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Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment

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Abstract

Community-based studies suggest that cannabis products that are high in Δ^9-tetrahydrocannabinol (THC) but low in cannabidiol (CBD) are particularly hazardous for mental health. Laboratory-based studies are ideal for clarifying this issue because THC and CBD can be administered in pure form, under controlled conditions. In a between-subjects design, we tested the hypothesis that pre-treatment with CBD inhibited THC-elicited psychosis and cognitive impairment. Healthy participants were randomised to receive oral CBD 600mg (n=22) or placebo (n=26), 210 min ahead of intravenous (IV) THC (1.5 mg). Post-THC, there were lower PANSS positive scores in the CBD group, but this did not reach statistical significance. However, clinically significant positive psychotic symptoms (defined a priori as increases ≥3 points) were less likely in the CBD group compared with the placebo group, odds ratio (OR)=0.22 (χ^2=4.74, p<0.05). In agreement, post-THC paranoia, as rated with the State Social Paranoia Scale (SSPS), was less in the CBD group compared with the placebo group (t=2.28, p<0.05). Episodic memory, indexed by scores on the Hopkins Verbal Learning Task-revised (HVLT-R), was poorer, relative to baseline, in the placebo pre-treated group (-10.6±18.9%) compared with the CBD group (-0.4%±9.7 %) (t=2.39, p<0.05). These findings support the idea that high-THC/low-CBD cannabis products are associated with increased risks for mental health.

Keywords

Delta-9-tetrahydrocannabinol, cannabidiol, THC, CBD, psychosis

Introduction

The cannabis plant contains over 60 different cannabinoid molecules (Izzo et al., 2009), but two in particular have relevance for psychiatry. Δ^9-tetrahydrocannabinol can induce acute psychotic symptoms, in medicated schizophrenic patients and in healthy controls, whereas cannabidiol (CBD) is showing promise as a possible anti-psychotic (D'Souza et al., 2009; Leweke et al., 2000; Zuardi et al., 2006).

The balance of these two molecules in 'street cannabis' appears to have changed over the last decade. For example, in the UK and Holland, cannabis products traditionally contained about 4% THC and 4% CBD, as compared with 16–22% THC and <0.1% CBD content in modern 'high-potency' products (Sinsemilla or 'skunk') (Slade et al., 2012). There is accruing evidence that sinsemilla carries a greater risk to mental health (Di Forti et al., 2009; Morgan and Curran, 2008; Schubart et al., 2011).

In a highly original design, Morgan and Curran measured trace cannabinoid levels in hair samples from regular cannabis users as well as psychosis proneness as rated by the OLIFE (Oxford Liverpool Inventory of Life Experiences) instrument. Regular users who were grouped as THC-positive/CBD-negative scored higher on scores of unusual experiences than regular users who were positive for both cannabinoids (Morgan and Curran, 2008). In an epidemiological study in South London, Di Forti and colleagues compared patterns of drug use in people presenting with a first episode of psychosis with healthy controls. Patients were approximately seven times more likely than controls to be users of sinsemilla (Di Forti et al., 2009).

In Holland, the most popular types of cannabis sold are measured annually for THC and CBD content. Schubart and colleagues combined this information with data on cannabis use from approximately 1900 people, and found that the THC/CBD ratio was related to subclinical psychotic experiences as rated by the CAPE scale (Community Assessment of Psychic Experiences).

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Subjects who used products with a high THC/CBD ratio reported significantly higher CAPE-total scores than those using products with a low THC/CBD ratio. In heavy users, higher CBD content was associated with lower scores on the CAPE-positive symptoms dimension (Schubart et al., 2011).

In laboratory-based experimental studies, the acute effects of specific cannabinoid molecules can be measured under tightly controlled conditions. For example, in the early 1980s, Zuardi and colleagues demonstrated that CBD (1 mg/kg) inhibited the anxiety provoked by THC (0.5 mg/kg) (Zuardi et al., 1982). More recently, in a neuroimaging study of 15 healthy volunteers, task-specific blood-oxygen-level-dependent (BOLD) responses were measured following the administration of oral THC (10 mg), CBD (600 mg) or placebo. Relative to placebo, THC and CBD evoked diametrically opposite task-specific BOLD responses in the hippocampus, the amygdala and the occipital cortex (Bhattacharyya et al., 2010), the right superior temporal gyrus (Winton-Brown et al., 2011) and the pre-frontal cortex and caudate nucleus (Bhattacharyya et al., 2012).

Previously we reported preliminary findings that pre-treatment with intravenous (IV) CBD (5 mg) inhibited IV THC (1.25 mg) evoked positive psychotic symptoms, as measured by the Positive & Negative Syndrome Scale (PANSS), although the small sample size (crossover, n=6) prevents definitive conclusions (Morrison et al., 2010). Here we report the first findings from a larger study (between groups, n=48) in which IV THC (1.5 mg) followed pre-treatment with either oral CBD (600 mg) or placebo. We hypothesised that, following IV THC, the group who had been pre-treated with CBD would show less positive symptoms and less cognitive impairment than the group that had been pre-treated with placebo.

Methods

The study was approved by the Joint Institute of Psychiatry and Maudsley Hospital Ethics Committee. All subjects provided written informed consent. Safety protocols have previously been described (Morrison et al., 2009).

Design

In a 2×3 mixed design, participants were randomly allocated in a counterbalanced fashion to placebo or CBD groups. Placebo/CBD capsules were administered under double-blind conditions. Each participant was assessed at three separate time-points: (1) baseline; (2) post-capsule; and (3) post-THC. (Baseline data were collected on a separate day at least 1 week before the experimental day.)

Participants

A total of 48 participants were recruited via the King's College e-mail lists. Inclusion criteria were: age between 21 and 50 years, previous cannabis use ≥1. Detailed screening was performed 1–2 weeks before the experimental session. In addition to clinical examination, the following screening tools were used: The MINI-SCID, The Michigan Alcohol Screening Test and The Drug Addiction Screening Test (Gavin et al., 1989; Selzer et al., 1975; Spitzer et al., 1992). Exclusion criteria were: current pregnancy, a history of mental illness, drug or alcohol dependence (excluding nicotine), current or past severe medical disorders or a history of major mental illness in a first-degree family member. Previous alcohol and drug use were recorded and a urine drug screen was carried out. Participants were asked to avoid alcohol (for 24 h) and drugs (for 1 week) before, and to abstain from driving for 24 h after the experimental session. Experimental sessions began between 9–10 am and were complete by 4–5 pm. Participants received a brief clinical examination prior to discharge, a 'check-up' phone call the following day and were reimbursed for their time.

Pharmaceuticals

Cannabidiol (2×300 mg capsules) and matching placebo were obtained from STI Pharmaceuticals UK. Synthetic THC was supplied by THC Pharm GmbH (Frankfurt am Main, Germany) and prepared as 1 mg/mL vials for IV injection, by Bichsel Laboratories (Interlaken, Switzerland) as previously described (Naef et al., 2004). After dilution in normal saline, preparations for injection contained 1.5% (v/v) ethanol absolute. Sterile cannulae were inserted into veins in the antecubital fossa of both arms: one for administration of THC and one for plasma sampling. THC was administered in 1 mL/min pulses over a period of 10 mins (total dose 1.5 mg). Blood samples were taken at 1 h, 2 h, 3 h 45 min (5 min post-THC), 4 h 10 min (30 min post-THC) and 5 h (80 min) post capsule. Doses of oral CBD and IV THC were selected on the basis of previous studies (Bhattacharyya et al., 2010; D'Souza et al., 2004; Morrison et al., 2009; Zuardi et al., 2006). Capsules (placebo/CBD) were administered 3 h 30 min prior to IV THC challenge, based on the available (albeit limited) knowledge regarding the pharmacokinetics of CBD (Bhattacharyya et al., 2010).

Psychopathological and cognitive measures

Baseline predictive instruments. Prior to the experimental session, participants completed the following questionnaires online: the Green et al. Paranoid Thoughts Scale (GPTS) Part B, which provides a measure of trait paranoia (Green et al., 2008); the Cannabis Experiences Questionnaire (CEQ), which quantifies psychotic/dysphoric experiences following recreational cannabis use (Barkus and Lewis, 2008); and the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). This permitted assessment of whether measures of 'psychosis-proneness' differed between the two groups. Participants also completed the Wechsler Test of Adult Reading (WTAR), which provides an estimate of IQ (Wechsler, 2001).

Experimental measures. In Table 1, the time course of events on the experimental day is illustrated.

Psychopathology. Under CBD/placebo and THC conditions, participants were instructed to report/score their experience based upon the peak intensity within the time-window since the previous drug administration.

Positive psychotic symptoms. The positive psychotic dimension was assessed using two instruments: the PANSS (Kay et al., 1987) as described previously (Morrison et al., 2009), and The State Social Paranoia Scale (SSPS) (Freeman et al., 2007). The PANSS was developed for schizophrenia research and consists of

Table 1. The time-course of the experimental day. Participants were instructed to report/score their experience based upon the peak intensity within the time-window since the previous drug administration (highlighted in bold).

Time (hours)	Experimental day
0h00min	**Oral CBD/Placebo administration**, Urinary drug screen
1h00min	Blood sampling CBD
2h00min	Blood sampling CBD
2h20min-2h25min	Post-tablet HVLT
2h25min-2h30min	Post-tablet Digit symbol recoding task
2h30min-2h35min	Post-tablet Digit span forward & reverse
2h35min-2h45min	Post-tablet NAB-Mazes
2h45min	Post-tablet HVLT-recall
Up to 3h00min	Post-tablet PANSS
3h00min-3h10min	Post-tablet Psychological Scales: uMACL, SSPS, BAI, SAM
3h30min-3h40min	**THC-infusion**
3h45min	Blood sampling CBD, THC
4h10min	Blood sampling CBD, THC
4h30min-4h35min	Post-THC HVLT
4h35min-4h40min	Post-THC Digit symbol recoding task
4h40min-4h45min	Post-THC Digit span forward & reverse
4h45min-4h55min	Post-THC NAB-Mazes
4h55min	Post-THC HVLT-recall
5h00min	Blood sampling CBD, THC
Up to 5h20min	Post-THC PANSS
5h20min-5h30min	Post-THC Psychological Scales: uMACL, SSPS, BAI, SAM
6h30min	Discharge

a positive subscale (seven items: delusions, conceptual disorganisation, hallucinations, hyperactivity, grandiosity, suspiciousness and hostility), a negative subscale and a general subscale. Items are rated from 1–7 (absent–severe), thus the range on the positive subscale is 7–49. There is a wide inter-individual variation in PANSS positive scores following THC and, as a group, positive symptoms are modest compared with acute schizophrenia. In earlier studies approximately 35–50% of healthy participants showed changes of ≥3–4 points (D'Souza et al. 2004; Morrison et al., 2009). The SSPS is a participant-rated instrument consisting of 10 persecutory items (e.g. 'Someone wanted me to feel threatened'), embedded within neutral and positive items. Responses are rated 1–5 (do not agree–totally agree). The SSPS has excellent internal reliability, adequate test-retest reliability, convergent validity with both independent interviewer ratings and self-report measures, and divergent validity with regard to measures of positive and neutral thinking (Freeman et al., 2007).

Affect. The University of Wales Mood Adjective Checklist (UMACL) was used to assess affect (Matthews et al., 1990). The UMACL is sensitive to change in the three major dimensions of affect: Hedonic Tone (pleasure–displeasure); Energetic Arousal (awake–tiredness); and Tense Arousal (tension–relaxation). On each dimension, participants rated their level of agreement with four positive and four negative adjectives. Scores within each dimension were summed to give a value between -12 and 12, as described previously (Morrison et al., 2009).

Cognition. Three of the four tasks that were employed make up part of the MATRICS Consensus Cognitive Battery (MCCB, PAR, Inc FL 33549) (exception: Digit span). Alternative versions of each task were used across the three different conditions, (baseline, post-capsule, post-THC), except for symbol-coding. All participants encountered each version in a consistent order. For each of the three conditions, cognitive tasks were presented in the following sequence (under THC conditions, cognitive testing began at 40 min post-THC injection).

The Hopkins Verbal Learning Task-Revised (verbal learning and memory). In the Hopkins Verbal Learning Task-Revised (HVLT-R), participants are tested in their immediate recall of 12 words (nouns from three taxonomic categories) after each of three learning trials. Here, delayed recall was assessed 20–25 min after the final learning trial.

Symbol coding (processing speed). This is a timed pencil-and-paper task in which participants are required to translate a symbol into a corresponding digit (1–9), whilst a reference key of symbol/digit pairs remains visible.

Digit-span forward and reverse (working memory). The digit span task (forward-condition) evaluates the capacity of working memory. Participants are tested for immediate recall of a sequence of digits; and given two attempts at each level of difficulty. In the reverse digit span condition, participants are required to recall the sequence in the reverse order, which places additional processing demands on working memory.

Neuropsychological Assessment Battery mazes (planning and organisational abilities). In the Neuropsychological Assessment Battery (NAB) mazes, participants are scored on a composite measure of accuracy and speed in a series of seven progressively more difficult maze-tracing tasks. Since only two equivalent versions are available, this task was only presented at the post-capsule and post-THC time-points.

Statistical analyses

All analyses were performed in SPSS 17.0 (SPSS Inc., Chicago). PANSS and SSPS data did not have a normal distribution and were analysed after log transformation as described previously (Kleinloog et al., 2012). In addition, for the PANSS we followed the approach of D'Souza and colleagues, which is to categorise clinically significant psychosis as increases from baseline of ≥3 points (D'Souza et al., 2005): thereafter the difference in the frequency of clinically significant THC-evoked psychotic reactions between the CBD and placebo groups was analysed using Pearson's Chi-square. Normally distributed data were analysed by a general linear model (GLM), specifically repeated-measures ANOVA. The within-groups factor was CONDITION (1. Baseline 2. Post-capsule 3. Post-THC). The between-groups factor was pre-treatment GROUP (1. CBD 2. Placebo). Greenhouse–Geisser statistics were used in cases where sphericity assumptions were violated. Post-hoc analyses were performed with Bonferroni correction. Relationships between psychosis scores and cognitive data were analysed using Spearman's rank correlation coefficient.

Table 2. Sample characteristics at baseline. The two groups (CBD & placebo) were adequately matched for demographic variables, 'psychosis-proneness' as indexed by the SPQ (Schizotypal Personality Questionnaire;), CEQ (Cannabis Experiences Questionnaire), Green et al. Paranoia Scale, BMI (Body Mass Index), and for previous illicit drug use. There was a trend for higher trait paranoia in the CBD pre-treated group.

Variable	Placebo group	CBD group	*p*
Age (years)	26 (±4)	25 (±3)	ns
Sex ratio (m:f)	14:12	13:9	ns
BMI	25 (±5)	25 (±4)	ns
Wechsler Test of Adult Reading	45.2 (±3.2)	44.3 (±3.4)	ns
SPQ (Total)	11.1 (±7.0)	12.1 (±11.2)	ns
CEQ (paranoia/dysphoria)	43.0 (±9.1)	42.8 (±10.4)	ns
The Green Paranoia scale	19.3 (±5.0)	23.7 (±10.2)	0.08
Previous cannabis use (episodes)	118 (±218)	137 (±234)	ns
Age at first cannabis use	16 (±2)	17 (±2)	ns
Previous drug use (Yes)			
'Ecstasy'	62.5%	48%	ns
Cocaine	54%	40%	ns
'LSD'	21%	20%	ns
Ketamine	21%	32%	ns
Amphetamines	13%	16%	ns
Mephedrone	17%	36%	ns

Significance was accepted at p values <0.05. All comparisons were two-tailed.

Results

In total, 48 subjects completed the experimental protocol (Placebo group n=26; CBD group n=22). In three subjects, failure of cannulation prevented the administration of THC, and data acquired up to that point were not used in any of the analyses. The two groups were adequately matched for demographic variables, baseline measures of 'psychosis-proneness' and previous drug use (Table 2). Previous cannabis exposure between the two groups was not significantly different whether data were analysed by comparing means (p=0.76) or ranks (p=0.98).

Pharmacokinetics

The plasma concentrations of CBD and THC over time are shown in Figure 1. Plasma concentrations of CBD were highest at the 3 h 45 min testing point, before beginning to decrease. THC concentrations were not significantly different between the group pre-treated with CBD and the group pre-treated with placebo at 5 min (p=0.5), 30 min (p=0.5) and 80 min (p=0.6) post-THC administration.

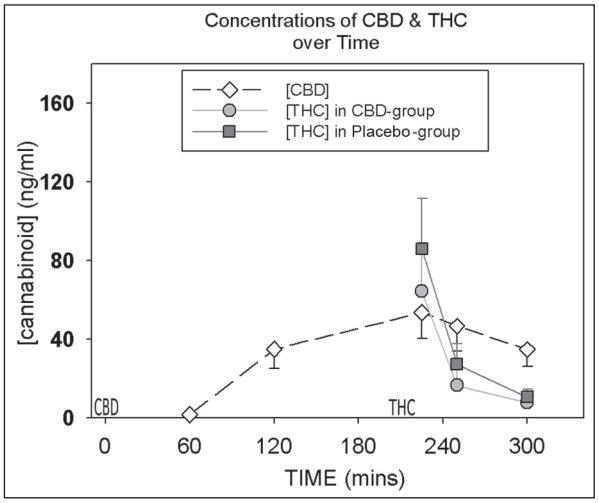

Figure 1. Plasma cannabinoid concentrations (mean±SEM). Oral CBD (600 mg) was administered at 0 min. THC (1.5 mg) was administered by slow IV injection from 210–220 min. In the CBD pre-treated group and the placebo pre-treated group, differences in plasma THC concentrations at three successive sampling points were not statistically significant. With respect to THC administration, plasma [THC] was assayed at 5, 30 and 80 min post-injection.

Positive psychotic symptoms

PANSS-positive scores. There was a main effect of CONDITION (F=27.9, p<0.000), but no effect of GROUP (F=1.7, p=0.19) and no interactive GROUP×CONDITION effect (F=2.28, p=0.14) (Figure 2). In the placebo group, PANSS positive scores, (mean±sd) increased by 2.4 (±3.1) points following THC, compared with 1.2 (±1.8) in the CBD group, a non-significant difference (t=1.5, p=0.15) (Figure 2). Clinically significant positive symptoms following THC, defined as an increase in PANSS positive scores of ≥3 points, were more common in the group pre-treated with placebo (11 of 26 cases) compared with the group pre-treated with CBD (3 of 22 cases), (χ^2=4.74, p<0.05) (Table 3).

SSPS scores. There was a main effect of CONDITION (F=7.5, p<0.005), but no effect of GROUP (F=2.5, p=0.12). There was a CONDITION×GROUP interaction (F=4.7, p<0.05) (Figure 3).

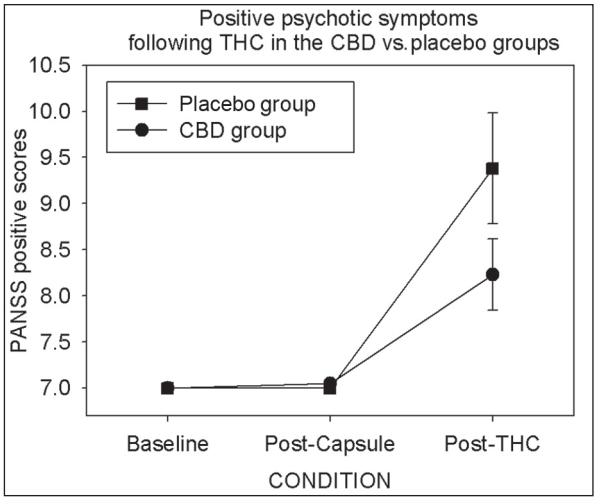

Figure 2. Pre-treatment with Cannabidiol, CBD (600 mg po) versus placebo reduced IV THC (1.5 mg) elicited increases in PANSS positive scores (mean±SEM), but between group differences did not reach statistical significance (t=1.5, p=0.15).

The increase in SSPS scores post-THC, with respect to baseline, was greater in the placebo versus the CBD group (t=2.28, p<0.05).

Affect

Hedonic tone. There were no main effects of CONDITION (F=1.5, p=0.23), GROUP (F=0.001, p=0.98) and no interactive CONDITION×GROUP effects (F=0.23, p=0.74).

Energetic arousal. There was a main effect of CONDITION (F=19.2, p<0.000) but no effect of GROUP (F=0.07, p=0.80) and no interactive CONDITION×GROUP effects (F=1.32, p=0.23). Energetic arousal decreased in the CBD group following the administration of CBD (p<0.01), whereas subsequent decreases following THC were not significant (p=0.13). Energetic arousal also decreased in the placebo group, at the level of a trend following the administration of placebo (p=0.08), whereas subsequent decreases following THC were not significant (p=1.00).

Tense arousal. There was a main effect of CONDITION (F=28.5, p<0.000) but no effect of GROUP (F=0.003, p=0.98) and no interactive CONDITION×GROUP effects (F=0.58, p=0.50). Tense arousal increased following the administration of THC in both groups (CBD group, p<0.005, placebo group, p<0.000).

Cognition

Scores on the cognitive battery at baseline, post-CBD/placebo, and post-THC are shown in Table 4.

The Hopkins Verbal Learning Task

Immediate recall. There was a main effect of CONDITION (F=22.64, p<0.000) but no effect of GROUP (F=0.079, p=0.78) and no interactive CONDITION×GROUP effects (F=0.92, p=0.88). Immediate recall was poorer following THC, regardless of group. Post-hoc analysis revealed differences between post-THC and baseline performance, significantly in the placebo group (p<0.005), and at the level of a trend in the CBD group (p=0.06). Differences between post-THC and post-capsule performance were significant in the CBD group (p<0.000) and the placebo group (p<0.005). Following THC, immediate recall was 2.9 (±5.3) and 3.6 (±4.5) items fewer in the CBD and placebo groups, respectively, compared with baseline, a non-significant between-groups difference (p=0.6), (Figure 4(a)).

Delayed recall. There was a main effect of CONDITION (F=7.25, p<0.005), but no effect of GROUP (F=1.75, p=0.19). There was a trend towards a CONDITION×GROUP interactive effect (F=3.26, p=0.058) (Figure 3). Post-hoc analysis in the placebo-group revealed differences between post-THC and baseline (p<0.05) and between post-THC and post-capsule performance (p<0.05). Corresponding analyses in the CBD group were p=1.0 and p=0.6, respectively. Following THC, delayed recall decreased from baseline by 10.6% (±18.9%) in the placebo group and by

Table 3. Pre-treatment with cannabidiol, CBD (600 mg po) reduced the odds of developing a clinically significant acute psychotic reaction to IV THC (1.5 mg), defined as a ≥3-point increase from baseline on the PANSS positive subscale.

THC psychosis	Pre-treatment		
	Placebo group		CBD group
No	Count;	15	19
	Expected count	18.4	15.6
Yes	Count;	11	3
	Expected count	7.6	6.4
Pearson Chi-Square=4.74, p<0.05			
(0 cells have expected count less than 5)			
Event rate (psychosis)		42%	14%
Odds of psychosis		0.73	0.16
Absolute risk reduction		28%	
Relative risk		0.33	
Relative risk reduction		67%	
Odds ratio		0.22	

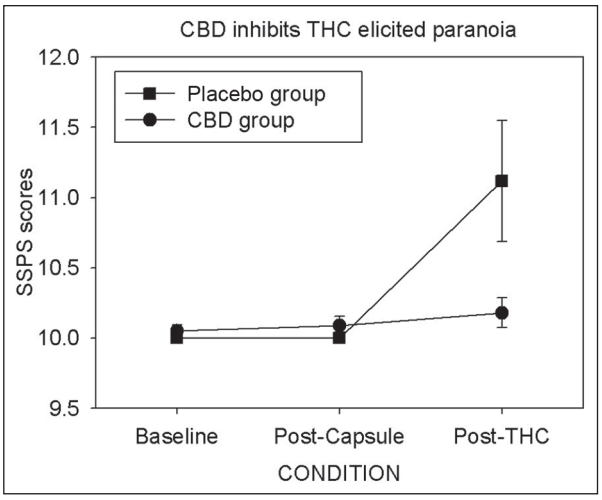

Figure 3. Pre-treatment with cannabidiol, CBD (600 mg po) inhibited IV THC (1.5 mg) evoked paranoia, as measured by the SSPS (mean ±SEM). The increase in SSPS scores [post-THC *minus* baseline] was greater in the placebo versus the CBD group (t=2.28, p<0.05).

0.4% (±9.7) in the CBD group, a significant between-groups difference (t=2.39, p<0.05), (Figure 4(b)).

A posteriori, we explored if there were relationships between impaired delayed recall and positive psychotic symptoms, post THC. In the placebo group, poorer delayed recall was related to the magnitude of PANSS-positive symptoms, at the level of a trend (Spearman's rho=0.3, p=0.09). The relationship between poorer delayed recall and higher scores on the SSPS was stronger and reached significance (Spearman's rho=0.5, p<0.05); corresponding findings in the CBD group were -0.3, p=0.9 and 0.5, p<0.05).

Symbol coding. There was a main effect of CONDITION (F=11.12, p<0.000) but no effect of GROUP (F=0.003, p=0.98) and no interactive CONDITION×GROUP effects (F=0.53, p=0.82). Performance improved in both groups from the baseline condition to the post-THC condition, (CBD group p<0.01; placebo group p<0.05).

Digit-span forward. There was a main effect of CONDITION (F=7.38, p<0.005) but no effect of GROUP (F=0.44, p=0.51) and no interactive CONDITION×GROUP effects (F=1.24, p=0.30). Post-hoc analysis in the placebo group revealed significant differences between digit-span performance in the post-THC condition compared with both the baseline (p<0.05) and post-capsule conditions (p<0.05). Corresponding post-hoc analyses in the CBD-group were p=1.00 and p=0.08, respectively.

Digit-span reverse. There was a main effect of CONDITION (F=9.46, p<0.000) but no effect of GROUP (F=0.000, p=0.99) and no interactive CONDITION×GROUP effects (F=1.53, p=0.86). Post-hoc analysis in the placebo group revealed differences between reversed digit-span performance in the post-THC condition compared with the baseline (p=0.08) and post-capsule conditions (p<0.05). Corresponding post-hoc analyses in the CBD-group were p=0.5 and p<0.01, respectively.

Mazes. There were no main effects of CONDITION (F=2.1, p=0.15), GROUP (F=2.4, p=0.13) and no interactive CONDITION×GROUP effects (F=0.015, p=0.90). Numerical differences between groups post-THC compared with baseline were not different (t=0.13, p=0.9).

Discussion

Our major findings are that pre-treatment with CBD inhibited THC-induced paranoia and inhibited the detrimental effects of THC on episodic memory. In addition, CBD decreased the proportion of participants who experienced clinically significant acute THC psychosis.

Table 4. Under THC (IV 1.5 mg) conditions, cognitive performance was generally poorer, except for the Symbol coding and NAB-MAZES tasks. THC-elicited deficits in delayed recall were inhibited by CBD (600 mg po).

Cognitive test	Placebo group			CBD group			Condition × Group
	Condition			Condition			
	Base	PLC	THC	Base	CBD	THC	
Immediate recall	30.4 (±3.0) F=12.6, p<0.000	31.2 (±2.6)	27.0 (±5.5)	30.4 (±2.8) F=10.5, p<0.005	31.3 (±3.0)	27.5 (±5.2)	F=0.92, p=0.88
Delayed recall	94.8% (±7.9%) F=7.7, p<0.01	96.0% (±7.0%)	84.2% (±20.9)	93.8% (±9.1%) F=1.5, p=0.2	97.1% (±5.8%)	93.4% (±11.1)	F=3.26, p=0.058 Baseline - THC t=2.39, p<0.05
Symbol coding	67.7 (±9.2) F=4.4, p<0.01	70.1 (±9.8)	72.9 (±14.6)	67.6 (±10.4) F=6.7, p<0.01	70.7 (±11.7)	74.6 (±16.1)	F=0.53, p=0.98
Digit span forward	7.5 (±1.2) F=6.1, p<0.005	7.5 (±1.2)	6.6 (±1.2)	7.4 (±1.2) F=2.6, p=0.09	7.7 (±1.1)	7.1 (±1.5)	F=1.24, p=0.30
Digit span Reverse	5.9 (±1.2) F=5.6, p<0.01	6.00 (±1.2)	5.2 (±1.5)	5.7 (±1.4) F=4.1, p<0.05	6.1 (±1.3)	5.2 (±1.4)	F=1.53, p=0.88
NAB-MAZES	– F=1.1, p<0.3	22.6 (±4.1)	21.8 (±3.8)	– F=1.3, p=0.3	23.9 (±2.3)	23.2 (±2.8)	F=0.015, p=0.90

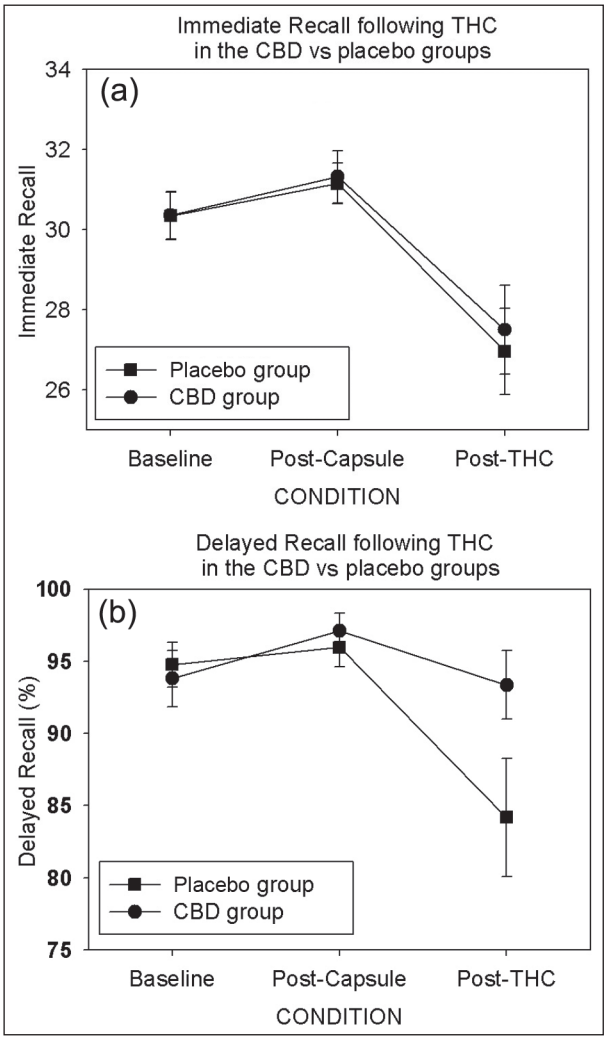

Figure 4. (a) Immediate recall in the HVLT-R (mean±SEM) was poorer following IV THC (1.5 mg), in both the placebo and CBD (600 mg po) pre-treated groups. (b) Delayed Recall was poorer following THC in the placebo but not the CBD pre-treated group. Relative to baseline, performance under THC was poorer in the placebo compared to the CBD group (t=2.39, p<0.05). HVLT-R, The Hopkins Verbal Learning Task-revised.

Cannabinoids and psychosis

The majority of community-based studies that have addressed the issue of specific cannabinoid components and psychosis have proposed that cannabis products lacking CBD are more psychotogenic than products that contain CBD (Di Forti et al., 2009; Morgan et al., 2008; Schubart et al., 2011; but see Morgan et al., 2010). The findings in the present study provide strong support for this idea. Here, on the PANSS (an investigator-rated scale), clinically significant THC psychosis was less likely under CBD versus placebo conditions, and on the SSPS (a participant-rated scale) THC-induced paranoia was inhibited under CBD conditions. It is notable that there was a trend for higher *trait* paranoia in the CBD compared with the placebo group, suggesting that the CBD group might have been more prone to paranoia *at baseline*. Post-THC however, there was no apparent rise in paranoia in the CBD group, whereas by way of contrast, the placebo group reported significant paranoid symptoms.

Some caution is required, however, with regard to scores on the PANSS positive scale. Although the mean PANSS positive score in the CBD group was less, differences did not reach statistical significance. Lack of statistical power may be important, but it is also clear that CBD (in so far as it was administered here) does not completely abolish THC-induced positive psychotic symptoms.

Cannabinoids and memory

Cognitive performance was poorer following THC specifically in the domains of working and episodic memory, which is in keeping with previous reports (reviewed in Ranganathan and D'Souza, 2006; Solowij and Michie, 2007). Here, pre-treatment with CBD 'protected' episodic memory from the impact of THC, whereas working memory remained 'vulnerable' to a similar degree.

This result is in broad agreement with a study carried out by Morgan and Curran: volunteers were assessed at home under the influence of their own chosen type of cannabis, a sample of which was subsequently tested for THC and CBD content; higher levels of CBD in the cannabis used appeared to protect against impairments in immediate and delayed prose recall (Morgan et al., 2010). The reason for the differences with regard to immediate recall are unknown, but may stem from the different tasks employed.

Here there were marked performance deficits post-THC in three tests which require pre-frontal resources: immediate recall, digit-span forward and digit-span back. CBD did not appear to attenuate THC-induced deficits in any of the three tasks. This contrasted with the protective effect of CBD on delayed recall and paranoid symptoms. It is also notable that THC-induced impairment in delayed recall and THC-induced paranoia were correlated, and it is feasible that both measures load onto a common factor.

Mechanisms

Molecular neuropharmacology. The molecular neuropharmacology of THC is well understood: partial-agonism at CB_1 receptors (Pertwee, 2008). For CBD, the picture is more obscure. In vitro work has shown that CBD (in the nanomolar range) can antagonise the pharmacological effects of CB_1 agonists, despite having low affinity (in the micromolar range) for the CB_1 receptor (Pertwee et al., 2002). CBD targets a number of other proteins/processes, including (in descending order of potency): the orphan receptor GPR55, K^+ and Ca^{2+} channels, adenosine re-uptake transporters; $TRPV_1$ receptors, anandamide re-uptake; and 5-HT_{1A} receptors (Pertwee, 2008). Clearly, further in vitro work will be required to identify which action underlies a particular psychopharmacological effect, at the systems and the behavioural levels.

Systems pharmacology. How THC impacts upon episodic memory is reasonably well understood. Episodic memory depends upon the integrity of hippocampal circuitry. Numerous animal studies have shown that CB_1 agonists disrupt processes within the hippocampus that are believed to be at the heart of learning and memory – network oscillations, neuronal synchrony and plasticity (Fan et al., 2010; Hajos et al., 2000; Holderith et al., 2011; Robbe

and Buzsaki, 2009). Recently, CB_1 agonists have become a useful tool in hippocampal research. This is because CB_1 agonists disrupt synchronicity, without altering the firing rates of individual neurons in the network – a unique property amongst drugs which impact on hippocampal function (Robbe et al., 2006).

The mechanisms underlying the pro-psychotic properties of THC are less well understood. Theoretical accounts have invoked excessive, pathological dopamine release (Kuepper et al., 2010; Murray et al., 2007), but experimental support for this has been weak (Barkus et al., 2011; Bossong et al., 2009; D'Souza et al., 2008; Kleinloog et al., 2012; Stokes et al., 2009; but see Liem-Moolenaar et al., 2010). Other accounts have focussed on disrupted network oscillations (Sewell et al., 2009). Here the experimental evidence has been stronger (Morrison et al., 2011; Stone et al., 2012) but remains at an early stage.

In the present dataset, we were interested by the apparent relationship between THC psychosis and THC-elicited impairments in episodic memory. However, the presence of such a relationship was not hypothesised a priori, and replication is required.

Strengths and limitations

In laboratory-based pharmacological studies, pure synthetic preparations can be administered at a set dose under controlled conditions. This is particularly relevant for cannabinoid studies because 'street cannabis' contains a multitude of other molecules, many of which are known to be pharmacologically active. One example is Δ^9-Tetrahydrocannabivarin (THCV), a CB_1 receptor antagonist at low doses, an agonist at higher doses (Pertwee, 2008). Compared with 'street cannabis', pure synthetic preparations are ideal for studying the behavioural pharmacology of specific cannabinoid molecules, because pharmacodynamic and pharmacokinetic influences from other constituents can be disregarded from the outset. A limitation in the present study is that only one dose of CBD was investigated. Future studies could examine if higher CBD doses, or indeed extended dosing over several days, produce stronger 'protective effects', or if protection extends to additional domains such as working memory.

Conclusions

Previous epidemiological and experimental studies have suggested that cannabis products lacking CBD are more psychotogenic than products containing CBD. The findings here provide strong support for this view. Under controlled experimental conditions, CBD decreased THC-elicited positive psychotic symptoms and 'protected' hippocampal-dependent memory from the impact of THC.

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Conflict of interest

PDM has received an unrestricted grant from GW Pharmaceuticals and honoraria from Valeant Pharmaceuticals and STI Pharmaceuticals. SK and RM receive salary support from the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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