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ORIGINAL INVESTIGATION

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Cognitive and subjective dose-response effects of acute oral Δ^9-tetrahydrocannabinol (THC) in infrequent cannabis users

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Abstract *Rationale:* Although some aspects of memory functions are known to be acutely impaired by Δ^9-tetrahydrocannabinol (Δ^9-THC; the main active constituent of marijuana), effects on other aspects of memory are not known and the time course of functional impairments is unclear. *Objective:* The present study aimed to detail the acute and residual cognitive effects of Δ^9-THC in infrequent cannabis users. *Methods:* A balanced, double-blind cross-over design was used to compare the effects of 7.5 mg and 15 mg Δ^9-THC with matched placebo in 15 male volunteers. Participants were assessed pre and 1, 2, 4, 6, 8, 24 and 48 h post-drug. *Results:* Δ^9-THC 15 mg impaired performance on two explicit memory tasks at the time of peak plasma concentration (2 h post-drug). At the same time point, performance on an implicit memory task was preserved intact. The higher dose of Δ^9-THC resulted in no learning whatsoever occurring over a three-trial selective reminding task at 2 h. Working memory was generally unaffected by Δ^9-THC. In several tasks, Δ^9-THC increased both speed and error rates, reflecting "riskier" speed-accuracy trade-offs. Subjective effects were also most marked at 2 h but often persisted longer, with participants rating themselves as "stoned" for 8 h. Participants experienced a strong drug effect, liked this effect and, until 4 h, wanted more oral Δ^9-THC. No effects of Δ^9-THC were found 24 or 48 h following ingestion indicating that the residual effects of oral Δ^9-THC are minimal. *Conclusions:* These data demonstrate that oral Δ^9-THC impairs episodic memory and learning in a dose-dependent manner whilst sparing perceptual priming and working memory.

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Introduction

Marijuana (cannabis) remains one of the most widely used social drugs in the world and is generally perceived by users to be a relatively benign substance (Ashton 2001). However, several studies comparing marijuana users with non-drug using controls suggest that prolonged, frequent use of this drug can impair aspects of cognitive functioning. Among these, a study by Block and Ghoneim (1993) found heavy marijuana users displayed subtle deficits in retrieval and mathematical reasoning, along with improved concept formation. A large prospective study by Fletcher et al. (1996) which successfully matched non-using controls with marijuana users reported that prolonged use of the drug was associated with deficits on recall of word lists and with impairments in both selective and divided attention. More recently, Pope et al. (2001) showed word recall deficits in heavy marijuana users (compared with controls) when tested 1 and 7 days following last use of the drug but these were no longer evident after 28 days of abstinence. Pope et al. (2001) conclude that verbal recall impairments detectable a few days after heavy cannabis use are related to recent cannabis exposure and are reversible with abstention from use.

Verbal recall impairments are one of the more consistent findings of laboratory studies of the acute effects of cannabinoids. These studies have administered either marijuana in the natural plant form of cannabis or its primary active ingredient, Δ^9-tetrahydrocannabinol (Δ^9-THC). Natural cannabis preparations contain many cannabinoid constituents besides Δ^9-THC (Turner et al. 1980) and in the current debate on the medical use of cannabinoids, a central issue concerns whether the effects of the whole plant differ from those of pure Δ^9-THC (e.g. Joy et al. 1999; Wachtel et al. 2002). Studies of acute cognitive effects have differed widely in methodology,

for example administering marijuana or Δ^9-THC at differing doses, in various ways (e.g. in a cigarette to be smoked, as "cookies" to be eaten) and have assessed effects at varying time points post-ingestion in people with varying levels of tolerance to marijuana and who have used the drug more or less recently before testing. It is not surprising, therefore, that such studies have often produced a mixed pattern of results.

Although the DSM-IV (American Psychiatric Association 1994) criteria for marijuana intoxication include impaired judgement and difficulty carrying out complex mental operations, a recent study of acute Δ^9-THC effects in heavy (daily) users of marijuana showed minimal Δ^9-THC impairment of performance on complex cognitive tests (Hart et al. 2001). Hart et al. showed that Δ^9-THC smoked in a cigarette (at 3.9% Δ^9-THC concentration) increased the time to complete some tests, impaired the immediate (but not delayed) reproduction of an 8-digit sequence on a keyboard and at the same time improved performance on pursuit tracking in a task requiring simultaneous vigilance to separate visual stimuli. Even with simple psychomotor tasks, reaction times following acute marijuana have been shown to be both unaffected (Heishman et al. 1997) and impaired (Borg et al. 1975).

Memory impairment would be a predictable effect of Δ^9-THC given the uneven distribution of cannabinoid receptors in the brain with highest densities in the hippocampus, basal ganglia and cerebellum (Herkenham et al. 1990; Ameri 1999). A recent in vitro study suggests that cannabinoids inhibit the formation of new synapses between hippocampal neurons in culture (Kim and Thayer 2001). Several studies in humans have reported impairments following smoked Δ^9-THC on the recall or recognition of word lists or digit sequences (e.g. Hooker and Jones 1987; Heishman et al. 1997; Leweke et al. 1998). However, the range of memory assessments used has been generally restricted to these types of tests and it is not known whether Δ^9-THC affects performance on implicit memory tasks or on explicit tasks which are more predictive of everyday memory function (e.g. prose recall; Sunderland et al. 1986).

The time course of functional impairment following acute Δ^9-THC or cannabis use is also unclear. Many studies have used assessments only around the peak action of the drug and it is not clear whether effects may persist for longer. For example, Leirer et al. (1989, 1991) examined the carry-over effects of smoking cannabis in experienced aircraft pilots and reported that performance on a flight simulator was impaired for as long as 24 h after marijuana use although the pilots themselves were unaware of any persisting drug effects. In reviewing the effects of heavy marijuana use, Pope et al. (1995) concluded that there was evidence of a drug "residue" effect on memory and attention 12–24 h after an acute dose but insufficient evidence regarding a longer lasting impairment.

The present study therefore aimed to examine the cognitive and subjective effects of acute oral Δ^9-THC administration on memory and cognitive function over a prolonged period from before to 48 h after consumption. Δ^9-THC was administered orally as dronabinol (Marinol). The two dose levels used (7.5 mg and 15 mg) were chosen as representative of social use, as a typical "joint" will deliver a dose of 5–25 mg Δ^9-THC. Assessments were selected to tap a range of memory functions (working memory, episodic memory, perceptual priming) as well as attentional, psychomotor and subjective effects. Given previous studies and the distribution of cannabinoid receptors in the brain, we predicted that Δ^9-THC would produce impairments on explicit memory tasks tapping episodic memory whilst preserving performance on an implicit task tapping perceptual priming.

Materials and methods

Design and participants

A crossover design was used to compare the effects of Δ^9-THC 15 mg and 7.5 mg with matched placebo capsules. Participants were tested on three occasions each separated by a 1-week interval. The order of administration of drugs was balanced and participants were randomly allocated to treatment order. Double-blind procedures were used throughout. The study was carried out in accordance with the Declaration of Helsinki, approved by the institutional ethical committee and all participants gave written, informed consent.

Fifteen healthy male volunteers aged between 18 and 30 (mean 24.2±2.1) years were recruited through advertisement and paid for participation. A detailed drug history was taken before volunteers could enter the study. Only participants who had prior experience with cannabis were selected. Regular current users (any participants who reported smoking cannabis more than once a week; Pope et al. 1995) were excluded from the study. Volunteers who used any other psychotropic drug on a regular basis or who exceeded the recommended weekly amount of 21 units of alcohol or had any psychiatric history were also excluded.

Participants had to agree not to smoke cannabis for 3 weeks before commencing and throughout the study and this was checked by urine testing at the beginning of each day of the study. They were instructed to consume their normal caffeine intake with a low fat breakfast on the mornings of the 3 test days and were provided with caffeine free drinks and a standardized, low fat lunch during test days.

Procedure

One week prior to commencing the study all participants attended an individual training session in order to familiarize them with the core assessments. Subsequently, each participant was tested individually beginning at 8 or 9 a.m. and remained under supervision in individual rooms during the 9 h of each full study day. They were allowed home at the end of each study day and returned to the laboratory at 8 or 9 a.m. for the 24- and 48-h assessments. They performed a series of tests at the following time points: 1 h prior to ingesting drug (time 0) and 1, 2, 4, 6 and 8, 24 and 48 h after drug ingestion. An extended battery of tests was given at 0, 2 and 6 h. All tests had the appropriate number of versions so that no version was administered twice (with the exception of Gibson's maze, for which there is only one version). Test versions were balanced across participants and design.

Assessments

Assessments were selected to tap working and episodic memory as well as related functions (attention; response speed).

Core tasks (administered at all time points)

Buschke Selective Reminding Task. This test was used to index free recall and rate of verbal learning. Sixteen unrelated bisyllabic words were presented individually for 2 s with 1-s interval between each word (Buschke 1974). Participants were instructed to recall as many words as possible. They were then "reminded" of any words not recalled from the list (i.e. these words only were presented again) and again asked to recall the entire list. This procedure is repeated for a third trial. After a 30-min delay, participants were asked to recall the list again.

Rapid visual information processing task. This was used to index sustained attention and working memory (Wesnes and Warburton 1984). In the 10-min task, single digits were presented at the rate of 100 digits/min and participants were instructed to press a response key to either 3 consecutive odd or 3 consecutive even digits.

Baddeley reasoning task. Participants were asked to verify a series of statements on a VDU such as "A does not precede B...BA" (Baddeley 1968) by pressing a "true" or a "false" key. Sixty-four trials were presented involving four different grammatical constructions. This task loads on central executive function.

Serial sevens subtraction task. Chosen as a brief working memory task, this task requires the ability to hold information in memory whilst manipulating it. Participants were instructed to repeat a 3-figure number read by the experimenter and to deduct 7 away from this and then the resulting number and so on for 90 s; number of correct subtractions and errors were recorded.

Choice reaction time task. A four-choice reaction time task was used (Maylor and Rabbitt 1989) which loads on attentional function and psychomotor speed. Participants were instructed to respond to four targets (A, B, C, D) which were each presented at different response-stimulus intervals (50, 100 200, 400 and 800 ms), randomly generated with no letter repeated twice in succession over approximately 3 min. Participants were instructed to press a corresponding key (A-1, B-2, C-3, D-4) on a separate response box as quickly as possible after presentation. A response immediately removed the stimulus from the screen. Any responses made within 100 ms of stimulus onset were classed as anticipatory and excluded.

Single and double target digit cancellation tasks. As a measure of simple focused attention, participants were presented with a sheet of paper with 400 random numbers and asked to cross out all the number 4s (single target) as quickly and as carefully as they could. The task was then repeated but with two targets (2 and 6) to be crossed out. The time to complete each task and errors were recorded.

Simple reaction time task. Participants responded by a key press as quickly as possible when they saw a target symbol on an otherwise blank computer screen. There were 24 presentations and the inter-stimulus intervals were randomly generated (100–3000 ms). Reaction time and errors were recorded automatically.

Additional assesments (administered at 0, 2 and 6 h only)

Prose recall. Participants listened to a pre-recorded tape of a short prose passage similar to a "news bulletin" on the radio. Participants were asked to recall the story immediately after presentation and again after a delay of 45 min filled by other tests. Each of the nine parallel versions of the story is divided into 21 "idea" units and recall is scored by allocating 2 points to each unit correctly recalled (or an exact synonym) and 1 point for each partial recall of a unit (or partial synonym).

Verbal fluency. Participants were required to generate as many words as possible in 60 s which began with a given letter of the alphabet. This task taps speeded retrieval from semantic memory. Names of people and places and plurals were not allowed. The letters were selected such that each began a similar number of words listed in the Oxford Mini-dictionary.

Gibson spiral maze. In this perceptual motor task, participants are instructed to place a pencil on an arrow in the center of the maze and to make their way out of the maze as quickly as possible without touching the sides of the maze or the circles around the maze. Time to complete the task and errors are recorded.

Perceptual priming task (administered at 2 h only). In this implicit memory task, participants are presented with a list of words and asked to rate on a scale of 1–5 how much they like or dislike the word. After a filled 90-s delay, participants are given a sheet of three-letter word stems and were asked to complete each word using the first English word that came to mind. Half of the stem list contained the beginning three letters of the words that had been presented for rating of liking. Parallel versions of this task were used such that baseline measures of stem completion were obtained (Curran and Gorenstein 1993).

Subjective ratings

Mood rating scale (Bond and Lader 1974)

This 16-item visual analogue scale (VAS) was chosen as a measure of mood. Principal components analysis of the 16 items yields three mood factors: alertness, contentedness and calmness.

Subjective effects rating scale

This VAS consists of a range of bodily symptoms thought to be side effects of cannabis use (e.g. dryness of mouth, problems focusing, impairment of memory or of concentration). The scale also included an item of "stoned". Each scale is anchored with "no symptom present" on one side of the scale to "symptom severe" on the other. On all post-drug assessments, four additional items, adapted from Kirk et al. (1998), were used to measure participants' subjective feelings about the capsules they had ingested. These required participants to rate (i) the overall effects of the capsules (anchored as "I feel no effect" at one end of the scale to "I feel a very strong effect" at the other end); (ii) how much they liked the effects of the capsules (anchored "like a lot" to "dislike a lot"); (iii) whether they wanted more of the drug (anchored "want more-want less"); (iv) how much they felt like smoking cannabis (no desire-strong desire for a joint).

Plasma Δ^9-THC levels

Participants were cannulated via a forearm vein prior to the study and blood was taken before and at each time point after drug administration. Samples were taken into silanized glass tubes, centrifuged immediately and stored deep frozen at –20°C pending analysis for cannabinoids. Δ^9-THC and 11-hydroxytetrahydrocannabinol (11-OH-THC) were extracted from plasma using a hexane/ethyl acetate mixture. The extracts were derivatized using BSTFA before the analysis. THC-d3 and 11-OH-THC-d3 were used as internal standards. The extracts were analyzed on a Hewlett Packard MS Engine (GC-MS) in SIM mode (EI ionisation). A splitless injection technique was used. The analytical column was a HP-5, 25 m×0.20 mm×0.33 μm.

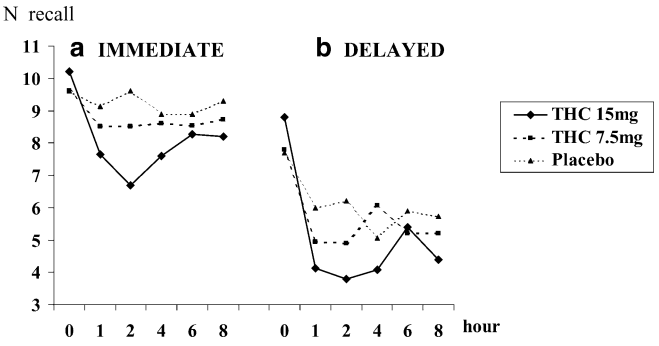


Fig. 1 Mean number of words recalled (**a**) in the first three trials of the Bushke selective reminding task at each assessment time (**b**) after a delay

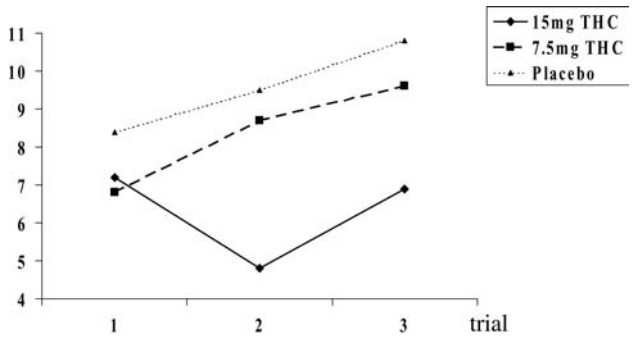


Fig. 2 Mean number of words recalled on each of the three trials at the two hour assessment (Bushke selective reminding task) according to treatment condition

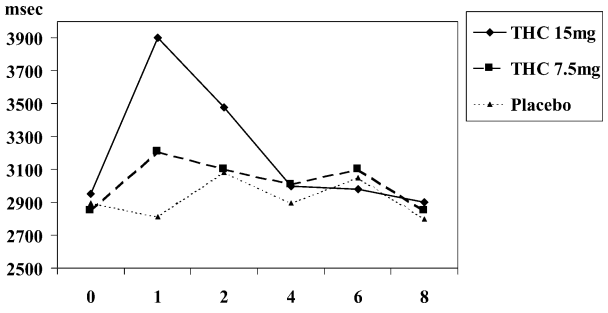


Fig. 3 Median response times in the Baddeley reasoning task at each assessment point by each treatment condition

Urine samples and analysis

Each participant provided a urine sample at the beginning of each study day and these were analysed for recent use of psychotropics. Cut-off levels on these tests were set to detect cannabis use in the previous 2–3 days.

Statistical analyses

Repeated measure multivariate analyses of variance (RMANOVAs) were carried out on all variables with both drug (Δ^9-THC 15 mg, 7.5 mg, placebo) and times (hour of testing) as within subject variables. Acute (0, 1, 2, 4, 6 and 8 h) and residual (0 versus 24 and 48 h) effects were analyzed separately. Post-hoc comparisons were computed using multivariate tests of simple effects with Bonferroni correction for multiple comparisons.

Results

Core tasks

Bushke selective reminding task

Analysis of the first three acquisition trials revealed three main effects: drug [$F(2,13)=5.18$, $P<0.025$]; testing time [$F(5,10)=7.17$, $P<0.005$] and trial [$F(2,13)=74.4$, $P<0.001$] but no interactions emerged. As seen in Fig. 1a, the higher dose produced marked impairments which were most pronounced at 2 h and showed some recovery over subsequent times. Drug differences at 2 h showed the high dose differed from placebo ($P<0.01$). Delayed recall was significantly affected by drug [$F(2,13)=4.69$, $P<0.03$] and by time [$F(5,10)=15.88$, $P<0.001$] and an interaction between these two factors approached significance [$F(10,5)=3.77$, $P<0.08$]. As seen in Fig. 1b, there were dose dependent impairments by Δ^9-THC which were most marked at 1 and 2 h. Analysis of forgetting (trial 3 recall minus delayed recall) revealed no significant drug effects.

At 2 h, immediate recall showed there was a drug×trial interaction [$F(4,11)=4.51$, $P<0.025$] which reflected a complete lack of learning over trials under the higher dose of Δ^9-THC compared with other treatments. As seen in Fig. 2, trial 3 recall following 15 mg Δ^9-THC was the same level as trial 1, and trial 2 was recall was poorer than either.

Rapid visual information processing task

Proportion of hits (correct detections of consecutive odd or even digit sequences divided by the number presented) on this task showed a main effect of testing time [$F(2,13)=10.4$, $P<0.001$] and a trend towards a main effect of drug [$F(2,13)=3.0$, $P<0.09$]. Tests of simple effects showed no differences between either Δ^9-THC dose and placebo. Median response time showed no significant drug effects.

Baddeley reasoning task

There was a trend towards a main effect of drug on median response times [$F(2,13)=3.44$, $P<0.07$] and simple effects tests showed significant increase in response times following both 7.5 mg ($P<0.05$) and 15 mg doses of Δ^9-THC ($P<0.01$) at 1 h compared with placebo (Fig. 3). Errors showed no drug effects.

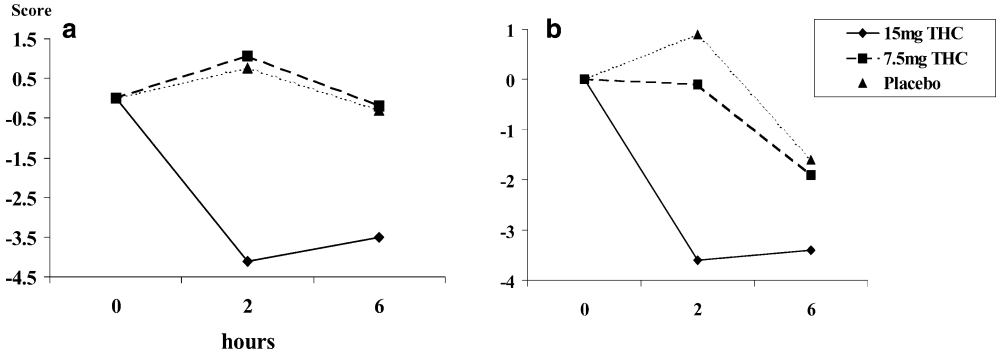


Fig. 4 Mean (**a**) immediate and (**b**) delayed prose recall scores at each assessment point by each treatment condition

Serial sevens

Neither response time nor errors showed any Δ^9-THC effects.

Choice reaction time test

No drug effects emerged on reaction times [only a times main effect: $F(5,10)=11.7$, $P<0.001$]. Errors showed a significant effect of drug [$F(2,13)=10.79$, $P<0.002$] and of time [$F(5,10)=5.29$, $P<0.015$] but no interaction. Tests of simple effects showed that, compared with placebo, errors were increased by Δ^9-THC 15 mg at 1 h ($P<0.05$) and by Δ^9-THC 7.5 mg at 2 ($P<0.05$) and 8 h ($P<0.05$).

Digit cancellation tasks

Single target cancellation. Time to complete the task showed no significant drug effects. A main effect of time [$F(2,13)=3.61$, $P<0.04$] reflected improvement under all treatments over time. *Errors* showed a main effect of drug [$F(2,13)=4.64$, $P<0.03$] and of time [$F(5,10)=4.60$, $P<0.02$] but no interaction. Errors were increased by both doses of Δ^9-THC at 2 h ($P<0.01$) and by the high dose at 4 h ($P<0.01$).

Double target cancellation. Time to complete the task again showed only a main effect of time [$F(5,10=4.22$, $P<0.025$] but drug only approached significance [$F(2,13=2.8$, $P<0.10$]. Test of simple effects showed that at 4 h participants were slower given placebo (mean±SD: 91.3±7.6 s) than 7.5 mg Δ^9-THC (80.6±6.1 s; $P<0.01$) but not different from 15 mg Δ^9-THC (87.0±5.8 s). *Errors* showed a main effect of drug [$F(2,13)=6.53$, $P<0.01$], a trend towards a main effect of time [$F(5,10)=3.14$, $P<0.06$] but no significant interaction between the two. Errors were increased by both doses of Δ^9-THC at 1 h ($P<0.05$ for both comparisons) and by the higher dose at 2 h ($P<0.05$).

Simple reaction time

Trends emerged towards drug×times interaction [$F(10,5)=3.98$, $P<0.07$], drug [$F(2,13)=2.8$, $P<0.10$] and times [$F(5,10)=3.19$, $P<0.06$]. Tests of simple effects showed the higher dose prolonged reaction times compared with placebo at 2 h ($P<0.05$).

Additional assessments (0, 2 and 6 h)

Prose recall

Immediate recall showed a significant interaction of drug with testing time [$F(4,11)=5.13$, $P<0.015$] as well as a testing time main effect [$F(2,13)=10.13$, $P<0.01$]. As seen in Fig. 4, the higher dose produced marked effects at 2 h which persisted at 6 h. Tests of simple effects confirmed significant impairment only by the high dose ($P<0.001$) with the lower dose not differing from placebo.

Delayed recall

The pattern of results was similar for delayed recall, although the drug with time interaction only approached significance ($P<0.08$); there was a main effect of time [$F(2,13)=12.56$, $P<0.001$] (Fig. 4). Tests of simple effects showed significant drug differences only at 2 h with the high dose impairing performance compared with placebo ($P<0.05$). The low dose did not differ significantly from placebo.

Perceptual priming task

Performance on this implicit memory task was not affected by Δ^9-THC. Completion of target words was 2–3 times higher than baseline rates in each treatment condition showing that priming was clearly preserved (Fig. 5).

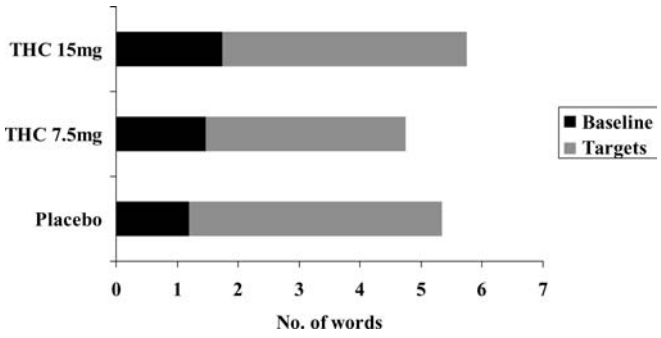


Fig. 5 Mean number of stems completed with words previously rated for liking (targets) with base rates (displayed in black) of completion by each treatment condition

Verbal fluency

Number of correct exemplars, excluding repetitions and errors, was analyzed. There was a significant drug with time interaction [$F(4,11)=5.27$, $P<0.015$] as well as a main effect of time [$F(2,13)=5.76$, $P<0.05$]. At 6 h people on the higher dose produced significantly more exemplars than when on the lower dose ($P<0.01$; Table 1).

Gibson's spiral maze

Time to complete showed a significant drug×time interaction [$F(4,11)=3.75$, $P<0.04$] and a main effect of time [$F(2,13)=7.33$, $P<0.01$]. As seen in Table 1, compared with placebo, performance was faster on both doses of Δ^9-THC at 2 h and, by the higher dose, at 6 h. *Errors* showed a significant drug effect [$F(2,13)=4.77$, $P<0.03$, Table 1], reflecting more errors under Δ^9-THC than placebo. The increase in errors at 6 h was dose-related and simple effects showed a significant difference between the two doses of Δ^9-THC ($P<0.01$).

Subjective effects

Mood rating scale

Mood Factor 1 (alertness-drowsiness) showed a significant interaction of drug with testing time [$F(10,5)=5.65$, $P<0.05$] as well as a main effect of time [$F(5,10)=3.90$, $P<0.05$]. The higher dose increased drowsiness most especially at 2 h ($P<0.05$). Mood factors 2 and 3 showed no significant treatment effects. There was a main effect of time on mood factor 3 [$F(5,10)=8.7$, $P<0.002$], reflecting increased anxiety until 2 h, which then decreased over subsequent testing times.

Subjective effects scale

Six side effect scales showed significant drug effects.

Table 1 Means (SD) for number of words generated in the verbal fluency task, time to complete and errors on Gibson's maze

Fluency	0	2	6 h
15 mg	14.20 (6.36)	14.40 (5.90)	18.53 (5.05)
7.5 mg	14.87 (4.59)	16.33 (5.34)	15.20 (4.94)
Placebo	14.80 (4.39)	15.93 (4.25)	16.47 (5.81)
Maze time 15 mg	47.57 (19.92)	45.28 (19.74)	41.33 (13.09)
7.5 mg	44.06 (12.69)	39.79 (12.91)	41.24 (9.24)
Placebo	44.27 (15.49)	43.91 (15.20)	42.06 (14.22)
Maze error 15 mg	3.30 (2.54)	5.93 (5.92)	7.13 (6.22)
7.5 mg	4.00 (3.50)	6.33 (6.08)	5.27 (4.14)
Placebo	4.27 (3.22)	4.07 (2.34)	3.67 (2.79)

Dizziness. There was a main effect of drug [$F(2,13)=4.14$, $P<0.05$]. Drug effects were significant at 8 h [$F(2,13)=3.93$, $P<0.05$] with Δ^9-THC slightly increasing rating of dizziness.

Dry mouth. There was a main effect of drug [$F(2,13)=5.84$, $P<0.015$] whereby the higher dose produced marked dry mouth especially at 1 and 2 h but persisting to some degree throughout the testing day. The lower dose had no effect.

Impaired memory. A drug×times interaction emerged [$F(10,5)=5.02$, $P<0.05$] and a times main effect [$F(5,10)=11.38$, $P<0.001$]. There was a clear dose related increase in ratings of impaired memory most marked at 2 h but persisting to 4 h (Fig. 6a). Tests of simple effects confirmed that the high dose differed significantly from placebo at 2 and 8 h ($P<0.01$).

Impaired concentration A main effect of time [$F(5,10)=8.83$, $P<0.002$] emerged and a drug main effect approached significance [$F(2,13)=3.13$, $P<0.08$]. Tests of simple effects showed significant drug differences at 2 h with the high increasing ratings compared with placebo ($P<0.01$).

Palpitations. A main effect of drug [$F(2,13)=5.27$, $P<0.025$] reflected increased ratings of palpitations on the high dose of Δ^9-THC, especially at 1 and 2 h.

"Stoned". There were significant main effects of drug [$F(2,13)=7.38$, $P<0.007$] and time of testing [$F(5,10)=19.21$, $P<0.001$] (Fig. 6b). On the higher dose, participants rated significantly higher feelings of being stoned than on placebo at 2 ($P<0.005$), 4 ($P<0.01$) 6 ($P<0.05$) and 8 h ($P<0.05$) post-drug. The lower dose produced intermediate effects between placebo and the high dose and did not differ significantly from either.

Feel an effect of the drug. There were significant main effects of both drug [$F(2,13)=10.74$, $P<0.002$] and time [$F(4,11)=12.11$, $P<0.001$] but no interaction (Fig. 7a). Simple effects showed significant drug differences at 1 ($P<0.001$), 2 ($P<0.005$) and 6 h ($P<0.02$).

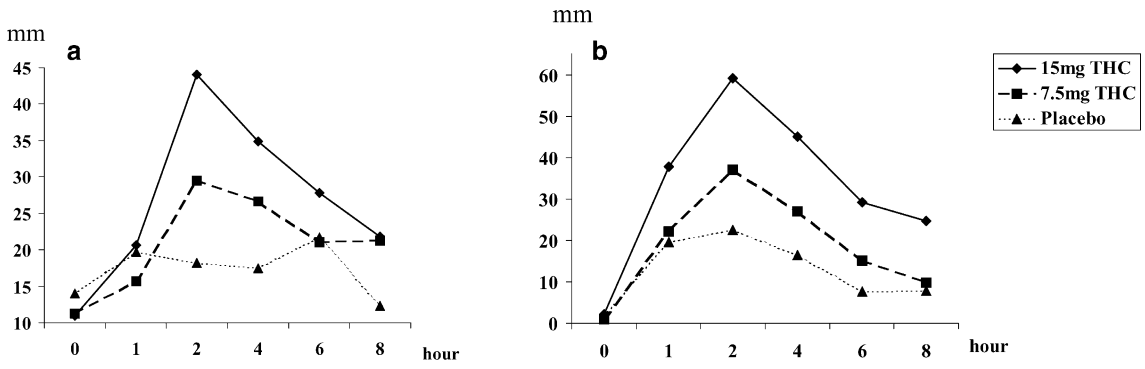
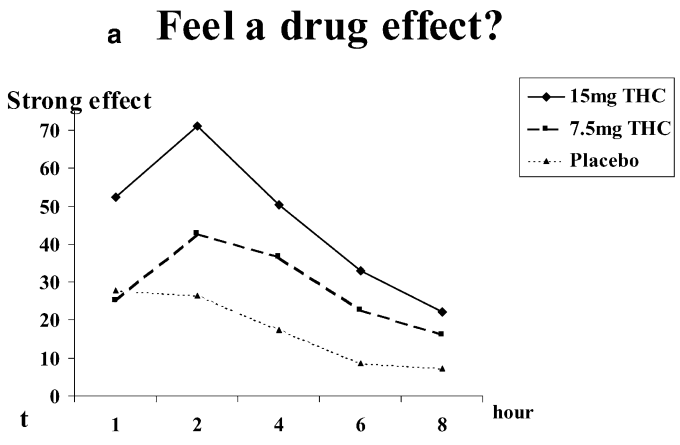
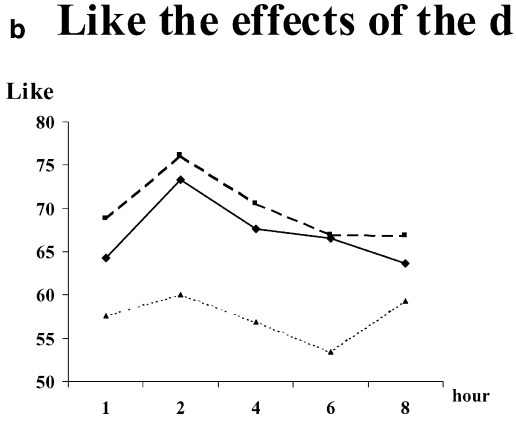


Fig. 6 Subjective ratings of (**a**) impaired memory and (**b**) feeling "stoned" at each assessment point by each treatment condition





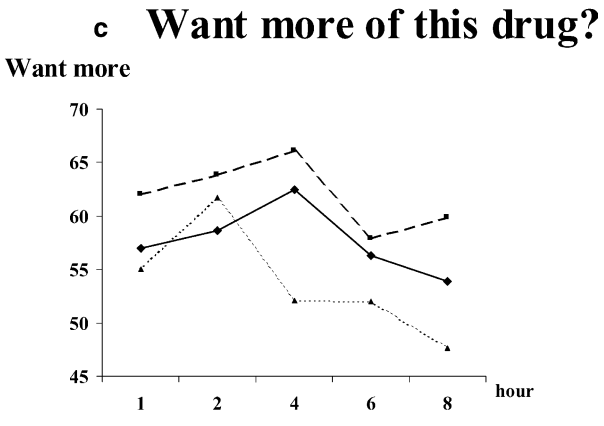


Fig. 7 Subjective effects of THC on ratings of (**a**) feeling a strong effect of the drug (**b**) liking the effect (**c**) wanting more of the drug

Like the effect of the drug. A significant main effect of drug [$F(2,13)=4.58$, $P<0.05$] emerged with both the lower and higher doses of Δ^9-THC producing increased ratings of liking the drug compared with placebo (Fig. 7b).

Want more of the drug. There was only a trend towards a drug with time interaction [$F(8,7)=3.37$, $P<0.07$] (Fig. 7c). Simple effects analysis showed significant drug differences only at 4 h ($P<0.01$) with both doses of Δ^9-THC increasing ratings of "wanting more drug" compared with placebo.

Desire for a joint of cannabis. Δ^9-THC had no significant effect on desire for cannabis.

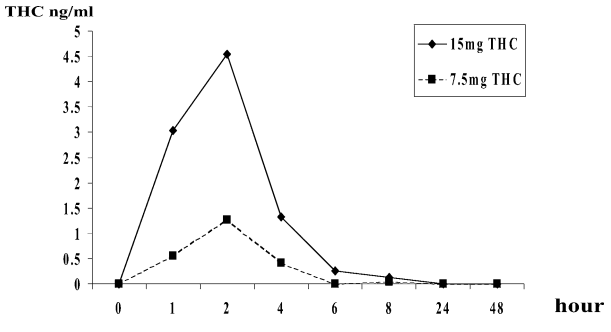


Fig. 8 Mean plasma levels of THC at each assessment point

Residual effects

No significant effects of Δ^9-THC on any measure were evident 24 or 48 h after the drug was administered.

Urine screens and plasma levels of Δ^9-THC

Screens with the cut-offs described at the beginning of each test day showed no detectable levels of Δ^9-THC or evidence of any other recreational drug in any participant's urine sample. Time-concentration curves (Fig. 8) demonstrate that Δ^9-THC was detectable in plasma for several hours with peak concentrations occurring at 2 h after both high dose and low dose. The profile of 11-OH-THC levels showed the same pattern. Levels at 24 h and 48 h were below the limit of detection.

Discussion

The findings of this study profile the acute effects of a single, oral dose of Δ^9-THC over an 8-h period and residual effects 24 and 48 h later. In terms of cognitive function, impairments were induced by the higher dose and were most evident 2 h after consumption. In terms of subjective effects, oral Δ^9-THC produced a similar profile to smoked Δ^9-THC and, although these effects were also more marked at 2 h, some subjective effects were more persistent than cognitive effects with participants on the higher dose rating feeling significantly "stoned" 8 h after the drug. However, no residual effects of acute oral Δ^9-THC were found 24 or 48 h later, supporting the findings of Fant et al. (1998) with acute smoked Δ^9-THC that cognitive deficits do not persist 24 h after a single, moderate dose of the drug.

Δ^9-THC 15 mg impaired performance on two explicit memory tasks (selective reminding and prose recall). Impairments on the selective reminding task were most pronounced 2 h post-drug but also evident at both 1 and 4 h. By 6 h there were no impairments on this task (either for immediate or delayed recall), although immediate prose recall showed persisting impairment at this time. Given that prose recall is a reasonable predictor of real-life memory performance (Sunderland et al. 1986), this implies that people may display poor memory for events for 6 h following Δ^9-THC.

The higher dose of Δ^9-THC resulted in no learning whatsoever occurring over trials in the selective reminding task at the time of peak plasma concentration (2 h). On the lower dose, as on placebo, participants showed a standard learning curve over trials. However, following Δ^9-THC 15 mg, recall on the third trial was at the same level as it had been on the first trial. These findings suggest that 15 mg of Δ^9-THC effectively disrupts acquisition and blocks new learning.

In contrast, as predicted, at the same time point that Δ^9-THC reached peak plasma concentration and exerted maximal effects on the explicit memory tasks, performance on the implicit memory task (word-stem completion) was not affected by the drug. As far as we aware, this is the first demonstration that perceptual priming is preserved by Δ^9-THC. Thus, as seen in organic amnesia, implicit memory is preserved despite explicit memory deficits. This pattern of preserved performance on implicit memory tasks co-existing with impaired performance on explicit tasks characterizes many amnestic drugs including anticholinergics, most benzodiazepines (except lorazepam) and alcohol (Curran 2000).

Retrieval from semantic memory as reflected in verbal fluency showed no drug impairment, and some indication of facilitation by the high dose at 6 h. It is unclear whether this reflects a form of retrieval disinhibition. Previous studies have also suggested some facilitation associated with use of cannabinoids, for example, Block and Ghoneim (1993) reported some improvement in concept formation (alongside explicit memory impairment) in heavy marijuana users compared with non-drug using controls. Performance on two of the tasks tapping working memory (serial sevens task and RVIP) was unaffected by Δ^9-THC. Performance on the logical reasoning task showed no disruption to accuracy but there was an increase in response time at 1 h by both doses. This task is thought to tap the central executive component of working memory, and as this is also involved (along with the phonological loop) in the serial sevens and RVIP, this subtle slowing of response times was not enough to produce parallel impairments on these two tasks at the same time point. At 2 h, there were no significant effects of Δ^9-THC on any of these three tasks, which implies that the decrement in performance on the prose recall and Bushke tasks (found at 2 h) reflected impairments of episodic memory and not working memory. Subjective ratings of memory suggest that participants were *aware* of Δ^9-THC-induced impairments for several hours post-drug administration. This may have meant that they were aware of performance decrements on the memory tasks they were completing and perhaps actively compensated for such decrements in performing the tasks. In daily life, when there are not such repeated tests, such awareness of impairment may not occur and compensatory strategies may not be used. In contrast to ratings of memory impairment, ratings of attentional

impairment by Δ^9-THC were short-lived with significant differences between treatments emerging only at 2 h.

On several tasks, Δ^9-THC produced an increased error rate alongside either no change in speed of performance (choice reaction time task, single digit cancellation) or faster performance on Δ^9-THC than placebo (Gibson's maze, double digit cancellation). These findings indicate that Δ^9-THC altered participants' trade off between speed and accuracy so that they maintained or increased their speed at the cost of increased errors. Whether such effects would translate into 'riskier' strategies in real life tasks is not known although cannabis is thought to affect speed-accuracy trade-off in driving (Ashton 2001).

Our participants, who all used cannabis infrequently (less than once a week), experienced a strong drug effect, liked this effect and were prone to want more of the drug up until 4 h. Indeed, one participant asked if he could be paid in the Δ^9-THC capsules rather than in money. The increased wish to take Δ^9-THC in those who had already taken it, but not in those who had been given matched placebo, suggests that Δ^9-THC clearly activates certain appetites within the brain. However, despite the desire for drug on the occasions when the drug was administered, Δ^9-THC did not increase participants' desire for cannabis in the more socially common form of a "joint". Oral Δ^9-THC is currently given medicinally for the treatment of anorexia associated with AIDS and for nausea and vomiting associated with chemotherapy. It is possible that the medicinal uses of this compound may be extended in the future. Used in medicinal contexts, our results indicate that while oral Δ^9-THC may be enjoyed by patients and they may desire more, it would be unlikely to induce a desire for smoking plant-based cannabis.

Other subjective effects replicated the well known side-effects of Δ^9-THC including dry mouth, sedation and feeling "stoned" (Kirk et al. 1998; Kirk and de Wit 1999). Recently, Wachtel et al. (2002) carried out two studies to compare the subjective effects of Δ^9-THC with those of marijuana in people who had used marijuana recreationally on more than ten occasions. In one study the two compounds were ingested orally and in the other study they were both smoked. Both studies showed comparable plasma THC levels and very similar subjective effects of Δ^9-THC and marijuana suggesting that the psychoactive effects of marijuana are primarily due to THC. The mechanism of the subjective effects of cannabis is less well understood than that produced by opioids or stimulants. Ameri (1999) argues that, like these other drugs of abuse, cannabinoids produce facilitation of the mesolimbic dopamine 'reward' system. However, animals do not self-administer Δ^9-THC in drug discrimination paradigms (Wiley 1999). Anandamide (from "ananda", the Sanskrit word meaning "bliss") is an endogenous ligand at cannabinoid receptors and Δ^9-THC's subjective effects may be linked to the density of cannabinoid/anandamide receptors in limbic, cerebellar and related areas of the brain.

Understanding the cognitive effects of psychoactive drugs is important whether the drugs are used in the treatment of medical and psychiatric disorders or self-administered drugs of abuse. Drugs that impair cognitive functions may impede progress in learning based therapies often used conjointly with psychiatric drugs or with clients who abuse psychotropics. Thus drugs that impair episodic memory may reduce learning in cognitive behavioural therapy and drugs that impair judgement may hinder progress in motivationally based approaches to drug dependence. Drugs may also contribute to maintain substance use, for example by impairing inhibitory processes involved in impulse control or by blurring the user's memory for personal events which occurred whilst s/he was intoxicated.

In summary, the present study examined the dose-response effects of oral Δ^9-THC over an extended time period. The higher dose produced the most marked impairments at 2 h post-ingestion, the time at which peak plasma levels were obtained. At this time point, 15 mg Δ^9-THC impaired episodic memory and verbal learning but aspects of working memory and performance on an implicit memory task were preserved intact.

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