4.8 (4.1)	n.s.

Standard deviations in parentheses; n.s.: non-significant difference; Age: reported in years; IQ test score: measured by a shortened version of Raven's Standard Progressive Matrices; Monthly cannabis use: consumption of cannabis cigarettes (joints); Monthly alcohol use: consumption of alcohol units; Monthly nicotine use: consumption of cigarettes.

this compensation appears to have its limits due to impaired inhibitory control—a critical element in the top-down control over information processing (Botvinick et al., 2001).

Moreover, both the neurocognitive and the subjective effects of cannabis have been demonstrated to be highly dependent on the specific dose of THC administered (Hart et al., 2001; Ramaekers et al., 2006; Hart et al., 2010; D'Souza et al., 2012; Hunault et al., 2014). Consequently, when investigating the effect of cannabis on error monitoring, different results may be expected depending on the combination of the dose and history of cannabis use of the studied sample. For instance, a relatively low dose of THC may not produce visible changes in the error monitoring system of chronic cannabis users, while the compensatory mechanism may not be sufficient to prevent the impairments caused by a relatively high dose of THC.

In order to test these speculations, we examined the impact of two different doses of vaporized cannabis (5.5 mg or 22 mg of THC; see Section 2.2) and placebo on the amplitudes of the ERN and Pe. Moreover, we recruited only frequent cannabis users in our sample due to their partial tolerance to the impairing effects of cannabis (Hart et al., 2001; Kelleher et al., 2004; D'Souza et al., 2008; Ramaekers et al., 2009; Hart et al., 2010; Theunissen et al., 2012). Accordingly, based on the characteristics of the studied sample and on the reported effects of a relatively high dose of THC on the ERN (16 mg in total; Spronk et al., 2011), we expected to observe a decreased ERN amplitude following administration of the high, but not low cannabis dose or placebo. Since no studies have investigated the acute effects of cannabis on the Pe, we could only speculate that it will be affected in a similar manner to the ERN. The ERN and Pe were assessed in the context of a modified version of the Flanker task (Eriksen and Eriksen, 1974). Since administration of cannabis to regular users does not usually lead to overt error impairments (Hart et al., 2001; Ramaekers et al., 2009; Hart et al., 2010), we did not expect to observe any effects at the behavioral level.

2. Experimental procedures

The current research was part of a larger study which included other tasks and measurements.

2.1. Participants

The program fpower (Friendly, 2014) was used to estimate the approximate number of participants needed for detecting medium ($d = 0.5$) or large effect sizes ($d = 0.8$). With an estimated sample size of 60, three conditions, and a set alpha of 0.05, the power to detect main effects with a medium or large effect size for a between-groups ANOVA was estimated at 0.679 and 0.979, respectively.

Sixty-one healthy frequent cannabis users (53 males and 8 females) took part for a small financial compensation. Participants were recruited through advertisements on the internet, on community bulletin boards, and in coffee shops (outlets in which the sale of minor quantities of cannabis to consumers is allowed by Dutch law), and by word of mouth. Specific demographic and substance use information is displayed in Table 1. Written informed consent was obtained from all subjects, after a complete explanation of the nature of the research. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

The subjects were assigned at random to one out of three experimental groups: placebo, 5.5 mg or 22 mg THC. The conditions were comparable with regard to sex, age, IQ test score, and substance use characteristics, except for years of alcohol exposure. All participants were requested to be frequent users (use cannabis minimally 4 times a week, for at least 2 years) and to be native Dutch speakers. The exclusion criteria were: (1) history or presence of an axis I psychiatric disorder (DSM-IV; assessed with the use of the Mini International Neuropsychiatric Interview; M.I.N.I: Lecrubier et al., 1997); (2) clinically significant medical disease; (3) use of psychotropic medication; (4) current or previous regular use of other drugs except cannabis (regular use defined as having used a drug more than 4 times in a lifetime); (5) abuse of alcohol (more than 14 units a week). Compliance with the inclusion and exclusion criteria was evaluated by means of self-report. Moreover, participants were required to abstain from chocolate, caffeine, and alcohol 12 h before the experiment and not to use nicotine 2 h before the session. Cannabis use was also not allowed within 2 days before the study. Subjects' compliance with these criteria was evaluated by means of a personal interview and the application of a saliva drug test, which identified the recent use of cannabis, morphine or cocaine (Oral-View™ Saliva Multi-Drug of Abuse Test; Alfa Scientific Designs Inc., Poway, CA, U.S.A.).

From the initial sample of 61 subjects, one male participant withdrew from the experiment before completing the flanker task, without providing any explanation. Another subject experienced anxiety before cannabis administration and had to quit the study. In case of adverse events related to drug administration, one participant reported anxiety, combined with fatigue and nausea, which

led to excluding him from the experiment. In addition, one female subject requested a break in the experiment, which prevented her from completing the flanker task. Moreover, the data of another participant was excluded from the analysis due to a technical malfunction. In addition, initial screening of the behavioral data revealed that there was one participant with an extremely low percentage (marked as extreme outlier in SPSS, <1st quartile minus 3.0 IQR) of correct trials. Consequently, this subject was excluded from the analyses. This left 55 subjects for the final analysis (49 males and 6 females).

2.2. Study drugs

The active drug substance was composed of the dried, milled and homogenized flowers of the plant *C. sativa* (variety "Bedrocan"®; 19% THC). It was acquired from Bedrocan BV (Veendam, The Netherlands) where it was cultivated under standardized conditions in line with the requirements of Good Agricultural Practice (GAP). The placebo (variety "Bedrocan"®; <0.5% THC) administered in the experiment had a moisture content and terpenoid profile (providing the typical smell and taste of cannabis) matching the active drug. Study medication was prepared by ACE Pharmaceuticals BV (Zeewolde, The Netherlands). For each specific dose, precise amounts of active cannabis and placebo were mixed so that each dose was equal to 250 mg total weight but with varying concentrations of THC (placebo/5.5 mg/22 mg THC). Study medication was kept in a refrigerator (2–8 °C) in triple-layer laminated foil pouches (Lamigrip). Shelf life stability was determined to be at least 1 year under these conditions.

On the experiment day, each participant was administered a randomized single dose of cannabis by means of a Volcano® vaporizer (Storz&Bickel GmbH, Tüttlingen, Germany) – a safe and reliable method of intrapulmonary administration of THC (Hazekamp et al., 2006; Zuurman et al., 2008). Cannabis was vaporized at a temperature of 230 °C into a standard Volcano balloon as supplied with the vaporizer. For the purpose of blinding, the Volcano balloon was covered with a non-transparent plastic bag in order that no differences in density of the vapor were visible between dosages.

When delivering THC by means of vaporizing, it needs to be noted that the dose present in the plant material is only partially vaporized into the balloon (Hazekamp et al., 2006), and that a part of the THC inhaled from the balloon is not absorbed by the lungs but is exhaled again (Zuurman et al., 2008). Therefore, in order to obtain an absorbed dose of approximately 2 and 8 mg of THC, we loaded the Volcano vaporizer with 5.5 and 22 mg of THC, respectively. Furthermore, since the Volcano vaporizer and cannabis joints deliver comparable amounts of THC (Abrams et al., 2007), the loaded vs. absorbed dose distinction can be applied to smoked cannabis as well.

During administration, subjects were requested to inhale deeply and hold their breath for 10 s after each inhalation. They were asked not to speak during the inhalation period and were instructed to empty the balloon within 5 min. Subjects had the possibility to practice the inhalation procedure using an empty balloon before drug administration.

2.3. Shortened Raven's standard progressive matrices (SPM; measure of intelligence)

Individual IQ test scores were evaluated by means of a reasoning-based intelligence test (Raven et al., 1988). Each element of this test is composed of a pattern or sequence of a diagrammatic puzzle with one item missing. The task is to complete the pattern or sequence by selecting the correct missing piece from a list of choices. The items become more difficult as the test taker proceeds through the test. The SPM test measures an individual's skill for creating perceptual relations and reasoning by analogy independent of language and formal schooling. The version of the test used in the experiment was composed of 14 items.

2.4. Flanker task (error monitoring)

In order to measure the ERN and Pe, an adapted version of the Flanker task was used (following Spronk et al., 2011). Subjects were instructed to respond with their right or left index finger to the letter they saw in the center of the screen (H or S), in a congruent (HHHHH or SSSSS) or incongruent (SSHSS or HHSHH) letter string. The assignment of H or S to the left or right index finger press was counterbalanced across subjects. A fixation point was initially presented (lasting 100 ms) with the stimulus following 300 ms later (lasting 100 ms). Afterwards the screen remained blank for 900 ms, followed by a visual feedback screen (lasting 1000 ms). The inter-trial interval was 100 ms. The visual feedback was composed of a yellow, blue, or red rectangle signaling that the previous response was correct, incorrect, or too late, respectively. Subjects were required to make a response as quick as possible to prevent feedback specifying that their reaction was too slow based on an individually determined preset reaction time (RT) deadline. Initially, the subjects were familiarized with the task in a practice block composed of 60 trials, during which the preliminary RT deadline was set at 800 ms. Afterwards, the average RT and SD of the correct responses were computed and the RT deadline was determined for each individual participant by adding 0.5 SD to the mean RT from the practice block. Consequently, this deadline was used during the main task. Note that the inclusion of this RT deadline is crucial to guarantee that error rates do not differ across the experimental conditions (see e.g. de Bruijn et al., 2004, 2006). The main task consisted of five blocks of 100 trials. After each part, subjects received information regarding the amount of incorrect and too late responses. Verbal instructions were provided to maintain response accuracy at around 80–90%.

2.5. Visual analog scales (VAS; subjective measure of drug effects)

Three scales were used to measure the subjective effects of cannabis (horizontal 100-mm lines, the left pole labeled "not at all" and the right "extremely") which refer to "(feeling) High", "Good drug effect (pleasant)" and "Bad drug effect (unpleasant)". Participants were instructed to mark a point at the continuous scale in order to indicate their experience.

2.6. EEG recording

EEG activity was recorded over 10 positions: F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2, and Pz of the 10/10 standard. Bipolar derivations of electro-oculogram (EOG) signals over the left and right outer canthus were used to calculate horizontal eye movements. Vertical eye movements were calculated by bipolar derivations of signals above and below the left eye. Monopolar recordings were referenced to the common mode sensor (CMS) and a driven right leg (DRL) electrode was used for drift correction (for details see http://www.biosemi.com/faq/cms&drl.htm). In order to re-reference the data offline, two electrodes were placed at the left and right mastoid. Signals were DC amplified and digitized with a BioSemi ActiveTwo system (BioSemi B.V., Amsterdam, The Netherlands) with a sampling rate of 512 Hz.

2.7. Design and procedure

The study used a randomized, double-blind, placebo-controlled, between-groups (placebo vs. 5.5 mg vs. 22 mg THC) design. All

Table 2 Mean percentages of correct, incorrect, omission, and too early responses to congruent and incongruent trials for each experimental condition.

	Congruent			Incongruent		
	Placebo	5.5 mg THC	22 mg THC	Placebo	5.5 mg THC	22 mg THC
% Correct	81.5	73.8	67	55.1	49.4	46.5
% Incorrect	9.4	13.2	11.5	24.4	28.9	22.2
% Omission	8	10.3	19.4	19	18.9	29.1
% Too early	1.1	2.7	2.1	1.5	2.8	2.2

subjects were tested individually. After arrival, the participants were instructed to complete the SPM test within the time limit of 10 min. This was followed by the study drug administration. Six minutes after cannabis administration, subjects were instructed to report the subjective effects of the drug by using the VAS. The evaluation of drug effects was then repeated twice-at 35 and 60 min after administration. After the initial VAS measurement, the subjects completed the Flanker task (in the time frame between 6 and 35 min after drug administration) on a computer using a Serial Response Box™ (Psychology Software Tools Inc., Sharpsburg, PA, USA).

2.8. Statistical analysis

Off-line analyses were conducted with Brain Vision Analyzer (Brain Products GmbH, Munich, Germany). After re-referencing the channels to the average mastoid, data was high-pass filtered 0.01 Hz (24 dB/oct), and ocular artifacts correction was performed using the standard Gratton et al. (1983) method. EEG artifacts were automatically identified with the use of four criteria: (1) bad gradient ($>50\,\mu V$/sample), (2) bad max-min difference ($>200\,\mu V$/200 ms), (3) bad amplitude (absolute value $>1000\,\mu V$), and (4) low activity ($<0.50\,\mu V$/100 ms). For the ERN and Pe components, epochs referring to correct and incorrect responses at incongruent trials were averaged individually and time-locked to response onset, starting 100 ms before and finishing 500 ms after the response, relative to a 100 ms pre-response baseline. In order to investigate if the impact of cannabis on the response-locked ERP components was not influenced by a general impairment of information processing or attention, additional stimulus-locked ERPs were analyzed (N1, N2, and P300). For these components epochs associated with correct responses were averaged separately for congruent and incongruent stimuli time-locked to stimulus onset, starting 100 ms before and finishing 500 ms after the stimulus, relative to a 100 ms pre-stimulus baseline. All ERPs were measured as the baseline-corrected average amplitude across a predetermined interval, relative to the response or stimulus onset. The ERN amplitude was determined on correct and incorrect incongruent trials in the 50 to 100 ms time-window relative to response onset, at electrodes Fz, FCz and Cz. The Pe was calculated on correct and incorrect incongruent trials in the period between 300 and 400 ms post-response, at electrode Pz. The N1 amplitude was measured in the 65 to 115 ms time-window after stimulus onset, at electrodes FCz, Cz and Pz. The N2 was determined in the period between 280 and 330 ms post-stimulus, at electrode FCz. The P300 amplitude was measured in the time-window between 350 and 400 ms relative to stimulus onset, at electrodes FCz, Cz and Pz.

The response-locked ERN was analyzed with the use of a repeated-measures ANOVA, with correctness (correct vs. incorrect) and electrode site (Fz vs. FCz vs. Cz) as within-subjects factor, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. A repeated-measures ANOVA was also used to analyze the Pe, with correctness (correct vs. incorrect) as a within-subjects

factor, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. In case of the stimulus-locked ERPs, the data was analyzed with the use of a repeated-measures ANOVA, with congruency (congruent vs. incongruent) and electrode site (for N1 and P300 only; FCz vs. Cz vs. Pz) as within-subjects factors, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. Moreover, repeated-measures ANOVAs were used to analyze individual means for RTs, with congruency (congruent vs. incongruent) and correctness (correct vs. incorrect) as within-subjects factors, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. In case of average error rates and percentage of "too late" responses, separate repeated-measures ANOVAs were run for both measures, with congruency (congruent vs. incongruent) as a within-subjects factor, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. In addition, in order to investigate post-error slowing (Rabbitt, 1966), we used the optimized measure recommended by Dutilh et al. (2012) that compares RTs of correct responses preceding an error to RTs of correct responses following an error. Only incongruent trials were included in this analysis in order to circumvent serial congruency effects. Consequently, a repeated-measures ANOVA was applied with trial type (pre-error vs. post-error) as a within-subjects factor, and condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor.

In case of the IQ test scores, age and substance use data, between-groups ANOVAs were conducted with condition (placebo vs. 5.5 mg vs. 22 mg THC) as a between-groups factor. Data referring to sex was analyzed with the use of a Pearson's chi-squared test. VAS scores were analyzed by means of repeated-measures ANOVAs with time after cannabis administration (6 vs. 35 vs. 60 min) as a within-subjects factor, and condition as a between-groups factor. All measures were analyzed separately. *Post-hoc* multiple comparisons *t*-tests were applied with Bonferroni correction. A significance level of $p < 0.05$ was adopted for all tests.

3. Results

3.1. Demographic and substance use data

No significant main effects of condition were found for age ($F(2, 52) = 1.478$, $p = 0.238$), IQ test score ($F(2, 52) = 0.5$, $p = 0.61$), monthly cannabis use ($F(2, 52) = 0.435$, $p = 0.649$), years of cannabis exposure ($F(2, 52) = 1.687$, $p = 0.195$), monthly alcohol use ($F(2, 52) = 0.44$, $p = 0.647$), monthly nicotine use ($F(2, 52) = 1.034$, $p = 0.363$), and years of nicotine exposure ($F(2, 52) = 0.57$, $p = 0.569$). The drug conditions did not also significantly differ by sex ($\chi^2(2, N=55) = 3.524$, $p = 0.172$). However, there was a significant main effect of condition on years of alcohol exposure ($F(2, 52) = 3.918$, $p = 0.026$); see Table 1.
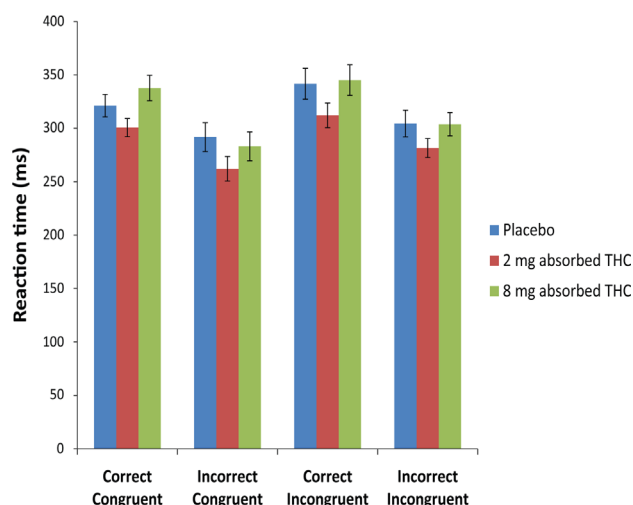
Figure 1 Average reaction times for correct and incorrect responses in both congruent and incongruent trials for each experimental condition. Error bars represent SE of the mean.

3.2. Behavioral effects

3.2.1. Performance

The percentage of responses for each of the four response options for each trial type and each experimental group is presented in Table 2. The analysis revealed that error rate was higher in incongruent than in congruent trials ($F(1, 52) = 234.172$, $p < 0.001$). Likewise, there were more response omissions in incongruent than in congruent trials ($F(1, 52) = 153.73$, $p < 0.001$). Moreover, there was a significant main effect of condition on response omissions. *Post-hoc* multiple comparisons revealed that subjects in the 22 mg THC condition displayed more omissions than subjects in the placebo condition ($t(35) = 3.828$, $p < 0.001$) and the 5.5 mg THC condition ($t(34) = 3.447$, $p = 0.001$). There were no significant interaction effects ($p > 0.05$).

3.2.2. Reaction times

Trials with response omissions were excluded from the analysis (see Figure 1). The ANOVA revealed main effects of congruency ($F(1, 52) = 66.188$, $p < 0.001$) and correctness ($F(1, 52) = 157.788$, $p < 0.001$). Specifically, participants responded faster in case of congruent trials (299 ms), as compared to incongruent trial types (315 ms). Moreover, subjects performed faster in incorrect (288 ms) than correct trials (326 ms). There were no significant main effects of condition, or interaction effects ($p > 0.05$).

3.2.3. Post-error slowing

A significant main effect of trial type ($F(1, 52) = 24.408$, $p < 0.001$) indicated that RTs following an incorrect response were significantly higher (328 ms) than those preceding an error (315 ms). There were no significant main effects of condition, or interaction effects ($p > 0.05$).

3.2.4. Drug subjective effects

A significant main effect of time after cannabis administration was found only in the case of the rating of "high" (with Huynh-Feldt correction; $F(1.887, 94.358) = 18.063$, $p < 0.001$).
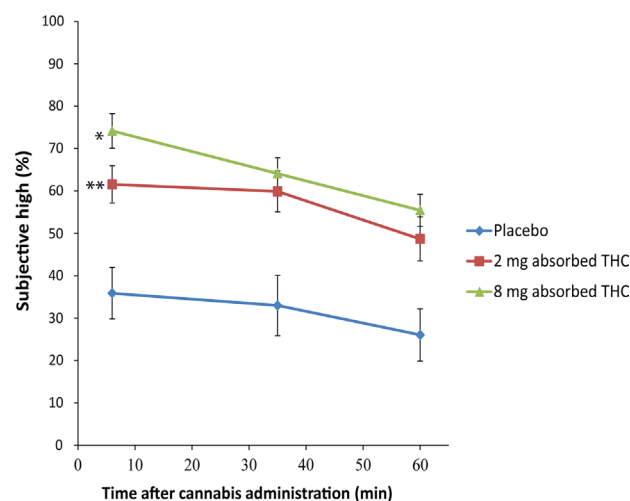

Figure 2 Average subjective high (rated as a percentage) experienced in each experimental condition as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.01$) difference between the 22 mg THC and placebo groups (*), and between the 5.5 mg THC and placebo groups (**). Error bars represent SE of the mean.
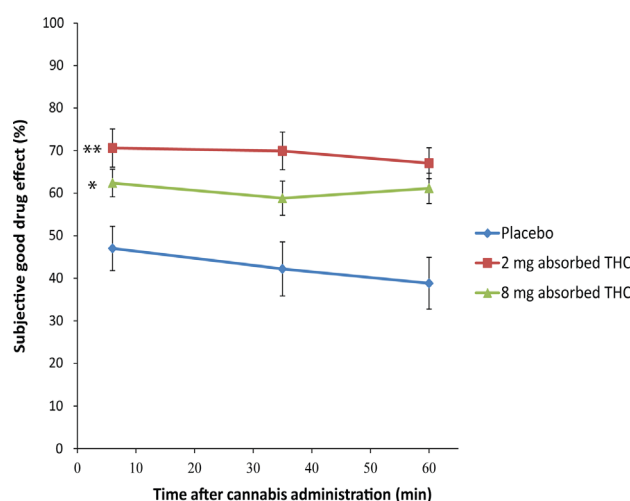

Figure 3 Average subjective good drug effect (rated as a percentage) experienced in each experimental condition as a function of time after cannabis administration. Symbols indicate a significant ($p < 0.01$) difference between the 22 mg THC and placebo groups (*), and between the 5.5 mg THC and placebo groups (**). Error bars represent SE of the mean.

Nevertheless, significant main effects of condition were revealed on all three measures: "high" ($F(2, 50) = 12.477$, $p < 0.001$), "good drug effect" ($F(2, 50) = 11.097$, $p < 0.001$) and "bad drug effect" ($F(2, 50) = 4.918$, $p = 0.011$). There were no significant interaction effects ($p > 0.05$).

Post-hoc multiple comparisons revealed that participants in the placebo condition showed significantly lower ratings of "high", compared to the 5.5 mg ($t(35) = 3.393$, $p = 0.001$) and 22 mg THC groups ($t(35) = 4.732$, $p < 0.001$); see Figure 2. Furthermore, the scores of "good drug effect" in the placebo group were significantly lower than in the 5.5 mg ($t(35) = 3.988$, $p < 0.001$) and 22 mg THC conditions

(t(35)=2.991, p=0.009); see Figure 3. For the measures of "high" and "good drug effect", no significant differences were obtained between the ratings in the 5.5 mg and 22 mg THC conditions (p>0.05). In contrast, in case of the ratings of "bad drug effect", subjects in the 22 mg THC group displayed significantly elevated scores, compared to placebo (t(35)=2.882, p=0.025) and 5.5 mg THC (t(34)=2.923, p=0.025); see Figure. 4. Moreover, the scores of "bad drug effect" did not significantly differ between the placebo and 5.5 mg THC groups (p>0.05).

3.3. ERP analyses

3.3.1. ERN amplitude
The response-locked ERP components for the three drug conditions are displayed in Figure 5. A significant interaction was found between condition and correctness (F(2, 52)=4.351, p=0.018), but not between condition, electrode and correctness (p>0.05). There was also a significant interaction between electrode and correctness (F(2, 104)=11.895, p<0.001). In addition, significant main effects of electrode (F(2, 104)=13.299, p<0.001), correctness (F(1, 52)=110.018, p<0.001) and condition (F(2, 52)=3.644, p=0.033) were found. A separate between-groups ANOVA revealed that the main effect of condition was driven only by incorrect responses in case of all three electrodes: Fz (F(2, 52)=4.13, p=0.022), FCz (F(2, 52)=4.99, p=0.01), and Cz (F(2, 52)=5.768, p=0.005).

Post-hoc multiple comparisons of the ERN collapsed across the three electrodes (Fz, FCz, and Cz) showed that participants in the 22 mg THC condition displayed a significant decrease in amplitude of the ERN between correct and incorrect responses, as compared to placebo (t(35)=2.915, p=0.014; −3.4 vs. −7.1 μV), but not 5.5 mg THC (t(34)=1.738, p=0.333; −3.4 vs. −5.5 μV). In addition, there was no significant difference between the 5.5 mg THC and placebo conditions (t(35)=1.239, p=0.595; −5.5 vs. −7.1 μV).

3.3.2. Pe amplitude
For the response-locked Pe amplitude a significant interaction between condition and correctness was found (F(2, 52)=5.184, p=0.009). In addition, there was a main effect of correctness (F(1, 52)=65.855, p<0.001).

Post-hoc multiple comparisons showed that participants in the 22 mg THC condition demonstrated a significant decrease in the amplitude of the Pe between correct and incorrect responses, as compared to placebo (t(35)=2.909, p=0.022; 2.8 vs. 6.2 μV), but not 5.5 mg THC (t(34)=0.04, p=1.0; 2.8 vs. 2.9 μV). Moreover, subjects in the 5.5 mg THC condition significantly differed from those in the placebo condition with regard to this measure (t(35)=2.615, p=0.024; 2.9 vs. 6.2 μV).

3.3.3. N1 amplitude
The stimulus-locked ERP components for the three drug conditions are presented in Figure 6. For the stimulus-locked N1 amplitude a main effect of electrode was found (F(2, 104)=35.765, p<0.001). There were no significant main effects of condition, or interaction effects (p>0.05).
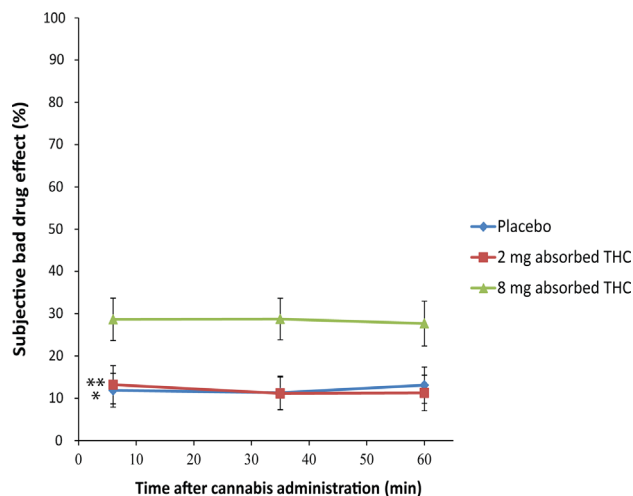

Figure 4 Average subjective bad drug effect (rated as a percentage) experienced in each experimental condition as a function of time after cannabis administration. Symbols indicate a significant (p<0.05) difference between the placebo and 22 mg THC groups (*), and between the 5.5 mg and 22 mg THC groups (**). Error bars represent SE of the mean.

3.3.4. N2 amplitude
In case of the stimulus-locked N2 amplitude a main effect of congruency was revealed (F(1, 52)=53.629, p<0.001). There were no significant main effects of condition, or interaction effects (p>0.05).

3.3.5. P300 amplitude
For the stimulus-locked P300 amplitude main effects of electrode (F(2, 104)=20.329, p<0.001) and congruency were found (F(1, 52)=32.769, p<0.001). There were no significant main effects of condition, or interaction effects (p>0.05).

4. Discussion

The present study shows for the first time that a low (5.5 mg THC) and high (22 mg THC) dose of vaporized cannabis differentially affects the neural correlates of error monitoring in frequent cannabis users. Specifically, a diminished ERN was observed in the high dose group in comparison to the placebo condition, whereas a diminished Pe amplitude was observed in both the high and low dose conditions, as compared to placebo.

Based on the available research, the finding of a decreased ERN in the high dose condition allows to speculate that a high dose of cannabis might affect the transmission of a reinforcement learning signal to the ACC (Holroyd and Coles, 2002; but see Yeung et al., 2004). Furthermore, the observation of a reduced Pe in both the high and low dose groups may suggest that even a relatively low dose of cannabis is already sufficient to influence the late (elaborate) neural processing of errors as reflected in the Pe. Previous research has linked the Pe to conscious detection of errors (Nieuwenhuis et al., 2001; Endrass et al., 2005), and the temporal dynamics of the Pe have been directly correlated with the emergence of error awareness (Murphy et al., 2012). Based on this, it might
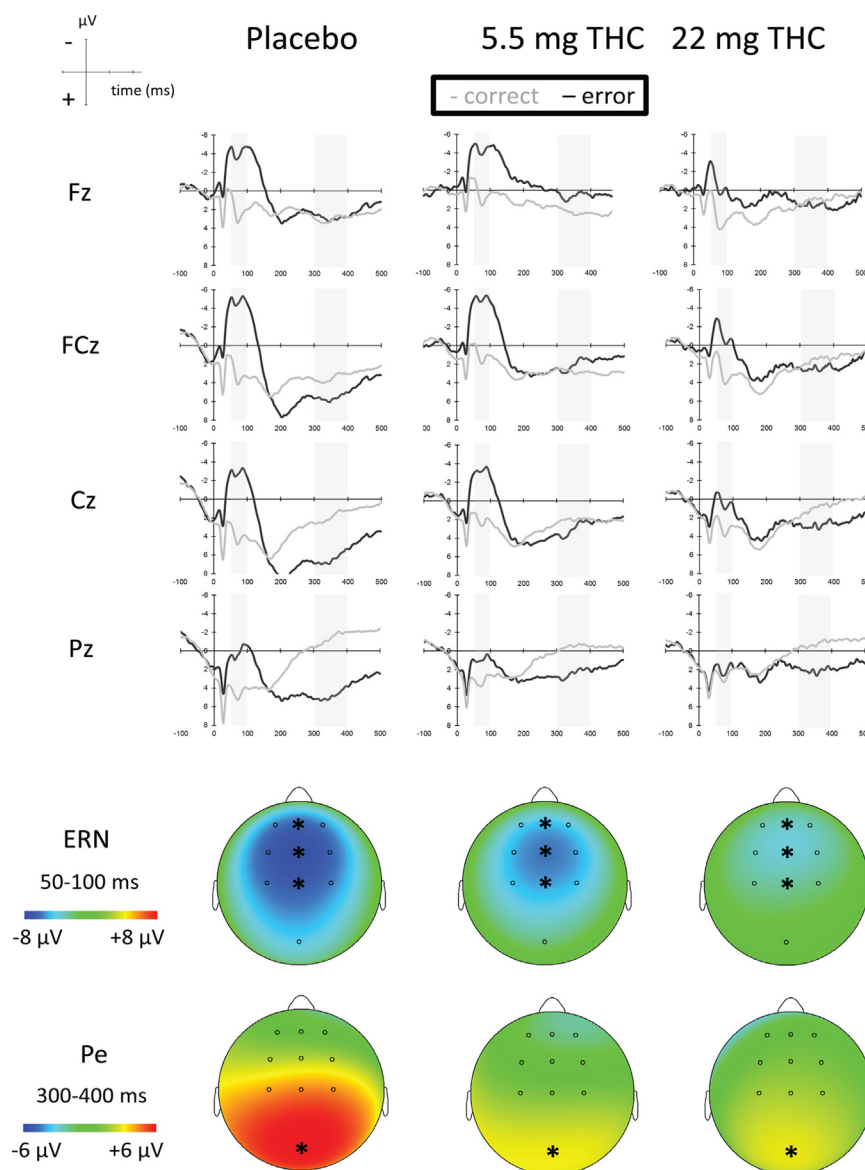
Figure 5 Grand average response-locked waveforms and topographical distributions of the difference between incorrect and correct responses at incongruent trials for each experimental condition.

be speculated that a low dose of cannabis is sufficient to affect error awareness, although such an assumption needs confirmation in future studies using independent behavioral measures.

Moreover, whereas previous studies on the chronic effects of cannabis use have shown that users are typically tolerant to most of the detrimental effects of cannabis (Hart et al., 2001; Kelleher et al., 2004; D'Souza et al., 2008; Ramaekers et al., 2009; Hart et al., 2010; Theunissen et al., 2012), and recruit compensatory mechanisms to prevent performance being affected (Harding et al., 2012; Fridberg et al., 2013), we showed that acute administration of cannabis still impacts the neural correlates of processes involved in error monitoring. Accordingly, based on the current observations and on the assumption that the ERN and Pe reflect two dissociable processes involved in error monitoring (Nieuwenhuis et al., 2001), it may be assumed that the changes in the neural correlates of the error monitoring

system observed in the current study are dose-dependent. Specifically, a high dose of cannabis seems to influence both the conscious (late), as well as the initial automatic processes involved in error monitoring, whereas a low dose of cannabis appears to affect only the conscious (late) processing of errors.

These potential dose-dependent effects of cannabis on the error monitoring system suggested by our data are in line with an earlier study pointing to dose-dependent effects of cannabis on executive control functions (Ramaekers et al., 2006). In particular, cannabis has been shown to diminish performance on a task measuring executive control (Tower of London), with a high dose of cannabis (500 μg/kg body weight THC) leading to a more pronounced deterioration of performance than a low dose (250 μg/kg body weight THC; Ramaekers et al., 2006). Consequently, combining this with various dose-dependent effects of cannabis on neural correlates of cognitive functions and
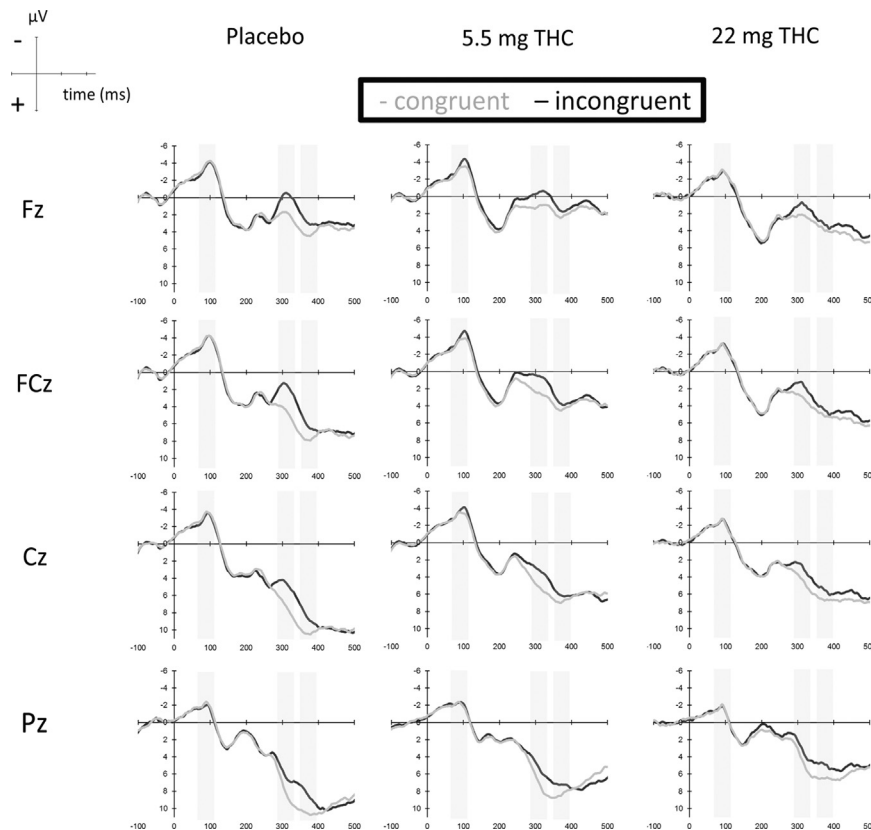
Figure 6 Grand average stimulus-locked waveforms of the difference between congruent and incongruent trials at correct responses for each experimental condition.

subjective effects (Hart et al., 2001; Hart et al., 2010; D'Souza et al., 2012; Hunault et al., 2014), one may speculate that the differential impact of the doses used in the current study reflects a dose-response relationship between cannabis and more general processes underlying executive function, including error monitoring.

4.1. Limitations

A significant limitation of the current study is its between-groups design, which at least theoretically raises the possibility that the observed differential impact of the cannabis doses was due to specific features of the studied sample. Another limitation was the lack of measurement of THC blood plasma levels, which did not allow us to assess the correlation between THC in the bloodstream and emergence of drug effects. In addition, the lack of this measurement makes it difficult to evaluate a dose-response curve, as it is possible that there were significant between-subjects differences in absorbed THC due to the lack of standardization of the duration and number of inhalations from the Volcano balloon. Furthermore, the application of a saliva test in order to verify the compliance of participants with the no-consumption criteria was not optimal, since it only provided an approximation of recent use of drugs. Evaluation of urinary levels of THC metabolites (11-COOH-THC) would have been a more accurate measure of drug use over an extended period of time. In addition, including a test for alcohol intoxication would have been another improvement in securing the compliance of subjects with

the study requirements. Moreover, it is possible that the observed results were affected by the fact that some subjects could had been experiencing cannabis withdrawal symptoms on the day of testing, due to the requirement to be abstinent from cannabis for 2 days prior the study (Bonnet et al., 2014).

5. Conclusion

The results of this ERP study show that even a low dose of cannabis may have an effect on the neural correlates of error monitoring of frequent cannabis users. Furthermore, this impact is more pronounced with highly-potent cannabis. Although any such speculations need to be confirmed by future studies, these observations raise the possibility that intoxicated frequent cannabis users might have difficulties to adapt to changing circumstances by monitoring and correcting their erroneous behavior. Consequently, it might be worthwhile to investigate the effects of using cannabis in situations which require flexible updating of behavior to changing conditions. Since such situations require efficient continuous error monitoring processes, any potential disturbances evoked by cannabis may lead to counterproductive, if not risky, results.

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the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Authors MAK, HS, LSC and BH designed the study. Author MAK wrote the protocol and managed the literature searches. Authors MAK, HS, LSC, AH, NJAW and BH contributed to setting up the study. Authors MAK, MM and JD collected the data. Authors MAK and HS managed the ERP and statistical analyses. Author MAK wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Arno Hazekamp and Mikael Kowal receive a salary from Bedrocan BV - the company which provided the study drugs. All other authors declare that they have no conflicts of interest.

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