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Effects of haloperidol on the behavioral, subjective, cognitive, motor, and neuroendocrine effects of Δ-9-tetrahydrocannabinol in humans

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Abstract

Introduction—Cannabinoids produce a spectrum of effects in humans including euphoria, cognitive impairments, psychotomimetic effects, and perceptual alterations. The extent to which dopaminergic systems contribute to the effects of Δ-9-tetrahydrocannabinol (Δ-9-THC) remains unclear. This study evaluated whether pretreatment with a dopamine receptor antagonist altered the effects of Δ-9-THC in humans.

Materials and methods—In a 2-test-day double-blind study, 28 subjects including healthy subjects (*n*=17) and frequent users of cannabis (*n*=11) were administered active (0.057 mg/kg) or placebo oral haloperidol in random order followed 90 and 215 min later by fixed order intravenous administration of placebo (vehicle) and active (0.0286 mg/kg) Δ-9-THC, respectively.

Results—Consistent with previous reports, intravenous Δ-9-THC produced psychotomimetic effects, perceptual alterations, and subjective effects including "high." Δ-9-THC also impaired verbal recall and attention. Haloperidol pretreatment did not reduce any of the behavioral effects of Δ-9-THC. Haloperidol worsened the immediate free and delayed free and cued recall deficits produced by Δ-9-THC. Haloperidol and Δ-9-THC worsened distractibility and vigilance. Neither drug impaired performance on a motor screening task, the Stockings of Cambridge task, or the delayed match to sample task. Frequent users had lower baseline plasma prolactin levels and blunted Δ-9-THC induced memory impairments.

Conclusions—The deleterious effects of haloperidol pretreatment on the cognitive effects of Δ-9-THC are consistent with the preclinical literature in suggesting crosstalk between DAergic and CBergic systems. However, it is unlikely that DA D_2 receptor mechanisms play a major role in mediating the psychotomimetic and perceptual altering effects of Δ-9-THC. Further investigation is warranted to understand the basis of the psychotomimetic effects of Δ-9-THC and to better understand the crosstalk between DAergic and CBergic systems.

Keywords

Schizophrenia; Cannabinoids; Dopamine; Antipsychotic; Cognition; Memory; Addiction; Attention; Haloperidol; Endocrine

Introduction

Cannabis is one of the most widely used illicit substances (Compton et al. 2004; SAMHSA 2004). The primary active cannabinoid in cannabis is Δ-9-tetrahydrocannabinol (Δ-9-THC), but cannabis also contains more than 60 other cannabinoids, some of which may contribute either directly or indirectly to the effects of Δ-9-THC. The spectrum of effects produced by cannabis includes euphoria, relaxation, anxiety, perceptual alterations, paranoia, and impairments in attention and memory. Laboratory experiments have demonstrated that synthetic and natural cannabinoids can induce transient psychotomimetic effects in healthy human subjects (D'Souza et al. 2004; Henquet et al. 2006; Leweke et al. 1999) and exacerbate psychosis in individuals with schizophrenia (D'Souza et al. 2005). Finally, a growing body of epidemiological studies (reviewed in Fergusson et al. 2006; Henquet et al. 2005) have drawn attention to the link between cannabinoids and psychosis (D'Souza 2007).

Converging preclinical evidence suggests interactions between cannabinoid (CB_1) and dopamine (DA) systems (reviewed in Gardner 2005; Laviolette and Grace 2006a). CB_1 and D_2 receptors are coexpressed in several brain regions (Hermann et al. 2002), and there is signal

transduction convergence in these regions (Meschler and Howlett 2001). Δ-9-THC activates DAergic mesolimbic neurons (French 1997; French et al. 1997; Gardner 2005; Gessa et al. 1998) and induces DA release in the striatum (Chen et al. 1990a; Tanda et al. 1997a) in animals. CB_1 agonists induce c-fos in the nucleus accumbens (Miyamoto et al. 1996) and A10 DArgic neurons within the ventral tegmentum (Patel and Hillard 2003). At a molecular level, DA D2 receptors are believed to have a significant modulatory role in determining the G-protein coupling specificity of CB_1 receptors (Jarrahian et al. 2004). Haloperidol and Δ-9-THC produce more catalepsy in rats than haloperidol alone (Marchese et al. 2003), haloperidol reverses Δ-9-THC reductions in prepulse inhibition and startle response in mice (Nagai et al. 2006); however, haloperidol has no influence on Δ-9-THC-induced catalepsy in mice (Kinoshita et al. 1994). Given the preclinical evidence of crosstalk between CB and DA systems, one logical question is to what extent, if any, are DA receptor mechanisms involved in the psychotomimetic and rewarding effects of cannabinoids in humans?

Haloperidol was hypothesized to reduce the psychotomimetic, perceptual altering, euphoric, and cognitive effects of Δ-9-THC in humans and that the two drugs would have additive cataleptic effects. Further, there are long-term changes associated with exposure to cannabinoids (reviewed in D'Souza et al. 2008: In review; Kolb et al. 2006; Lichtman and Martin 2005; Ranganathan et al. 2007), including regional changes in DA transmission (Jentsch et al. 1998; Verrico et al. 2003). Therefore, individuals who frequently used cannabis were hypothesized to differ in their response to the interactive effects of haloperidol and Δ-9-THC.

Materials and methods

The study was conducted at the Neurobiological Studies Unit (VA Connecticut Healthcare System, West Haven, CT) with the approval of the Institutional Review Boards of VA Connecticut Healthcare System and Yale University School of Medicine and in accordance with the Helsinki Declaration of 1975. Subjects were informed about the side effects of both haloperidol (sedation, akathisia, dystonia, etc.) and Δ-9-THC (euphoria, anxiety, paranoia, etc.). Subjects were recruited by public advertisement and compensated for their research participation. Confidentiality of study data was protected.

Participants

The sample consisted of two groups, frequent users of cannabis and healthy subjects. Frequent users were defined as (1) lifetime cannabis exposure greater than or equal to 100 times, (2) last exposure to cannabis within the past week, (3) recent cannabis exposure greater than ten times per month as quantified by Time Line Follow Back (Sobell and Sobell 1992), and (4) positive urine toxicological test for cannabis at screening. These subjects also met criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM) IV cannabis abuse disorder, while none of the healthy subjects did.

In addition to obtaining written informed consent, subjects had to successfully complete a questionnaire about the key risks and benefits of the study. Subjects (18–55 years) underwent a structured psychiatric interview for DSM (First et al. 2002; Spitzer 1990) and were carefully screened for any DSM axes I or II lifetime psychiatric or substance use disorder (except for cannabis in the case of frequent users) and family history of major axis I disorder. All subjects were asked to estimate their lifetime cannabis exposure (number of times), heaviest exposure, and last exposure to cannabis. Subjects were excluded for recent abuse (3 months) or dependence (1 year) to alcohol or any substances, other than nicotine in both groups. Cannabis-naïve individuals were excluded to minimize any risk of promoting future cannabis use/abuse. The history provided by subjects was confirmed by a telephone interview conducted with an individual (spouse or family member) identified by the subject before screening. A general physical and neurological examination, electrocardiogram, and laboratory tests (serum

electrolytes, liver function tests, complete blood count with differential, and urine toxicology) were also conducted. Subjects were instructed to refrain from alcohol, illicit drugs, or prescription drugs not approved by the research team for 2 weeks before the study and throughout study participation. Healthy subjects were required to have a negative urine toxicological test at screening. Frequent users were permitted to use cannabis until 24 h before each test day, to minimize cannabis withdrawal, a syndrome that has been described by several groups (Budney et al. 2003; Haney 2005; Haney et al. 1999a, b). Abstinence from cannabis in the 24 h before each test day was confirmed by subject interview on each test day. Self-reported cannabis use is a valid method of assessing cannabis use (Martin et al. 1988).

Experimental design

Subjects completed 2 test days during which they received placebo or active (0.057 mg/kg) haloperidol in random counterbalanced order, followed 90 min later by placebo Δ-9-THC (vehicle) and 215 min later by active Δ-9-THC (0.0286 mg/kg) administered intravenously (i.v.) over 20 min in a fixed order (Table 1).

Drugs

The dose and rate of administration of Δ-9-THC was chosen to mimic the dose range of recreational cannabis use and to be equivalent to about 0.5–1.5 of a standard National Institute of Drug Abuse cannabis cigarette. Further, in pilot studies, because subjects were unable to tolerate higher doses, Δ-9-THC (0.05, 0.035 mg/kg) was given as a 2-min bolus after receiving haloperidol. A 20-min infusion was selected to mimic the time frame of recreational cannabis consumption. The rationale for the route of Δ-9-THC administration and preparation of both Δ-9-THC and placebo is described previously (D'Souza et al. 2004, 2005). The psychoactive effects of cannabis in humans are due primarily to Δ-9-THC (Wachtel et al. 2002). Δ-9-THC of 99.6% purity was dissolved in 95% ethanol (Agurell et al. 1986) to yield a concentration of 2 mg/ml stock solution, which was then passed through a 0.22 μm polymer filter, subjected to sterility and pyrogenicity testing, assayed by gas chromatography–mass spectrometry to confirm its concentration, and stored at −20°C for future use. For the control condition, an equivalent volume (≅x2 ml) of ethanol (vehicle) was used, which would amount to a concentration of 0.0004% in an adult with average blood volume (4–5 l). Postinjection blood sampling at multiple time points failed to detect ethanol.

The DA receptor antagonist haloperidol was chosen because of its relative specificity for D2 receptors. In pilot studies, 0.05 mg/kg haloperidol (3.5 mg in a 70 kg individual) produced no appreciable effects, while at 0.071 mg/kg (5 mg in a 70 kg individual), it was associated with a high rate of dropouts related to side effects (D'Souza, unpublished observations). Therefore, an inter-mediate dose of haloperidol (0.057 mg/kg), equivalent to 4 mg in a 70-kg individual, was chosen. This dose was expected to produce antipsychotic effects without producing significant extrapyramidal side effects (Farde et al. 1992; Kapur et al. 1997, 2000) and is within the dose range recommended by the British Association of Psychopharmacology consensus conference for the use of haloperidol in healthy volunteers (King 1997). Further, at this dose, haloperidol is a relatively selective antagonist at DA D_2 receptors (Schotte et al. 1996) compared to actions at other receptors (e.g., muscarinic M_1 or histaminergic H_1) that might modulate Δ-9-THC effects.

Test days were separated by at least 1 week (greater than three times the elimination half life of Δ-9-THC) to minimize carryover effects (Wall et al. 1976). To keep both subjects and raters blind to study conditions and the order of drug administration, both the subjects and raters were told of a possibility of a third "very low" dose of both haloperidol and Δ-9-THC, deliberately described in ambiguous terms. In actuality, subjects never received the "very low" dose of both haloperidol and Δ-9-THC.

Schedule of testing

Urine toxicology was conducted on the morning of each test day to rule out recent illicit drug use. A positive urine drug screen resulted in exclusion from the study except when positive for cannabis in frequent users. Subjects fasted overnight, reported to the test facility around 8 A.M., and were provided a standard breakfast. A positive urine pregnancy test also resulted in exclusion.

The detailed schedule of test procedures is described in Table 1. Subjects were attended to by a research psychiatrist, a research nurse, and a research coordinator. Clear "stopping rules" were determined a priori, and rescue medications were available during testing (lorazepam and benztropine) if necessary and also at discharge (diphenhydramine). Subjects were recontacted at 1, 3, and 6 months post-study for safety follow-up.

Outcome measures

Behavioral and subjective ratings were conducted before and after haloperidol (active or placebo) and after placebo and active Δ-9-THC administration (Table 1). Positive, negative, and general symptoms associated with psychosis were assessed using relevant subscales of the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1989), perceptual alterations were measured using the Clinician-administered Dissociative Symptoms Scale (CADSS; Bremner et al. 1998), and feeling states associated with cannabis intoxication were measured using a self-reported visual analog scale of five items ("high," "calm and relaxed," "tired," "panic," and "anxious"; Haertzen 1965,1966). Subjects were also asked to rate on a 0–100 scale (0=not at all to 100=most of all) (1) the similarity of the experience compared to recreational cannabis use and (2) how much they enjoyed the experience. Inter-rater reliability sessions were conducted every 1–2 months, and, for example, intraclass correlation coefficient for the PANSS were consistently greater than 0.85.

A cognitive test battery was administered 30 min after receiving both placebo and active Δ-9-THC infusions. Learning and recall were measured using the Hopkins Verbal Learning Test (Brandt et al. 1992; Bylsma et al. 1991). This test consists of three consecutive trials of immediate free recall of a 12-item, semantically categorized list, followed 30 min later by testing of delayed free, cued, and recognition recall. Different but equivalent versions of the test were administered within and across test days. Vigilance and distractibility to visual stimuli were measured using a continuous performance task (Gordon 1986) in which subjects attended to numbers presented sequentially on a screen. The subject pushed a button to signal when a '1' was followed by a '9.' The distractibility task was identical to the vigilance task with the exception that numbers were presented sequentially in three contiguous columns. Subjects were instructed to attend to the middle column and ignore the outer two columns.

Executive function (Stockings of Cambridge: SOC), spatial working memory (SWM), visual recognition memory (delayed match to sample: DMTS), and motor screening were tested using the Cambridge Neuroscience Test Battery (CANTAB; http://www.camcog.com; Sahakian and Owen 1992). Intelligence quotient was remeasured as part of the CANTAB using the National Adult Reading Test (NART). A motor-screening task (MOT) was administered to ensure that subjects could point accurately and also to measure speed and accuracy, both of which are indices of motor skill. A series of crosses were shown in different locations on the screen. After a demonstration, the subject had to point to the crosses in turn. The time taken for the subject to touch the cross after it appeared was measured as MOT latency. The arithmetic mean was calculated from the latencies of the ten crosses presented, which were correctly responded to. The DMTS tests visual memory in a four-choice delayed recognition memory paradigm. Subjects were shown a complex visual pattern (the sample). After a variable delay (of 0, 4, or 12 s), three distractor patterns and the target pattern were shown (Robbins et al. 1994). Subjects

were instructed to choose the target pattern. The number of occasions upon which the subject selected the correct targets in trials was calculated as a percentage (DMTS percent correct score). In the SWM task, subjects had to find individually hidden "blue tokens" without returning to a box where one had previously been found (Owen et al. 1990). Errors included selecting boxes that had previously been found to be empty (within errors) and revisiting boxes that had already been found to contain a token (between errors). The SOC test is a spatial-planning task based upon the "Tower of London" test. Subjects had to move a set of balls to replicate a reference pattern. The number of occasions that a subject successfully replicated a reference pattern in the minimum possible number of moves was measured. CANTAB tests have satisfactory levels of test–retest reliability, with some outcome measures reaching correlations of better than 0.9. All the CANTAB tests used had parallel versions to facilitate repeated testing, and further, the tests tapped nonstrategic cognitive functions, which are less likely to be subject to significant practice effects.

Akathisia and drug-induced Parkinsonism were evaluated using the Barnes akathisia scale (Barnes 1989) and the Simpson Angus Scale (Simpson and Angus 1970), respectively. However, as subjects were not allowed to ambulate during testing because of safety concerns, the latter was modified to include only the items for tremor and a composite rigidity score (shoulders, elbows, wrist, head rotation) as described elsewhere (D'Souza et al. 2005).

Vital signs were recorded periodically, and blood was sampled for prolactin and cortisol from the intravenous line opposite to the one used for administering the study drug, to provide a behaviorally independent measure of cannabinoid effects. Immediately after collection, blood samples were placed on ice and centrifuged, and the extracted plasma was aliquoted into vials for storage at −70°C until the time of the assay. Prolactin and cortisol assays were run in duplicate pairs using radioimmunoassay kits to determine prolactin (Serono Diagnostics) and cortisol (Baxter Travenol Diagnostics) levels.

Statistical analyses

Initially, data were examined descriptively using means, standard deviations, and graphs. Each outcome was tested for normality using Kolmogorov–Smirnov test statistics and normal probability plots. Some, but not other, outcomes were approximately normal. Some of the skewed data were successfully normalized by log transformation. However, some skewed data could not be normalized by log transformation. These non-normal outcomes were analyzed using the nonparametric approach for repeated measures data (Brunner et al. 2002), where the data were first ranked and then fitted using a mixed-effects model with an unstructured variance–covariance matrix and p values adjusted for analysis of variance-type statistics (ATS). Linear mixed models were used to analyze normal or normalized (log-transformed) data. If data required normalization or could not be normalized, it is specified in "Results." For all the CANTAB data, vigilance and distractibility data, and the verbal recall models, each outcome, in turn, represented the dependent variable, while haloperidol (placebo vs active) and THC (placebo vs active) were included as within-subject explanatory factors, and group (frequent users vs healthy subjects) was included as a between-subjects factor. However, because no group differences were found, group was eliminated from the models for most of the outcomes except for endocrine, immediate recall, and SWM data. In addition, all CANTAB models were controlled for NART-IQ and motor function (latency). For verbal immediate recall, trial (1–3) was included as an additional within-subject factor. These models allowed for testing of all main and interaction effects of haloperidol and THC. When appropriate, post-hoc comparisons were performed. In the above models, subject was used as the clustering factor. Similar models as above were used to evaluate CADSS, PANSS, and VAS outcomes, except that the THC factor was replaced by time (−90, −30, 15, 65, 140, 190) as a within-subject factor. Data on the similarity to cannabis and enjoyment of the experience were

analyzed similarly except that measurements were taken only at time 65 and 190. Because there was little or no variance at earlier time points, analyses of the akathisia and Parkinsonism data were restricted to time 140 only; these models included only the within-subject factor haloperidol. Data were analyzed using SAS, version 9.1 (SAS Institute, Cary, NC). All results were considered statistically significant at $P<0.05$. Bonferroni correction was applied within but not across hypotheses. Thus, for the positive symptoms subscale of the PANSS, a cutoff alpha level of 0.05/2=0.025 was used to declare effects significant for PANSS positive.

Results

Of the 54 subjects who were screened, a total of 28 subjects (17 healthy subjects and 11 frequent users of cannabis) initiated the study (Table 2). Frequent users and healthy subjects were not significantly different across several measures except for years of education (Table 2) and cannabis use histories (Table 3). However, because there were no group differences found across most outcome measures, unless otherwise specified, the results are presented below for the combined sample. Eight subjects (five healthy subjects and three frequent users) did not complete the study because they disliked the psychotomimetic and anxiogenic effects of Δ-9-THC (n=2), scheduling difficulties (n=1), and/or nonstudy issues (n=5). One subject who did not disclose a history of migraine at screening experienced a headache on the placebo condition. No serious adverse events occurred during the study or during the follow-up period, as determined by face-to-face contact and telephone interview.

Psychotomimetic effects

PANSS and CADSS data were highly skewed. Δ-9-THC produced significant increases in PANSS Total (ATS=24.7, num df=2.9, unadjusted $P<0.0001$), PANSS positive symptoms subscale (ATS=10.1, num df=2.8, adjusted $P< 0.0001$), CADSS subjective [ATS=15.9, num df=3.5, unadjusted $P<0.0001$), and CADSS objective (ATS=20.8, num df=2.9, $P<0.0001$) scores. There were no significant effects of haloperidol or haloperidol by Δ-9-THC-interactive effects on any of these outcomes (Fig. 1a and b).

Visual analog scale feeling states

VAS "high," "anxious," and "panic" data were highly skewed, while "calm and relaxed" and "tired" data were approximately normal. Δ-9-THC produced significant increases in VAS "high" (ATS=44.6, num df=3.2, $P<0.0001$) and "tired" ($F[5, 27]=5.01$, $P=0.0022$) but did not significantly change any other feeling states. There were no significant effects of haloperidol or haloperidol by Δ-9-THC-interactive effects on any of these outcomes (Fig. 1c and d).

Similarity to cannabis and enjoyment of the experience

Data on these measures were skewed (Table 4). Δ-9-THC produced significant increases in ratings of the similarity of the experience to cannabis (ATS=116.5, num df=1, $P< 0.0001$) and enjoyment of the experience (ATS=41.7, num df=1, $P<0.0001$). Haloperidol reduced ratings of enjoyment of the experience (ATS=8.0, num df=1, $P=0.005$). There were no significant interactive effects of haloperidol and Δ-9-THC.

Verbal learning and recall

Immediate recall data were approximately normal while all other outcomes were highly skewed.

No significant practice effects both within and across test days were detected on verbal recall or any of the other cognitive measures (Table 4).

Immediate recall—Δ-9-THC significantly impaired immediate total recall (F[1, 27]=12.49, P=0.0015). Recall improved significantly across trials (learning) (F[2, 54]=145.9, P=0.0001). There was a trend toward a significant interaction between haloperidol and Δ-9-THC (F[1, 19] =3.4, P=0.08) with the haloperidol further worsening Δ-9-THC-induced recall deficits. There was a significant three-way interaction between haloperidol, Δ-9-THC, and group (F[1, 18] =6.0, P=0.025); this was a result of the combined effect of haloperidol and Δ-9-THC in producing significant recall deficits in healthy subjects (F[1, 18]=10.43, P=0.0046) but not in frequent users (F[1, 18]=2.66, P=0.12; Fig. 2).

Delayed free, cued, and recognition recall—Δ-9-THC (ATS=8.9, num df=1, P=0.0028) and haloperidol (ATS=3.6, num df=1, P=0.056) impaired delayed free recall. Δ-9-THC but not haloperidol impaired delayed cued recall (ATS=5.6, num df=1, P=0.0185). The interaction between haloperidol and Δ-9-THC was significant for delayed free recall (ATS=4.2, num df=1, P=0.04) and delayed cued recall (ATS=8.9, num df=1, P=0.003) with both effects explained by haloperidol further worsening Δ-9-THC-induced recall impairments. Neither Δ-9-THC nor haloperidol impaired delayed recognition recall (Fig. 3).

Errors—Δ-9-THC significantly increased the number of intrusions (ATS=7.9, num df=1, P=0.005) and false-positive (ATS= 22.1, num df=1, P<0.0001) responses but not perseverations. The interaction between haloperidol and Δ-9-THC trended to increase false-positive responses (ATS=3.5, num df=1, P=0.06) with the effects explained by haloperidol further increasing Δ-9-THC false-positive responses.

Attention

Both vigilance and distractibility data were highly skewed (Table 4).

Vigilance—Haloperidol (ATS=4.4, num df=1, P=0.037) and the interaction of Δ-9-THC and haloperidol (ATS=5.4, num df=1, P= 0.02) but not Δ-9-THC alone significantly increased omission errors. There were no significant effects of Δ-9-THC, haloperidol, or group on commission errors (Fig. 4a and b).

Distractibility—Δ-9-THC (ATS=10.0, num df=1, P=0.0016), haloperidol (ATS=25.6, num df=1, P<0.0001), and the interaction of Δ-9-THC and haloperidol (ATS=7.0, num df=1, P=0.008) significantly increased omission errors. The latter was driven by the effects of haloperidol. Haloperidol significantly (ATS=6.1, num df=1, P=0.014) and Δ-9-THC trended (ATS=3.5, num df=1, P=0.06) to increase commission errors, but there were no significant interactive effects between the two (Fig. 4c and d).

CANTAB

Motor screening—Δ-9-THC (F[1, 64]=6.4, P=0.01) but not haloperidol or the interactions between the two significantly reduced mean latency motor performance (Table 4).

Spatial working memory—Between-errors data were normalized by log transformation. Δ-9-THC increased between (F[1, 26]=5.2, P=0.03) but not within errors, while haloperidol had no effects on either type of error. This was one of the few measures where there was a significant interactive effect of group and Δ-9-THC on between errors (F[1, 25]=4.2, P=0.05); this was due to healthy subjects having higher Δ-9-THC induced between errors (F[1, 25]=9.88, P=0.004; Fig. 5).

Stockings of Cambridge—There were no significant effects of Δ-9-THC, haloperidol, group, or any interactions between the two on the number of occasions that subjects successfully replicated a reference pattern in the minimum possible number of moves.

Delayed match to sample task—Haloperidol significantly reduced percent correct performance (F[1, 62]=6.0, P=0.017). There were no effects of Δ-9-THC, group, or any interactions between Δ-9-THC, group, or haloperidol on any of the measures.

Akathisia, rigidity, and tremor—All outcomes were highly skewed. Δ-9-THC (ATS=5.1, num df=1.6, P<0.0098) but not haloperidol increased Barnes Global Akathisia scores. Neither Δ-9-THC nor haloperidol had any effect on tremor or rigidity (see Table S1 in Electronic supplementary material). There were no significant effects of haloperidol or group or the interactions between haloperidol, Δ-9-THC, and group on any of the other motor outcomes.

Neuroendocrine effects

Prolactin and cortisol levels were approximately normally distributed after log transformation. Serum cortisol levels decreased over time (F[2, 107]=51.05, P<0.0001), but there were no significant effects of haloperidol or interactions between haloperidol and Δ-9-THC (Fig. 6).

Haloperidol increased (F[1, 107]=77.7, P<0.0001) and time/Δ-9-THC decreased (F[2, 107] =10.8, P≤0.0001) serum prolactin levels. The interaction between haloperidol and time/Δ-9-THC was significant (F[2, 107]=56.8, P< 0.0001) where prolactin levels on the active haloperidol condition were significantly greater at 65 (F[1, 107]=15.8, P=0.0001) and 190 min (F[1, 107]=144.5, P<0.0001) but not at baseline (not significant). Of note, serum prolactin levels were lower in frequent users of cannabis (F[1, 102]=7.1, P=0.009).

Discussion

This is the first published report to our knowledge on the interactions between haloperidol and Δ-9-THC in humans. The principal finding of this study is that haloperidol, at a dose that produced effects consistent, e.g., with prolactin elevation with acute antagonism of DA D_2 receptors, failed to reduce any Δ-9-THC effects. Instead, haloperidol worsened some of the cognitive effects of Δ-9-THC.

Effects of haloperidol alone

Haloperidol worsened performance on some cognitive tasks similar to other reports (Saeedi et al. 2006). As expected, haloperidol increased serum prolactin levels. In addition, the observation that haloperidol did not produce any obvious behavioral or motor effects confirms the appropriateness of the dose that was selected. At this dose, most of haloperidol's effects would be expected to be related to its antagonism of DA D_2 receptors. Its affinity for histaminic H_1 and muscarinic M_1 receptors is greater than 600 and greater than 2,000 times less than its affinity for DA D_2 receptors. Similarly, any interactions between Δ-9-THC and haloperidol most likely converge through DAergic systems.

Effects of Δ-9-THC alone

The dose and rate of Δ-9-THC administration in this study were chosen in an attempt to mimic recreational cannabis use. The observation that subjects reported that the experience was similar to cannabis and that they enjoyed it supports the generalizability of the findings to recreational cannabis use.

The effects of intravenous Δ-9-THC observed in this study were similar to but of smaller magnitude than the effects produced by higher doses of intravenous Δ-9-THC (2.5 and 5 mg over 2 min; D'Souza et al. 2004, 2005, 2006). For example, the Δ-9-THC dose (2 mg over 20 min in a 70-kg individual) in this study produced peak self-rated perceptual alteration CADSS score (3.96) nearly four times lower than the effects (14.95) of a higher Δ-9-THC dose (5 mg over 2 min) (D'Souza et al. 2004). Nevertheless, the peak increases in PANSS positive

symptoms scores induced by this Δ-9-THC dosing paradigm were comparable to the peak increases in positive symptom scores induced by (1) amphetamine 0.25 mg/kg administered i.v. over 1 min (Krystal et al. 2005), (2) low-dose ketamine (bolus 0.081 mg/kg over 10 min followed by an infusion of 0.4 mg kg^{-1} h^{-1}; Krystal et al. 2006), and *m*-chlorphenyl-piperazine (D'Souza et al. 2006). As discussed earlier, we attempted a shorter infusion and higher dose of Δ-9-THC in combination with haloperidol, but this was poorly tolerated.

Some of the cognitive effects of Δ-9-THC that have been well described in animals but not in humans were measured in this study. Cannabinoids impair spatial memory in animals (Aigner 1988; Carlini et al. 1970a, b; Winsauer et al. 1999), and we now show for the first time in humans that Δ-9-THC impairs SWM as evidenced by an increase in between but not within errors. This profile of effects suggests that while subjects were able to perform the basic task, the longer they had to maintain information online, the worse they performed. Further, the observation that Δ-9-THC did not impair performance in frequent users of cannabis (Fig. 5) is consistent with the preclinical observations of tolerance to the effects of cannabinoids on SWM (Lichtman et al. 1995). Further, the absence of an effect in frequent users of cannabis is important to consider in interpreting the cannabis literature, as most studies have included frequent or heavy users of cannabis. Finally, the observation of group differences only on the SWM task suggests that the latter may be most sensitive in detecting differences between frequent users and healthy subjects.

In animals, cannabinoids impair performance on the DMTS, a visual recognition memory task, only when the delay is long (Heyser et al. 1993; Winsauer et al. 1999). Δ-9-THC did not impair DMTS in this study even when the delay was long. Other studies of Δ-9-THC on DMTS performance have had mixed results (Heishman et al. 1997; Lane et al. 2005). Perhaps, differences in the delay periods, other task parameters, Δ-9-THC doses, and degree of cannabinoid tolerance across samples might account for the disparate results. Consistent with a wealth of clinical data (reviewed in Ranganathan and D'Souza 2006), Δ-9-THC impaired several aspects of verbal recall. The fact that Δ-9-THC impaired free verbal recall but not visual and verbal recognition recall suggests that Δ-9-THC does not impair encoding but rather impairs retrieval and/or consolidation.

While Δ-9-THC reduced the number of problems solved in minimum moves on the SOC task (Table 5), these effects were not statistically significant. Of note, Ramaekers et al. (2006) showed that higher doses of Δ-9-THC impair performance on a task analogous to the SOC, the Tower of London task. They went on to argue that Δ-9-THC effects on executive function may be relatively small at low doses, similar to those used in this study, but may become "very substantial" at higher doses.

Δ-9-THC also reduced motor latency. Others have reported that Δ-9-THC produces an increase in the speed of responding along with worse performance suggesting that under the influence of cannabinoids, individuals trade speed for accuracy (Curran et al. 2002).

Interactive effects of haloperidol and Δ-9-THC

Behavioral and subjective outcomes

While both PANSS positive symptoms (Fig. 1a) and CADSS perceptual alterations (Fig. 1b) scores induced by Δ-9-THC were lower on the active vs the placebo haloperidol condition (see Table 4), these effects were not statistically significant. These results are not consistent with the report that "cannabis-induced psychosis" is responsive to treatment with DA D_2 receptor antagonists (Berk et al. 1999). In contrast, the current results are consistent with the observation that Δ-9-THC increased psychotomimetic symptoms in schizophrenic patients despite chronic treatment with DA D_2 receptor antagonists (D'Souza et al. 2005). Perhaps, the effects of Δ-9-

THC better model those positive symptoms that are resistant to DA D_2 receptor antagonist antipsychotic drugs. Further, whereas Δ-9-THC produces positive and negative symptoms and cognitive deficits (D'Souza et al. 2004,2005), amphetamine produces predominantly positive symptoms (Angrist et al. 1974b;Angrist and Gershon 1970;Griffith et al. 1972). Finally, haloperidol reverses psychosis induced by amphetamine (Angrist et al. 1974a). However, haloperidol pretreatment did not reduce the psychosis induced by ketamine (Krystal et al. 1999), lysergic acid diethylamide, and, in the current study, Δ-9-THC. Taken collectively, this suggests that DA D_2 mechanisms may not play a major role in the pathophysiology of Δ-9-THC-induced psychotomimetic effects. Perhaps, the use of a single and relatively low dose of haloperidol combined with the small increases in Δ-9-THC-induced psychotomimetic symptoms may explain the lack of a haloperidol effect in this study. Alternatively, the failure of haloperidol to block Δ-9-THC-induced psychotomimetic effects reflects a limitation in the relevance of the cannabinoid "model" of psychosis.

Similarly, the lack of any effect of haloperidol on Δ-9-THC-induced VAS measured subjective effects ("high," "tired," etc.) is consistent with our observations that chronic antipsychotic treatment did not blunt the euphoric effects of Δ-9-THC in schizophrenic patients (D'Souza et al. 2005). The failure of haloperidol to block the euphoric effects of Δ-9-THC was surprising given that the rewarding properties of cannabinoids, like other drugs of abuse, have been associated with an increased activity of mesolimbic DA transmission (Chen et al. 1990b, 1991; Fadda et al. 2006; French 1997; French et al. 1997; Ng Cheong Ton et al. 1988; Patel and Hillard 2003; Tanda et al. 1997a, b). Relevant to both the euphoric and psychotomimetic effects of Δ-9-THC, the DA D_2 receptor antagonist sulpiride failed to block Δ-9-THC-induced c-*fos* expression in both the striatum and nucleus accumbens (Miyamoto et al. 1996). Regardless, the current findings suggest that acute DA D_2 receptor blockade antagonists may not be useful in cannabis addiction or psychosis, but whether repeated dosing is useful remains unclear.

Cognitive outcomes

Together, haloperidol and Δ-9-THC impaired sustained attention (increased omission errors on both vigilance and distractibility tasks) and immediate and delayed verbal recall. Further, while the interactive effects of haloperidol and Δ-9-THC on visual recognition memory, SWM, and planning and execution did not reach statistical significance, the effects were in the direction of the combination of the two drugs worsening performance to a greater extent than either drug alone. The observed findings were not predicted and at present can only be speculated upon. Attention, execution function, visual recognition memory, SWM, verbal learning, and recall all require varying contributions of and complex interactions between the prefrontal cortex (PFC) and hippocampus. For instance, cannabinoids could alter PFC and hippocampal function via their effects on the release of DA, acetylcholine, glutamate, or norepinephrine. While it is out of the scope of this paper to discuss all these possibilities, we briefly discuss some of the preclinical evidence of crosstalk between CB_1 and DA systems in the PFC, which might explain some of the interactive cognitive effects of haloperidol and Δ-9-THC.

Systemically administered cannabinoids can modulate the activity of DAergic pathways in the PFC either directly or indirectly, by influencing the activity of DAergic neurons through either post- or presynaptic mechanisms (Egerton et al. 2006; Laviolette and Grace 2006b; Pistis et al. 2002). CB-induced DAergic hyperactivity in the PFC may contribute to working memory deficits associated with CB exposure (Diana et al. 1998; Jentsch et al. 1997). Acute administration of haloperidol may result in acute DA D_2 blockade but also compensatory DA release in the medial PFC and nucleus accumbens (Liegeois et al. 2002; Moghaddam and Bunney 1990; Moghaddam et al. 1990). Thus, the combination of Δ-9-THC and haloperidol

may result in additive DA release in the PFC. Given that either too high or low DAergic activity in the PFC can lead to impairments in PFC-related cognitive functions (Goldman-Rakic 1996; Murphy et al. 1996; Zahrt et al. 1997), this may explain the observations that the combination of haloperidol and Δ-9-THC worsened cognition.

Prolactin

Δ-9-THC produces an early and brief increase followed by a predominantly inhibitory effect on prolactin release (Harclerode 1984; Murphy et al. 1998) that is believed to be mediated by CB-1R activation of tuberoinfundibular (TIDA) DA neurons (Rodriguez De Fonseca et al. 1992). Of note, frequent users of cannabis had lower prolactin levels. Prolactin release is under tonic DA control (Selmanoff 1981), and prolactin controls its own release by altering DA release (Gregerson and Selmanoff 1988). Thus, the lower-baseline prolactin levels in frequent users may reflect increased DA tone in the TIDA pathway of frequent users that is related to either residual cannabis effects or long-term adaptive changes in DA function in response to chronic cannabis exposure. In a previous study, 5 mg but not 2.5 mg Δ-9-THC increased prolactin levels in healthy human subjects (D'Souza et al. 2004). Perhaps, the lack of a significant acute effect of Δ-9-THC on plasma prolactin in this study may be explained by the small dose (2 mg) and limited sampling.

Limitations

There were several limitations to this study. First, the use of multiple doses of haloperidol and Δ-9-THC may have been more informative than the current design but was not feasible, as discussed earlier. Second, because haloperidol has affinity for other receptors (D_1 and α_1), any interactions of Δ-9-THC and haloperidol cannot be attributed solely to interactions with D_2 receptors. Third, the smaller magnitude of Δ-9-THC induced behavioral and cognitive effects in this study compared to previous studies, which used higher doses and a faster infusion (D'Souza et al. 2004, 2005), may have reduced the likelihood of detecting a beneficial effect of haloperidol. Fourth, the limited sample size may, in part, contribute to the lack of significant findings. For example, the difference in Δ-9-THC-induced increase in PANSS positive symptom score between the placebo and active haloperidol test days was 0.65 (SD 1.56). This translates into a small to medium effect size (d=0.42) for the reduction in Δ-9-THC-induced positive symptoms, which, with 28 subjects, would not be adequately powered to detect. However, with 28 subjects, we still had 80% statistical power to detect medium/large effects size (d= 0.55) with 80% statistical power for any given outcome. Fifth, a random order of Δ-9-THC (placebo or active) administration would have been preferred. Sixth, in contrast to the cognitive assessments, the behavioral and subjective effects were measured repeatedly during each Δ-9-THC session. This should be noted in interpreting the effects of haloperidol pretreatment on Δ-9-THC effects.

Conclusions

The current study replicates a growing body of research characterizing the cognitive effects, perceptual altering, psychotomimetic, and euphoric of Δ-9-THC. The failure of haloperidol pretreatment to antagonize the psychotomimetic effects of Δ-9-THC suggests that these effects of Δ-9-THC are not likely mediated by DA D_2 receptor mechanisms and that novel pharmacologic approaches will be needed to block these effects. Given the growing interest in the link between cannabinoids and psychosis, future research should be directed toward understanding the precise mechanisms underlying the psychotomimetic symptoms produced by Δ-9-THC. While admittedly speculative, the search for drugs that block the psychotomimetic symptoms produced by Δ-9-THC may lead to novel approaches to the treatment of psychotic disorders. The deleterious effect of haloperidol pretreatment on the cognitive effects of Δ-9-THC is consistent with the preclinical literature in suggesting crosstalk

between DAergic and CBergic systems. However, further work is necessary to fully understand the crosstalk between the two systems in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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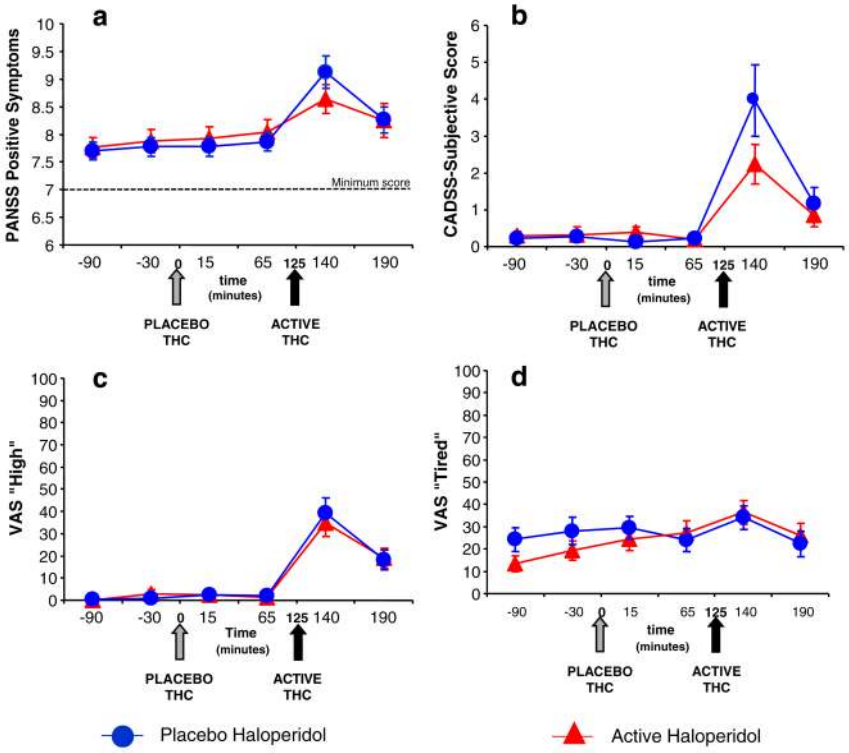


Fig. 1.

a Positive symptoms of psychosis measured by the Positive Symptoms subscale of the Positive and Negative Syndrome Scale (PANSS). **b** Perceptual Alterations measured by the Subject rated subscale of the Clinician Administered Dissociative Symptoms Scale (CADSS). **c** "High" measured by the visual analog scale (VAS). **d** "Tired" measured by the visual analog scale (VAS; *T bars* indicate SEMs)

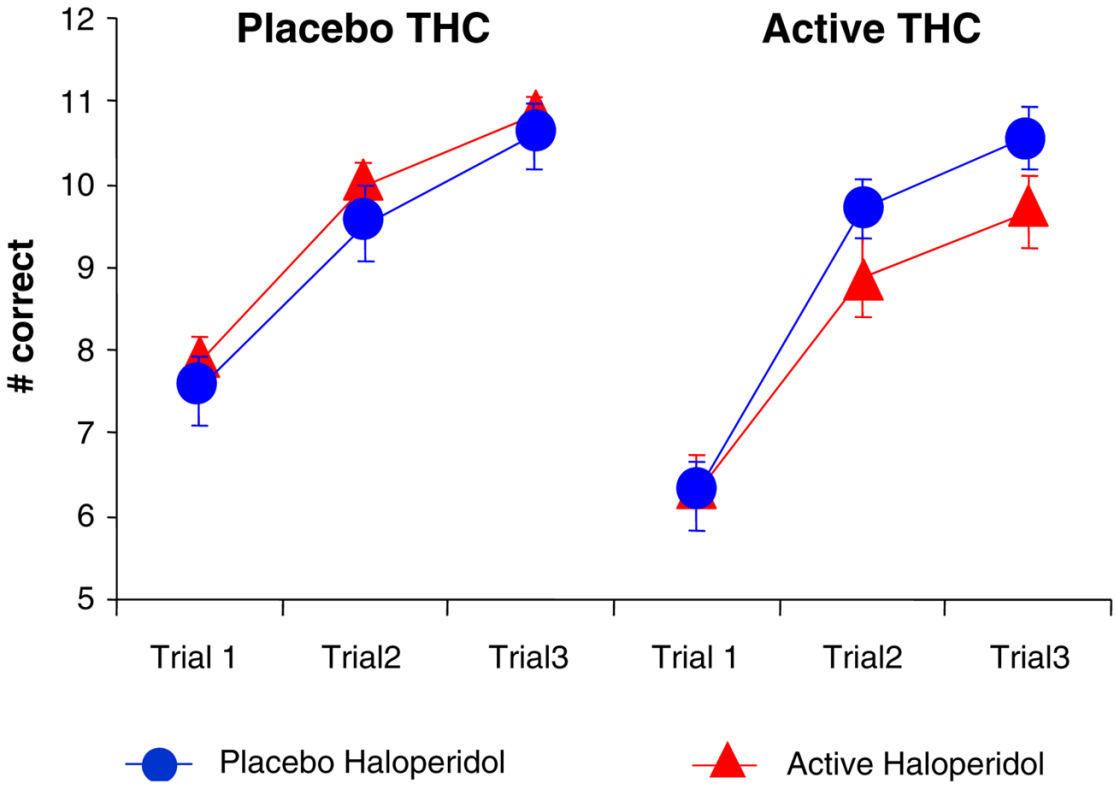


Fig. 2.
Immediate verbal recall measured by the Hopkins Verbal Learning Task (*T bars* indicate SEMs). Δ-9-THC impaired immediate recall and haloperidol worsened Δ-9-THC induced immediate recall impairments

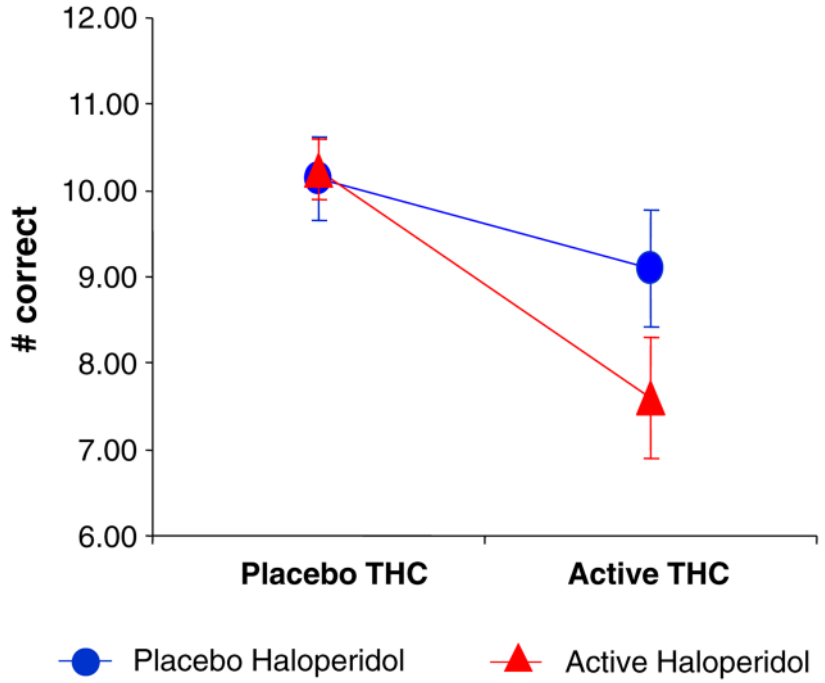


Fig. 3.
Delayed verbal recall measured by the Hopkins Verbal Learning Task (*T bars* indicate SEMs). Δ-9-THC impaired delayed free recall and haloperidol worsened Δ-9-THC induced delayed free recall impairments

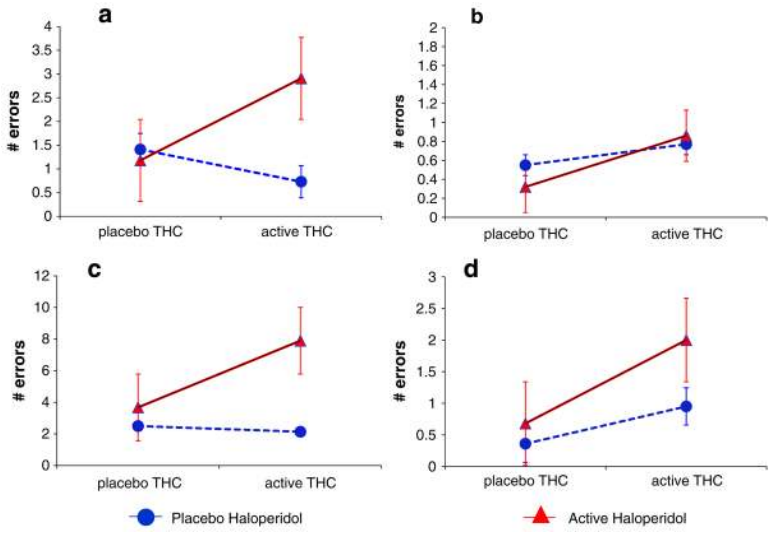


Fig. 4.

a, **b** Vigilance omission and commission errors measured by the Gordon Box Continuous Performance Task (CPT). Haldol alone and in combination with Δ-9-THC increased omission errors. **c**, **d** Distractibility omission and commission errors measured by the Gordon Box CPT. Δ-9-THC alone and haloperidol alone increased omission and commission errors. *T bars* indicate SEMs

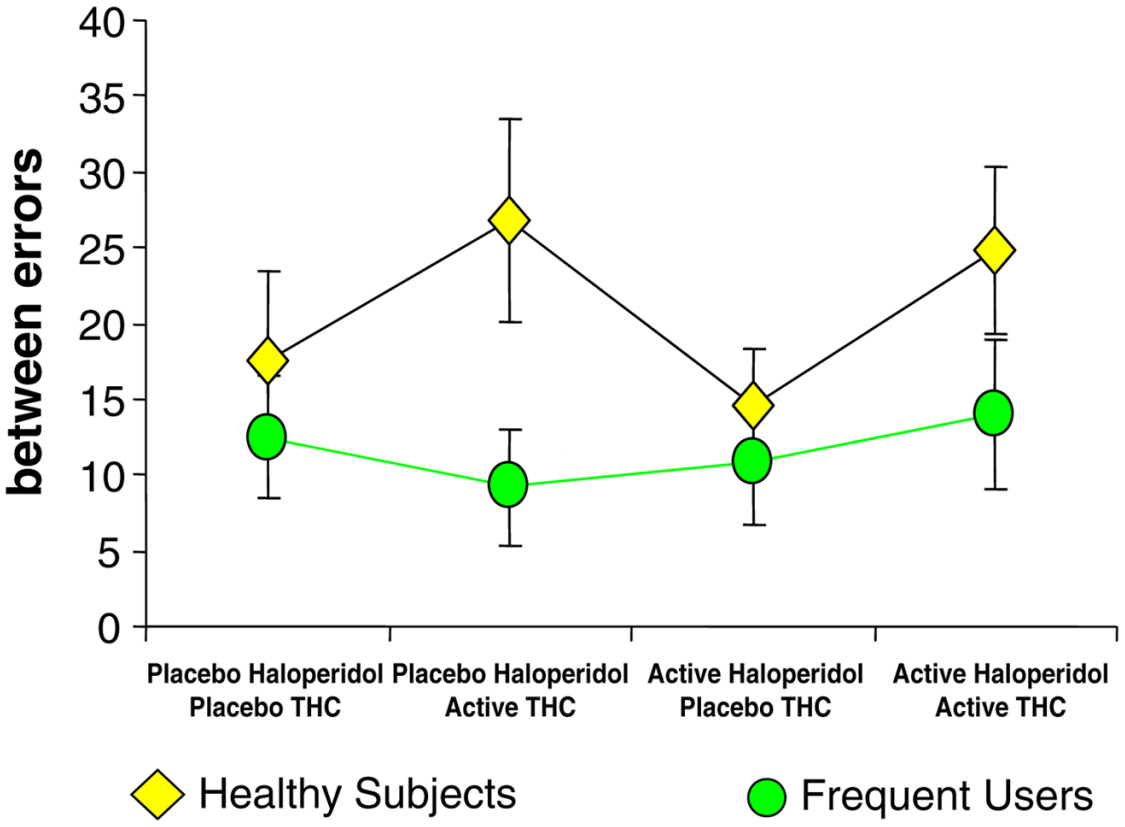


Fig. 5.
Spatial working memory measured by the CANTAB (Cambridge Neuroscience Battery; *T bars* indicate SEMs). Δ-9-THC and the combination of Δ-9-THC increased between errors only in healthy subjects

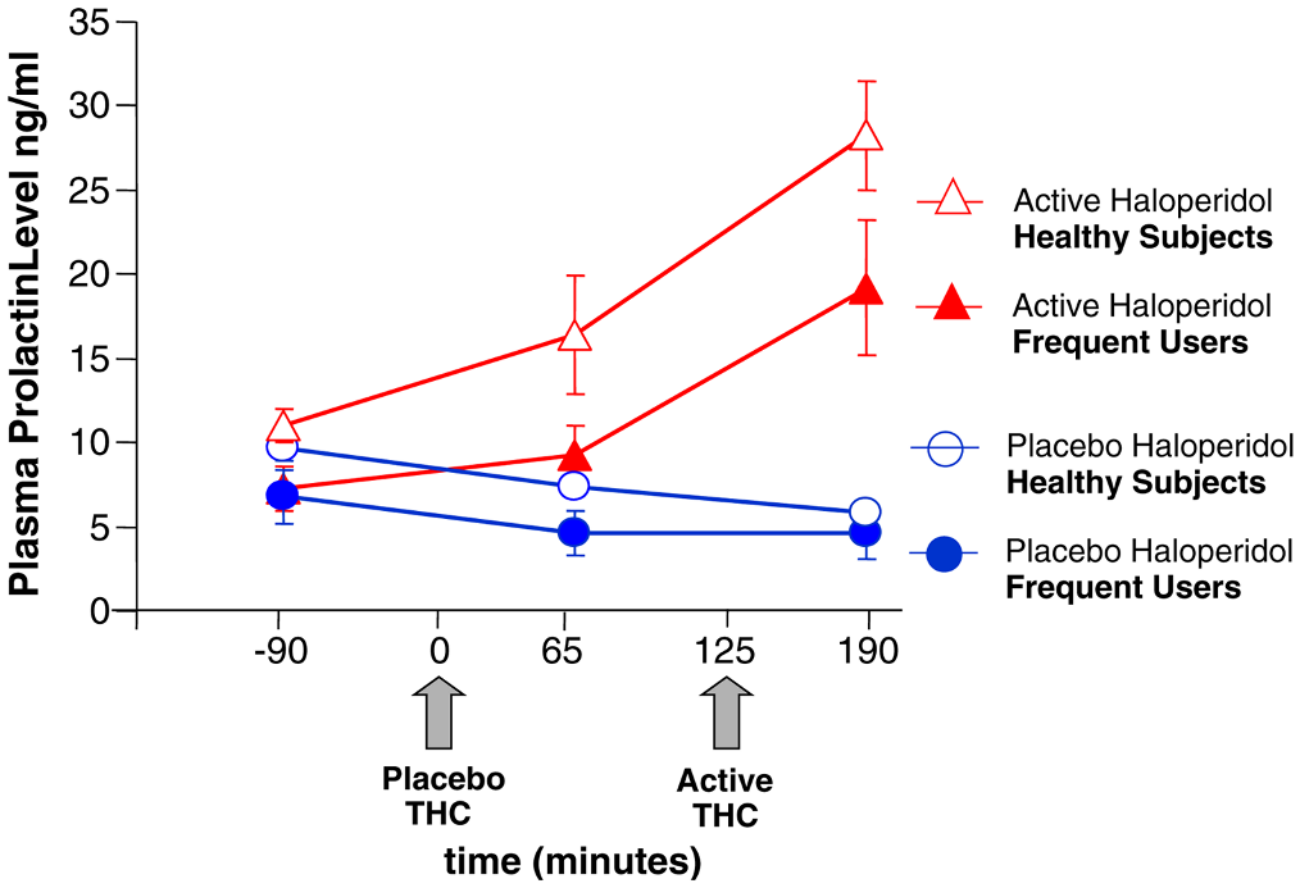
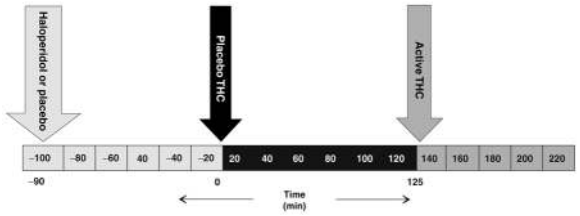


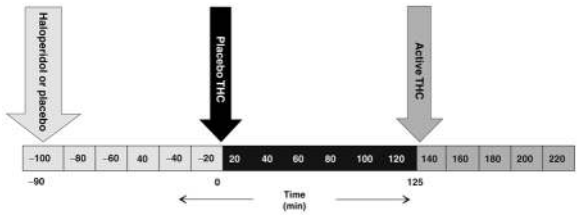
Fig. 6.
Plasma prolactin levels (*T bars* indicate SEMs). Lower baseline prolactin levels in frequent users. Haloperidol but not Δ-9-THC increases prolactin levels

Table 1

Schedule of procedures



Time (Min)	Procedures
−90	Screening: Urine drug screen and urine pregnancy test. Confirmation of abstinence from caffeine, alcohol, drugs and prohibited medications.
	Vital Signs (blood pressure, heart rate, temperature), standard light breakfast and placement of intravenous lines
	Baseline Serum Sampling for (1) prolactin (2) cortisol
	Behavioral Assessments: Positive and Negative Syndrome Scale (PANSS), Clinician Administered Dissociative Symptoms Scale (CADSS), Visual Analog Scale (VAS) for "high," "calm and relaxed," "anxious," "tired" and "panic," and Timeline Follow-Back (Day 1).
	Motor Assessments: Simpson Angus Scale for Parkinsonism (SAS), Barnes Akathisia Scale (BAS)
	Haloperidol or Placebo PO
−30	Behavioral ratings: PANSS, CADSS, VAS.
	Motor ratings: SAS, BAS
	Vital Signs
−10	**Bloods Levels: (1) prolactin (2) cortisol levels**
	Vital Signs
0	**Placebo Intravenous delta-9-THC over 20 min**
	Vital Signs Q 2 min.
+15	Vital Signs Q 5 min.
	Behavioral ratings: PANSS, CADSS, VAS.
	Motor ratings: SAS, BAS
+35	Vital Signs Q 10 min.
	Cognitive battery: Hopkins Verbal Learning Test Immediate and Delayed (30 min) recall (HVLT), Continuous Performance Task (CPT), Motor Screening (MS), Spatial Working Memory Task (SWMT), Stockings of Cambridge (SOC), Delayed Match to Sample (DMS)
+65	Vital Signs
	Behavioral ratings: PANSS, CADSS, VAS, Drug Liking Scale, Similarity to Cannabis Scale.
	Bloods Levels: (1) prolactin (2) cortisol levels
+85	Vital Signs
+125	**Active Intravenous delta-9-THC (0.0286 mg/kg) over 20 min**
	Vital Signs Q 2 min.
+140	Vital Signs Q 5 min.
	Behavioral ratings: PANSS, CADSS, VAS.
	Motor ratings: SAS, BAS
+160	Vital Signs: Monitoring set to q10 min. Switch to manual during cognitive battery.



Time (Min)	Procedures
	Cognitive battery: HVLT, CPT, MS, SWMT, SOC, DMTS
+190	Vital Signs
	Behavioral ratings: PANSS, CADSS, VAS, Drug Liking Scale, Similarity to Cannabis Scale.
	Bloods Levels: (1) prolactin (2) cortisol levels
+210	Vital Signs
End of each day	Safety Assessment: Field sobriety test, Minimental State Examination, vital signs, physician evaluation.
	Subject provided with Benadryl PRN for EPS and contact information for On-Call Research Psychiatrist.
Last day	**Exit interview**
Months 1, 3, 6	**Safety Follow up:** 1. Assessment of cannabis use, desire, craving, 2. Assessment for emergence of new psychiatric or medical problems.

Table 2

Demographics

		Mean (SD)
Total (*n*=28)	Healthy subjects	17
	Frequent users	11
Age (SD) years		24.89 (±6.98)
National Adult Reading Test (NART) IQ		113 (±7.3)
Years of education	All	15.78 (±1.9)**
	Healthy subjects	16.35 (±2.23)
	Frequent users	14.91 (±0.94)
Race	Caucasian	19
	Native American	0
	African American	3
	Hispanic	2
	Asian	4
Weight		159.35 (±28.59)

** *t* test; $p=0.054$

Table 3

Cannabis use histories

	Healthy subjects	Frequent users
Estimated self-reported lifetime cannabis exposure		
Less than 5 times	2	0
5–10 times	4	0
11–20 times	2	0
21–50 times	4	0
51–100 times	3	0
>100 times	2	11
Group difference (Wilcoxon signed rank test)	$P<0.0001$	
Last exposure to cannabis		
Past week	0	10
1 week–1 month	5	1
1–6 months	3	0
6months–1 year	3	0
1–5 years	5	0
5–10 years	1	0
>10 years	0	0
Group difference (Wilcoxon signed rank test)	$P<0.0001$	

Table 4

Behavioral, subjective, and motor results (means [±SD])

Outcome		Placebo haloperidol						Active haloperidol					
		−90	−30	15	65	140	190	−90	−30	15	65	140	190
		Pre THC		Placebo THC		Active THC		Pre THC		Placebo THC		Active THC	
PANSS	Positive	7.7 (0.76)	7.78 (0.8)	7.78 (0.8)	7.87 (0.81)	9.13 (1.39)	8.26 (1.14)	7.76 (0.93)	7.88 (1.05)	7.92 (1.08)	8.04 (1.17)	8.64 (1.29)	8.25 (1.54)
	Total	30.7 (3.53)	30.83 (2.72)	31.04 (3.08)	30.83 (2.44)	35.5 (3.6)	31.39 (2.25)	30.44 (2.65)	30.6 (2.6)	30.96 (2.79)	31.36 (3.05)	34.58 (2.89)	32.21 (3.27)
CADSS	Subject rated	0.22 (0.6)	0.26 (0.69)	0.13 (0.46)	0.22 (0.6)	3.96 (4.64)	1.17 (2.12)	0.28 (0.68)	0.32 (1.07)	0.38 (0.77)	0.2 (0.58)	2.24 (2.68)	0.84 (1.57)
	Clinician rated	0.09 (0.29)	0.14 (0.35)	0.17 (0.65)	0.17 (0.65)	2.43 (2.74)	0.52 (1.08)	0.04 (0.2)	0 (0)	0.24 (0.6)	0.28 (0.89)	1.96 (2.07)	0.92 (1.41)
VAS	Anxious	5.52 (13.5)	3.65 (10.45)	1.7 (4.19)	2.65 (6.11)	4.13 (8.15)	1.91 (5.2)	8.8 (13.3)	4.48 (9.24)	2.92 (5.28)	1.4 (2.74)	4.28 (10.44)	6.96 (19.77)
	Calm	76.91 (21.9)	78.96 (20.5)	76.74 (25.65)	76.74 (23.86)	80.13 (25)	80.43 (19.82)	69.76 (27.16)	74.2 (25.31)	77.76 (18.82)	72.96 (23.36)	73.6 (30.7)	70.67 (25.65)
	High	0.48 (0.99)	0.7 (1.11)	2.52 (5.23)	2.04 (4.57)	39.32 (31.15)	18.13 (20.9)	0.12 (0.33)	2.72 (10.06)	2.4 (5.63)	1.13 (4.08)	34.96 (30.71)	18.88 (21.88)
	Panic	0.65 (1.23)	0.65 (1.19)	0.57 (0.95)	0.61 (1.12)	0.74 (1.18)	0.91 (1.44)	0.28 (0.61)	0.32 (0.69)	0.48 (1.05)	0.4 (0.87)	1.4 (3.11)	1.29 (2.58)
	Tired	24.26 (25.5)	28.13 (28.88)	29.52 (24.26)	24 (25.39)	34.09 (25.91)	22.3 (27.26)	13.4 (18.31)	19.28 (22.47)	24.4 (25.7)	27.12 (27.22)	36.56 (26.42)	26 (26.36)
Similarity to cannabis					4.13 (10.99)		59.17 (30.64)				5.52 (15.58)		55.24 (29.65)
Enjoyment of experience					31.43 (25.97)		61.04 (26.64)				19.88 (22.98)		47 (26.24)

PANSS Positive and Negative Syndrome Scale, *CADSS* Clinician Administered Dissociative Symptoms Scale, *VAS* visual analog scale

Table 5

Cognitive measures results (mean [±SD])

Outcome			Placebo haloperidol		Active haloperidol	
			Placebo THC	Active THC	Placebo THC	Active THC
Verbal recall (HVLT)	Total immediate recall		27.61 (5.25)	26.52 (4.53)	28.64 (3.39)	24.84 (6.27)
	Delayed recall	Free	10.13 (2.32)	9.09 (3.25)	10.24 (1.74)	7.60 (3.46)
		Cued	10.00 (2.22)	10.30 (1.58)	10.40 (1.78)	8.72 (2.41)
		Recognition	11.57 (0.66)	11.65 (0.65)	11.80 (0.50)	11.32 (1.22)
	False positives		0.57 (0.90)	1.22 (1.68)	0.36 (0.76)	1.68 (1.97)
Vigilance	Omissions		1.41 (2.89)	0.68 (1.21)	1.18 (2.22)	2.91 (4.23)
	Commissions		0.55 (0.91)	0.77 (1.23)	0.32 (0.57)	0.86 (1.58)
Distractibility	Omissions		2.50 (4.70)	2.14 (2.98)	3.68 (4.36)	7.90 (6.66)
	Commissions		0.36 (0.58)	0.95 (1.81)	0.68 (1.25)	2.00 (2.66)
CANTAB	Motor function (MOT)	Latency	773.05 (198.3)	747.95 (224.6)	790 (155.09)	717.84 (165.04)
	Planning and execution (SOC)	Minimum moves	9.3 (1.69)	9.22 (1.98)	9.04 (1.9)	8.33 (2.01)
	Spatial working memory	Between errors	15.52 (18.74)	19.91 (22.3)	13.17 (13.48)	20.29 (19.08)
		Within errors	1.43 (2.86)	1.74 (3.79)	1.71 (4.37)	0.75 (1.07)
		Total errors	16.17 (19.38)	20.48 (23.24)	14.29 (14.25)	20.63 (19.34)
	Visual recognition memory (DMTS)	Percent correct	87.54 (8.6)	86.67 (10.05)	82.13 (12.28)	80.83 (12.17)

HVLT Hopkins Verbal Recall Test, *MOT* motor screening task, *SOC* Stockings of Cambridge, *DMTS* delayed match to sample

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