

REGULAR RESEARCH ARTICLE

Psychosis-Relevant Effects of Intravenous Delta-9-Tetrahydrocannabinol: A Mega Analysis of Individual Participant-Data from Human Laboratory Studies

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Abstract

Introduction: There is increasing interest in the relationship between cannabinoids and psychosis. While individual human laboratory studies have been critical in demonstrating that cannabinoids (e.g., delta-9-tetrahydrocannabinol [THC]) can induce acute transient psychosis-like effects in healthy human volunteers, combining data from multiple studies offers a fine-grained view of these effects.

Methods: THC-induced psychosis-relevant effects were examined using a data repository of 10 double-blind, randomized, placebo-controlled, crossover studies with 400 i.v. THC infusions in healthy human volunteers. The Positive and Negative Syndrome scale was used to measure psychotomimetic effects. The profile of symptoms, frequency of a response, its relationship to THC dose and substance use, latent structure in Positive and Negative Syndrome scale response, and the relationships between psychotomimetic and perceptual alteration symptoms were evaluated.

Results: Clinically meaningful increases in positive symptoms were noted in 44.75% infusions; conceptual disorganization, hallucinations, blunted affect, somatic concern, motor retardation, and poor attention were the items most frequently altered by THC. The increase in Positive and Negative Syndrome scale positive symptoms was positively associated with THC dose ($\beta = 11.13$, $SE = 4.94$, Wald $\chi^2 = 19.88$, $P < .001$) and negatively associated with frequent cannabis use ($\beta = -0.575$, $SE = 0.14$, Wald $\chi^2 = 18.13$, $P < .001$). Furthermore, positive symptoms were strongly correlated with Clinician Administered Dissociative States Scale perceptual alterations score ($r_s = 0.514$, $P < .001$).

Conclusion: Intravenous administration of THC consistently induces psychotomimetic effects that include symptoms across Positive and Negative Syndrome scale domains. Moreover, healthy individuals who frequently use cannabis have a blunted psychotomimetic response.

Key Words: cannabinoid, delta-9-THC, human laboratory model, PANSS, psychosis, schizophrenia

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Significance Statement

Human laboratory studies of drug-induced psychosis such as the delta-9-tetrahydrocannabinol (THC) model have made significant contributions to our understanding of psychosis. Taking advantage of the largest repository of individual participant data from 10 double-blind, randomized, placebo-controlled studies of THC-induced acute psychosis, we examine the symptom profile, factor structure, and determinants of psychosis severity. Acute administration of THC induces a transient psychosis characterized by specific symptoms from positive, negative, excitement, and emotional dimensions of psychopathology in a dose-dependent fashion. This psychotomimetic response is blunted by prior frequent cannabis use and tobacco smoking. The results define the aspects of schizophrenia phenomenology that can be successfully modelled with THC and are relevant to the design of future human laboratory studies with THC and other pharmacological agents.

Introduction

Drug-induced psychosis models in humans have substantially contributed to our current understanding of the underlying neurobiology (Murray et al., 2013). These models permit an objective evaluation of schizophrenia-like phenotype in healthy human volunteers in safe and well-controlled laboratory environments. The ability to study human behavioral and subjective effects in real time, while engaging specific neuroreceptors with known physio-chemical properties and tissue distribution, renders these models suitable to investigate network-level changes that may mimic the psychopathology in psychosis. Drugs acting on diverse neurotransmitter systems, including dopamine (amphetamine), glutamate (ketamine), serotonin (lysergic acid diethylamide, psilocybin, dimethyltryptamine), and cannabinoid (delta-9-tetrahydrocannabinol [THC]), have been used to induce transient psychosis states in healthy human volunteers to “model” the symptoms of psychosis (Paparelli et al., 2011; Murray et al., 2013; Steeds et al., 2015). Given the heterogeneity in the expression of psychoses, manipulation of a specific neurotransmitter system is likely to recapitulate only some aspects of the rich phenomenology that characterizes psychoses (Murray et al., 2013). Furthermore, the different drug-induced psychotomimetic effects may reflect potential neurotransmitter and circuit-level biology that are most relevant to a specific symptom dimension. This calls for an in-depth examination of the phenotype induced by each drug.

A potential role of endocannabinoid system dysfunction in the pathophysiology of psychosis, leading to an “endocannabinoid hypothesis,” was proposed more than 2 decades ago (Emrich et al., 1997). Accumulating evidence (listed below) regarding the relationship between cannabis, cannabinoids, and psychosis have further given rise to the “exocannabinoid hypothesis” (Tikka and D’ Souza, 2019), which complements the endocannabinoid hypothesis. First, the administration of cannabinoid receptor agonists to healthy humans induces transient behavioral and cognitive effects, and electrophysiological information-processing abnormalities akin to those seen in schizophrenia (D’Souza et al., 2009; Cortes-Briones et al., 2015; Broyd et al., 2016; Skosnik et al., 2016). Second, a small yet significant proportion of individuals who abuse phyto- and synthetic cannabinoids manifest psychosis characterized by paranoid ideations, delusions, and hallucinations resembling the positive symptoms of schizophrenia (Núñez and Gurpegui, 2002). Third, epidemiological studies demonstrate a strong positive relationship between cannabis use (frequency and potency) and the incidence of first-episode psychosis (Di Forti et al., 2019). Fourth, among the cases of drug-induced psychosis, the highest rate of conversion to schizophrenia is noted for cannabis (Starzer et al., 2018). Fifth, in laboratory studies, THC exacerbates symptoms in those with established schizophrenia,

and, related to this, cannabis use is known to have a negative impact on the course and expression of schizophrenia (Foti et al., 2010). Sixth, genome-wide association studies adopting Mendelian randomization methods demonstrate possible bidirectional causal relationships between schizophrenia and lifetime cannabis use (Pasman et al., 2018; Vaucher et al., 2018). Lastly, studies in animal models demonstrate the emergence of schizophrenia-relevant behavioral abnormalities on chronic and subchronic cannabinoid administration (Chesworth and Karl, 2017). Collectively, the evidence supports a relationship between cannabinoids and psychosis and suggests that a “human laboratory model-cannabinoids (HLM-cannabinoids)” has utility in understanding the contributions of the cannabinoid system to the pathophysiology of psychosis.

Several research groups, including ours, have examined acute, transient psychosis-like effects induced by administration of THC, the principal psychoactive constituent of cannabis, in healthy human volunteers [for comprehensive reviews, see Englund et al. (Englund et al., 2012) and Sherif et al. (Sherif et al., 2016)]. Briefly, laboratory studies of cannabis and cannabinoids (THC, cannabidiol, nabilone, dronabinol) in human volunteers have been undertaken over the past several decades (Domino, 1971; Hollister and Gillespie, 1973; Emrich et al., 1991; Leweke et al., 2000). These studies have adopted different routes of administration (smoking, inhalation, oral, and i.v.) and have examined diverse cognitive and behavioral outcomes. Notwithstanding the heterogeneity in study design, many of these early studies noted psychosis-relevant behavioral and cognitive responses such as frank hallucinations (Domino, 1971), temporal disorganization and delusion-like ideas (Melges et al., 1974; Mathew et al., 1998), attention and memory impairment (Hooker and Jones, 1987), alterations in binocular depth perception (Leweke et al., 1999), and emotional word recognition (Leweke et al., 1998). More recent double-blind, randomized, placebo-controlled studies have adopted tools used to assess psychosis of schizophrenia to measure psychotomimetic effects of THC (vide infra): Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Brief Psychiatric Rating Scale (Overall and Gorham, 1962), Community Assessment of Psychic Experience (Konings et al., 2006), Psychotomimetic States Inventory (Mason et al., 2008), and Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998). Among these scales, the PANSS has been most frequently utilized both by our group and several others.

While the results of individual THC studies from our group have been reported elsewhere (D’Souza et al., 2004, 2008a, 2008b, 2009, 2012), pooling individual participant data provides the necessary sample size to examine, for the first time to our knowledge, the PANSS symptom profile, correlates of symptoms

severity, latent dimensions in the symptoms, and the relationship between psychotic and perceptual alteration following i.v. THC administration in healthy human volunteers.

Methods

Studies conducted at the Schizophrenia Neuropharmacology Research Group at Yale University to characterize acute psychotomimetic response to intravenous THC in healthy human volunteers were included in this analysis. The data were anonymized and curated in a secure online database with a common protocol approved by the local institutional review boards of VA Connecticut Healthcare System (VACHS), West Haven, CT, and Yale University School of Medicine (YUSM). Demographic information, cannabis use measures, experimental conditions (THC/placebo dose, duration of infusion), and behavioral measures were extracted from the database. The studies were conducted under an IND (#51671: DSouza) at the VACHS Neurobiological Studies Unit. The individual studies were approved by the institutional review boards of VACHS and Yale University School of Medicine. Capitalizing on this largest known data repository of HLM-cannabinoid studies, we aimed to address the following 5 questions:

- 1) Does i.v. THC reliably induce a psychotomimetic response in healthy individuals?
- 2) What is the dose-response relationship?
- 3) Do demographic variables and history of recent cannabis use influence the severity of the psychotomimetic response?
- 4) Are there similarities in the PANSS symptom profile and factor structure between the THC psychotomimetic response and schizophrenia?

- 5) Are the THC response PANSS scores related to the subjective experience of high and perceptual alterations?

Studies and Setting

The methods employed in participant screening, inclusion and exclusion criteria, recruitment, randomization, blinding, THC/placebo infusion and pre- and post-infusion assessments, and safety monitoring have been published elsewhere (D'Souza et al., 2004, 2008a, 2008b; Carbuto et al., 2012; Ranganathan et al., 2012b, 2019; Radhakrishnan et al., 2015). Study participants had a wide range of cannabis exposure (D'Souza et al., 2008a); cannabis-naïve individuals were not permitted to participate in the studies. Participants were required to abstain from drugs and medications 1 week prior to the test day to avoid any potential interactions. Studies of frequent users of cannabis were allowed cannabis use no closer than 8 hours from the start of a test session (8 AM). Six of the 10 studies examined the interaction between THC and other compounds such as cannabidiol (D. C. D'Souza, unpublished observations), haloperidol (D'Souza et al., 2008b), iomazenil (Radhakrishnan et al., 2015), naltrexone (Ranganathan et al., 2012b), tolcapone (Ranganathan et al., 2019), and physostigmine (D. C. D'Souza, unpublished observations). In these studies, only the data from THC alone and placebo-alone test days were used for the analysis. Of the 239 participants, 114 (47.7%) received more than 1 dose of THC (2–6 infusions) on different test days.

THC and placebo (<2 mL of sterile vehicle: 190-proof USP ethanol) were administered i.v. into a rapidly flowing saline infusion by manual injection or via an infusion pump over 2 to 5 minutes ("rapid"), 10 minutes ("brief"), or 20 minutes ("extended") (Table 1). The dose of THC ranged from 0.015 mg/kg to 0.070 mg/kg, with some studies testing 2 doses of THC in the

Table 1. Summary of Studies Included in Analysis

Study#	Study title	Sample size ^a	THC doses in mg/kg	Duration of infusion in minutes	Other drugs if tested	THC infusions with PANSS - sample size (n)	Placebo infusions with PANSS - sample size (n)
1	THC response in healthy frequent and infrequent cannabis users	44	0.035 and 0.07	2–5	n/a	87	44
2	Interactions between haloperidol and THC	31	0.0286	20	Haloperidol	31	31
3	Genetics of THC response and interaction with tolcapone	78	0.05	20	Tolcapone	78	78
4	THC effects in people with family history of alcoholism	30	0.018 and 0.036	20	n/a	60	30
5	Electrophysiological effects of THC	33	0.015 and 0.030	10	n/a	66	30
6	Interactions between iomazenil and THC	23	0.015	10	Iomazenil	23	23
7	Interactions between naltrexone and THC	6	0.025	20	Naltrexone	6	6
8	Interactions between physostigmine and THC	6	0.015	10	Physostigmine	6	6
9	Interactions between cannabidiol and THC	29	0.035	20	Cannabidiol	29	29
10	THC effects on information processing	7	0.015 and 0.030	10	n/a	14	7
	Total	287 ^b				400	284

Abbreviations: n/a, not applicable; PANSS, Positive and Negative Syndrome scale.

^a Sample sizes represent participants with complete PANSS information on the 28 items for THC condition in each study.

^b39 individuals participated in more than 1 study, resulting in a total sample size of 287.

same participants on 2 separate test days (D'Souza et al., 2004, 2008a). This dose range is roughly equivalent to the amount of THC delivered by one-quarter to a full joint (Lee et al., 2015; Boggs et al., 2018).

Assessment Scales

Demographic variables including age, gender, race, and ethnicity were collected. Lifetime and past 30-day cannabis exposure were assessed using the Scale for the Assessment of Lifetime Cannabis Use developed in our laboratory and/or the Time Line Follow Back Approach (Sobell and Sobell, 1992; Hjorthøj et al., 2012a, 2012b). Current and past history of psychiatric disorders and use of alcohol and tobacco products were assessed using the Structured Clinician Interview for DSM IIR or IV (First and Gibbon, 2004). The National Adult Reading Test was used to rule out participants with diminished capacity to provide consent.

Positive, negative, and general symptoms were assessed using relevant subscales of a modified version of the PANSS that excluded irrelevant items (N4: passive/apathetic social withdrawal, and G16: active social avoidance) to repeated measurements within a short time (D'Souza et al., 2004). We adopted an empirical cut-off of a 2-point change in each PANSS item to define a positive psychotomimetic response on that item. PANSS items are scored on a 7-point Likert scale ranging from 1 to 7 (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe, and 7=extreme) (Kay et al., 1987). The 2-point cutoff in item change scores was chosen to ensure a definitive and clinically meaningful change. For the 3 PANSS subscales, we set an empirical cut-off of 2-point change in ≥ 2 PANSS items amounting to a minimum change of 4 in each subscale. This threshold is more stringent than some of the previous HLMs drug studies that have used a cutoff score of 3 in PANSS positive subscale to define a positive psychotomimetic response (D'Souza et al., 2004).

THC-induced quasi-psychotic perceptual alterations were measured using the 27-item CADSS (Bremner et al., 1998). Subjective effects of "high" induced by THC were measured with a 100-point visual analog scale (VAS) (0=not at all to 100=most of all). Participants were assessed at baseline prior to THC/placebo infusion and at regular intervals up to 5 hours after the infusion. The maximum score noted on each item following THC infusion was used to define the post infusion score. Pre-infusion baseline scores were subtracted from the post infusion scores on each item to derive the change scores as measures of THC/placebo response.

Statistical Analysis

A clinically significant psychotomimetic response was defined as a ≥ 2 -point increase in at least 2 items on the PANSS positive subscale (primary outcome). A ≥ 2 -point change in at least 2 items of negative and general psychopathology subscales and at least 5 items of the full PANSS scale were measured as secondary outcomes. The proportion of infusions that resulted in response above these threshold scores were computed.

The data distribution of PANSS scores as continuous measures were examined with histograms and box plots. The PANSS data exhibited positive skewness and floor effects. PANSS positive total scores were fitted with generalized estimating equations (GEE) with main effects of dose, infusion-rate, age, gender, and cannabis use frequency. The GEE used tweedie distribution with a log-link function (to model zero-inflated data with positive skew) with an unstructured working correlation matrix. GEE is a robust statistical method to handle correlated measures,

missing data, and non-normal distributions (D' Souza et al., 2019). The effect of dose*infusion-rate interaction was further examined in the GEE model. The resulting marginal means for PANSS positive scores were plotted using bar graphs in the 3 infusion-duration categories. Holm-Bonferroni correction was used to adjust for multiple comparisons when appropriate. Further, dose response was also examined in a subgroup of participants who received 2 different doses of THC. The difference in PANSS positive scores between past-month users and nonusers and between tobacco smokers and nonsmokers were examined with the Mann-Whitney-U test.

An exploratory factor analysis was conducted to examine the latent structure in the THC-induced psychotomimetic response as measured by the 28-item PANSS scale. Data characteristics were assessed prior to factor analysis with the Kaiser-Meyer-Olkin test for sampling adequacy and Bartlett's test for sphericity. Orthogonal varimax rotation was used to derive the rotated component matrix; this has been most frequently used to derive latent PANSS dimensions in schizophrenia (Wallwork et al., 2012). The resulting factor loadings were compared with the PANSS factor solutions in schizophrenia literature. Lastly, the relationships between PANSS and CADSS scores, and PANSS and VAS (high) scores were assessed using Spearman's rank correlation. Statistical analyses were carried out using IBM SPSS statistics version 26.

Results

Sample Characteristics

The sample consisted of 239 healthy individuals (71 females, 29.71%) who received a total of 400 i.v. THC infusions and 284 placebo infusions (supplementary Table 1). Four of the 10 studies tested 2 doses of THC against a single placebo infusion (Table 1). Seventy-six (31.8%) participants were characterized as "frequent" cannabis users with a history of use ≥ 2 times/wk. The remaining 163 (68.2%) participants reported occasional (≤ 1 use/mo) to very occasional (≤ 1 use/4 mo) cannabis use. Thirty-nine (15.5%) participants had participated in more than 1 study, and 114 (47.7%) of the participants had THC response data available on at least 2 different doses. The mean (SD) age of the sample was 25.29 (7.49) years, and only 32 (13.4%) participants were older than 30 years.

Psychotomimetic Response to THC

A clinically significant psychotomimetic response was noted in 179 (44.75%) of the 400 THC infusions. A clinically significant increase in THC-induced PANSS negative, general psychopathology, and global symptoms was noted in 177 (44.25%), 253 (63.25%), and 223 (55.8%) infusions, respectively. In contrast, no clinically significant psychotomimetic responses were noted with the placebo infusions. In the subsample of 114 participants who received 2 or more doses of THC, 24 (21.05%) participants had a clinically significant psychotomimetic response on every THC dose they received, while 41 (35.96%) did not have a psychotomimetic response on any of the infusions. An additional 27 (23.68%) participants had a clinically significant psychotomimetic response only with higher THC doses (>0.03 mg/kg).

Among the individual PANSS items, a significant response was most frequently noted for conceptual disorganization (P2) (46.25%), hallucinations (P3) (45%), blunted affect (N1) (46.75%), somatic concern (G1) (54.5%), motor retardation (G7) (43.75%), and poor attention (G11) (46.5%). In contrast, the items of grandiosity (P5), hostility (P7), stereotyped thinking (N7), guilt feelings (G3), depression (G6),

uncooperativeness (4.5), disorientation (G10), lack of judgment and insight (G12), and poor impulse control (G14) yielded a positive response in <5% of the infusions. The proportion of infusions resulting in a positive psychotomimetic response for each PANSS item, the 3 subscales, and PANSS total using different cut-off thresholds are presented in [supplementary Tables 2.1 and 2.2](#).

Relationship of Dose and Rate of Infusion to Psychotomimetic Response

There was a significant effect of dose on the PANSS positive symptom response to THC (beta=11.13, SE=4.94, Wald $\chi^2=19.88$, $P<.001$). A greater psychotomimetic response was noted for “brief” followed by “rapid” and “extended” infusion protocols, respectively ([Figure 1a](#)). Plotting the estimated marginal means of dose categories across the 3 infusion-rate protocols demonstrated a doserelated increase in the psychotomimetic response (PANSS positive) in the “rapid” and “brief” infusion protocols, while the pattern of response was complex in the “extended” infusion protocol ([Figure 1b-d](#)). A similar pattern of dose-response relationships was noted across the PANSS negative and general psychopathology symptoms and PANSS total scores ([supplementary Figure 1](#)). Lastly, we compared the PANSS positive symptoms in participants who had THC response data available on 2 different doses of THC from 2 different time-points. The magnitude of response was significantly higher for the higher dose of THC (mean [SD]=4.73 [3.71]) compared with the lower dose (3.59 [3.73], $P=.002$).

Factors Influencing the THC Response

Frequent cannabis use (beta=-0.575, SE=0.14, Wald $\chi^2=18.13$, $P<.001$) ([Figure 2](#)) and age (beta=-0.14, SE=0.006, Wald $\chi^2=5.05$,

$P=.025$) were associated with a blunted psychotomimetic response. There was no significant effect of gender. In the subsample with available past-month cannabis use data (n=159 infusions, 39.75%), past month users had a blunted PANSS positive response compared with nonusers, and the mean difference was marginally significant. Similarly, in a subsample with data about current tobacco smoking (n=269 infusions, 67.25%), smokers had a significantly lower psychotomimetic response ([supplementary Table 3](#)). The main effects of THC dose and frequent cannabis use on PANSS negative, general symptom scores, and PANSS total scores were also significant ([supplementary Table 4](#)).

Factor Structure of PANSS Items in THC Psychotomimetic Response

Exploratory factor analysis was conducted on THC response measured with 28-item PANSS. A Kaiser-Meyer-Olkin value of 0.848 suggested adequate sample size to carry out a factor analysis. Further, a highly significant Bartlett's test (approx. $\chi^2=5033.75$, $P<.001$) suggested redundancy between variables that can be summarized with factor analysis. An initial analysis yielded 8 components with eigen values above the Kaiser's criteria of 1. Analysis of the scree plot ([supplementary Figure 2](#)) suggested an optimal fit for a 5-factor solution that cumulatively explained 53.94% of variance, and these 5 factors were retained in the final analysis. [Table 2](#) presents the rotated component matrix with factor loadings of individual PANSS items. These results suggest that THC-induced psychotomimetic response is characterized by positive/THC-response (factor 1), negative (factor 2), emotional (factor 3), excitement (factor 4), and disorganization like (factor 5) symptoms that broadly resemble the

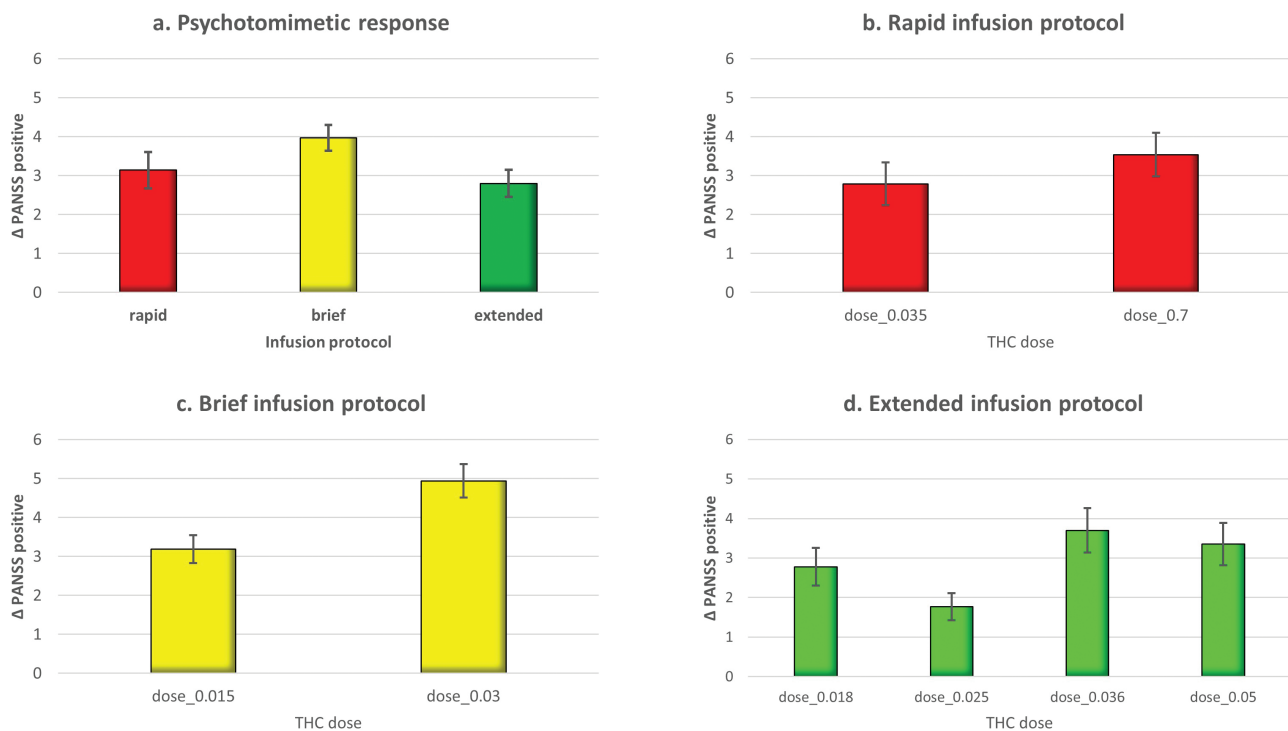


Figure 1. Bar graph presenting estimated marginal means of Positive and Negative Syndrome scale (PANSS) positive symptom change score, error bars (\pm SE). (a) Three delta-9-tetrahydrocannabinol (THC) infusion protocols. (b) Two THC doses in rapid infusion protocol. (c) Two doses in the brief infusion protocols. (d) Four THC doses in the extended infusion protocol.

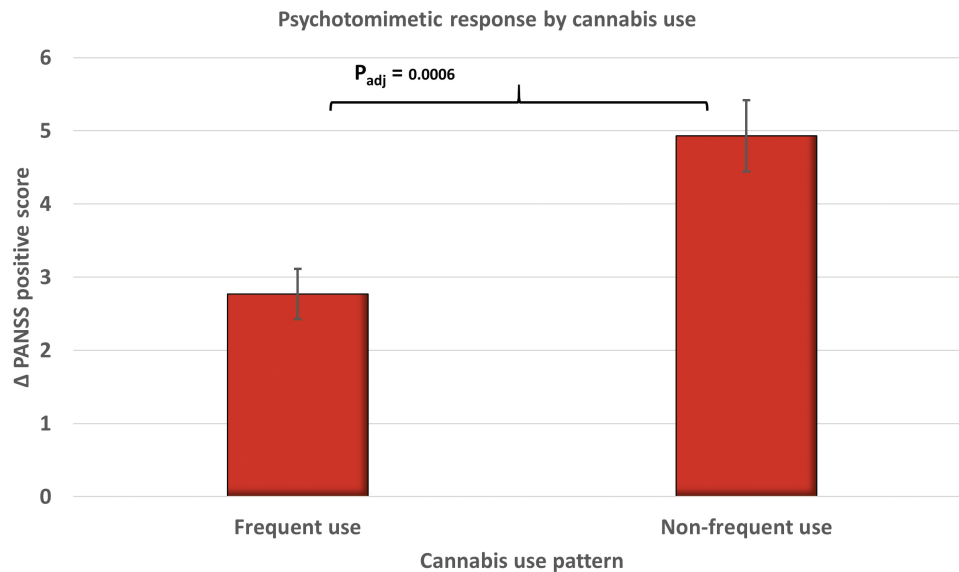


Figure 2. Bar graph presenting estimated marginal means of Positive and Negative Syndrome scale (PANSS) positive symptom change score between frequent and nonfrequent cannabis users with error bars (\pm SE). P_{adj} , adjusted P value in the generalized estimating equations (GEE) model.

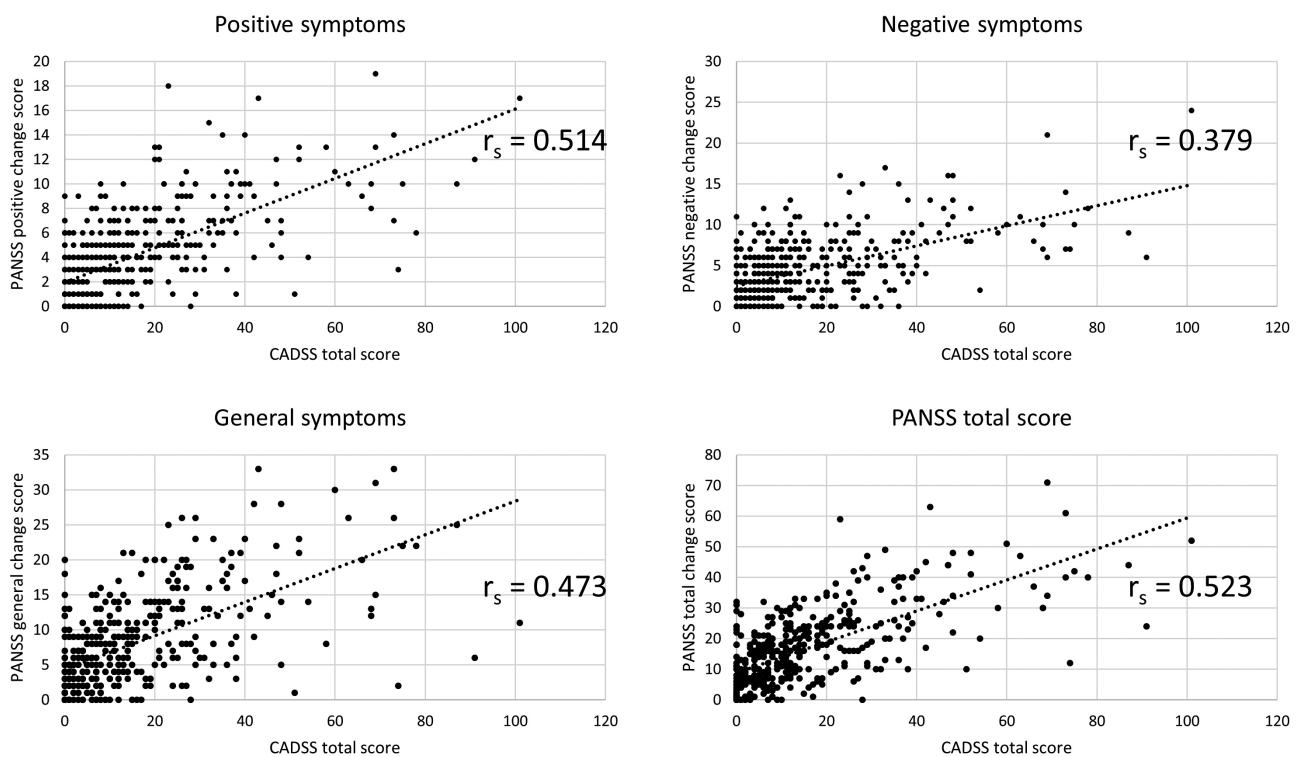


Figure 3. Scatter plots depicting relationship between Clinician Administered Dissociative States Scale (CADSS) total scores with (a) Positive and Negative Syndrome scale (PANSS) positive, (b) PANSS negative, (c) PANSS general psychopathology, and (d) PANSS total scores. r_s , Spearman's rank order correlation coefficient.

PANSS dimensions noted in schizophrenia literature (van der Gaag et al., 2006; Wallwork et al., 2012).

Relationship of PANSS Response With Perceptual Alteration and Subjective Experience Measures

A dose response relationship was also noted for perceptual alterations measured by the CADSS (supplementary Figure 3). PANSS

positive symptoms had the strongest correlation ($r_s=0.514$, $P<.001$) with CADSS scores followed by PANSS general psychopathology ($r_s=0.473$, $P<.001$) and PANSS negative symptoms ($r_s=0.379$, $P<.001$). Further, there was a strong positive correlation between CADSS scores and PANSS total scores ($r_s=0.523$, $P<.001$) (Figure 3). In contrast, the strength of the relationship between subjective effects of high (VAS-high) and the PANSS positive [$r_s=0.293$ ($z=3.75$)], negative [$r_s=0.207$ ($z=2.66$)], and

general psychopathology [$r_s=0.291$ ($z=3.02$)] subscales and the PANSS total scores [$r_s=0.31$ ($z=3.66$)] was significantly smaller than for the perceptual alterations (CADSS).

Discussion

Capitalizing on the largest known repository of individual participant data on the psychotomimetic response to i.v. THC, we have characterized this phenotype at individual symptom-level resolution, leading to some novel insights. In addition, these results provide some useful directions for future studies using HLM cannabinoids to examine the behavioral, cognitive, and biological aspects of psychosis. THC induces a clinically meaningful psychotomimetic response in a substantial proportion of the participants; this response is often driven by specific PANSS items (conceptual disorganization, hallucinations, affective blunting, somatic concern, motor retardation, and poor attention). Furthermore, exploratory factor analysis suggests an overlap in the symptom domains between the psychotomimetic response to THC and schizophrenia captured by the PANSS (van der Gaag et al., 2006). A strong relationship is noted between the measures of positive symptoms (PANSS) and perceptual alterations (CADSS), suggesting a continuum between these non-normative quasi-psychotic perceptual alterations that may precede the onset of outright positive symptoms. In contrast, we note a weak correlation between THC-induced feelings of “high” and positive symptoms suggesting a dissociation in these symptom domains.

With respect to the experimental design, while some individuals experienced a psychotomimetic effect at a dose as low as 0.015 mg/kg, our results suggest that a 10-minute dosing protocol with THC doses in the range of 0.03 to 0.036 mg/kg will be optimal for HLM-cannabinoid studies of psychosis. Based on our previous studies, this dose range results in a plasma THC concentration more than 60ng/dL, approximating the concentrations reached by smoking three-quarters to a full standard joint (Lee et al., 2015; Boggs et al., 2018). While we demonstrate a linear dose-response relationship in the severity of the psychosis-relevant phenomena, it is moderated by rate of THC infusion, frequency and recency of cannabis use, and ongoing tobacco use. It will be vital to account for these factors in future studies of HLM cannabinoids. The findings of blunted psychotomimetic response in persons with a history of frequent and recent cannabis use (D'Souza et al., 2008a) confirm some of the previous findings reported by our group related to the symptom profile, severity, and predictors of THC response (D'Souza et al., 2004).

Compared with earlier studies, we used stringent cut-off criteria to define psychotomimetic response to THC in the PANSS positive subscale (D'Souza et al., 2004). We note that a substantial proportion of healthy participants (~45%) experience clinically meaningful psychotomimetic responses. This finding confirms the previously reported rates of response in healthy volunteers to i.v. THC from independent research groups (Bhattacharyya et al., 2010). A substantial proportion of the participants had consistent responses to THC (i.e., those who did experience a clinically significant psychotomimetic response on a THC study had the same response on other THC studies). Similarly, there was consistency to those who did not have a clinically significant response across studies. This suggests that a participant's unique vulnerabilities attributable to genetic or developmental factors may determine the psychotomimetic response to cannabinoids. Studies that examine biological endophenotypes and polygenic risk burden for psychosis in the context of HLM cannabinoids may further our understanding of these vulnerabilities.

Dose-related psychotomimetic effects were evident in 2 of the 3 dosing protocols (“rapid” and “brief” infusions). Likewise, higher psychotomimetic responses were observed with higher doses of THC. Lastly, THC dose was one of the significant predictors of severity of psychotomimetic response in PANSS total and all 3 subscale scores in the regression model after controlling for the effects of infusion rate and other covariates such as age, gender, and frequent cannabis use. These results support a dose-dependent effect of THC in inducing transient psychotic states. Thus, the well-known biphasic effects of cannabinoids (e.g., anxiety with low dose are anxiolytic while high doses are anxiogenic) do not extend to their psychotomimetic effects. The complex dose-response relationship in the psychotomimetic effects observed in the “extended” infusion protocol can be attributed to the variation in the sample profiles (recent cannabis use, family history of substance use) for the first 2 doses of this protocol.

Greater cannabis exposure was associated with lower THC-induced PANSS positive symptoms. This was further corroborated in a subsample of participants for whom detailed past 30-day cannabis use data were available; there was a blunted THC-induced psychotomimetic response in cannabis users compared with nonusers. These results suggest the development of tolerance to THC-induced psychotomimetic response, confirming our previous findings (D'Souza et al., 2008a) or that these reflect inherent resilience to cannabinoids that are unrelated to tolerance. The mechanism of tolerance in the context of HLM is intriguing as this brings to the fore potential differences between dopamine and cannabinoid models of psychosis. In the case of the former, the mechanism of “sensitization” has been proposed in the development of psychosis (Peleg-Raibstein et al., 2009). Thus, studying the neural substrate of cannabinoid-induced psychosis might provide valuable clues in contrast to other drug models of schizophrenia.

Differences in the profile of psychotomimetic effects induced by different drugs may offer clues to the contributions of different neurotransmitter systems underlying the neurobiology of these phenomena. Acute administration of stimulants that act on dopaminergic pathways model some positive symptoms of psychosis. However, stimulants do not induce negative symptoms acutely and might even improve some negative symptoms (e.g., emotional withdrawal) and cognitive deficits (e.g., attention) (Lindenmayer et al., 2013). Serotonergic drugs such as lysergic acid diethylamide and psilocybin induce a range of positive symptoms of psychosis marked by visual hallucinations (Geyer and Vollenweider, 2008). The NMDA receptor antagonist ketamine models disorganization and negative symptoms in addition to positive symptoms (Abi-Saab et al., 1998). THC appears to induce a range of positive and negative symptoms, specifically conceptual disorganization, hallucinations, affective blunting, somatic concern, motor retardation, and poor attention. In addition, while not analyzed in this paper, THC reliably induces cognitive deficits when administered acutely (D'Souza et al., 2008b, 2012). The profile of THC-induced symptoms encompassed the symptoms frequently disrupted by dopaminergic, serotonergic, and glutamatergic agents, suggesting that the THC model of psychosis is distinct from other drug models (see [supplementary Table 5](#)).

While this study did not investigate the precise mechanism/s by which THC induces acute psychotomimetic effects, we provide some potential explanations based on preclinical and human studies. One obvious candidate neurotransmitter system implicated in acute psychotomimetic states is dopamine (DA). As stated by Bloomfield et al. (Bloomfield et al., 2016), the effects

Table 2. Rotated component matrix presenting factor loadings of PANSS items

Rotated component matrix (Varimax ^d)					
	1	2	3	4	5
PANSS items	Positive	Negative	Emotional	Excitement	Disorganization
P3 Hallucinations	0.778				
G1 Somatic concern	0.682				
G9 Unusual thought content	0.677		0.422		
P1 Delusions	0.666				
G11 Poor attention	0.614	0.454			
G7 Motor retardation	0.596	0.433			
G4 Tension	0.56				0.475
N1 Blunted affect	0.559	0.454			
P2 Conceptual disorganization	0.532				
G13 Disturbance of volition	0.445				
N3 Poor rapport		0.697			
N2 Emotional withdrawal		0.643			
N6 Lack of spontaneity and flow of conversation conversation		0.631			
G15 Preoccupation		0.569			
G8 Uncooperativeness		0.552			
G10 Disorientation		0.441			
P7 Hostility		0.413	0.669		
N7 Stereotyped thinking			0.636		
P6 Suspiciousness/persecution			0.582		
G2 Anxiety	0.441		0.568		
G6 Depression			0.482		
G3 Guilt feelings					
G14 Poor impulse control				0.746	
G12 Lack of judgement and insight				0.743	
P4 Excitement				0.597	
P5 Grandiosity				0.558	
N5 Difficulty in abstract thinking					0.735
G5 Mannerisms and posturing	0.401				0.452

Abbreviations: PANSS, Positive and Negative Syndrome scale.

^dItems are ordered on the magnitude of factor loadings and values <0.4 are suppressed.

of THC on the DA system are complex and diverse. Fitoussi et al. demonstrated that administration of THC into the shell of the nucleus accumbens in rats resulted in dose-dependent potentiation of emotional salience for fear conditioning cues. This was paralleled by increased activity of dopaminergic neurons in the ventral tegmental area, suggesting that acute administration of THC could modulate dopaminergic transmission in the ventral tegmental area (Fitoussi et al., 2018). In contrast, relative to DA stimulants such as amphetamine, which induce significant DA release and also induce positive symptoms of psychosis in healthy individuals and exacerbate psychosis in schizophrenia patients (Laruelle et al., 1995; Abi-Dargham et al., 2009), the effects of THC on dopamine release in humans are very small (Bossong et al., 2009; Stokes et al., 2009; Barkus et al., 2011) and not commensurate with its capacity to induce psychosis.

The interplay between GABA and CB1-R systems (Eggan et al., 2010) provides another mechanism underlying the capacity of cannabinoids to induce psychosis in healthy individuals and exacerbate psychosis in schizophrenia. Pharmacological induction of a GABA deficit can enhance the psychosis-relevant behavioral and psychophysiological effects of THC (Radhakrishnan et al., 2015). This could further be explained by the disruption of endocannabinoid signaling by exogenous THC (Wilson et al., 2001; Wilson and Nicoll, 2001) and the interplay between GABA and CB1-R systems (Eggan et al., 2010). For instance, if CB1-R activation could lead to disinhibition and desynchronization of

pyramidal cell activity, leading to perturbations in gating, associative functions, and neurocognition, this could culminate in psychotic symptoms as suggested by Radhakrishnan et al. (Radhakrishnan et al., 2015). If this were to occur in the presence of a GABAergic deficit, as may be the case in schizophrenia, it would explain why cannabinoids exacerbate psychosis in schizophrenia.

The mechanisms underlying the blunted psychotomimetic response noted in chronic users merits discussion. We and others have reported that chronic cannabis users show in vivo evidence of downregulation of cannabinoid receptor (Hirvonen et al., 2012; Ceccarini et al., 2015; D'Souza et al., 2016) that would explain a blunted response to THC. Additionally, Bloomfield et al. have demonstrated in vivo evidence of reduced dopamine synthesis in the striatal and limbic region in cannabis users (Bloomfield et al., 2014) that may explain the blunted response to THC. Future investigations that examine neurobiological correlates of psychotomimetic states in acute, chronic, and acute-on-chronic cannabis exposure would better elucidate the underlying mechanisms in the relationship between THC, cannabinoids, and schizophrenia.

The factor structure of THC-related psychosis was comparable with schizophrenia with an optimal 5-factor solution and factors corresponding to positive, negative, emotional, excitement, and disorganization symptom domains. However, there were specific differences in the item loading, with items that measure positive,

negative, and disorganization symptoms in the 5-factor solutions of schizophrenia, loading on a common factor (factor 1, Table 2) in THC-induced transient psychosis. These findings suggest that while PANSS captures levels of psychopathology along multiple schizophrenia relevant items in THC-induced psychosis, the 2 phenotypes differ in the covariation of these symptoms.

Lastly, we observed large correlations between PANSS positive symptoms and the measures of perceptual alterations captured with CADSS. Hence, the acute experience induced by THC involves several perceptual and cognitive alterations that are not typically classified as psychotic experiences but co-vary with these symptoms. Collectively, the CADSS and PANSS together capture a wide range of THC-induced effects. In contrast, only modest correlations were observed between THC-induced positive symptoms and subjective effects of high. These data suggest some dissociation between the euphoric and psychotomimetic effects of THC.

Some limitations should be considered in the interpretation of these results. As these data were collected over 2 decades, we have included those variables that were common across the studies in our analysis. While the analysis-related variables were standardized, there was heterogeneity in the questionnaires used to capture cannabis use, family history of psychiatric disorders, and other substance use. Based on these scales, participants were dichotomized as frequent and nonfrequent cannabis users and as past month users and nonusers. But across both categorical variables, there was a consistent pattern of blunted psychotomimetic response. In the absence of definite cut-offs defining a positive psychotomimetic response, we used empirical criteria to define a positive response on global PANSS measures and the 3 subscales. To overcome this limitation, we have also presented the data with multiple cut-off thresholds. The PANSS was developed for typological and dimensional assessment in schizophrenia. We used a modified PANSS (without items N4: passive/apathetic social withdrawal, and G16: active social avoidance) removing 2 items that are not relevant to capturing acute psychotomimetic effects in healthy individuals. This modified version has been used extensively to capture the effects of a range of psychotomimetic drugs, including ketamine (Krystal et al., 2005), amphetamine (Krystal et al., 2005), and salvinorin A (Ranganathan et al., 2012a). We analyzed the PANSS in this report as it was the commonly used measure in the 10 primary studies included in the analysis. While formal studies have not established sensitivity of PANSS in the context of acute psychotomimetic response, this has been the most commonly used scale in HLM studies of drug-induced psychosis. Furthermore, the factor structure presented in our analysis provides vital clues to the PANSS domains that are most representative of acute psychotomimetic response to THC.

Conclusions

Intravenous administration of THC reliably induces a psychotomimetic response in a substantial proportion of the participants in a dose-dependent fashion. Frequent cannabis users demonstrate a blunted psychotomimetic response. While this experience broadly mimics the psychosis in schizophrenia, specific symptoms spanning the positive, negative, excitement, and emotional domains are most frequently elicited by THC. In sum, human laboratory model with cannabinoids can be useful to examine specific aspects of the phenomenology and neurobiology of psychosis.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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