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Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users

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Abstract

Performance impairment during Δ^9-tetrahydrocannabinol (THC) intoxication has been well described in occasional cannabis users. It is less clear whether tolerance develops to the impairing effects of THC in heavy users of cannabis. The aim of the present study was to assess neurocognitive performance during acute THC intoxication in occasional and heavy users. Twenty-four subjects (12 occasional cannabis users and 12 heavy cannabis users) participated in a double-blind, placebo-controlled, two-way mixed model design. Both groups received single doses of THC placebo and 500 μg/kg THC by smoking. Performance tests were conducted at regular intervals between 0 and 8 h after smoking, and included measures of perceptual motor control (critical tracking task), dual task processing (divided attention task), motor inhibition (stop signal task) and cognition (Tower of London). THC significantly impaired performance of occasional cannabis users on critical tracking, divided attention and the stop signal task. THC did not affect the performance of heavy cannabis users except in the stop signal task, i.e. stop reaction time increased, particularly at high THC concentrations. Group comparisons of overall performance in occasional and heavy users did not reveal any persistent performance differences due to residual THC in heavy users. These data indicate that cannabis use history strongly determines the behavioural response to single doses of THC.

Key words

cannabis use history; cognition; impulsivity; performance; THC; tolerance

Introduction

Cannabis is the most widely used illicit drug in Europe and the USA. At least 65 million European adults (about 20%, aged 15–64) have reported cannabis use at least once in their lives and 22.5 million (about 7%) Europeans have reported cannabis use in the previous year (EMCCDA, 2006). In 2004, 40% of US citizens (12 years and older) reported lifetime use of cannabis and about 10% reported cannabis use in the previous year (DHHS/SAMHSA, 2004).

Experimental, placebo-controlled studies have repeatedly demonstrated that single doses of Δ^9-tetrahydrocannabinol (THC) between 40 and 300 μg/kg cause a dose-dependent reduction in performance at laboratory tasks measuring memory, divided and sustained attentions, reaction time, impulse control, tracking and motor functions and actual driving performance (Ameri, 1999; Casswell and Marks, 1973; Chait and Zacny, 1992; Curran, *et al*., 2002; Hart, *et al*., 2002; Heishman, *et al*., 1988, 1989, 1990; Kelly, *et al*., 1990, 1993; Lamers and Ramaekers, 2001; Ramaekers, *et al*., 2006b; Weil, *et al*., 1968). Performance impairments are maximal during the first hour after smoking and sharply decline over 2–4 h after THC use. Performance impairments are strongly related to THC concentration in serum, although the magnitude of these impairments may vary considerably. Objective performance impairments have been shown to emerge at serum THC concentrations as low as 2–5 ng/ml, whereas maximal performance impairments have been observed at serum concentrations >30 ng/ml (Ramaekers, *et al*., 2006c). From a public health perspective, the major concern about the acute effects of cannabis is the possibility of accidents if users drive or operate machinery while intoxicated (Hall and Solowij, 1998). Cannabis induced impairment of driving performance has been demonstrated in on-the-road driving tests (Ramaekers, *et al*., 2000, 2004).

The majority of experimental performance studies have been conducted in occasional users of cannabis, who display a

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low frequency of lifetime use as compared to heavy, daily users. The implicit assumption in these experimental studies is that acute effects of cannabis on performance persist unabated for so long as the drug is taken. It is not unlikely, however, that acute effects mitigate in frequent cannabis users as a consequence of tolerance (Hart, *et al*., 2001; Nordstrom and Hart, 2006). Early studies of cannabis tolerance in humans found that high doses of THC for prolonged periods are required to observe tolerance to subjective (Mendelson, 1976) and physiological effects (Nowlan and Cohen, 1977). The best indication for the existence of tolerance to subjective high following prolonged cannabis administration comes from a series of studies in experienced THC smokers by Jones, *et al.* (1981) and Haney, *et al*. (1999). They concluded that tolerance develops after short periods of cannabis administration (50% reduction in intoxication ratings after 4 days of exposure to THC) when the conditions are optimal, i.e. when dose, dose frequency, duration and route of administration are such that sustained blood/brain levels of THC are achieved. Another interesting finding was that tolerance developed more rapidly, while the subjects were constantly treated with the lower, more frequent oral doses (Jones, *et al*., 1981). Thus, if the doses of THC are small and infrequent, little tolerance seems to develop. The latter had been noted previously as well by Cappel and Pliner (1974), who found no differences between frequent and infrequent users' self administration of THC cigarettes to achieve a desirable high. These data indicate that frequent or long-term users of cannabis may not develop substantial tolerance unless they are in a constant state of 'high' as evinced by steady-state THC concentrations in blood.

It is not clear whether repeated use of cannabis will also induce tolerance to the impairing effects of THC on performance, because systematic studies are lacking. A few studies examined whether cannabis use history affected a subjects' response to single doses of THC. Kirk and de Wit (1999) reported that ratings of subjective high and sedation were lower in frequent cannabis users than in infrequent cannabis users when challenged with a single dose of 15 mg THC. The groups did not differ, however, in objective, cognitive performance on a digit symbol substitution task suggesting that tolerance was limited to subjective measures. About the only indication for behavioural tolerance in a range of performance measures comes from a study by Hart, *et al.* (2001), who reported the absence of any acute effects of smoking cigarettes containing 1.8% and 3.9% THC on complex cognitive functions in heavy, daily users of cannabis. The authors suggested (Hart, *et al*., 2001; Nordstrom and Hart, 2006) that the presence or absence of THC induced performance impairments depends on cannabis use history. Thus, cognitive impairment is likely to occur in occasional users and unlikely to occur in frequent users due to tolerance. Yet this claim cannot be evaluated on the basis of the study by Hart, *et al.* (2001) alone because it is unclear how THC doses administered in their study in daily users compared with THC doses administered in studies employing occasional users. In addition, (residual) cognitive impairments may have been present during both THC and placebo treatments, because all subjects tested positive to THC in urine prior to smoking the experimental cigarettes. The finding that cognitive performance of frequent cannabis users was comparable during THC and placebo treatments may thus also have reflected a presence of cognitive impairment during both treatment conditions (Ramaekers, *et al*., 2006a).

The aim of the present study was to compare the acute effects of a high dose of THC (500 μg/kg THC) on neuropsychological performance in heavy and occasional cannabis users during 8 h after smoking in a placebo-controlled study. Placebo and THC cigarettes were administered using a standardized smoking regime and THC concentrations were determined in serum. Residual THC effects were assessed by comparing the performance of heavy users and occasional users, independent of the experimental THC or placebo treatment.

Methods

Subjects

Twelve occasional cannabis users (eight males, four females) and 12 heavy cannabis users (nine males, three females) participated in the present study. A summary of their demographics and history of drug use is given in Table 1. Subjects were

Table 1 Subject characteristics (mean, SD) and history of drug use for occasional and heavy cannabis users

Demographic variables	Occasional users (N = 12)	Heavy users (N = 12)
Age (years)	22.8 (2.3)	23.2 (3.3)
Weight (kg)	71.9 (16.6)	66.6 (8.4)
Frequency of cannabis use/year	55 (36)	340 (86)
Joints per occasion (number)	1.2 (0.5)	2.3 (1.2)
History of cannabis use (years)	7.4 (2.7)	6.2 (3.4)
Occasional use of other drugs (no. subjects)		
Alcohol	12	12
MDMA	6	8
Amphetamine	2	2
Cocaine	2	4
LSD	0	0
Mushrooms	7	4
Other	2	1
Combined use of THC and alcohol (no. subjects)	11	11
Combined use of THC and MDMA (no. subjects)	3	4
No. subjects attesting to driving under the influence of cannabis (DUIC)	6	11
Frequency of DUIC/year	0.5 (0.5)	93.6 (138.4)
Visits to coffee shops/year	14.1 (22.5)	68.1 (93.3)
Visits to bars/year	68 (42.2)	65.8 (47.1)

recruited through advertisements in coffee shops. Initial screening comprised of a questionnaire on medical history. Subjects were examined by the medical supervisor who checked vital signs and took blood and urine samples. Standard blood chemistry, haematology and drug screen tests were conducted on these samples. General inclusion criteria pertaining to both occasional and heavy users were: free from psychotropic medication; good physical health as determined by medical examination and laboratory analysis; absence of any major medical, endocrine and neurological conditions; normal weight, body mass index (weight/length^2) between 18 and 28 kg/m^2 and written informed consent. Specific inclusion criteria were frequent use of cannabis (>smoking on more than 4 days/week) during the previous year in case of heavy users and weekly use or less in case of occasional cannabis users. Exclusion criteria were: history of drug abuse (excluding marijuana) as assessed by drug urine screens and questionnaires; non-cigarette smokers; pregnancy or lactation or failure to use reliable contraceptives; colour blindness, excessive drinking (>25 standard alcoholic consumptions a week); hypertension (diastolic >100; systolic >170) or history of psychiatric disorders.

The study was conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Edinburgh (2000). All subjects were fully informed of study procedures, adverse reactions to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without penalty or censure. A permit for obtaining, storing and administering marijuana was obtained from the Dutch drug enforcement administration.

Design, doses and administration

The study was conducted according to a double-blind, placebo-controlled, two-way mixed model design. Groups of occasional and heavy cannabis users received THC placebo and 500 μg/kg THC. Treatment orders were randomly assigned to subjects according to a balanced block design. A minimum wash-out of 7 days transpired between experimental treatments. Smoking started in the morning of test days and lasted for about 10 min. The cigarettes were prepared beforehand for each individual from stock provided by the Dutch Bureau for Medicinal Cannabis. Marijuana cigarettes were prepared from batches containing 13% THC, a standard potency for marijuana sold at Dutch pharmacies for medical use. The total amount of cannabis was weight calibrated for each individual subject and mixed with tobacco to achieve a standard cigarette size and weight. Placebo cigarettes equalled weight and size of active marijuana cigarettes, but contained no active THC. Subjects were instructed to smoke the cigarette according to a standardized procedure (Ramaekers, *et al*., 2006b) to minimize the subject's possibility of dose titration and to increase optimal absorption of THC, i.e. inhalation for 4 s, hold breath for 10 s and exhale/break for 15 s. This sequence was repeated until the cigarettes were smoked as completely as possible. Mean (SD) number of puffs smoked from the cigarette in the placebo and THC condition were 25 (6.4) and 28 (15.4), respectively, by occasional users and 22 (7.5) and 22 (8.2), respectively, by heavy users.

Procedures

Occasional cannabis users were asked to refrain from any drugs during the study period. Heavy cannabis users were asked to refrain from drugs other than cannabis. Subjects were not allowed to use alcohol on the day prior to an experimental session and were requested to arrive at experimental sessions well rested. Drug and alcohol screens were performed prior to experimental sessions upon arrival of the subject. Drug screens assessed for the presence of morphine, cocaine, marijuana, methampethamine and amphetamine. In case of occasional cannabis users, THC or THC placebo cigarettes were only administered if a subject had passed the alcohol and drug screens on a given test day. In case of a positive drug screen, occasional users were sent home to return to the laboratory at a later time. In case of heavy cannabis users, THC placebo and THC cigarettes were administered if subjects tested positive for THC, but negative for other drugs and alcohol. In total, two occasional users tested positive for amphetamine, and one occasional user tested positive for THC on single test days. These subjects were sent home to return to our laboratory at a later time. Heavy cannabis users always tested positive for THC on test days. Subjects received a standardized breakfast prior to smoking. Performance tests were conducted at fixed intervals during 8 h post-smoking. The critical tracking task (CTT) was conducted at 10 min, 3 h 05 min, 5 h 05 min and 7 h 05 min post-smoking; a divided attention task (DAT) was conducted at 20 min, 3 h 20 min, 5 h 20 min and 7 h 20 min post-dosing; the stop signal task (SST) was conducted at 35 min, 3 h 30 min, 5 h 30 min and 7 h 30 min post-smoking and a Tower of London (TOL) task was conducted at 60 min, 3 h 40 min, 5 h 40 min and 7 h 40 min post-dosing. Performance tasks were selected because of their demonstrated sensitivity to the impairing effects of THC (Ramaekers, *et al*., 2006b). Subjects received a training session prior to onset of the experimental sessions to familiarize them with the tests and procedures and minimize practice effects.

Performance assessments

The 'critical tracking test' measures the subject's ability to control a displayed error signal in a first-order compensatory tracking task. Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The subject's compensatory response increases in frequency with an increasing phase lag. Control is lost at the point where the compensatory response lags the cursor's last movement by 180°. The response frequency at this point is defined as the critical frequency or lambda-c. The test includes five trials of which the lowest and the highest scores

were removed. The average of the remaining scores is taken as the final score (Jex, *et al*., 1966).

The 'divided attention task' measures the subject's ability to divide attention between two tasks performed simultaneously. The primary task consists of tracking task as described above, but at a constant level of difficulty set at 50% of the subject's maximum capacity. Tracking error is measured as the difference in mm between the position of the cursor and the midpoint of the scale. In the secondary task, the subject monitors a central display upon which single digits are presented at 1-s intervals. The occurrence of the digit '2' is a signal for the subject to remove the foot from a pedal as rapidly as possible. Inter stimulus interval varies between 1 and 2 s. Mean absolute tracking error (mm), number of correct detections and number of control losses are the main performance measures (Moskowitz, 1973).

The 'stop signal task' measures motor impulsivity, which is defined as the inability to inhibit an activated or pre-cued response leading to errors of commission. The current test is adapted from an earlier version of Fillmore, *et al.* (2002) and has been validated for showing stimulant and sedative drug effects (Ramaekers and Kuypers, 2006). The task requires subjects to make quick key responses to visual go signals, i.e. the letters ABCD presented one at a time in the middle of the screen, and to inhibit their response if a subsequent visual stop signal, i.e. '*', appears in one of the four corners of the screen. The stop signal is presented at predefined delays of 50, 150, 250 and 350 ms. The main parameters were stop reaction time and response accuracy. Stop reaction time represents the estimated mean time required to inhibit a response. Stop reaction time is calculated by subtracting the stop signal delay from the reaction time on go-trials associated with *n*-th percentile of the reaction time (RT) distribution. The *n*-th percentile corresponds to the percentage of commission errors (Logan, *et al*., 1984).

The 'Tower of London' is a decision-making task that measures executive function and planning (Shallice, 1982). The original version of the TOL consists of three coloured balls, which must be arranged on three sticks to match the target configuration on a picture, while only one ball can be moved at a time. The present version consists of computer-generated images of begin- and end-arrangements of the balls. The subject decides as quickly as possible, whether the end-arrangement can be accomplished in 2, 3, 4 or 5 steps from the begin arrangement by pushing the corresponding coded button. Number of correct decisions and mean reaction time are the main outcome measures.

Subjective high

Subjects rated their subjective high on visual analogue scales (100 mm) directly after smoking and at 45 min, 1 h 20 min, 2 h 20 min, 3 h 20 min, 5 h 20 min and 7 h 20 min, as a percentage of the maximum 'high' ever experienced.

Physiological measures

Blood pressure (systolic and diastolic pressure) and heart rate were measured directly after smoking and at each subsequent hour.

Pharmacokinetic assessments

Blood samples (6 ml) were taken at baseline, 5, 15, 30, 45 and 60 min during the first hour after smoking and subsequently at the hour between 2 and 8 h after smoking. Blood samples were centrifuged and serum was frozen at −20 °C until analyses for pharmacokinetic assessments. THC concentrations and its main metabolites (THC-COOH, OH-THC) were determined using a validated and accredited routine method for the analysis of cannabinoids in forensic blood samples. The procedure essentially consists of an automated solid phase extraction and gas chromatography with mass spectrometric detection with a limit of quantification of 1 ng/ml, which has also been successfully used for the analysis of THC in oral fluid (Kauert, *et al*., 2006).

Statistics

All performance measures were analysed with SPSS 13.0 using a GLM repeated measures analysis of variance with THC (two levels) and time after smoking (four levels) as within-subject factors and cannabis use history (two levels) as between-subject factors. Subjective high and physiological measures were analysed according to the same model with the exception that the levels for the factor time after smoking increased to 7 or 9. In addition, data collected during THC was converted into difference scores from placebo for further analyses of the association between high (>10 ng/ml) and low (<10 ng/ml) THC concentrations and performance on tasks showing a significant THC effect. The 10 ng/ml threshold was chosen, because previous research has shown that THC concentrations over this threshold produced consistent impairment over a large range of performance tasks (Ramaekers, *et al*., 2006c). Corresponding change scores of task performance were classified either as showing 'impairment' or 'no impairment' for all individual cases. Binomial tests were applied to measure whether the proportion of observations showing impairment or no impairment significantly differed from the hypothesized proportion. It was hypothesized that in case of no effect of cannabis on task performance, the proportion of observations showing impairment or no impairment would be equal, i.e. 50%.

Results

A general summary of significant overall effects of THC on subjective high, physiological and performance measures is given in Table 2.

Table 2 Summary of significant ($P < 0.05$) within and between factor effects on performance, subjective and physiological measures according to GLM repeated measures analyses

Variable	THC	Cannabis use history	Time after smoking	THC × cannabis use history	THC × time after smoking	THC × cannabis use history × time after smoking
CTT-Lambda-c	0.022	0.032	0.000	0.027	–	–
DAT-Tracking error	0.013	–	0.000	–	–	0.003
DAT-Hits	0.024	–	–	–	0.021	0.024
DAT-Control losses	0.032	–	0.000	0.034	0.001	0.003
SST-Go RT	–	–	–	–	–	–
SST-Stop RT	–	–	–	–	0.010	–
SST-Accuracy	0.034	–	–	–	–	–
TOL-Correct decisions	–	–	0.000	–	–	–
TOL-RT	–	–	0.005	–	–	–
Subjective high	0.000	0.026	0.000	–	0.000	–
Heart rate	0.000	0.000	0.000	–	0.000	–
Systolic BP	–	–	0.000	–	–	–
Diastolic BP	–	–	0.000	–	–	–

CTT, critical tracking task, DAT, divided attention task, SST, stop signal task, TOL, Tower of London task.

Missing data

One subject in the group of occasional users did not complete testing between 2 and 8 h after THC smoking. The subject complained of dizziness and nausea and was no longer able to adhere to testing procedures.

Subjective high and physiological data

Mean (SE) values for subjective high, heart rate, systolic and diastolic blood pressure as a function of Time after smoking are shown in Figure 1. Subjective high ($F_{1,21} = 39{,}22$; $P = 0.000$) and heart rate ($F_{1,21} = 23{,}98$; $P = 0.000$) significantly increased after smoking THC. Increments were highest during the first hour after smoking, but significantly decreased as a function of Time after smoking for subjective high ($F_{6,126} = 14{,}7$; $P = 0.000$) as well as heart rate ($F_{8,168} = 11{,}51$; $P = 0.000$). Cannabis use history also affected subjective high ratings. These were generally higher in occasional cannabis users than in heavy cannabis users ($F_{1,21} = 5{,}7$; $P = 0.026$). Systolic and diastolic blood pressure were not affected by THC or THC-related factors.

Performance measures

Mean (SE) values for performance at the CTT, the DAT and the SST as a function of time after smoking THC or placebo are given in Figures 2 and 3.

THC increased Lambda-c in the CTT ($F_{1,21} = 6{,}13$; $P = 0.022$). However, THC induced impairment of critical tracking performance only occurred in occasional cannabis users when compared with heavy users as indicated by a significant THC × cannabis use history interaction ($F_{1,21} = 5{,}62$; $P = 0.027$). In addition, cannabis use history also affected critical tracking performance. The latter was generally worse in occasional cannabis users when compared with heavy users, independent of treatment condition ($F_{1,21} = 5{,}28$; $P = 0.032$).

Performance in the DAT was significantly affected by THC. THC increased tracking error ($F_{1,21} = 7{,}38$; $P = 0.013$) and the number of control losses ($F_{1,21} = 5{,}28$; $P = 0.032$) in the primary task and decreased the number of hits in the secondary task ($F_{1,21} = 5{,}93$; $P = 0.024$). The overall effect of THC was most prominent during the first hour after smoking and only in occasional cannabis users relative to heavy users. The latter was evinced by a significant THC × cannabis use history × time after smoking interaction for tracking error ($F_{3,63} = 5{,}17$; $P = 0.003$), number of control losses ($F_{3,63} = 5{,}26$; $P = 0.003$) and number of hits ($F_{3,63} = 3{,}39$; $P = 0.024$).

In the SST, stop reaction time was affected by THC × time after smoking ($F_{3,63} = 4{,}08$; $P = 0.01$). Inspection of the data shows that stop reaction time primarily increased during the first hour of smoking. Accuracy of responses generally decreased following THC ($F_{1,21} = 5{,}13$; $P = 0.034$). Reaction time on go trials was not affected by THC.

Performance in the TOL task was not affected by THC.

THC concentrations and performance

A summary of mean (SD) THC, THC-COOH and OH-THC concentrations in serum as a function of time after smoking is given in Table 3. THC concentrations were generally higher in heavy users than in occasional users during the THC condition. At baseline and throughout the placebo condition, heavy users displayed residual levels of THC ranging between 2 and 4 ng/ml (mean). Occasional users tested negative for THC during placebo and at baseline prior to smoking THC. Binomial tests showed a significant increase in the proportion of observations showing impairment in the CTT and the DAT in occasional users ($P < 0.05$). In case of the SST, significant increases in the

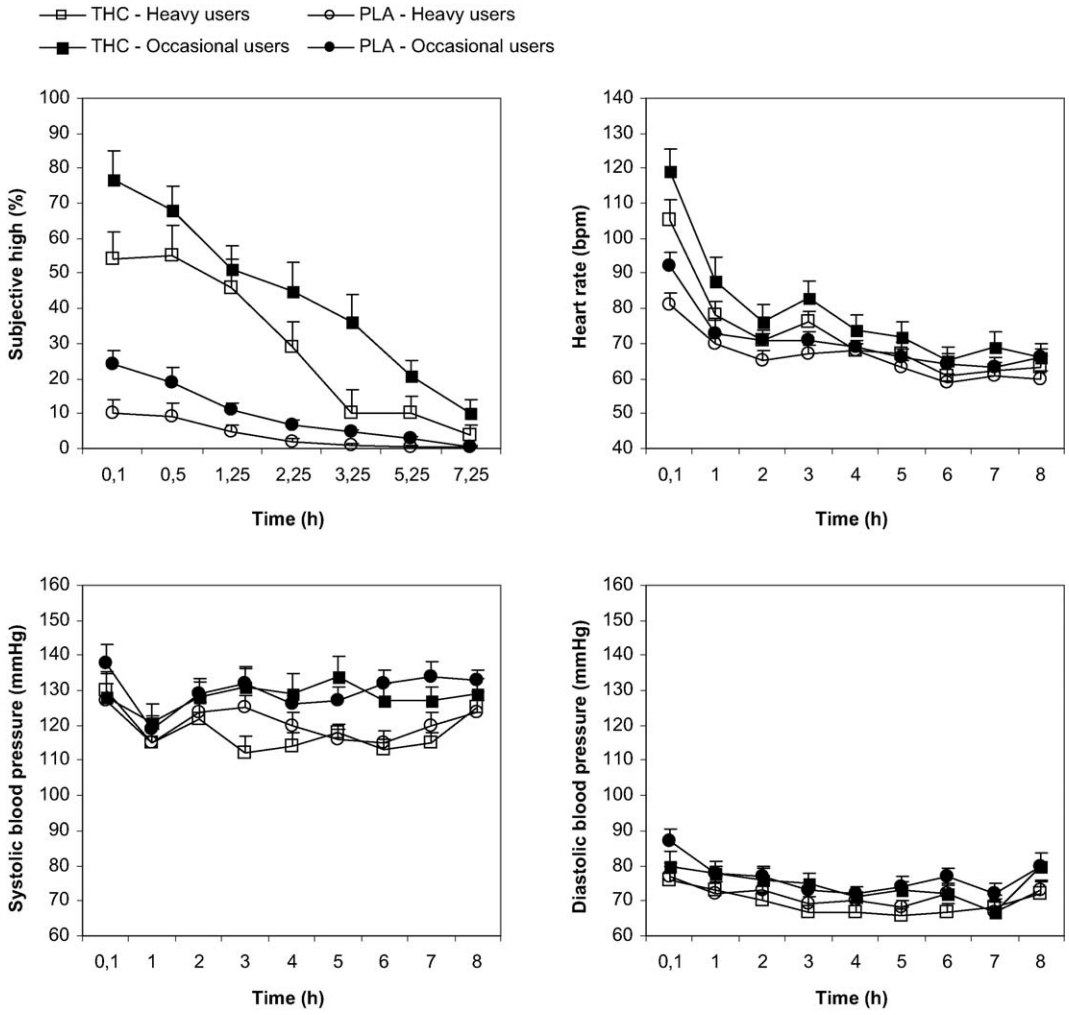

Figure 1 Mean (SE) values for subjective high, heart rate, systolic and diastolic blood pressure as a function of time after smoking THC or placebo in heavy and occasional cannabis users.

proportion of observations showing impairment were found for serum THC concentration >10 ng/ml ($P < 0.05$) in occasional cannabis users as well as heavy users. Distributions of observations showing 'impairment' and 'no impairment' in each performance task as a function of serum THC (i.e. ≤ or >10 ng/ml) are shown in Figure 4.

Discussion

The present study was designed to assess the effects of a single dose of THC on a range of performance measures in occasional and heavy cannabis users. Results demonstrate that a single dose of 500 µg/kg THC impairs tracking performance, divided attention and inhibitory control in occasional cannabis users. Heavy cannabis users, however, did not display acute impairments on most of the performance tasks although impulse control decreased at high THC concentrations.

Performance at the CTT and the DAT significantly decreased after a single dose of THC. These impairments were prominent in occasional cannabis user and virtually absent in heavy cannabis users as also evinced by significant statistical interactions of THC × cannabis use history and THC × cannabis use history × time after smoking. The latter interaction effect not only indicated that impairments were most prominent in occasional users but also that performance impairments decreased over time. Impairments were maximal during the first hour after smoking and then gradually declined. THC induced performance impairments in occasional cannabis users are in line with a large number of previous studies reporting similar findings (see Introduction). The absence of any performance impairments in the CTT and the DAT in

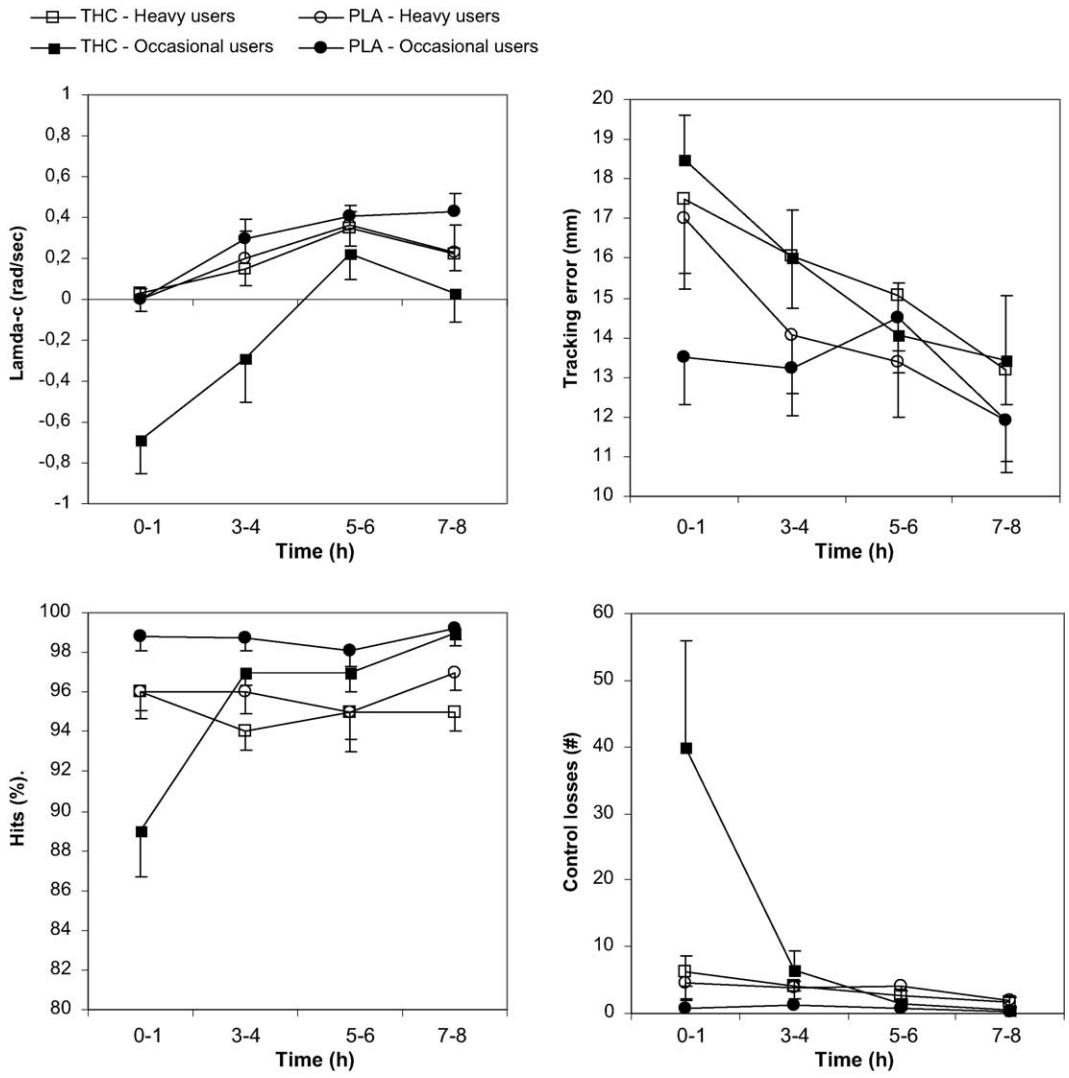

Figure 2 Mean (SE) values for lambda-c in the critical tracking task, and tracking error, hits and control losses in the divided attention task as a function of time after smoking THC or placebo in heavy and occasional cannabis users.

heavy cannabis users, however, indicates that cannabis use history strongly determines whether acute THC impairment will occur. The present data indicate that heavy cannabis users have developed tolerance to most of the acute effects of THC and are no longer susceptible to THC-induced impairments of tracking and divided attention. Alternatively, it has been suggested that (abstinent) heavy cannabis users recruit alternative neural networks as a compensatory mechanisms during task performance. Eldreth, *et al.* (2004) demonstrated that cannabis users whose performance on a modified Stroop task was not impaired, did show hypoactivity in the left perigenual anterior cingulate cortex and the left lateral prefrontal cortex and hyperactivity in the hippocampus bilaterally, when compared with a control group. Kanayama, *et al.* (2004) showed that compared with controls, cannabis users exhibited increased activation of brain regions typically used during spatial working memory performance. However, cannabis users also utilized additional regions not typically used for spatial working memory, i.e. they compensated by working harder and recruiting compensatory networks.

However, heavy cannabis users did not display tolerance to impairments in every performance domain. Stop signal reaction increased after a single dose of THC in both occasional and heavy cannabis users. Mean increments in stop reaction time appeared bigger in heavy cannabis users than in occasional cannabis users, although the interaction THC × cannabis use history did not reach significance. Binomial tests comparing frequency of impairments at low and high doses of THC

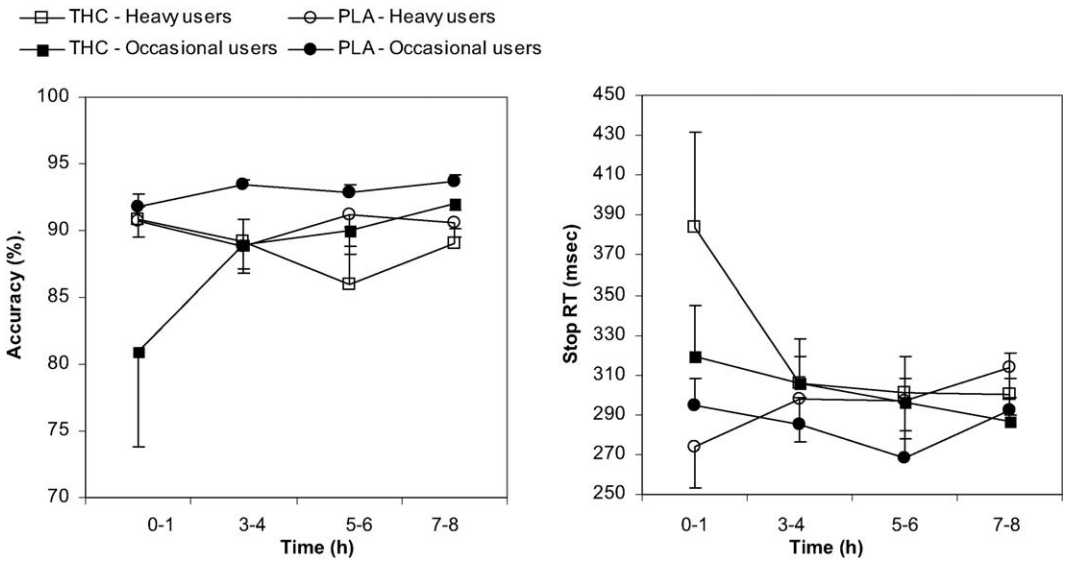

Figure 3 Mean (SE) values for accuracy and stop reaction time in the stop signal task as a function of time after smoking THC or placebo in heavy and occasional cannabis users.

confirmed results from GLM repeated measures analyses. They showed that at concentrations >10 ng/ml, the number of observation indicative of impairment of impulse control (i.e. stop reaction time) increased in occasional and heavy users. The latter may be very relevant to hypotheses suggesting that long-term drug use impairs inhibitory control functions mediated by the prefrontal cortex and the associated limbic brain circuitry, leading to a loss of inhibition or to impulsivity (Jentsch and Taylor, 1999). Loss of behavioural control and impulsivity are generally seen as a criterion of substance addiction. The dopaminergic mesolimbic system, which originates in the ventral tegmental area, and projects to the nucleus accumbens, has been implicated in the reinforcing and disinhibiting effects of drugs of abuse (Koob, *et al*., 1998; Kreek, *et al*., 2005).

THC increased subjective high and heart rate in occasional and heavy cannabis users to similar degrees. Increments were highest during the first hour after smoking, but significantly decreased as a function of time after smoking. In the past, some studies have reported tolerance to acute effects of THC on subjective high and heart rate after repeated administration of high doses (Haney, *et al*., 1999; Jones, *et al*., 1981). In contrast, the present data seem to indicate that no tolerance occurred to acute THC effects on subjective high and heart rate in heavy cannabis users. However, it should be noted that THC serum concentrations in heavy cannabis users where much higher than those observed in occasional cannabis users. In heavy cannabis users, a single dose of 500 µg/kg THC produced a mean peak concentration of 120.9 ng/ml, whereas the same dose produced a mean peak concentration of 49.1 ng/ml in occasional cannabis users. All occasional and heavy cannabis users were instructed to adhere to the same smoking protocol, i.e. inhale for 4 s, hold breath for 10 s and exhale/break for 15 s. This sequence was repeated until the cigarettes were smoked as completely as possible. On average, occasional and heavy users smoked 28 and 22 number of puffs of the THC cigarette. The present study, however, did not control for puff volume, which has been shown to produce dose-related changes in plasma levels of THC (Azorlosa, *et al*., 1992, 1995). Present differences in THC concentrations seem to indicate that puff volume of occasional and heavy cannabis users may have differed and that heavy cannabis users needed higher THC concentrations to achieve their desired high. This of course, would be a classic indication of tolerance.

The present study also offered the opportunity to assess general performance differences between occasional cannabis users and heavy cannabis users resulting from residual THC concentrations or chronic use. It has been suggested that chronic cannabis use may produce persistent, long-term deficits in attention, memory and psychomotor functions which are not caused by an acute pharmacological effect and persist beyond the elimination phase of THC from the body (Solowij, *et al*., 1991, 1995, 2002). However, most studies on the long-term effects of THC have measured cognitive function in heavy users after only 12 and 72 h of abstinence. It is, therefore, impossible to determine whether such deficits are temporary, i.e. due to residual THC in the brain or resulting from acute withdrawal, or long lasting. A study conducted by Pope *et al.* (2001) suggested that cognitive deficits in long-term heavy users of cannabis are reversible and related to recent cannabis exposure rather than related to cumulative lifetime use of THC. The investigators demonstrated that heavy users scored significantly below control subjects on memory tasks before

Table 3 Mean (SD) serum concentrations (ng/mL) of THC, THC-COOH and OH-THC as a function of time after smoking in heavy users and occasional users

	Time after smoking (h)														
	Baseline	0.1	0.25	0.5	0.75	1	1.5	2	3	4	5	6	7	8	
Heavy cannabis users after smoking THC															
THC	3.4 (3.5)	120.9 (78.1)	47.4 (28.2)	30.3 (18.6)	22.6 (12.2)	19.0 (10.5)	13.9 (7.4)	10.4 (5.8)	6.1 (3.5)	5.2 (3.5)	5.5 (6.9)	4.2 (4.1)	3.5 (3.0)	3.5 (2.9)	
THC-COOH	71.0 (79.0)	107.3 (95.8)	114.8 (96.2)	114.9 (92.3)	113.9 (92.6)	102.5 (85.4)	94.3 (82.0)	88.3 (79.5)	80.8 (81.1)	68.8 (73.6)	63.2 (77.7)	64.3 (75.5)	61.8 (75.3)	62.4 (75.7)	
OH-THC	1.6 (1.7)	12.0 (10.7)	10.5 (8.5)	9.5 (7.8)	8.5 (6.7)	7.5 (5.7)	6.2 (4.3)	5.0 (3.3)	3.4 (2.2)	2.7 (1.8)	2.5 (2.6)	2.1 (1.8)	1.8 (1.5)	1.7 (1.4)	
Occasional cannabis users after smoking THC															
THC	0.0 (0.0)	49.1 (24.9)	20.7 (9.3)	13.3 (5.3)	10.9 (4.4)	8.5 (3.3)	6.7 (2.2)	5.1 (2.1)	2.9 (1.9)	2.1 (1.3)	1.3 (0.8)	0.9 (0.6)	0.7 (0.4)	0.6 (0.3)	
THC-COOH	1.6 (0.5)	12.0 (11.8)	10.5 (12.0)	9.5 (11.1)	8.5 (10.3)	7.5 (9.1)	6.2 (7.6)	5.0 (6.7)	3.4 (5.5)	2.7 (4.3)	2.5 (3.8)	2.1 (4.3)	1.8 (4.1)	1.7 (3.9)	
OH-THC	0.0 (0.0)	6.6 (5.1)	5.7 (3.7)	4.7 (2.9)	4.0 (2.4)	3.3 (1.8)	2.9 (1.3)	2.4 (1.1)	1.6 (0.7)	1.2 (0.4)	0.8 (0.3)	0.7 (0.3)	0.5 (0.3)	0.5 (0.3)	
Heavy users after smoking placebo															
THC	2.9 (3.2)	3.0 (3.7)	3.0 (3.8)	2.9 (4.0)	2.9 (3.7)	3.0 (4.2)	2.7 (2.9)	2.7 (3.1)	2.6 (3.1)	2.8 (3.4)	2.5 (2.7)	2.6 (3.1)	2.3 (2.5)	2.4 (3.0)	
THC-COOH	96.3 (177.5)	82.9 (135)	81.7 (156.5)	84.1 (136.9)	83.2 (139.1)	86.4 (142.8)	87.1 (140.7)	73.5 (117.2)	76.7 (126.7)	66.5 (111.7)	66.8 (118.2)	71.2 (127.3)	72.1 (135.5)	65.9 (113.6)	
OH-THC	1.9 (3.1)	1.9 (3.3)	1.7 (2.8)	1.9 (3.1)	1.8 (2.8)	1.7 (2.9)	1.6 (2.3)	1.4 (2.1)	1.3 (2.0)	1.3 (1.9)	1.2 (1.7)	1.0 (1.6)	0.9 (1.4)	0.9 (1.3)	

and after 1 and 7 days of abstinence. By day 28, however, there were virtually no significant differences between the groups' neuropsychological performance. Persistent performance deficits were only observed among those who commenced cannabis use prior to the age of 17 (Pope, *et al*., 2003). In the present study, heavy cannabis users always tested positive for cannabis use prior to smoking THC or placebo. Mean (SD) serum THC concentration at baseline prior to smoking THC and placebo were 3.4 (3.5) and 2.9 (3.2) ng/mL, respectively. During placebo treatment, residual THC concentrations remained relatively constant throughout an 8-h window, whereas THC concentrations after smoking an active THC cigarette returned to baseline levels at 8 h after smoking. In theory, the presence of residual THC concentrations in heavy cannabis users may have produced differences in baseline performance levels of occasional and heavy cannabis users. Yet, direct comparisons of performance (independent of treatment condition) in occasional and heavy users revealed no significant differences in any of the performance tests, with the exception of the CTT. Critical tracking performance of heavy cannabis users was generally worse during placebo treatment, but superior during THC intoxication when compared with occasional users. However, differences between tracking performance of both groups during placebo were always very small. In general, the between group comparisons seem to indicate that residual, low doses of THC did not produce any notable performance impairment in heavy cannabis users.

The finding that heavy cannabis users develop tolerance to the impairing effects of acute THC doses may bear an important implication for researchers involved in epidemiological case–control studies on the role of THC in traffic injuries and death. Ideally, a crash risk ratio for THC would be determined from a direct comparison between the frequency of THC positives among crash victims and the frequency of THC positives among the general driving population. However, crash risk may be easily underestimated if THC positives in the general driving population were generally representatives of heavy cannabis users and if THC positives in crash victims were generally representatives from occasional cannabis users. This is not an unlikely scenario as may be illustrated by one particular demographic of subjects participating in the present study. Among occasional users, six out of 12 attested to ever driving under the influence of cannabis (DUIC). The average frequency of DUIC per year in occasional users, however, was relatively low, i.e. 0.5. Among heavy cannabis users, 11 of 12 attested to DUIC on a regular basis. Their mean frequency of DUIC was relatively high, i.e. about 94 times per year. Heavy cannabis users thus seem accustomed to driving under the influence of cannabis, whereas occasional users are not. Heavy users are likely to show up in the general driving population regularly as acute THC impairments are minor in this group. Occasional users, however, do not DUIC on a regular basis. But if they do they are more likely to show up among crash victims because of their sensitivity to THC induced performance impairments. In other words, crash risk calculations may be confounded by cannabis use history of drivers. The

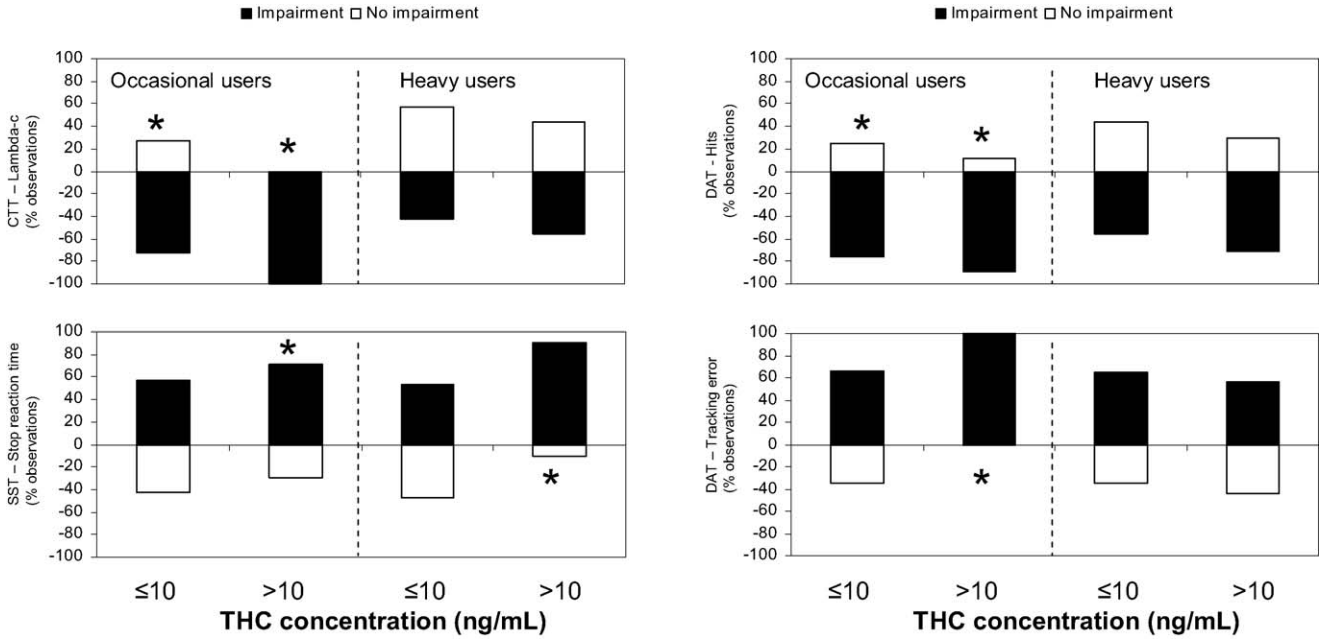

Figure 4 Distribution of observations showing 'impairment' or 'no impairment' for THC concentrations lower or higher than 10 ng/ml in the critical tracking task (CTT), divided attention task (DAT) and the stop signal task (SST).

frequency of THC positives may be relatively low among crashed drivers (i.e. the cases) because DUIC frequency in occasional users is low, whereas the frequency of THC positives may be high in the general driving population (i.e. the controls) because DUIC frequency in heavy users is high. Confounding factors such as cannabis use history may explain current controversies in case–control studies showing that THC either increases crash risk (Dussault, *et al.*, 2002) or not (Movig, *et al.*, 2004).

A final comment should be made regarding binomial tests for comparing frequency distributions of observations showing 'impairment' or 'no impairment'. This methodology has previously been used successfully for assessing performance impairments as a function of THC in serum (Ramaekers, *et al.*, 2006c). It should be noted that the present study was not designed to measure performance along the full scale of the pharmacokinetic curve of THC. Performance measures were taken between 0 and 1 h after smoking and repeated between 3 and 4, 5 and 6, 7 and 8 h after smoking. The practical implication is that no performance correlates were present for THC concentrations between 1 and 3 h after smoking when mean THC concentrations were between 6 and 19 ng/ml in heavy users and between 3 and 9 ng/ml in occasional users. Consequently, binomial tests of impairment were only applied in two wide concentration ranges: i.e. THC ≤10 ng/ml and THC >10 ng/ml. The a priori aim of this analysis was to separately assess the influence of high and low THC concentrations in heavy and occasional cannabis users. The analyses showed that THC impaired performance of occasional users at low and high THC concentrations, whereas THC only impaired stop reaction time of heavy users at high THC concentrations. Low concentration THC effects on performance of occasional users do not imply that performance was impaired at each individual concentration below 10 ng/ml, but that impairment was present for this cluster of concentrations. Previous research (Ramaekers, *et al.*, 2006c) has shown that performance impairment only starts to emerge at THC concentrations between 2 and 5 ng/ml.

In conclusion, the present study demonstrated that an acute dose of 500 μg/kg THC produces impairment of critical tracking, divided attention and motor impulse control in occasional cannabis users. In heavy cannabis users, performance impairment was limited to a loss of motor impulse control at high concentrations. Together, these data suggest that cannabis use history strongly determines the behavioural response to single doses of THC.

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