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A study investigating the acute dose–response effects of 13 mg and 17 mg Δ 9- tetrahydrocannabinol on cognitive–motor skills, subjective and autonomic measures in regular users of marijuana

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Abstract

Heavy use of marijuana is claimed to damage critical skills related to short-term memory, visual scanning and attention. Motor skills and driving safety may be compromised by the acute effects of marijuana. The aim of this study was to investigate the acute effects of 13 mg and 17 mg Δ 9-tetrahydrocannabinol (THC) on skills important for coordinated movement and driving and on subjective and autonomic measures in regular users of marijuana. Fourteen regular users of marijuana were enrolled. Each subject was tested on two separate days. On each test day, subjects smoked two low-nicotine cigarettes, one with and the other without THC.
Seventeen mg THC was included in the cigarette on one test day and 13 mg on the other day. The sequence of cigarette types was unknown to the subject. During smoking, heart rate and blood pressure were monitored, and the subjects performed a virtual reality maze task requiring attention and motor coordination, followed by 3 other cognitive tasks (Wisconsin Card Sorting Test (WCST), a "gambling" task and estimation of time and distance from an approaching car). After smoking a cigarette with 17 mg THC, regular marijuana users hit the walls more often on the virtual maze task than after smoking cigarettes without THC; this effect was not seen in patients after they smoked cigarettes with 13 mg THC. Performance in the WCST was affected with 17 mg THC and to a lesser extent with the use of 13 mg THC. Decision making in the gambling task was affected after smoking cigarettes with 17 mg THC, but not with 13 mg THC. Smoking cigarettes with 13 and 17 mg THC increased subjective ratings of pleasure and satisfaction, drug "effect" and drug "high". These findings imply that smoking of 17 mg THC results in impairment of cognitive–motor skills that could be important for coordinated movement and driving, whereas the lower dose of 13 mg THC appears to cause less impairment of such skills in regular users of marijuana.

Key words

attention; marijuana; maze; motor skills; THC

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Introduction

Marijuana has become the most popular illicit drug in the western world and is becoming a major concern for healthcare authorities (Substance Abuse and Mental Health Services Administration, 2004). It has been established that the acute use of marijuana damages motor skills and can thus affect driving safety. Studies of the incidence of reckless driving due to the acute effects of marijuana, cocaine and alcohol, indicated that, after alcohol, marijuana is responsible for the highest rate of car crashes and consequent death (Soderstrom, *et al*., 1995; Stoduto, *et al*., 1993; Chipman, *et al*., 2003). Moreover, it is also known that an increased level of Δ9-tetrahydrocannabinol (Δ9-THC), the active ingredient in marijuana, is related to a higher risk of car crashes (Ramaekers, *et al*., 2004).

There have also been studies showing the acute effects of marijuana on cognitive–motor function. Liguori, *et al*. (2002) found that marijuana may increase body sway and imbalance without affecting braking speed, whereas alcohol prolongs braking time without affecting body tilt. Curran, *et al*. (2002) have reported that recreational users of marijuana made more errors in the Gibson spiral maze task when they smoked cigarettes with 15 mg THC.

Mixed findings have been reported by others regarding impaired performance in cognitive tests on THC. Hart, *et al*. (2001) showed impaired cognitive performance in regular users of marijuana at two doses of THC, but impairment was only significant at the higher dose, equivalent to approximately 30 mg THC (Nordstrom and Hart, 2006). Participants who were heavy users of marijuana (24 cigarettes a week) showed impaired performance on 30 mg THC on reaction time on an immediate recall test and on mental calculation task and also made more premature responses on a reaction time task. They were not impaired on other measures of accuracy of response on attention, memory, visuo-spatial processing, reasoning, flexibility and mental calculation tasks. Ramaekers, *et al*. (2006) also showed dose-related impaired performance in cognitive tasks in recreational users of marijuana. They measured the effects of two doses, equivalent to 17.5 mg THC and 35 mg THC, on tasks which measured perceptual-motor control (critical tracking task), motor impulsivity (stop signal task) and cognitive function (Tower of London), with significant effects still present at the lower dose used.

Maze tasks have been used extensively for measuring cognitive–motor skills and brain metabolic activity in healthy volunteers and clinical populations and for measuring the effects of drugs or medication on human subjects, in particular in nicotine dependence (Ghatan, *et al*., 1995, 1998; Levin and Simon, 1998). Ghatan, *et al*. (1995, 1998) used maze tasks together with positron emission tomography imaging to show that maze performance involves brain areas responsible for attention, motor skills and visual processing. Virtual reality tasks can mimic real-life situations, and recent applications in psychology and psychiatry have included use of a virtual maze task for diagnosis of schizophrenia (Sorkin, *et al*., 2006).

In our preliminary study (Brickner, *et al*., 2005), we used a virtual reality maze task to check the effects of Δ-9 THC on maze performance in regular users of marijuana. Findings suggested that on 13 mg Δ-9 THC, users had difficulties in moving accurately in the maze (bumping into walls) and in learning the rules governing exit from the maze. It has become evident that the task required visuo-spatial and memory abilities. Another preliminary study by Ronen, *et al*. (2005) compared the effects of 13 mg THC and 17 mg THC on behaviour in a driving simulator in recreational users of marijuana (subjects who smoke on weekends only). They found a dose–response effect on driving performance as well as subjective and autonomic measures. A previous study by Perez-Reyes, *et al*. (1982) has also shown that THC produces dose–response effects on Δ-9 THC plasma concentration, heart rate acceleration and psychological ratings within the range of 10 mg–20 mg THC.

Based on these preliminary studies and the work of others described above, it is apparent that the acute effects of marijuana use may include impairment of cognitive function that could impact driving safety. However, many important parameters relating to this impairment are not yet well defined. This study aims to contribute to the knowledge of the THC dose at which marijuana use may pose a risk to driving safety in regular users and the specific aspects of cognitive function that are affected by THC. Thus the principal aims of the current study were to investigate the acute effects of 13 mg and 17 mg doses of Δ-9 THC on cognitive–motor skills (i.e. speed and accuracy) during maze performance in regular users of marijuana and three cognitive tasks that measure mental flexibility – Wisconsin Card Sorting Task (WCST), decision making - the "Gambling Task," and a task requiring estimation of time and distance from an approaching car. Finally, it was our aim to compare the acute effects of smoking 13 mg and 17 mg THC on measures of heart rate and blood pressure and subjective effects of the drug in regular users of marijuana.

Methods and materials

Subjects

Fourteen subjects were recruited by contacts and advertisements among students. They were all regular users of marijuana, 10 males and 4 females of average age 27 (s.d. = 7.45), and had used at least one cigarette with marijuana a day for at least 5 years. The average age at first use was 19 years and 6 months. Subjects reported that they did not regularly use other drugs, as supported by the results of urine testing on each of the two days of testing. All subjects fulfilled the study criteria of drinking less than 2 units of alcohol a day, smoking less than 20 cigarettes with nicotine a day, drinking less than 3 cups of coffee a day and normal body weight. They were assessed by a psychiatrist (MB) who confirmed their suitability to give informed consent and that they met the DSM-IV (American Psychiatric Association, 1994) criteria for marijuana dependence. As a further check and precautionary measure,

they also testified that they have not been diagnosed before as suffering from a psychiatric or neurological disorder. Subjects confirmed that they did not take any medication and had no medical history or current condition that might affect the central nervous system. Pregnancy was also an exclusion criterion since subjects also participated in an imaging protocol and radiation exposure is risky for the foetus. They were requested to refrain from using marijuana the night before testing, but no testing was carried out to confirm this. During the day of testing, starting two hours before testing, subjects were not allowed to drink coffee or any drink but water, smoke cigarettes or eat. All subjects were right handed with normal or corrected-to-normal vision. They were paid $50 for both sessions.

Δ-9 Tetrahydrocannabinol

Δ-9 THC was prepared in the laboratory of RM (see Gaoni and Mechoulam, 1964, for preparation and synthesis of Δ-9 THC). It was mixed with 95% ethanol and it was then injected into cigarettes containing 0.1 mg nicotine. The ethanol evaporated leaving the cigarette with pure Δ-9 THC. A plastic filter was attached to each cigarette instead of the cigarette's original filter. A rolling paper was rolled around the cigarette to hide the stains of THC. The experiment was approved by the IRB committee of Sourasky Medical Centre in Tel Aviv and the Pharmacy Division of the Ministry of Health in Israel. The principal investigator obtained a special license to maintain and use THC from the District Pharmacist in Tel Aviv. All subjects were insured for the quality of Δ-9 THC to cover possible damage by the drug. Due to the lack of facilities for analysis of THC in the blood, no blood samples were taken for such analysis. It is established that after smoking THC, the plasma concentration of THC increases to reach a peak (approximately 3 to 8 min) and then decreases quickly (half-life of approximately 30 min; Verstraete, 2004).

Psycho-motor tasks

The virtual maze task This version is based on a commercial computer game Wizardry 8 (Sirtech Canada Ltd; for details see http://www.wizardry8.com). The player wore eye glasses with an eye tracker attached (InterTrax2/i-O Display SVGA I-Glasses PC with Head Mounting System bundle; for details see http://www.i-glasses.com). The virtual reality glasses and tracker enabled the player to see the maze in three-dimensional displays, and it avoided distraction from visual items outside this visual field. In the computer simulated task, the player was situated on a desert island and was required to open a door and move inside a maze by using the arrow keys of the computer keyboard. The players navigated the maze via corridors and had to choose between different routes in order to reach the exit door. Subjects were instructed to perform the task as quickly and accurately as they could and that reaction times and number of hits of the walls would be recorded. They were not instructed about any trade off between speed and accuracy. After a few practice trials, all subjects learned how to move with optimal speed and accuracy and how to finish the maze in about a minute. Subjects performed the task repeatedly for 25 min. Time to complete the maze and accuracy (number of collisions with the walls in each trial) were recorded manually.

Further cognitive tasks. The following tasks measure cognitive abilities such as executive function and estimates of time and space. They do not specifically measure the visuo-spatial attention and memory abilities that are required in the maze task. The "Wisconsin Card Sorting Task" (WCST) was previously used to measure attention and mental flexibility in multiple clinical populations including marijuana users (Bolla, *et al*., 2002) and opiate-dependent patients (Rotheram-Fuller, *et al*. 2004). We used the version described by Rotheram-Fuller, *et al*. (2004) with a larger number of trials (200 instead of 128). It required sorting of cards into 3 different conditions of matching, according to colour, shape and number. Each block consisted of 10 presentations that were all of the same matching condition (i.e. colour, shape or number). After each block, the criterion was changed. There were 20 blocks of presentations, thus in total 200 presentations. It took between 15 and 20 min to complete the task, depending on speed of response of individual subjects. Task performance was assessed by 5 measures: 1) Total number of blocks without error (10 items in each block). 2) Errors of perseverance due to disregarding changes of category (colour, shape or number), indicating inflexibility. 3) Non-perseverance errors – errors within categories indicating inattention. 4) Total number of errors = perseverance + non-perseverance. 5) Number of trials required to complete the first category without errors.

The "gambling task" (Bechara, et al., 1994, 1996) This has been used to demonstrate impaired decision making in heavy marijuana users (Whitlow, *et al*., 2004) and in poly-drug abusers (Rogers, *et al*., 1999a; Grant, *et al*., 2000). In our study, we used the gambling task described in detail by Rogers, *et al*. (1999b). There were five conditions of probability (10 vs. 90, 20 vs. 80, 30 vs. 70, 40 vs. 60 and 50 vs. 50) and 40 presentations of each of the 5 conditions, 200 altogether. It took between 15 and 20 min to complete the task depending on the speed of response of each subject.

The data analyses looked at two main features: 1) speed of decision making, 2) quality of decisions – per cent of choice of the most likely outcome (i.e., the colour with the highest number of boxes).

Estimate of time and distance from a car Since marijuana is known to affect the perceptions of time and space (Block, *et al*., 2000), we set out to assess whether marijuana affects estimates of time and distance. We have designed a novel test in which we recorded time and distance estimates of a real-life approaching car to assess the effects of THC on these skills. Subjects stood by a pedestrian crossing and were required to estimate the time and distance with respect to an approaching

car. A research assistant recorded the actual time with a stopwatch. The actual distance from the car, i.e., the distance from the distant pedestrian crossing to the pedestrian crossing where the subject stood, was measured. The actual range of time of arrival was between 4 and 19 s and the distance between the two pedestrian crossings was 48 meters throughout the study. There were 5 estimates in each condition of the study.

Procedure

Each participant was tested on two days separated by a week. At the start of each test day, there were practice trials of each of the tasks; these practice trials were excluded from analysis and were followed by baseline measures (10 maze trials, 1 WCST trial, 1 gambling task trial and 5 car estimate trials) until all subjects reached a ceiling performance at baseline. After this practice, baseline heart rate and systolic/diastolic blood pressure were measured. Subjects were then given a cigarette and were requested on each breath to hold the smoke in their lungs for 1 min and then to exhale for 10 s. Cigarettes were finished within 5 min (5–10 puffs). It should be mentioned that some subjects could not hold the smoke in their lungs for 1 min and exhaled earlier. Measures of heart rate and blood pressure were then taken again immediately after the subjects finished smoking the cigarettes. The subjects were then allowed to take up the virtual maze task for 25 min. Time to complete the maze and the number of collisions against the walls were recorded manually. Forty minutes after the beginning of smoking, the subjects were asked to fill in a questionnaire on the subjective effects of marijuana. The timing of filling in of the questionnaire was chosen in view of previous evidence that peak subjective effects of marijuana are experienced from approximately 15–40 min after smoking (Perez-Reyes, *et al*., 1982). After filling in the questionnaire, subjects performed the WCST, gambling task and car estimate task. Two hours after the first cigarette, subjects were given a second cigarette to smoke, and the subjects followed exactly the same procedure as that for the first cigarette. Heart rate and blood pressure were measured again immediately before and after smoking the cigarette and subjects then proceeded to complete the same sequence of maze task, questionnaire and other cognitive tasks again.

On one test day (test day 1), the first cigarette contained 17 mg THC, while the second cigarette was without THC; the condition after smoking this cigarette is referred to subsequently in this paper as non-THC 1. On the other test day (test day 2), the first cigarette was without THC (this condition is referred to as non-THC 2), whereas the second cigarette contained 13 mg THC. The two test days were counter-balanced among the subjects, so six of them underwent test day 1 first and six underwent the test day 2 first.

The research assistant who gave the cigarettes to the subjects was blinded with regard to the THC content of the cigarettes. Five subjects identified the cigarettes with THC according to their effects, whereas others did not.

Questionnaire

Subjective measure questionnaire was aimed at describing subjective experience of the effect of the drug, including ratings on visual analogue scales with distinct points (1, 2, 3, 4, 5, 6, 7) on 3 subscales:

1) Symptoms: dry mouth, "high," muscle tension, pain in the jaw, prickly pain.
2) Subjective feelings: pleasure, satisfaction, feeling the drug, enjoyment, want, desire, alertness, relaxation, concentration, sense of memory function.
3) Mental states: Paranoia, fear, depersonalisation, psychotic, dissociation, depressed.

Statistical analysis

Statistical analysis of all tasks, autonomic measures (heart rate, systolic and diastolic blood pressure) and questionnaire ratings was performed using paired *t*-tests. For analysis of autonomic measures, to allow for daily variations, rather than analyzing heart rate and blood pressure values, we analyzed differences between pre- and post measures for each cigarette smoked, thus using the pre-smoking measures in each case as a baseline for the measurements made immediately after smoking.

In view of the crossover treatment design and the possibility of time of day and learning effects on cognitive tasks, and the numerous comparisons, ANOVA was also performed. Within-subject effects were tested for sequential day (1st vs. 2nd day) and order within day (baseline vs. 1st cigarette vs. 2nd cigarette) as well as drug effect (no THC vs. 13 mg, THC vs. 17 mg THC). In the case of the pre–post cigarette differences in heart rate and blood pressure, and the questionnaire, where there were no baseline measurements, order within day was defined with only two states (1st vs. 2nd cigarette). Between-subject variability was assumed to be a random effect.

Results

Autonomic measures

Mean heart rate, systolic and diastolic blood pressures increased on smoking all cigarettes, both with and without THC, though there was considerable inter-subject variability, with heart rate and blood pressure decreasing in a few subjects. To avoid potential problems due to fluctuations in autonomic measures, rather than analyzing blood pressure and heart rate *per se*, statistical analysis was performed throughout on the increases in blood pressure and heart rate from pre- to post-smoking. ANOVA indicated no significant drug effect for heart rate and only a slight drug effect for increase in systolic blood pressure [$F(2,37) = 2.94$; $P = 0.1$] and diastolic blood pressure [$F(2,37) = 2.65$; $P = 0.1$]. It also indicated no significant order within day effects for increases in heart rate and in systolic and diastolic blood pressures.

Analysis of specific effects using paired *t*-tests showed that cigarettes with 17 mg THC did not significantly raise mean heart rate, systolic and diastolic blood pressures, compared with the non-THC 2 cigarettes (first cigarette on test day 2). Significant differences were found between mean elevations in heart rate ($t = 2.48$; $P < 0.05$) and systolic blood pressure ($t = 2.47$; $P < 0.05$) on 17 mg THC compared with the non-THC 1 cigarette (second cigarette on test day 1). Significant increases in heart rate ($t = 2.87$; $P < 0.05$) and systolic blood pressure ($t = 2.58$; $P < 0.05$) were also found with 17 mg THC compared with 13 mg THC.

Mean increase in diastolic blood pressure was significantly higher with 13 mg THC compared with the non-THC 1 cigarette ($t = 2.72$; $P < 0.05$), but otherwise increases in mean heart rate and blood pressure with 13 mg THC did not differ significantly compared with the non-THC cigarettes. See Figure 1 for summary of the effects of THC on autonomic measures.

The effects of tetrahydrocannabinol on the questionnaire of subjective measures

ANOVA revealed significant drug effects for subjective measures of pleasure [$F(2,37) = 4.53$; $P < 0.05$], satisfaction [$F(2,37) = 3.36$; $P < 0.05$], drug "effect" [$F(2,37) = 3.93$; $P < 0.05$], "high" [$F(2,37) = 4.38$; $P < 0.05$], alertness [$F(2,37) = 4.58$; $P < 0.05$], and dry mouth [$F(2,37) = 4.19$; $P < 0.05$]. Order within day effects were also identified for alertness [$F(1,37) = 8.57$; $P < 0.01$] and for muscle tension [$F(2,37) = 7.23$; $P < 0.05$].

Analysis of specific effects using paired *t*-tests showed that subjects rated smoking the cigarette with 17 mg THC as significantly more pleasurable than smoking the non-THC 2 cigarette ($t = 2.72$; $P < 0.05$) and felt more satisfied ($t = 2.25$; $P < 0.05$). They also felt more "high" ($t = 2.33$; $P < 0.05$), and less alert ($t = 2.72$; $P < 0.05$), and felt more sense of a dry mouth ($t = 2.58$; $P < 0.05$). In comparison with the same non-THC 2 cigarette, subjects also rated smoking the cigarette with 13 mg THC as significantly more pleasurable ($t = 3.37$; $P < 0.01$) and felt more satisfied ($t = 2.25$; $P < 0.05$), felt greater drug effect ($t = 3.98$; $P < 0.01$), more "high" ($t = 3.68$; $P < 0.01$), dry mouth ($t = 3.23$; $P < 0.01$), and less alertness ($t = 4.31$; $P < 0.001$), though this effect on alertness may have been due at least in part to the order effect which indicated lower alertness later in the day. Subjects also reported significantly more muscle tension ($t = 2.59$; $P < 0.05$), though this again may have been due at least in part to the order effect which showed increased muscle tension later in the day, and more desire ($t = 2.52$; $P < 0.05$), after smoking the 13 mg THC cigarette than after smoking the non-THC 2 cigarette.

Figure 2 shows subjective ratings of pleasure, satisfaction, "drug effect" and "high" after smoking cigarettes with 17 mg THC, non-THC 1, non-THC 2 and 13 mg THC. Note that while the differences between non-THC 1 and non-THC 2 are not significant, these subjective ratings were all higher for non-THC 1 than for non-THC 2.

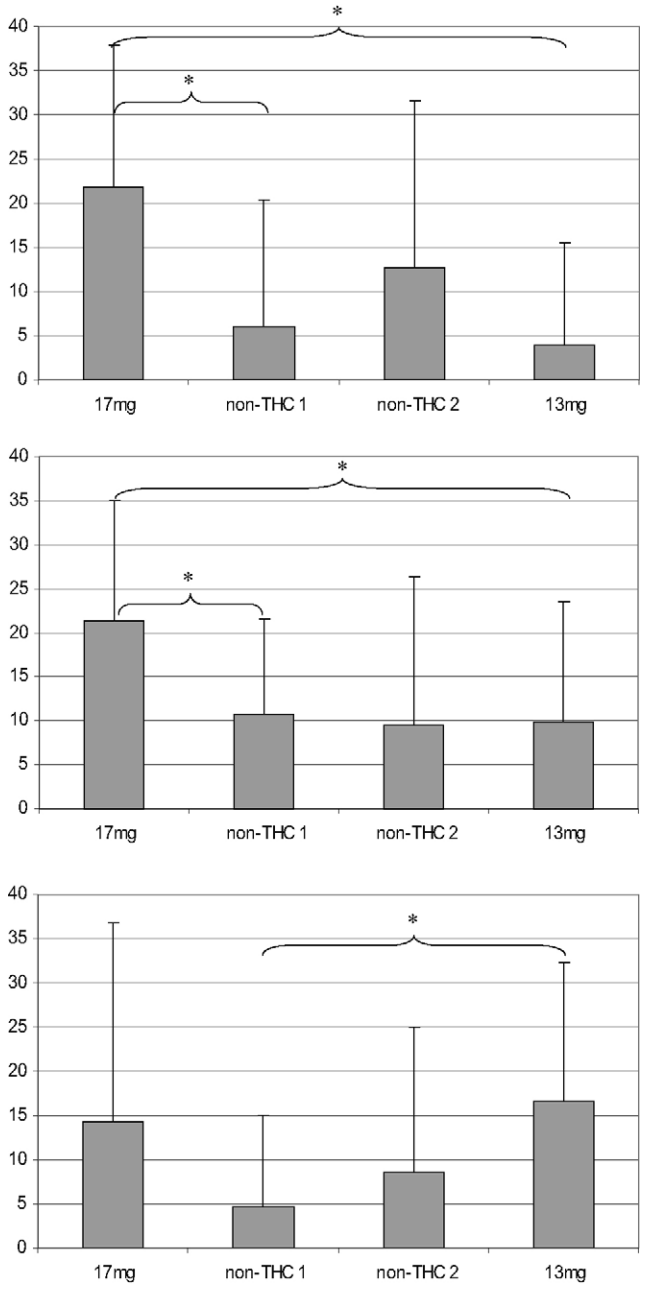

Figure 1 Autonomic measures: mean and standard deviations for changes in 1a) heart rate (beats per minute), 1b) systolic blood pressure (mmHg) and 1c) diastolic blood pressure (mmHg) due to smoking of cigarettes on day 1; with 17 mg THC, without THC (non-THC 1), and on day 2: without THC (non-THC 2), and 13 mg THC, in 14 regular users of marijuana. Non-THC 1 and 2 refer to the cigarettes without THC smoked on test day 1, 2 h after the smoking of the 17 mg THC cigarette, and the first cigarette smoked on test day 2, respectively. The figure indicates where differences between THC and non-THC cigarettes were significant[a]. [a] * $P < 0.05$.

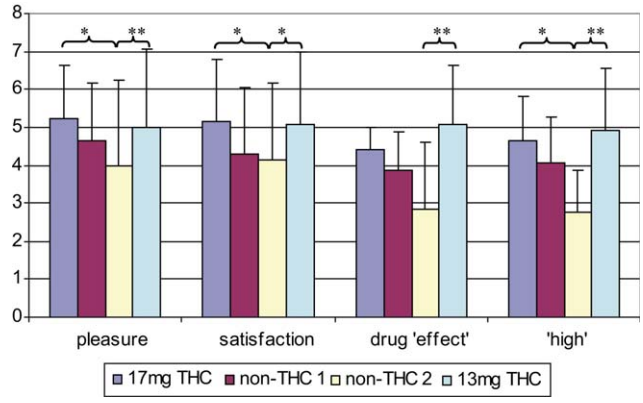

Figure 2 Measures of subjective ratings of pleasure, satisfaction, "drug effect" and "high" on the visual analogue scales (1, 2, 3,... 7) in 14 regular smokers of marijuana after they smoked cigarettes on day 1 with 17 mg THC, and without THC (non-THC 1), and on day 2 without THC (non-THC 2), and 13 mg THC. The figure shows significantly increased subjective ratings of pleasure, satisfaction, "drug effect" and "high" in subjects after they smoked cigarettes with 17 mg THC and 13 mg THC compared with non-THC 2. The figure indicates where differences between the THC cigarettes and non-THC 2 were statistically significant [a].
[a] $*P < 0.05$; $**P < 0.01$.

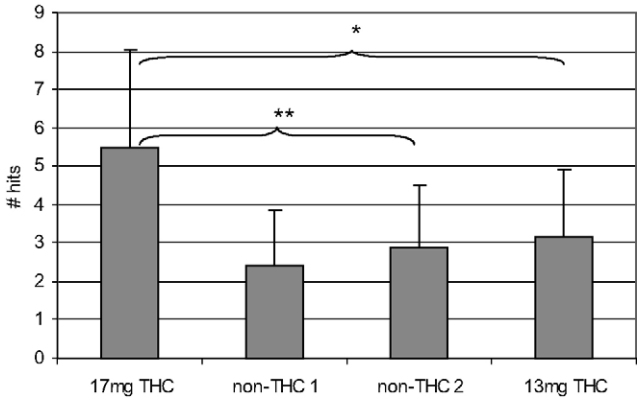

Figure 3 Measures of number of collisions during performance of the virtual maze task after smoking cigarettes with 17 mg THC, in 14 regular smokers of marijuana after they smoked a cigarette without THC (non-THC 1), without THC (non-THC 2) and with 13 mg THC. The figure shows increased number of collisions by subjects after smoking cigarettes with 17 mg THC compared with smoking non-THC cigarettes (non-THC 1 and non-THC 2) and compared with smoking cigarettes with 13 mg THC[a].
[a] $*P < 0.05$; $**P < 0.01$.

Virtual maze task

Response time for completion of the maze ANOVA indicated no significant drug effect on time for completion of the maze and highly significant order effects, for sequential day [$F(1,63) = 27.60$; $P < 0.001$] and for order within day [$F(2,63) = 12.03$; $P < 0.001$].

Mean times to complete the maze were 63.6 and 61.2 s for 17 mg THC and non-THC 1, respectively, and 61.7 and 60.5 s for non-THC 2 and 13 mg THC, respectively.

Number of collisions per trial ANOVA indicated a significant drug effect [$F(2,63) = 10.04$; $P < 0.001$), significant sequential day [$F(1,63) = 25.37$; $P < 0.001$] and order within-day [$F(2,63) = 7.07$; $P < 0.005$] effects on number of collisions with maze walls. Paired *t*-tests indicated the drug effect seen on ANOVA, showing higher collision rate in the 17 mg THC than in the non-THC 2 condition ($t = 3.57$; $P < 0.01$; mean numbers of collisions, 5.5 vs. 2.9, respectively), and higher collision rates after smoking a cigarette with 17 mg THC compared with those after smoking a cigarette with 13 mg THC ($t = 2.8$; $P < 0.05$; mean numbers of collisions 5.5 vs. 3.2, respectively) though this effect may be moderated by the "order" effect. There was no significant difference between 13 mg THC and non-THC 1 conditions (mean numbers of collisions, 3.2 vs. 2.4, respectively). Figure 3 shows the effect of THC on accuracy in performance of the maze task as indicated by the number of collisions per trial.

Wisconsin card sorting task

ANOVA identified significant drug effects for the total number of blocks completed without error [$F(2,63) = 3.45$; $P < 0.05$] as well as non-perseverance errors [$F(2,63) = 3.45$; $P < 0.05$]. There were no significant order effects on any of the categories measured.

Paired *t*-tests showed differences between 17 mg THC and the non-THC 2 condition in the number of blocks completed without error (means 16.2 vs. 17.8 blocks; $t = 2.47$; $P < 0.05$), errors of non-perseverance (means 5.3 vs. 3.2 errors; $t = 2.47$; $P < 0.05$) and total errors (means 5.7 vs. 3.8 errors; $t = 2.21$; $P < 0.05$). Significant differences were also found between 13 mg THC and non-THC 2 in number of blocks completed without error (means 16.6 vs. 17.8 blocks; $t = 3.16$; $P = 0.01$), errors of non-perseverance (means 4.3 vs. 3.2 errors; $t = 2.60$; $P < 0.05$) and total errors (means 5.0 vs. 3.8 errors; $t = 2.88$; $P < 0.05$). Note that the results for total errors relate mostly to the non-perseverance errors. No other significant effects were found.

Figure 4 shows the average performance on total number of blocks without error, non-perseverance errors and total errors over all subjects under all conditions of the experiment.

Gambling task

Speed of decision making ANOVA indicated no significant drug effect but highly significant order effects, both for sequential day and for order within day for response time in the gambling task for all odds. Table 1 shows speed on the gambling

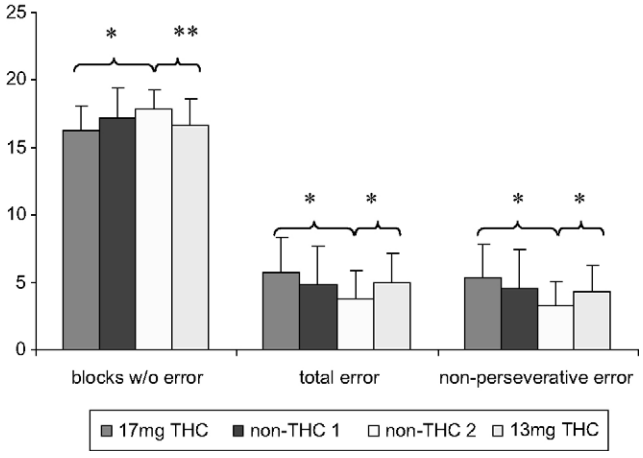

Figure 4 Measures of performance of WCST: total blocks completed without error, total number of errors, non-perseverance errors, in 14 regular smokers of marijuana after they smoked cigarettes on day 1: with 17 mg THC and without THC (non-THC 1), and on day 2: without THC (non-THC 2) and with 13 mg THC. The figure indicates where differences between the THC cigarettes and non-THC 2 were statistically significant[a].
[a] $*P < 0.05$; $**P < 0.01$.

task over all subjects under all conditions of the experiment, as well as F and P values for the order effects for each condition.

Quality of decision making – analysis of response choice Per cent of choice of the most likely outcome – ANOVA identified no significant drug effects and no significant order effects on any percentages of response choice. Analysis of simple effects using paired t-tests showed that in case of 17 mg THC, the percentage choices of the less likely outcomes, 20 vs. 80 and 10 vs. 90, were significantly higher than those on non-THC 2 ($t = 2.54$; $P < 0.05$; $t = 2.15$; $P < 0.05$, respectively). Comparison of 17 mg THC with non-THC 1 yielded no significant differences. Comparison of 13 mg THC with non-THC 2 and non-THC 1 both showed no significant differences.

Table 2 shows response choices on the gambling task in all subjects under all conditions of the experiment.

Estimate of time of arrival and distance from an approaching car

Estimate of time of arrival of a car ANOVA showed no significant drug effects and no significant order effects on estimates of arrival time.

Table 1 Reaction times, mean (standard deviation), in milliseconds, on all probability categories completed in the gambling task

Probability/condition	Test day 1			Test day 2			Order within-day effect	
	Base 1	17 mg THC	Non-THC 1	Base 2	Non-THC 2	13 mg THC		
50 vs. 50	1018 (387)	771 (169)	624 (253)	809 (445)	674 (296)	510 (202)	F(2,65) = 8.08	$P < 0.01$
40 vs. 60	953 (340)	717 (171)	562 (201)	767 (445)	627 (306)	508 (274)	F(2,65) = 7.34	$P < 0.01$
30 vs. 70	958 (251)	716 (204)	575 (203)	763 (390)	613 (269)	531 (217)	F(2,65) = 12.34	$P < 0.01$
20 vs. 80	919 (283)	725 (228)	571 (236)	872 (458)	666 (334)	519 (247)	F(2,65) = 10.19	$P < 0.01$
10 vs. 90	851 (272)	707 (199)	570 (231)	800 (535)	659 (313)	477 (197)	F(2,65) = 5.49	$P < 0.01$

These measures were taken on day 1 at baseline, after the subjects smoked cigarettes with 17 mg THC, without THC (non-THC 1) and on day 2 at baseline, after the subjects smoked cigarettes without THC (non-THC 2) and 13 mg THC.

Table 2 Quality of decisions in gambling task: mean (standard deviation) per cent of response choices in all probability categories

Probability/ condition	Test day 1			Test day 2			Diffs
	Base 1	17 mg THC	Non-THC 1	Base 2	Non-THC 2	13 mg THC	
50 vs. 50	67.6 (14.0)	66.2 (11.7)	70.9 (11.1)	64.8 (10.8)	70.0 (10.5)	71.2 (7.7)	Not significant
40 vs. 60	68.5 (7.4)	72.1 (8.6)	71.7 (7.3)	64.4 (12.4)	68.4 (10.0)	72.1 (9.9)	Not significant
30 vs. 70	72.5 (7.2)	69.5 (8.6)	71.7 (6.8)	68.3 (9.7)	70.0 (8.9)	71.4 (4.3)	Not significant
20 vs. 80	74.1 (8.1)	74.4 (6.0)	74.7 (9.4)	71.7 (9.9)	69.6 (7.1)	74.6 (9.9)	$P < .05$*
10 vs. 90	75.1 (9.4)	74.8 (8.8)	70.0 (12.0)	72.6 (9.2)	68.3 (10.5)	69.6 (12.3)	$P < .05$*

These measures were taken on day 1 at baseline, after smoking cigarettes with 17 mg THC, without THC (non-THC 1) and on day 2 at baseline, after smoking cigarettes without THC (non-THC 2) and 13 mg THC.
$*P < 0.05$ for difference between 17 mg THC and non-THC 2 conditions.

Table 3 Measures of mean differences between estimated and actual of time of arrival of a car (in seconds) and estimated and actual distance from a car (in meters) under all conditions over all subjects

Time estimates						
Time difference (secs)	Test day 1			Test day 2		
	Base 1	17 mg THC	Non-THC 1	Base 2	Non-THC 2	13 mg THC
Mean (S.D.)	−2.7 (3.4)	−1.7 (3.2)	−1.5 (2.9)	−2.1 (2.9)	−1.4 (2.8)	−3.1 (2.3)
Distance estimates						
Distance difference (metres)		Test day 1			Test day 2	
	Base 1	17 mg THC	Non-THC 1	Base 2	Non-THC 2	13 mg THC
Mean (S.D.)	−2.6 (13.1)	−2.1 (10.0)	−1.5 (8.0)	−3.3 (8.7)	−5.3 (7.9)	−5.7 (9.3)

These measures were taken on test day 1 at baseline, after the subjects smoked cigarettes with 17 mg THC, without THC (non-THC 1) and on test day 2 at baseline, after the subjects smoked cigarettes without THC (non-THC 2) and 13 mg THC.

Estimate of distance from a car ANOVA showed no significant drug effects and no significant order effects on estimates of distance.

Table 3 shows mean estimates of time of arrival and distance from an approaching car over all subjects under all conditions of the experiment.

Discussion

The main findings in this study relate to the impairments seen in the cognitive tests after smoking THC. There was a significant increase in collisions against the walls in the virtual maze task due to the effect of 17 mg THC. Impaired accuracy occurred without significant effect on speed. Effects of both 13 mg and 17 mg THC were also significant in some of the WCST tests (total number of blocks completed without error, non-perseverance errors and total number of errors). Significant increase in risk-taking in the gambling task (slight increase in the percentage of less probable choices offering high gain) was also seen in subjects on 17 mg THC.

Analysis of the results revealed two important issues – an "order" or "time of day" effect, and the possibility of a "carry-over" effect, namely, that performance after smoking the non-THC cigarette on test day 1 may have been affected by smoking the 17 mg THC cigarette 2 h earlier. As described, ANOVA indicated that order or "time of day" significantly affected performance, giving rise to improvement during each test day in both speed and accuracy in the maze task and in speed on the gambling task. As a result, differences between performance measures in these tasks at different times of day cannot be interpreted as being due only to THC, because of the confounding effect of the time of the day. It is well known that frequent repetition of computer games and tasks can result in faster and more accurate performance, presumably due to a learning effect. There was also a "time of day" effect on two questionnaire items, indicating reduced alertness and increased muscle tension during the test day. Reduced alertness over the course of several hours of tests is not surprising. Where no significant "time of day" order effects were present, differences between test conditions could be interpreted as resulting only from the effects of THC.

Regarding the "carry over" effect, we found that for performance in the WCST and quality of decisions in the gambling task, as well as ratings on most questionnaire items, the differences between THC and non-THC on test day 2 were greater than the differences between THC and non-THC on test day 1, calling into question the equivalence of the effects of the two non-THC cigarettes. This led us to suspect a "carry-over" effect on performance and questionnaire ratings following smoking the non-THC cigarette on test day 1 from the 17 mg THC cigarette smoked 2 to 3 h earlier. However, direct comparisons of performance following non-THC cigarette on test day 1 and non-THC cigarette on test day 2 did not yield significant differences, indicating that this "carry-over" effect must be small. The presence of a "carry-over" effect on subjective assessment of the drug extending 2–3 h after smoking THC is in line with the findings of Perez-Reyes, *et al.* (1982) and Hart, *et al.* (2001), both indicating that subjective perception of drug-related effects decreases in intensity, but does not return to baseline levels within this time. Ongoing effects of THC on cognitive function have been documented by Ramaekers, *et al.* (2006), who found cognitive impairment lasting up to 6 h in recreational users of marijuana. Thus although the subjects in our study were regular users and therefore perhaps had greater tolerance, presence of a low level of residual impairment 2–3 h after smoking 17 mg THC, as suggested by our results, would not be surprising.

The specific effect of THC on movement accuracy in the corridors of the maze is heavily dependent on motor and visuo-spatial skills, and subjects also had to rely on memory to learn how to complete the maze quickly. One possible factor that might have affected performance is the sustained attention required for repetition of this task over 25 min, which may have resulted in fatigue. The finding of impaired performance of subjects using 17 mg THC in the maze task supports the results of a previous study (Curran, *et al.*, 2002). However, the study by Curran, *et al.* (2002) used less experienced (infre-

quent) marijuana users, a different maze task without much repetition and different doses of THC. In our study, there was no significant difference in performance in the maze task between 13 mg THC and the non-THC 1 condition, but this may have been due in part to reduced accuracy in case of non-THC 1 due to residual effects of 17 mg THC smoked 2 h earlier, as described above. Other comparisons with 13 mg THC cannot be readily interpreted due to the order effect. However, it is possible that the regular marijuana users in our study might have developed tolerance to the relatively low dose of 13 mg THC, resulting in little effect on maze performance. Previous studies showing performance impairments after comparable low doses were carried out only in recreational users of marijuana (Curran, *et al*., 2002, Ronen, *et al*., 2005).

It may be noted that our maze task was not identical to that used by Ghatan, *et al*. (1995, 1998) where the subjects saw the whole maze in front of them and had a choice of strategy for exiting from the maze. In our maze, subjects could not see the exit in advance, so they had to find their way out by trial and error initially and thereafter to rely on memory to cut short the trial and error process and complete the maze quickly. Furthermore, unlike the maze of Ghatan, *et al*. (1995, 1998), and the task we used in our preliminary study (Brickner, *et al*., 2005), in the maze that we report now, the difficulty of the task remains constant and does not become more complicated with improved performance. In this way, the factor of intelligence or problem solving is reduced, and the challenge of the task is focused on the accuracy of movement.

Impaired accuracy of movement and increased collisions with maze walls in subjects on 17 mg THC is an important finding. Accurate movement is required for activities such as walking, driving, sportive activity and flying. One of the important aspects of these activities is the ability to keep the body or the vehicle in the centre of the road. Our results are in conformity with those of a study of behaviour in a driving simulator after using marijuana (Liguori, *et al*., 2002).

In addition to impaired performance in the maze task, our study indicated some impairment in performance of the WCST, as well as slight increased risk in decision making in the gambling task. In the WCST, both in subjects using 13 mg and in those using 17 mg THC, fewer blocks were completed without error, and the number of non-perseverance errors, as well as total number of errors, was higher. Although performance was impaired both in subjects using 13 mg and in those using 17 mg THC, more severe performance impairment was observed in subjects using 17 mg THC, indicating a dose-dependent response. These effects were seen despite the fact that the WCST task was performed from approximately 45 to –60 min after smoking THC, and thus after the peak effect of the drug.

Previous studies reported that marijuana reaches its peak effect after 30 min of smoking or i.v. administration when it is also associated with impairment to time (Mathew, *et al*., 1997, 1998). See also Lundqvist (2005) for comprehensive review on cognitive consequences of cannabis use.

The impaired performance in some categories of the WCST is in concordance with that in previous studies, showing impaired performance in cognitive tasks in subjects using THC who are regular users of marijuana (Hart, *et al*., 2001) and in recreational users of marijuana (Ramaekers, *et al*., 2006). The increase in errors in the WCST in case of subjects using THC may indicate an effect on general visual attention, noting that significant difference in the WCST was seen in non-perseverance errors which would reflect reduced mental flexibility. This finding is compatible with our result of the higher number of collisions in case of subjects on 17 mg THC in the virtual maze task and it indicates an attentional impairment.

The effects of 17 mg THC in the gambling task were seen in terms of significantly increased risk-taking, without significant effect on the response time. These effects were seen despite the fact that the gambling task was performed at 60–85 min after smoking, which was well after the peak effect of the drug. This finding is a post-hoc finding which was tested for because of previous evidence of risk-taking behaviour in marijuana users. The observation of more risky decision-making in the gambling task in subjects on 17 mg THC in our study is in concordance with evidence of impulsivity and risk-taking behaviour in a risk-taking task that has been reported in occasional marijuana users on THC (Lane, *et al*., 2005). There is also evidence for increased risk-taking as a chronic effect of marijuana use in heavy users in Bechara's gambling task (Whitlow, *et al*., 2004).

The car task, involving estimating distance of an approaching car and its estimated approach time, was a novel procedure, devised for this study to evaluate perception of time and distance because of its relevance for driving skills. Definition of this task was exploratory and no validity or reliability data were available. The absence of the typically found changes in time perception indicates that it was not very sensitive to the effects of the drug, though this may also relate to the timing of the test (approximately 85 min from the start of smoking).

Smoking cigarettes containing THC also affected autonomic measures, resulting in average in increases in heart rate and blood pressure. However, smoking non-THC cigarettes also resulted in increases, presumably due to expectancy of THC and due to this, as well as the high variability in heart rate and blood pressure responses between the 14 subjects, differences between THC and non-THC cigarettes were not all significant. Our data indicated somewhat more significant increases in heart rate and blood pressure in subjects on 17 mg than in those on 13 mg THC. This post-hoc finding is in accordance with the literature that shows that acute physiological effects of marijuana include a substantial dose-dependent increase in heart rate, generally associated with a mild increase in blood pressure. In a study of the effects of THC in occasional marijuana users, Lane, *et al*. (2005) demonstrated a dose-dependent increase in heart rate, with no significant changes in systolic or diastolic blood pressure. However, since development of tolerance to the acute effects of marijuana smoking has been documented (Jones, 2002), this too may contribute to the lack of stronger and more consistent effects seen among these regular users of marijuana.

Autonomic measures showed lower mean increase in heart rate in non-THC 1 (smoked 2 h after smoking 17 mg THC) compared with non-THC 2 (smoked as the first cigarette on test day 2). Hart, *et al*. (2001) described dose-dependent increases in heart rate 10 min after smoking THC cigarettes, but decreasing gradually down to levels lower than baseline around 2 h after smoking, with doses of THC similar to those in our study, and also in a group of regular marijuana users. Jones (2002) describes modified cardiac function and autonomic responses extending for some hours after smoking THC, though some tolerance to this effect might be expected in regular users. It is thus possible that responsiveness of the autonomic system might be depressed after the initial rise in heart rate in response to 17 mg THC, accounting for low responsiveness to the non-THC 1 cigarette.

We also found significant effects of THC on subjective responses, as reflected in the questionnaire. Subjective ratings of "satisfaction," "pleasure," "high" and "drug effect" were significantly increased both in subjects on 13 mg and in those on 17 mg THC, as compared to the non-THC 2 condition. As discussed previously, subjective responses in the non-THC 1 condition may have been modified by ongoing effects of the 17 mg THC smoked 2 h earlier.

There were aspects of the study design that could have had an impact on the results. In particular, despite all precautions to ensure that all participants and assistants were blinded to the contents of the cigarettes, not entirely surprisingly, 5 of the subjects identified correctly the cigarettes containing 13 mg and 17 mg THC. In these cases, their responses to the subjective questionnaires were not impartial. Furthermore, this may indicate that those who did not identify the cigarettes containing THC were tolerant to the acute effects of marijuana and might require stronger doses of marijuana to show more significant impairment in performance in the various tasks used in this study.

Limitations of this study include issues relating to the difficulties of working with a population of illicit drug users, while attempting to preserve natural conditions for meaningful investigation of subjective experience of drug use. We relied on self-report, supported by a urine sample test for THC, and therefore cannot entirely rule out the possibility of marijuana use the night before testing, and this might have affected the results. No blood samples were taken due to the lack of facilities for analysis of THC in blood. However, in this context, it should be noted that neither subjective nor cognitive effects of THC appear to follow the same time course as concentration of THC in blood (Perez-Reyes, *et al*., 1982). Also, despite negative findings of the recent use of heavy drugs and alcohol, we cannot entirely rule out unreported previous use of other drugs or psychiatric and neurological disorders that may have affected the results. It is also plausible that abstinence from nicotine and the administration of a low dose (0.1 mg) of nicotine might have affected the results, though comparison of effects of THC cigarettes with non-THC cigarettes with the same dose of nicotine should control for this, at least in those cigarettes smoked at the same time of the day. Finally, the 13 mg and 17 mg THC doses chosen for this study were based on doses used in preliminary studies, and we acknowledge that a wider range of doses, for example, 10 mg and 20 mg THC might yield clearer dose–response effects in regular users of marijuana.

In conclusion, the regular marijuana users in our study showed cognitive impairment in the maze task and in the WCST on 17 mg THC, with evidence also of increased risk-taking in the gambling task and effect on heart rate measures. In addition, the results show attentional impairment albeit less severe, in subects using 13 mg THC, thus suggesting a dose–response effect, and indicate the possibility of residual cognitive impairment up to 3 h after smoking 17 mg THC. It seems that smoking a cigarette containing doses in the range 13–17 mg THC caused cognitive and motor impairment in this small group of regular users of marijuana, despite the tolerance they have developed to the drug. This evidence is compatible with previous studies showing impaired cognitive function in regular users of marijuana.

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