Psychopharmacology (2009) 204:85–94
DOI 10.1007/s00213-008-1440-0

ORIGINAL INVESTIGATION

Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC)

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Received: 20 March 2008 / Accepted: 5 December 2008 / Published online: 20 December 2008

Abstract
Rationale Δ^9-Tetrahydrocannabinol (THC) is the main active constituent of cannabis. In recent years, the average THC content of some cannabis cigarettes has increased up to approximately 60 mg per cigarette (20% THC cigarettes). Acute cognitive and psychomotor effects of THC among recreational users after smoking cannabis cigarettes containing such high doses are unknown.
Objectives The objective of this study was to study the dose–effect relationship between the THC dose contained in cannabis cigarettes and cognitive and psychomotor effects for THC doses up to 69.4 mg (23%).
Materials and methods This double-blind, placebo-controlled, randomised, four-way cross-over study included 24 non-daily male cannabis users (two to nine cannabis cigarettes per month). Participants smoked four cannabis cigarettes containing 0, 29.3, 49.1 and 69.4 mg THC on four exposure days.
Results The THC dose in smoked cannabis was linearly associated with a slower response time in all tasks (simple reaction time, visuo-spatial selective attention, sustained attention, divided attention and short-term memory tasks) and motor control impairment in the motor control task. The number of errors increased significantly with increasing doses

Trial registration: ClinicalTrials.gov identifier, NCT00225407.

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in the short-term memory and the sustained attention tasks. Some participants showed no impairment in motor control even at THC serum concentrations higher than 40 ng/mL. High feeling and drowsiness differed significantly between treatments.

Conclusions Response time slowed down and motor control worsened, both linearly, with increasing THC doses. Consequently, cannabis with high THC concentrations may be a concern for public health and safety if cannabis smokers are unable to titrate to a high feeling corresponding to a desired plasma THC level.

Keywords Cannabis · THC · Cognitive impairment · Psychomotor impairment · Acute · High dose · Cognitive functions

Introduction

Cannabis is by far the most commonly used recreational drug worldwide today (World report 2006). The pleasurable effects sought by recreational users are usually euphoria, relaxation and feeling 'high'. Other common acute effects on cognitive function are changes in sensory perception and attention, impairment in short-term memory, judgment and motor performance (Ameri 1999; Curran et al. 2002). The effects of cannabis on human behaviour may vary with the dose, route of administration, subject's expectations, susceptibility and previous cannabis experience. The effects on cognition are mainly due to Δ^9 tetrahydrocannabinol (Δ^9-THC), i.e. the principle psychoactive component of cannabis that activates type 1 cannabinoid receptors (CB1). These receptors have been found mainly in brain and peripheral nerves of both animals and humans. Reduction in performance after smoking cannabis includes in particular a dose-related impairment in motor control, which is of interest for partly predicting the alterations in human behaviour related to operating motor vehicles (Barnett et al. 1985; Ramaekers 2003).

In a recent report, there appears to be an upward trend in the average THC content of confiscated cannabis (El Sohly 2004). The issue of increased THC potency contained in cannabis cigarettes is not new, since several researchers have addressed this issue in the 1970s and 1980s (Mikuriya and Aldrich 1988). Cannabis is available as commercial grade and designer grade. The latter, especially, is bred, locally grown and carefully cultivated using advanced cultivation techniques. The designer grades, known as 'sinsemilla' and 'nederweed' tend to have a much higher THC content than the commercial grade (Pijlman et al. 2005; Niesink et al. 2007; Potter et al. 2008). The average levels of Δ^9-THC in nederweed cannabis cigarettes sold in The Netherlands rose from 11.3% in 2000/2001 to 20.4% in 2003/2004 and 16% in 2006/2007 (Niesink et al. 2007). In England, sinsemilla appears to have become the most widely used form of cannabis, and the median sinsemilla potency was found to be 13.98% over the period 1995 to 2003 (Potter et al. 2008). These concentrations correspond to absolute THC doses of about 34, 61 and 48 mg for The Netherlands and about 42 mg for England, respectively, since a European joint is usually made of a mix of 300 mg cannabis and 700 mg tobacco. In North America, the average THC concentration in the 2003 illicit cannabis samples was 6.25%, meaning about 60 mg THC for a 952-mg American cannabis cigarette (El Sohly 2004).

The majority of the published studies on human performance used pure cannabis cigarettes provided by the American National Institute of Drug Abuse containing 35 mg THC at the most (Fant et al. 1998; Hart et al. 2001; Lane et al. 2005). A recent Dutch trial reported impairment in executive functions and motor control after smoking tobacco mixed with cannabis at a 500-μg/kg dose (Ramaekers et al. 2006a). In the Ramaekers' study, subjects smoked cannabis 3.4 times per month for 3.9 years on average. The 500-μg/kg dose used in the Ramaekers' study represents about 37 mg THC for an adult of 74 kg, which is still far under the THC dose of about 60 mg that is observed in designer grade cannabis samples.

Despite numerous studies on human performance after smoking cannabis, it remains unknown what the acute cognitive, psychomotor and subjective effects are of cannabis at doses of THC frequently found in cannabis cigarettes nowadays. The present study was performed to determine the effects of high THC doses—doses up to 69.4 mg of THC (23% THC)—on various aspects of behaviour in regular but non-daily cannabis users. This article focuses on the cognitive and psychomotor effects of such THC doses. The pharmacokinetics and effects on heart rate and blood pressure after smoking cannabis cigarettes with high THC doses have been reported elsewhere (Hunault et al. 2008). We previously showed that smoking cigarettes containing a mix of tobacco and cannabis at THC doses up to 69 mg induced a linear increase in serum THC concentration (Hunault et al. 2008). In the present article, we examined whether the relationship between exposure dose and behavioural impairment was linear at THC doses up to 69 mg (23%).

Materials and methods

The cannabis data used in the analyses were obtained from a double-blind, placebo-controlled, four-way cross-over randomised trial (Hunault et al. 2008). The Human Ethics Committee of the medical centre approved the trial, and written informed consent was obtained from all participants prior to their inclusion. Participants received a fixed fee for their participation. The study was carried out in accordance

with the declaration of Helsinki (1964) and amended in Edinburgh (2000).

Twenty-four male subjects aged 18–33 years were recruited through advertisements in newspapers. Individual demographic characteristics of the subjects have been published elsewhere (Hunault et al. 2008). Participants' demographics and drug use history are shown in Table 1. Participants smoked four joints on four exposure days, separated by a washout period of at least 7 days. The joints consisted of a mixture of 300 mg cannabis and 700 mg tobacco. The cannabis contained various concentrations of THC: 0.003% for the placebo, 9.8% for the low dose (29.3 mg per joint), 16.4% (49.1 mg per joint) for the middle dose and 23.1% for the high dose (69.4 mg per joint). The order of the THC doses was random (no dose escalation), but the THC doses were equally distributed across sessions. The smoking procedure was standardised by means of computer-generated instructions based on a pilot study conducted 2 months before the study and aimed to mimic the recreational cannabis use of the participants (3 s for getting ready, 2 s for inhalation, 3 s for holding breath and 32 s for normal breathing and relaxation). The whole joint was smoked in about 22 min.

Frequent blood sampling occurred during and after smoking to measure the serum concentrations of THC and its main metabolites (11-OH-THC and THC-COOH). Participants were asked to refrain from any drugs 15 days before and during the study period. Urine drug screens were performed upon arrival of the participants using DrugControl® tests to assess for the presence of amphetamines, barbiturates, benzodiazepines, cocaine metabolite, methaqualone, opiates, MDMA (ecstasy), MDA (3,4-methylenedioxyamphetamin) and THC (cutoff level 50 ng/ml THC-COOH). Participants with a baseline THC serum concentration higher than the limit of quantification (LOQ) were excluded from the analyses since this indicates they had smoked a cannabis cigarette aside from the study. Participants were required to stay overnight in our unit (within a hospital) prior to each test day and were therefore obliged to refrain from alcohol use at least 10 h before the onset of smoking.

Table 1 Participants' demographics and drug use history

	N
Total number	23[a]
Included in the placebo analyses	20/23
Included in the low THC dose analyses	18/23
Included in the middle THC dose analyses	20/23
Included in the high THC dose analyses	20/23
Employment status[b]	
Student	14/20
Not working	1/20
Working full- or part-time (not student)	5/20
Race (Caucasian)	23/23
Cocaine or ecstasy exposure (occasional)	4/23 & 1/23
	Mean (SD)
Age (years)	24.1 (4.0)
Weight (kg)	74.3 (5.2)
BMI (kg/m^2)	22.1 (1.7)
Past year cannabis use (number of joints, monthly)	7.7 (3.7)
Duration of cannabis use (years)	7.7 (4.2)
Past year number of tobacco cigarettes smoked daily[c]	8.4 (5.8)
Past year alcohol consumption (g of ethanol per day)	19.4 (15)

[a] Subject no. 21 was excluded from all analyses
[b] Three missing values for 'employment status'
[c] Among tobacco smokers (n=18), five participants did not smoke pure tobacco

Outcome measures

Cognitive and psychomotor measurements

The participants performed six different cognitive and psychomotor tasks at different time points after smoking cannabis. Outcome measures were speed (in ms), precision in motor control and accuracy (number of errors). The psychometric tasks were completed by means of the software package ERTS v3.05 (Experimental Run Time System, Berisoft, Germany). The performed tasks were the following: (1) the simple reaction time (SRT) test was performed at 37 min, 3 and 5 h after onset of smoking, for approximately 3 min. Participants had to respond as quickly as possible to an asterisk symbol appearing 90 times at random time intervals and locations by pressing the response key. (2) Visuo-spatial selective attention (VSSA) was evaluated using the Erickson flanker task performed 44 min after onset of smoking for approximately 5 min. A central stimulus (< or >) appeared 120 times, flanked by two sets of three identical symbols (<, = or >, for example: = = = > = = =). Participants had to respond by pressing the response button corresponding to the stimulus. There were three different levels of difficulty: congruent (stimulus and flankers identical), neutral (flankers were = symbols) and incongruent (stimulus and flankers opposite). (3) Short-term memory (STM) was tested using the Sternberg's memory scanning test performed 60 min after onset of smoking for about 5 min. Participants had to memorise a set of two to five digits, and subsequently, stimuli (112 total) were presented sequentially. If a stimulus belonged to the memorised set, participants had to press the right button, otherwise the left. The difficulty of the task increased with the number of digits the participants had to memorise (between two and five). (4) The motor control (MC) task was performed 70 min after onset of smoking, for approximately 6 min, using the unstable tracking test. A vertical bar moved continuously across the screen at varying speeds and the participant had to counteract with a joystick to keep the bar in the central position. There were three levels of difficulty that differed by

the velocity of the bar's deviation. The deviation from centre, recorded at 6-s time intervals, was expressed and recorded in root mean square (RMS) units. (5) A divided attention (DA) task was performed 80 min after onset of smoking for about 6 min. The subject's attention was divided by performance of two simultaneous tasks: a MC task (middle level of difficulty) and a STM task (with three digits). (6) The sustained attention (SA) task was performed 90 min after onset of smoking for about 10 min. Two hundred forty block patterns of four squares, in a 3×3 grid framework, were flashed continually. Most frequently, the patterns changed, but sometimes, they remained the same. Subjects had to press the response button as quickly as possible when two consecutive block patterns were identical. On the evening prior to the first exposure, subjects were individually trained to familiarise themselves with these six tasks. All tasks were performed once during this training session.

Measurement of subjective effects and heart rate

Participants' subjective assessment of drowsiness and capability to perform a task were measured at baseline, 108 min and 4 h after the onset of smoking. Participants were required to rate their own capability and drowsiness on two 100-mm-long visual scales ranging between "I am 100% able' and 'I am 0% able to perform a task' and "I am 0% drowsy' and 'I am 100% drowsy'. Participants were also asked to report their 'high' feeling, i.e. the subjective intensity of intoxication on a 100-mm-long visual scale (anchored by '0—not at all' and '100—tremendous high'). The high feeling score was recorded at baseline and regularly during 8 h after the onset of smoking. Heart rate was monitored with a Passport 2®monitor model (Datascope, USA). Heart rate was measured at baseline and during 8 h after the onset of smoking.

Statistical analyses

Multilevel models with dose as a continuous variable (THC 29.3, 49.1, 69.4 mg, placebo) and, when appropriate, time and degree of difficulty were used to assess the effect of THC dose on the response time or tracking deviation. Observations were clustered within individuals. Body mass index (BMI, defined as weight/length^2), time to smoke and previous cannabis use (in joints/month) were included as confounders in the analyses (see Appendix 1). Previous cannabis use was measured by the self-reported average number of joints smoked during the last 12 months. The PROC MIXED statement (SAS v9.1) was used to test the hypothesis that the relationship between THC exposure dose and effects was linear. A Bonferroni correction was used to specify what alpha value should be used for the analyses (see Appendix 1).

Differences in numbers of errors across THC doses were analysed using non-parametric median tests.

A mixed model with THC serum concentration at 1 h post-smoking was used to assess whether the known dose–effect relationship (Ramaekers 2003) between THC serum concentration and motor control impairment continued at THC doses up to 69 mg. In this model, the outcome variable was the average deviation from centre in the highest difficulty level of the motor control task, 70 min post-smoking. Body mass index, time to smoke and previous cannabis use were included as covariates in the analysis. A similar model including 11-OH-THC serum concentration at 1 h post-smoking instead of THC serum concentration was also used.

Subjective capability and subjective drowsiness scores at baseline were not normally distributed. Differences in participants' subjective capability and drowsiness at baseline were therefore tested by means of the non-parametric Friedman test. Mixed models with dose (THC 29.3, 49.1, 69.4 mg, placebo) were used to assess the effect of THC dose on the changes in heart rate, high feeling, subjective capability and subjective drowsiness between pre-smoking and post-smoking situations. BMI (defined as weight/length^2), time to smoke the joint and previous cannabis use were included as confounders in the analyses.

Results

Despite the use of a paced smoking procedure, the time used to smoke the cannabis cigarette was dose-dependent, increasing from 19.0 min on average (SD=3.4) with the placebo cigarette to 21.6 (SD=5.0), 23.1 (SD=4.6) and 24.4 min (SD=4.4) with the 29.3, 49.1 and 69.4 mg THC cigarettes, respectively. Participants 8, 15, 21 and 24 with the placebo dose, participants 1, 6, 11, 21, 23 and 24 with the low dose, participants 1, 12, 20 and 21 with the middle dose and participants 1, 16 and 21 with the high dose were excluded because of a THC serum concentration higher than the LOQ at baseline. Another participant (participant 11) was also excluded from the analyses involving the high dose because eight (out of 14) blood samples were missing. The final analyses include 20, 18, 20 and 20 participants, respectively, for the placebo, low, middle and high THC doses.

Table 2 summarises the results from the cognitive and psychomotor tests concerning response time and motor control precision. The data are presented by level of difficulty within a task (e.g. four levels in the short-term memory task). The response time increased with increasing task difficulty, between tasks (e.g. the response time was longer in the sustained attention task than in the simple reaction tasks) and within a task (e.g. in case of placebo

Table 2 Response time (RT) or tracking deviation (RMS) in the six cognitive or psychomotor tasks

Parameters	Time (min)[a]	Mean ± SD per dose				THC dose effect (linear term)		
		Placebo (0%), n=20	29.3 mg THC (9.75%), n=18	49.1 mg THC (16.38%), n=20	69.4 mg THC (23.12%), n=20	F	df	P value
Simple RT						15.2	1, 207	<0.001
	37	230 (28)	247 (30)	252 (37)	271 (62)			
	180	230 (28)	259 (42)	263 (37)	280 (47)			
	300	227 (26)	249 (46)	253 (46)	256 (45)			
Visuo-spatial selective attention (RT)[b]	44	374 (37)	386 (47)	398 (45)	416 (77)	35.7	1, 208	<0.001
Congruent		352 (34)	367 (53)	379 (40)	395 (73)			
Neutral		356 (39)	370 (45)	380 (46)	399 (81)			
Incongruent		417 (46)	426 (51)	439 (54)	458 (81)			
Short-term memory (RT)[b]	60	480 (60)	549 (83)	571 (95)	613 (117)	54.1	1, 286	<0.001
Load 2		409 (52)	450 (78)	487 (127)	485 (87)			
Load 3		429 (48)	482 (81)	508 (85)	542 (130)			
Load 4		483 (65)	551 (107)	565 (105)	629 (114)			
Load 5		537 (84)	632 (106)	652 (135)	700 (171)			
Motor control (RMS)	70	3.4 (1.1)	4.1 (1.1)	4.7 (2.1)	6.1 (3.6)	26.6	1, 208	<0.001
Easy		1.7 (1.0)	1.6 (0.5)	2.0 (1.1)	2.7 (2.3)			
Middle		2.9 (0.9)	3.8 (1.3)	4.4 (2.2)	5.2 (3.8)			
Heavy		5.6 (1.6)	6.9 (2.1)	7.9 (3.8)	10.3 (5.5)			
Divided attention (dual)	80							
Short-term memory (RT)		521 (78)	562 (118)	572 (105)	594 (133)	16.1	1, 130	<0.001
Motor control (RMS)		3.6 (2.2)	4.9 (2.0)	5.0 (2.7)	6.1 (4.1)	15.3	1, 130	<0.001
Sustained attention (RT)	90	550 (101)	595 (81)	617 (60)	619 (92)	10.3	1, 53	0.002

RMS is the outcome in the motor control task and in the tracking part of the divided attention task. In all other cases, the outcome is 'response time'

[a] Time after onset of smoking (in min)

[b] Means of response times when the given answer was right (no error)

exposure, the response time in the short-term memory task ranged from 409 to 537 ms). According to the task, response time or tracking deviation or both, increased significantly with increasing THC doses which means a linear dose–effect relationship was observed (Table 2). Concerning the SRT task with the low, middle and high THC doses, response time differed significantly between 37, 180 and 300 min post-smoking [$F(2,19)=27.7$, $P<0.001$]. The interaction term dose × time was not significant ($P=0.54$), meaning that the SRT was still impaired 5 h post-smoking.

Figure 1 shows the average number of errors made per test. The average number of errors differed significantly between the four THC doses in the short-term memory and the sustained attention tasks ($\chi^2=8.0$, $P=0.047$ and $\chi^2=9.8$, $P=0.02$, respectively), but not in the selective attention task nor in the short-term memory part of the divided attention task ($\chi^2=1.03$, $P=0.79$ and $\chi^2=3.40$, $P=0.33$, respectively).

Figure 2 illustrates large inter-individual differences in motor control impairment after exposure to high THC doses. Some participants showed decreasing motor control precision with increasing THC serum concentrations (see the individual results represented by diamond symbols in Fig. 2), but others showed no motor control impairment even at very high THC serum concentrations (see the individual results represented by circle and triangle symbols in Fig. 2). Four participants among the 24 participants included in the study did not show motor control impairment with THC concentrations higher than 40 μg/L. Their median age was 24 years (range 18–33), the median BMI 20.7 (range 19–23), the median cannabis use during the 12 previous months, eight joints (range 2–14) and the median duration of use 11 years (range 2–17). Their median THC concentration at the time the motor control task was performed was 62 μg/L (versus 24 μg/L for the whole group).

Inter-individual differences in motor control impairment could be explained by differences in THC concentration at 1 h post-smoking [$F(1,20)=4.84$, $P=0.04$]. 11-OH-THC serum concentration at 1 h post-smoking was also a significant explanatory variable of motor control impairment at 70 min post-smoking when this variable was included in the model instead of THC serum concentration [$F(1,20)=9.30$, $P=0.01$].

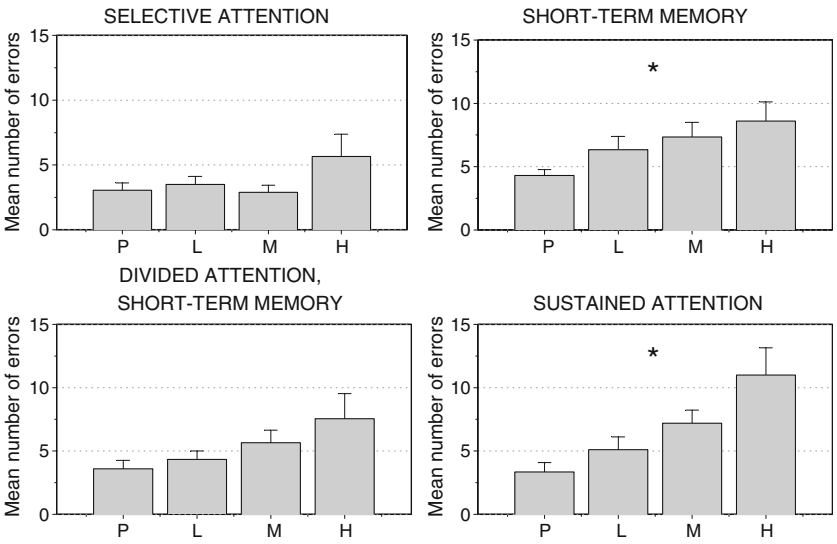

Fig. 1 Mean number of errors by task. *P* placebo, *n*=20 participants; *L* low dose (29.3 mg THC), *n*=18 participants; *M* middle dose (49.1 mg THC), *n*=20 participants; *H* high dose (69.4 mg THC), *n*=20 participants. *Asterisks* show tasks that had a significant difference in number of errors between THC doses

Heart rate, subjective capability to perform a task and subjective drowsiness did not differ across the different treatments at baseline (χ^2=0.3, *P*=0.97, χ^2=0.6, *P*=0.89 and χ^2=3.8, *P*=0.28, respectively; Table 3). Changes in heart rate and 'high' feeling between the pre- and post-smoking situations reflected the level of intoxication and increased with increasing THC doses (Table 3). Analyses with mixed models showed that changes in heart rate, high feeling and subjective capability differed significantly between treatments [heart rate $F(1,20)=83.7$, $P<0.001$; high feeling $F(1,20)=147.0$, $P<0.001$; subjective capability $F(1,20)=20.7$, $P<0.001$]. No significant differences were observed in change in drowsiness between treatments [$F(1,20)=3.8$, $P=0.06$]. Vomiting was observed in seven out of the 58 non-placebo experiments (12%, one in low-dose, three in middle-dose and three in high-dose experiments) by five of the participants (22%). One participant experienced a short episode of anxiety and another participant a fit of euphoria. In all these cases, no medication was necessary.

Figure 3 shows the mean serum THC and 11-OH-THC concentrations and Fig. 4 shows the mean 'high' score at the time the different tasks were performed.

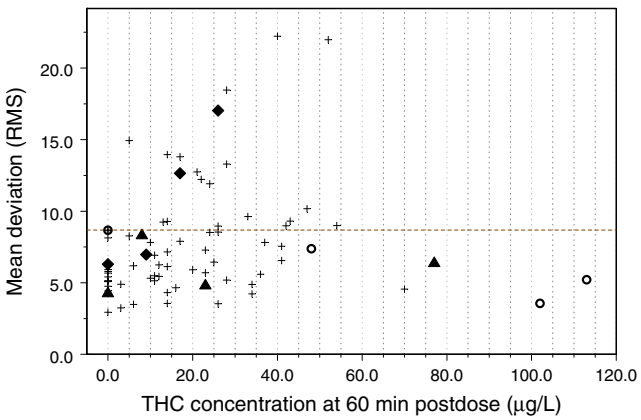

Fig. 2 THC serum concentrations at 60 minutes post-exposure versus mean deviation in the motor control task (heavy level). The plot contains 78 data points (20, 18, 20 and 20 subjects, respectively, for the placebo, low, middle and high THC doses). Three participants were assigned *diamond*, *circle* and *triangle symbols*, respectively, in order to single them out. The *horizontal dashed line* represents the upper limit of the participants' performance with the placebo

Discussion

The present study provides unique data about the extent of cognitive and psychomotor impairments after smoking cigarettes containing tobacco and cannabis at THC doses up to 69 mg. Response time slowed down and motor control worsened, both linearly, with increasing THC doses in the cannabis cigarette. The number of errors linearly increased with increasing THC doses in the short-term memory and sustained attention tasks. Some participants showed no impairment in motor control even at high THC serum concentrations. Heart rate and high feeling linearly increased with increasing THC doses.

Response time increased with increasing THC doses in all cognitive tasks, but accuracy (number of errors) was affected in only two tasks. Subjective ratings of the high and of the capability to perform a task suggested that participants were aware of delta-9-THC-induced effects for several hours post-smoking (Table 3 and Fig. 4). This may have meant that they were aware of performance impairment in the tasks they were completing and perhaps actively compensated for such impairment in performing the tasks more slowly. This is less probable when the instructions given to the participants stressed speed than when they stressed accuracy. In the present study, no specific instructions were given to stress speed or accuracy.

Table 3 Mean (SD) cardiovascular and subjective parameters at baseline and after smoking

	Placebo THC (0%, *n*=20)	29.3 mg THC (9.8%, *n*=18)	49.1 mg THC (16.4%, *n*=20)	69.4 mg THC (23.1%, *n*=20)
Baseline measure				
Heart rate (bpm)	74.4 (10.9)	73.6 (14.1)	75.5 (11.9)	73.2 (14.1)
'I am able to perform the task' (mm)	80.1 (18.0)	75.4 (21.8)	82.2 (19.7)	72.3 (21.4)
'I feel drowsy' (mm)	31.2 (29.8)	41.7 (30.8)	34.0 (29.4)	42.4 (31.2)
Change				
Heart rate (beats per min)[a]	+11.3 (10.2)	+48.5 (13.3)	+50.00 (14.8)	+56.45 (21.0)
'I feel high' (mm)[a,b]	+7.4 (13.6)	+46.7 (26.0)	+52.1 (25.4)	+72.0 (20.3)
'I am able to perform a task' (mm)[c]	−1.3 (19.7)	−13.1 (18.5)	−19.3 (23.1)	−31.9 (33.2)
'I feel drowsy' (mm)[c]	−0.4 (31. 3)	+14.3 (27.4)	+16.6 (41.0)	+26.1 (35.6)

[a] Change = measurement at 17 min post-smoking—baseline measurement
[b] Baseline measurements of high feeling were all equaled to 0
[c] Change = measurement at 108 min post-smoking—baseline measurement

Slower reaction time was observed in our study from 37 min until 5 h after onset of smoking. This slower response time at 90 min was probably related to the high THC serum concentration, whereas the slower reaction time at 300 min may be related to coexistent drowsiness. Slower reaction times had consequences on the other tasks performed in the meantime, as these tasks included a reaction time as well. The reaction time component includes processing stages such as identification of the stimulus and preparation and execution of the response. Contradictory results have been reported in previous studies for the reaction time task. A dose–effect relation between decrease in motor speed and THC dose was reported after smoking cannabis cigarettes at much lower doses than in our study. Reaction time increased from 400 to 430 ms after THC exposure to doses ranging between 0 and 250 μg/kg (i.e. a maximum dose of circa 18.5 mg for 74 kg body weight) in cannabis users smoking three or less times per week (Borg et al. 1975). The reaction times were longer in the Borg study than in our study because in the former, the participants had to move their hand, whilst in our study, they only had to press a button. In another study, reaction time was unaffected immediately after 16 puffs of a 3.55% THC cigarette that

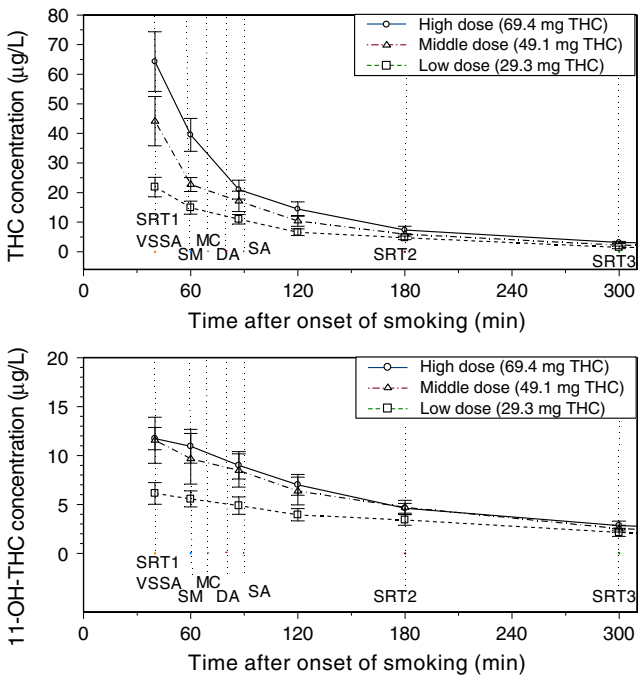

Fig. 3 Mean (±SEM) THC (*top graph*) and 11-OH-THC (*bottom graph*) serum concentrations at the times the cognitive and psychomotor tasks were performed (*n*=18, 20 and 20 participants, respectively, for the low, middle and high THC doses). *SRT1* first simple reaction time, *VSSA* visuo-spatial selective attention, *STM* short-term memory, *MC* motor control, *DA* divided attention, *SA* sustained attention, *SRT2* and *SRT3* second and third simple reaction time tasks

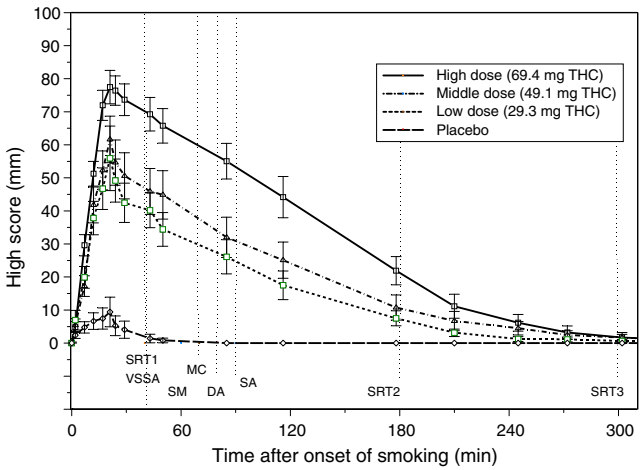

Fig. 4 Mean (±SEM) high scores over time (*n*=18, 20 and 20 participants, respectively, for the low, middle and high THC doses). *SRT1* first simple reaction time, *VSSA* visuo-spatial selective attention, *STM* short-term memory, *MC* motor control, *DA* divided attention, *SA* sustained attention, *SRT2* and *SRT3* second and third simple reaction time tasks

resulted in a mean THC Cmax of 188 ng/mL (Heishman et al. 1997). Unfortunately, no reaction times were reported in this article for the simple reaction task. This lack of cannabis effect could be explained by the fact that the participants included in the Heishman's study were heavier cannabis users than those included in the present study.

A general linear effect on response time was observed in the three attention tasks (the selective attention, the divided attention and the sustained attention tasks) for THC doses up to 69.4 mg. Attention has been defined by W. James as follows: "[Attention] is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalisation, concentration of consciousness are of its essence" (James 1890). In the present study, we assessed different aspects of attention that were already recognised in James's definition. Selective attention, referring to the capacity to maintain a behavioural set in the face of competing stimuli; sustained attention, that is the capacity to maintain a consistent behavioural response during continuous and repetitive activity; and divided attention or the capacity to respond simultaneously to multiple tasks (a motor control task and a short-memory task in the present study). The number of errors significantly increased with increasing THC doses in the sustained attention task. In this task, the participants had to detect infrequent stimuli over a prolonged period of approximately 10 min, whilst their THC serum concentration had already substantially decreased. At that time, however, the THC serum concentration was still 2.22 and 3.12 ng/mL on average, respectively, with the 49.1 mg and 69.4 mg THC cigarettes (Fig. 3).

Short-term memory impairment continued to increase in terms of response time and number of errors with increasing dose of THC up to 69.4 mg. Contradictory results have been reported in the literature. In the Heishman's study, the Sternberg test was also used with sets of digits consisting of five to seven digits (Heishman et al. 1997). It was not affected by cannabis in spite of 16 puffs of a 3.55% THC cigarette in heavier cannabis users. No response time and no number of errors were reported for the task. However, in the same study, another memory task was impaired, the so-called word recall task. This task consisted of the presentation of words the participants had to remember and then write down during a 2-min free recall period. The number of correct responses was found to be dose-related, with eight right answers on average after four puffs versus five after 16 puffs. It seems much harder to show drug effects on recognition memory tasks than on free recall tasks. Despite the fact that the short-term memory task employed in this study could be characterised as a short-term recognition memory task, we did show acute cannabis effects.

In Hart's study, an eight-digit recall task was impaired after administrating three puffs of a 3.9% THC cigarette, but not after three puffs of a 1.8% THC cigarette (Hart et al. 2001). No response times and no numbers of errors were mentioned in the article. Subjects included in the Hart study were smoking 24 joints per week and were likely tolerant to the effects of cannabis and insensitive to the test battery. Deficit in short-term memory has been shown to contribute to poor performance in decision-making tasks (Bechara and Martin 2004). Two recent studies conducted in controlled laboratory conditions have reported that acute exposure to cannabis produced measurable change in decision making (Lane et al. 2005; Ramaekers et al. 2006a). Several studies conducted in natural settings have shown that cannabis use is associated with risky behaviour like high-risk sexual activity or crime (Watts and Wright 1990, Brook et al. 1999; Duncan et al. 1999; Staton et al. 1999).

The dose-related tracking impairment was already known from previous studies (Barnett et al. 1985; Ménétrey et al. 2005) and was also clear in our study. In the present study, the tracking test, used to measure driving impairment indirectly (Ramaekers 2003), revealed significant impairment even at the easiest level with the highest dose (69.4 mg THC). A dose-related tracking impairment has been reported previously after smoking cannabis cigarettes with THC in doses between 70 and 250 μg/kg in cannabis users smoking cannabis three or less times per week (Borg et al. 1975; Barnett et al. 1985). However, the association between serum THC concentration and the magnitude of motor impairment seemed to be weak at a 500-μg/kg dose (Ramaekers et al. 2006b). Some studies reported no impairment of motor control after exposure to cannabis. In a study in which a concurrent pursuit tracking and vigilance task was performed, the tracking portion was actually improved following the high THC dose, i.e. three puffs of a 3.9% THC cigarette as compared to the other lower doses (0% and 1.8%; Hart et al. 2001). The absence of impairment could be explained by the fact that the participants included in this previous study were daily users of cannabis, in other words, people who might have developed tolerance to the effects of cannabis (Hollister 1986; D'Souza et al. 2008; Cooper and Haney 2008).

The dose–effect relationship observed in the study population, however, was not observed in four participants. They did not disclose acute psychomotor impairment above the placebo effect range despite increased THC serum concentrations. Two main reasons may explain those subjects to be insensitive to THC effects: tolerance or innate differences. Prolonged and heavy treatment with cannabis produces a tolerance phenomenon for most of the pharmacological effects of these substances (Jones et al. 1981; Hollister 1986). At the cellular level, attenuation of both CB1 receptor binding (down-regulation) and CB1 agonist-stimulated G-protein activation (desensitisation) are believed to contribute to tolerance (Martin et al. 2004;

D'Souza et al. 2008). Age, BMI and average number of joints smoked during the previous months by those participants were comparable with the rest of the group, but those four participants had smoked cannabis for a longer time. No significant relation was found between motor control impairment and participants' past cannabis use, but we could not check the veracity of participants' declarations. In fact, recent studies have shown that even light users of cannabis show blunted responses to effects of THC that are suggestive of tolerance (D'Souza et al. 2008). Concerning innate differences, a recent study has shown that polymorphism of the catechol-methyl-transferase (COMT) gene moderates the response to cannabis and may influence the susceptibility to the psychomimetic effects of cannabis (Henquet et al. 2006). Innate differences could not be investigated in our study since no DNA material was collected. Anyway, the fact that some of the participants did not show any impairment despite THC serum concentrations higher than 40 μg/L demonstrates that knowing only the THC serum concentration of a subject, no definitive conclusions can be made on a possible psychomotor impairment of this subject.

Some study limitations should be mentioned. Firstly, for safety reasons, a maximum heart rate limit of 170 bpm and a minimum mean arterial blood pressure limit of 55 mmHg were imposed by the protocol (Hunault et al. 2008). In six out of 72 non-placebo exposures (8%), it was necessary to interrupt smoking temporarily (Hunault et al. 2008). This slowed down the THC absorption rate and may have weakened the psychomotor effects. This underestimation of risk may have been counterbalanced by the experimental conditions in which participants were required to smoke the entire joint even if it caused unpleasant effects. In spite of this possible limitation, linear dose–effect relations have been observed for the vast majority of outcome measures. Secondly, we used a mix of tobacco and cannabis and not pure cannabis as in the majority of the previous studies. We wanted to assess the potential risks of cannabis cigarettes with high THC content similar to the cigarettes currently available on the Dutch market, and our experiment reflects therefore better the practice of Dutch cannabis users than the majority of the studies hitherto published. Interaction between nicotine and THC has been studied in mice with very high THC doses (5 until 10 mg/kg, administered 5 days long). The authors observed that nicotine increased the latency of response in a tail immersion test and a hot plate test (Valjent et al. 2002). As far as we know, no study has been conducted in humans about interaction between THC and nicotine. In our study, nicotine may have strengthened the impairment in motor control and the increase in heart rate by cannabis. Thirdly, only males were included in the present study because of differences in adipose tissue distribution between male and female that could have induced differences in the cannabis pharmacokinetics. Finally, in the experimental conditions of the study, participants were required to smoke entire joints even if it caused unpleasant effects. It is unclear how cannabis users handle high THC-containing cigarettes in the natural ecology and whether they are able to modify their smoking behaviour to titrate to a high feeling corresponding with a desired plasma THC level. In this study, we observed that the participants had no time to titrate before the occurrence of physical effects. Heart rate reaching 170 bpm or blood pressure dropout, when they occurred, occurred within the first minutes and sometimes required a transitory stop (Hunault et al. 2008). After such a transitory stop, the participants usually smoked less deeply, thus effectively titrating dose after they felt physical effects or a high feeling.

In conclusion, the linear relationship between THC dose and cognitive, psychomotor and subjective effects continued at THC concentrations up to 69 mg. Effects were observed for participants already used to cannabis. If cannabis smokers are unable to titrate to a high feeling corresponding to a desired plasma THC level when smoking cannabis cigarettes, cannabis with high THC concentrations may be of greater concern for public health and safety than cannabis with lower THC concentrations.

Acknowledgements This study was funded by the Dutch Ministry of Health, Welfare and Sport which had no further role in study design, data collection, analysis and interpretation of data and writing the reports. The authors declare that the study complies with the current Dutch laws, i.e. the country in which the study was performed. The authors wish to express their gratitude to Andrew Clark for his linguistic advice. The authors also acknowledge the anonymous reviewers of *Psychopharmacology* whose suggestions greatly improved this article.

Appendix 1

Table 4 Multilevel models used for the different tasks: the PROC MIXED was used to fit mixed effects models (SAS v9.1)

	Outcome variable	Fixed effect(s)	Confounders
SRT	Response time	THC dose Time THC dose × time	BMI Previous cannabis use Time to smoke the joint
VSSA	Response time	THC dose	BMI Previous cannabis use Time to smoke the joint Congruency
STM	Response time	THC dose	BMI Previous cannabis use Time to smoke the joint Load
MC	Tracking deviation	THC dose	BMI Previous cannabis use

Table 4 (continued)

	Outcome variable	Fixed effect(s)	Confounders
			Time to smoke the joint
			Level of difficulty
DA-STM	Response time	THC dose	BMI
			Previous cannabis use
			Time to smoke the joint
DA-MC	Tracking deviation	THC dose	BMI
			Previous cannabis use
			Time to smoke the joint
SA	Response time	THC dose	BMI
			Previous cannabis use
			Time to smoke the joint

P values for the tests of the within-subject effects were adjusted using a Bonferroni correction computed as $\alpha \equiv 1-(1-\pi)^{1/n} = 1-(1-0.05)^{1/9} = 0.006$, *n* being the number of variables tested (column 'Fixed effects' in the table). *SRT* simple reaction time, *VSSA* visuo-spatial selective attention, *STM* short-term memory, *MC* motor control, *DA-STM* short-term memory part of the divided attention, *DA-MC* motor control part of the divided attention, *SA* sustained attention tasks, *BMI* body mass index (weight/length^2)

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