Published in final edited form as:

Psychiatry Res. 2020 November ; 293: 113380. doi:10.1016/j.psychres.2020.113380.

Cannabinoid use in psychotic patients impacts inflammatory levels and their association with psychosis severity

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Abstract

Inflammatory abnormalities are well-documented in individuals with chronic psychotic disorders. Particular attention has focused on interleukin-6 (IL-6) and its correlation with psychotic symptom severity. Cannabis use is associated with an increased risk of psychosis and also has immunomodulating properties. It has been hypothesized that inflammatory disturbances are a common underlying pathology between cannabis use and psychosis. We measured inflammatory markers in individuals admitted to a psychiatric unit with acute psychosis who had toxicology positive for natural and/or synthetic cannabinoids ($n = 59$) compared to patients with negative cannabinoid toxicology ($n = 60$). Psychosis severity was assessed using the Positive and Negative Syndrome Scale (PANSS). While PANSS scores were similar between groups, cannabinoid-positive participants were more likely to receive *pro re nata* (PRN or as-needed) medications for agitation in the psychiatric emergency room, particularly synthetic cannabinoid-positive participants. In unadjusted models, cannabinoid-positive participants had lower interferon- γ (IFN- γ) levels ($p = 0.046$), but this finding was not significant after adjusting for covariates and multiple comparisons. Among cannabinoid-positive participants, IL-6 levels negatively correlated with PANSS total score ($p = 0.040$), as well as positive ($p = 0.035$) and negative ($p = 0.024$) subscales. Results suggest inflammatory alterations among psychotic individuals with comorbid cannabinoid use.

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Declarations of interest: none.

Keywords

schizophrenia; cannabis; synthetic cannabinoids; marijuana; IFN- γ ; IL-6; inflammation

1. Introduction

Psychotic disorders have long been associated with abnormalities in the inflammatory and immune systems based on multiple lines of evidence (Khandaker and Dantzer, 2016; Muller and Schwarz, 2010). Genetic analyses, including the initial 108 schizophrenia-associated gene loci study, consistently report immune-related susceptibility genes for schizophrenia (Horvath and Mirnics, 2014; Schizophrenia Working Group of the Psychiatric Genomics et al., 2014). Birth cohort studies find increased rates of schizophrenia in offspring of women who have elevated peripheral cytokines during pregnancy, which indicate the presence of prenatal infections or inflammatory conditions (Brown and Derkits, 2009). Similarly, individuals with chronic psychotic disorders have elevated peripheral cytokine levels (Radhakrishnan et al., 2017). Meta-analyses report that multiple inflammatory markers are elevated during acute psychotic relapse including (but not limited to) interferon- γ (IFN- γ), interleukin-1 β (IL-1 β), IL-6, IL-8, IL-12, soluble IL-2R (sIL-2R), and tumor necrosis factor- α (TNF- α) (Goldsmith et al., 2016; Miller et al., 2011).

Of the multiple inflammatory markers, IL-6, a key inflammatory cytokine, has received the most attention. IL-6 is among the cytokines capable of crossing the blood-brain barrier (Pan and Kastin, 2004) and reduces monoamine neuron survival *in vitro* (Jarskog et al., 1997). In schizophrenia, peripheral levels of IL-6 correlate positively with total duration of illness (Akiyama, 1999) and psychopathology scores (Chase et al., 2016; Dahan et al., 2018), although this latter relationship does not always replicate (Kim et al., 2001) and a negative relationship between positive psychotic symptoms and IL-6 levels has also been reported (Stojanovic et al., 2014). Multiple confounding variables may explain replication failure (Na et al., 2014). One key potential confound is participants' use of cannabis, a drug associated with psychosis (Radhakrishnan et al., 2014) whose active compounds are known to impact inflammation (Tanasescu and Constantinescu, 2010).

The link between cannabis use and psychosis has been recognized for centuries (Warnock, 1903). For example, acute intoxication with THC or synthetic cannabinoids, commonly known as K2 or spice, can induce psychotic-like symptoms in healthy individuals (D'Souza et al., 2004; Papanti et al., 2013). Cannabis use is associated with a dose-dependent increased risk and earlier onset of psychotic disorders (Di Forti et al., 2009; Di Forti et al., 2014; Marconi et al., 2016). Individuals with psychotic disorders are more susceptible to the acute effects of cannabis (Haney and Evins, 2016); even when receiving antipsychotic medications, patients with psychotic disorders are at an increased risk of psychotic relapse while using cannabis (Alvarez-Jimenez et al., 2012; Muller et al., 2010). Similarly, among psychiatric inpatients, the use of either synthetic cannabinoids or natural cannabis is associated with increased odds of being psychotic (Bassir Nia et al., 2016). In particular, synthetic cannabinoids, the majority of which are highly potent full agonists at cannabinoid

receptors (Castaneto et al., 2014), are associated with greater agitation and aggression, normally reflective of more severe psychotic episodes (Bassir Nia et al., 2016).

Inflammatory perturbations that are associated with psychosis are strongly regulated by cannabis. The cannabinoid receptor type 2 (CBR2) is one of the primary receptors to which cannabinoids bind and is primarily expressed on immune cells, directly regulating immune function. Pre-clinical studies demonstrate that administration and potentiation of endogenous cannabinoids as well as administration of cannabinoid agonists like delta-9-tetrahydrocannabinol (THC) results in multiple immunosuppressive and anti-inflammatory effects, including reductions in cytokine production (Burstein and Zurier, 2009; Klein and Cabral, 2006). However, the effects of either natural or synthetic cannabinoids on the immune system of recreational users remains poorly understood. Of the few studies, accumulating evidence suggests that cannabis use reduces IL-6 levels. For example, alveolar macrophages recovered from chronic cannabis users produce lower levels of IL-6 when stimulated with a pathogen (Baldwin et al., 1997), and cannabis users were reported to have lower peripheral IL-6 levels compared to non-drug using participants (Keen II et al., 2014).

Although inflammation may be one pathway through which cannabis use modulates the risk of psychotic disorders and relapse (Suarez-Pinilla et al., 2014), few studies have measured peripheral cytokine levels in patients with psychosis who use cannabis. Miller et al. (2018) reported a tendency for reduced IL-6 levels among cannabis-using psychotic patients compared to patients with negative urine drug screens. Interestingly, IL-6 levels were positively correlated with both the total score and the negative subscale of the Positive and Negative Syndrome Scale (PANSS; an assessment of psychotic symptom severity) in the cannabis users, but not among all patients with negative urinary drug screens.

To further expand current knowledge regarding psychosis, cannabis, and the immune system, we explored the relationship between cannabinoid use and inflammation among psychotic patients admitted to a psychiatric unit with recent use of natural cannabis or synthetic cannabinoids, compared to inpatients without recent cannabis use. The following inflammatory markers were measured: IFN- γ , IL-12 (the active heterodimer, IL-12 p70), IL-6, IL-2, IL-1 β , TNF- α , IL-10, IL-21, IL-8, C-reactive protein (CRP), and soluble IL-2 receptor α (sIL-2Ra). We hypothesized that: (1) cannabinoid users will have more severe psychoses, evidenced by having higher PANSS scores and receiving more pro re nata (PRN; provided as needed) medications for agitation; (2) cannabinoid users will have lower inflammatory marker profiles; and (3) among cannabinoid users alone, IL-6 levels will be predictive of PANSS scores.

2. Methods

2.1 Participants

One-hundred and nineteen patients with psychosis were recruited from a psychiatric unit at Mount Sinai Beth Israel, a hospital located in Manhattan, New York City. After an on-site attending clinically diagnosed patients as having acute psychosis based on DSM-V (Association, 2013) criteria and having capacity for informed consent, research staff approached patients for study recruitment within one week of hospitalization. Exclusion

criteria included history of a significant traumatic brain injury, active seizure disorder, brain surgery, dementia, brain masses, pervasive developmental disorders, or not being conversationally fluent in English. Procedures were explained to patients and written informed consent was obtained before study participation. This study was approved by the Internal Review Board at the Mount Sinai Hospital, New York City, New York (study ID 16-00472).

2.2 Psychiatric assessments

The Positive and Negative Syndrome Scale (PANSS) was used to measure the severity of psychosis. PANSS is a widely-used, 30-item scale to assess the presence and severity of positive, negative, and general symptoms of schizophrenia (Kay et al., 1987). The scale has been internally and externally validated and demonstrates high inter-rater reliability (Bell et al., 1992). PANSS interviews were conducted by three trained psychiatrists and one trained medical student. A subset of interviews was scored by two individuals to verify inter-rater reliability. In the rare case that a scale item was missing, it was input with that item's mean.

Data regarding participant hospital course, medical history and comorbidity, hospital admissions labs (including complete blood count [CBC] results), physiological measurements (body mass index [BMI], temperature, sleep length), and medication administration (including PRN medication) were obtained through chart review after patient discharge.

2.3 Biospecimen collection and toxicology

Blood samples were obtained once eligible participants were deemed able to provide informed consent; the mean number of days between hospital admission and sample collection was 2.3 days (SD =1.8 days). Blood was collected in sodium heparin tubes (BD Vacutainer, Mississauga, ON, Canada) before immediate centrifugation to collect plasma; 2mL of plasma was then aliquoted into separate cryovials. Blood and plasma samples were stored at -80°C until assay commencement. Urine for hospital urinary toxicology screens and blood for admission labs were collected and processed by hospital staff. Urine for mass spectrometry toxicology was collected from participants in a urine collection cup (BD Vacutainer). If available, urine collected at the emergency department was also retrieved for mass spectrometry toxicology testing. Urine samples were aliquoted into 5mL tubes and stored at -20°C until processing.

Mass spectrometry was used to assess the presence of synthetic cannabinoids and to confirm the presence of tetrahydrocannabinol (THC) metabolites in blood and urine specimens. Supplementary material 1 lists all synthetic cannabinoids that were assessed. If a participant had no toxicology results due to refusal to provide a specimen sample ($n = 3$), self-reported drug history and chart review was used to determine toxicology status.

2.4 Analyte testing

Analytes were measured using commercially available multiplex cytokine/chemokine panels (EMD Millipore, Billerica, Massachusetts) as per the manufacturer's instructions on Luminex-200 multiplex immunoassay system. Data were analyzed using Milliplex Analyst

5.1 software. Analytes with values below the limit of detection on standard sensitivity kits were measured using high sensitivity kits, including IL-6, IL-1 β , IL-12p70, IL-2, and IL-21. In the case that a sample's analyte concentration was still below the limit of detection, half the limit of detection was used as an input. For example, if a kit's limit of detection was 1.00 pg/mL, and a sample resulted below this limit, we inputted 0.50 pg/mL for that sample. Samples were measured (in duplicate) in four 96 well plates (80 wells for 38 samples measured in duplicate, 14 wells for standard curve measurements, and 2 for assay quality control). Duplicate sample measurements were averaged together to give 38 individual sample measurements in each plate.

Samples were assayed in three batches and the resulting raw data from each batch were normalized so that the mean analyte level was the same for each analyte across batches. A subset of samples was measured in duplicate across the three batches and was used to validate the batch normalization method. The batch effect and the similarity of duplicate samples from the same patient were assessed using the area under the receiver operating characteristic curve (AUC) produced from sample-sample similarity measurements. Further, a similarity matrix generated from this normalization method showed that duplicate samples from the same patient run in different batches clustered closely and that samples from the same patient run in duplicate were more similar than samples from different patients.

2.5 Data analyses

2.5.1 Power calculation—Based on our study timeline and patient recruitment rate, we planned 50 patients per group. No prior studies had tested our selected inflammatory markers between cannabinoid-positive and cannabinoid-negative individuals with psychosis, so a power calculation was estimated using the study of van Kammen et al. (1999) that compared IL-6 levels between patients with psychosis and healthy controls. Fifty patients per group, 80% power, an α threshold of 0.05, and an assumed standard deviation of 2.56 ng/mL, would allow a minimum detectable difference of 1.44 ng/mL between the participant groups.

2.5.2 Statistical plan—Baseline characteristics are presented as means $\pm$ standard deviations; two-sided t-tests were used to compare means between cannabinoid-negative and cannabinoid-positive participants. Chi-square tests or Fisher's exact tests were used to compare distributions of categorical variables across groups. In the case of significant results, standardized residuals assessed cells of interest; standardized residuals ≥ 2.0 were considered significant. Pearson's correlation coefficient was used to assess interrater reliability in PANSS scores and an F-test was used to test for an effect of PANSS administrator on PANSS total and subscale scores. PANSS scores between cannabinoid-negative and cannabinoid-positive participants were compared using a two-sided t-test. A logistic regression model was used to assess the effect of cannabinoid type (natural versus synthetic) on PRN medication administration.

Analysis of covariance (ANCOVA) models were used to compare mean inflammatory factor levels between cannabinoid-negative and cannabinoid-positive participants. All cytokines as well as CRP and sIL-2Ra were tested in separate models. After batch normalization,

analytes were transformed using a log base-10 algorithm. Untransformed analyte data is included in supplementary material 2. Data were first analyzed without controlling for possible covariates, which are reported as unadjusted results. Next, adjusted models accounted for possible covariates, including age, sex, presence of an illness that may impact inflammation, smoking status, BMI, temperature, hours slept the night before the blood draw, administration of antipsychotic medication during hospitalization before the blood draw, and administration of benzodiazepine medication during hospitalization before the blood draw. In the rare case that a covariate data point was missing, it was input with that item's mean (continuous variables) or median (categorical variables). Covariates whose mean values differed between cannabinoid-positive and negative groups at $p < 0.1$ were included in the model. Additionally, for each analyte, a backward selection algorithm was applied in a multivariate analysis and all explanatory variables with p -values less than 0.1 were included in the final model. The presence of significant interaction effects between group and included covariates were assessed and interaction terms with p -values < 0.05 were included. Final covariates are listed in the footnote beneath each data table (Table 2 and Table 3). Multicollinearity was assessed in all fitted models and any covariate with variance inflation factor (VIF) greater than five was viewed as a signal of multicollinearity. To account for multiple comparisons, p -values were compared against p -values derived using the Benjamini–Hochberg procedure; a main effect with a false discovery rate less than or equal to 0.15 were viewed as demonstrating a significant between group difference in inflammatory factor level.

Linear regression modeling was used to assess the relationship between log-transformed IL-6 levels and PANSS scores. Cannabinoid-negative and cannabinoid-positive participants were analyzed separately. Models were built for PANSS total score and each subscale (positive, negative, and general). Covariate selection followed the same algorithm as used in the ANCOVA model, including the use of all covariates whose mean values differed between groups ($p < 0.1$). Covariates that were significantly related to either IL-6 (predictor variable) or PANSS scores (outcome variables) were also included in the final models. The estimated effects and p -values associated with IL-6 are reported.

Data were analyzed using IBM SPSS Statistics. Unless otherwise described (e.g. for the ANCOVA models), significance level was set at p -value 0.05 for all analyses.

3. Results

Baseline characteristics of the 119 participants are reported in Table 1. In total, 60 participants had negative toxicology for both cannabis and synthetic cannabinoids, and 59 participants had positive toxicology for cannabinoids. Of these, seven participants had positive toxicology for synthetic cannabinoids, four of whom were positive for natural cannabis as well. The synthetic cannabinoids that were identified include: FUB-AMB 3-methyl-butanoic acid (seven participants) and MDMB-FUBINACA 3,3-dimethyl-butanoic acid (two participants). Inflammatory marker data was available for 56 cannabinoid-negative participants and 51 cannabinoid-positive participants. Supplementary material 3 reports CBC and differential data from hospital admission labs; there were no significant differences in leukocyte profiles between participant groups. Supplementary material 4 lists participant

discharge medications. A smaller portion of cannabinoid-positive participants were prescribed atypical antipsychotics at discharge compared to cannabinoid-negative participants ($p = 0.025$).

Cannabinoid-positive participants were significantly younger ($p = 0.005$), had lower BMIs ($p = 0.038$), and had trend-level lower rates of medical conditions that may impact inflammation ($p = 0.061$). For a complete listing of these conditions, see supplementary material 5. Other baseline characteristics were similar between the groups.

3.1 Severity of psychosis and cannabinoid use

Inter-rater reliability was assessed by sampling 10 PANSS interviews with a resulting Pearson's correlation coefficient of 0.763. There was no significant effect of PANSS administrator on PANSS total score [$F = 0.630$, $p = 0.597$] or any subscale ($p > 0.2$ for each).

There was no significant difference between the cannabinoid groups on PANSS total score [$t = 1.323$, $p = 0.188$], positive subscale [$t = -0.816$, $p = 0.416$], negative subscale [$t = 1.841$, $p = 0.068$], or general subscale [$t = 1.669$, $p = 0.098$] (Figure 1).

Significantly more cannabinoid-positive participants (49.2%) received PRN medications in the psychiatric emergency room compared to cannabinoid-negative participants (28.3%; $p = 0.020$) (Figure 2). A logistic regression demonstrated that synthetic cannabinoid-positive patients drove this finding, OR = 15.176 (95% CI: 1.698 – 135.633), $p = 0.015$. However, there was no difference in PANSS scores for synthetic cannabinoid-positive patients compared to natural cannabinoid-positive patients ($p > 0.05$). There was no significant difference in PRN medication administered during hospitalization on the psychiatric unit between cannabinoid-positive and cannabinoid-negative patients ($p = 0.773$).

3.2 Inflammatory profile comparisons between cannabinoid negative and cannabinoid-positive participants

Logarithmically transformed IFN- γ levels were lower in the cannabinoid-positive group (0.869 ± 0.310) compared to the cannabinoid-negative group (0.997 ± 0.340), $F = (1,105) = 4.062$, $p = 0.046$ (Figure 3). This finding did not remain significant after adjusting for covariates in the ANCOVA model or for multiple comparisons. There were no significant between group differences for any other tested analyte, though the majority of the inflammatory markers tested were lower amongst cannabinoid positive participants. In the ANCOVA model, IFN- γ , CRP, IL-21, IL-2, and IL-12 were reduced at an α threshold of $p = 0.1$. Table 2 provides the full ANCOVA results and included covariates; for graphical representation, see supplementary material 6.

3.3 Relationship between IL-6 levels and PANSS scores

Pearson correlations between PANSS scores and log(IL-6) levels revealed a marginally significant negative association between log(IL-6) levels and PANSS negative subscale for the cannabinoid-positive group alone ($R = -0.273$, $p = 0.052$). The remaining correlations

between log(IL-6) levels and PANSS total, positive, and general scores were not significant (supplementary material 7).

The results from linear regression modeling of log(IL-6) levels and PANSS scores, stratified by cannabinoid-positive and negative groups, are summarized in Table 3. Among the cannabinoid-positive group, log(IL-6) levels were significantly negatively associated with PANSS total scores ($\beta = -0.283$, $p = 0.040$), positive subscale ($\beta = -0.277$, $p = 0.035$), and negative subscale ($\beta = -0.303$, $p = 0.024$); there was no significant association between log(IL-6) levels and the general subscale. Among the cannabinoid-negative group, there were no significant associations between log(IL-6) levels and PANSS total or subscale scores. Significant covariates included in each model are listed below Table 3.

4. Discussion

Few investigations have examined inflammation in cannabis-using individuals with psychosis. The current study of 119 actively psychotic inpatients characterized the association between use of cannabinoids, peripheral inflammatory markers, and psychosis severity. The results support alterations in cytokine levels and an inverse correlation between IL-6 and PANSS scores in individuals with psychosis and comorbid cannabinoid use.

4.1 Severity of psychosis and cannabinoid use

Cannabinoid-positive participants were significantly more likely to receive PRN medications in the psychiatric emergency room for agitation compared to cannabinoid-negative participants, which was especially driven by synthetic cannabinoid-positive participants. This replicates our previous findings (Bassir Nia et al., 2016) and provides further support for several lines of evidence that synthetic cannabis induces more severe psychotic presentations. However, neither PANSS total score nor any subscale differed between groups, perhaps due to the small number ($n = 7$) of synthetic cannabis users. Moreover, since patients who presented with very severe psychoses and agitation were enrolled only after they were deemed eligible to give informed consent, the effects of cannabinoids on psychotic severity may have diminished at the time of the PANSS interview.

4.2 Inflammatory profile differences between cannabinoid-positive and cannabinoid-negative participants

No overall group differences were detected for the inflammatory markers tested, but the inflammatory profiles of participants who tested positive for cannabinoids were characterized by reductions of IFN- γ levels compared to those who were cannabinoid-negative. However, this finding did not survive in the models adjusted for covariates or correction for multiple comparisons, so caution must be taken with interpreting this result. Of interest, the majority of the inflammatory markers tended to be lower among participants who tested positive for cannabinoids, with CRP, IL-21, IL-2, and IL-12 reaching trend-level reductions.

IFN- γ is an inflammatory cytokine capable of crossing the blood brain barrier with roles in the innate and adaptive immune responses against a variety of pathogens (Pan and Kastin, 2004). While few studies in humans exist, the tendency for IFN- γ to be reduced in the

current cannabis-using cohort is consistent with the literature showing that, in general, exposure to THC and cannabinoid agonists reduces expression of IFN- γ (Klein, 2005; Klein et al., 2000; Smith et al., 2000; Zgair et al., 2017). Nevertheless, there are inconsistencies in the literature with some studies showing no difference in IFN- γ levels in individuals with cannabis use disorder who do not have comorbid psychiatric disorders (Bayazit et al., 2017). However, in patients with psychosis, IFN- γ levels measured *in vivo* are higher compared to healthy controls (Kim et al., 2009). Interestingly, immune cells of patients with psychosis produce less IFN- γ when stimulated *in vitro* (Arolt et al., 2000). Some suggest that suppressed IFN- γ corresponds to a blunted type-1 immune response in patients with psychosis (Müller et al., 2015). Accordingly, administration of IFN- γ in a small number of patients with treatment resistant schizophrenia has shown encouraging results (Grüber et al., 2014). Further research is needed to determine whether the inflammatory system is more affected in cannabis users who have psychotic disorders.

4.3 Relationship between IL-6 levels and PANSS scores

A key *a priori* focus of our study was based on the published association of IL-6 with psychosis and psychotic symptoms (Chase et al., 2016; Dahan et al., 2018). We observed that IL-6 levels negatively correlated with PANSS total scores, as well as negative and positive subscale scores in patients with cannabinoid use. No association was detected between IL-6 levels and PANSS scores in the cannabinoid negative group. The majority of the previous literature reports either a positive correlation between IL-6 levels and PANSS scores or no relationship (Chase et al., 2016; Dahan et al., 2018; Kim et al., 2001; Miller et al., 2011). Such studies largely exclude patients with substance abuse disorders or do not assess substance use, making them consistent with our null findings in the cannabinoid negative group. However, a negative correlation between PANSS scores and IL-6 levels has previously been reported. Stojanovic et al. (2014) observed that, among outpatients with psychotic disorders, IL-6 levels were *negatively* correlated with PANSS positive subscale scores (but positively correlated with PANSS negative subscale scores). Interestingly, in relation to the current study, the population in their investigation included a large cohort of cannabis users — 26% of participants reported daily cannabis use.

The only prior study that specifically examined inflammatory markers in cannabinoid using participants with psychosis reported a positive correlation between PANSS total and negative subscale scores and IL-6 levels (Miller et al., 2018). However, that investigation was based on data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project in which the majority of the participants studied were stable outpatients (Lieberman et al., 2005). In contrast, our participants were exclusively inpatients experiencing acute psychosis. Inflammatory factors are known to fluctuate rapidly and IL-6 has been shown to stabilize post-treatment (Miller et al., 2011), which may in part explain the dissimilar findings.

4.4 Study limitations

The current observational study faced several limitations and challenges. We had a relatively small sample size; however, our power calculation demonstrated that we were powered to detect meaningful differences in analyte levels between cannabinoid-positive versus negative

participants. Because few synthetic cannabis users were recruited, it was not possible to discern differences in inflammatory markers between synthetic and natural cannabis users. Nevertheless, despite the small number, synthetic cannabinoid users still drove greater use of PRN medications for agitation in the cannabis group.

We measured inflammatory markers at a single time point; thus, we were unable to assess the longitudinal effects of antipsychotic treatment or cannabinoid abstinence on the inflammatory profiles of participants over time. We had few exclusion criteria, making our study sample representative of a typical inpatient psychiatric unit. For example, we included participants who had recently used other substances, including alcohol. We also did not exclude participants with inflammatory medical conditions, which may have impacted inflammatory marker levels. However, we accounted for the presence of inflammatory illnesses in our regression models. Finally, cannabinoid use was determined using toxicology alone. We were not able to assess how duration, frequency, or quantity of cannabinoid use impacted psychotic symptom severity or inflammatory markers.

To account for the multiple tests required by the ANCOVA models, we adjusted p -values using the Benjamini-Hochberg procedure using a false positive rate of 0.15. While our finding of reduced IFN- γ levels among participants who tested positive for cannabinoids did not survive the correction factor, given the exploratory nature of the study, this finding can guide future hypothesis development. The generally lower inflammatory marker levels (in particular CRP, IL-21, IL-2, and IL-12) suggest a broad reduction in inflammation in the cannabinoid-positive group, an interesting trend for further investigation.

4.5 Conclusion

We examined psychotic symptom severity and inflammatory markers in cannabinoid-positive compared to cannabinoid-negative participants with acute psychosis. The findings suggest that cannabinoid users may have inflammatory dysregulation, as evidenced by the trend for generally lower levels of inflammatory markers, especially IFN- γ . Among cannabinoid-using patients, lower levels of the pro-inflammatory cytokine IL-6 correlated with higher psychopathology scores, suggesting that impaired inflammatory response in acute psychosis, potentially related to the use of cannabinoids, is associated with more severe psychotic symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This research project would not have been possible without the contributions of the Beth Israel clinical research volunteer team, including Rachel Concha, Trevor Friedman, Samantha Jancowski, HanLim Kim, Nina Rodriguez, Kendra Terry, Joanny Valerio, and Zain Warriach, as well as administrative assistant Lyla Parvez and Anna Opreescu. A special thank you to Dr. Gary Winkel for his statistical guidance.

Funding:

This project was generously supported by the National Institutes of Health TL1 grant, TR001434 and internal Mount Sinai funds from the Addiction Institute (YLH). Anahita Bassir Nia was supported by the National Institute of Health K12 DA000167 grant.

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Figure. 1.

Cannabinoid-positive participants have similar PANSS scores compared to cannabinoid-negative participants. PANSS = Positive and Negative Syndrome Scale.

Figure 2.

Synthetic cannabinoid-positive participants received significantly more pro re nata (PRN or as-needed) medications in the psychiatric emergency room compared to cannabinoid-negative and natural cannabinoid-positive participants ($p = 0.015$). SC = synthetic cannabinoid.

Figure 3. Comparing Log(IFN- γ) levels between cannabinoid-positive and cannabinoid-negative participants, *p*-value represents analyses controlling for covariates.

Table 1.

Participant baseline characteristics and hospitalization data

Variable count (%) or mean (SD)	Cannabinoid-negative (n = 60)	Cannabinoid-positive (n = 59)	p-value
Gender, women	18 (30%)	19 (32%)	0.795
Age	39.0 (12.9)	32.9 (10.4)	0.005
Race			0.222
Black	27 (45%)	16 (27%)	
White	8 (13%)	15 (25%)	
Hispanic	13 (21%)	16 (27%)	
Asian	11 (18%)	11 (19%)	
Unknown	1 (2%)	1 (2%)	
Living Situation			0.635
Independent or living with family/friends	27 (47%)	32 (57%)	
Transitional housing, shelter, or homeless	28 (49%)	22 (39%)	
Other	2 (4%)	2 (4%)	
Length of hospital stay, days	15.0 (9.5)	12.7 (6.1)	0.117
Received PRN medication in psychiatric emergency room	17 (28%)	29 (49%)	0.020
Diagnosis at discharge			0.420
Schizophrenia	20 (33%)	18 (31%)	
Schizoaffective disorder	20 (33%)	13 (22%)	
Bipolar disorder	11 (18%)	13 (22%)	
Other psychotic disorder / NOS	8 (13%)	9 (15%)	
MDD with psychotic features	1 (2%)	2 (3%)	
Substance-induced psychotic disorder	0	2 (3%)	
No psychotic disorder at discharge	0	2 (3%)	
Other positive toxicology ^a	17 (28%)	14 (24%)	0.426
Cocaine	5 (8%)	7 (12%)	
PCP	1 (2%)	3 (5%)	
Amphetamines	4 (7%)	2 (4%)	
Barbiturates	0	2 (3%)	
Opiates	4 (7%)	1 (2%)	
Methadone	2 (3%)	1 (2%)	
Benzodiazepines	4 (7%)	0	
Not available	9 (15%)	9 (15%)	
Body Mass Index	26.6 (6.1)	24.3 (5.9)	0.038
Current tobacco smoker	41 (70%)	44 (76%)	0.440
Inflammatory disorder ^b	25 (42%)	15 (25%)	0.061

Bold values indicate significance at $p < 0.05$; Chi-Square testing and Fisher's exact test (for variables with cells < 5) were used for categorical variables; two-sided t-tests were used for continuous variables

^aToxicology for substances other than alcohol based on hospital acquired urine toxicology alone

^bDiagnosed with an acute or chronic disorder at time of blood draw that could affect a patient's inflammatory marker levels, see supplementary material 5 for a full listing

PRN = pro re nata (medication administered as needed for agitation in psychiatric emergency room, prior to admission to hospital); NOS = not otherwise specified; MDD = major depressive disorder

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Table 2.

ANCOVA results comparing inflammatory factors between cannabinoid-negative and cannabinoid-positive groups

Factor	Cannabinoid-negative (mean $\pm$ SD)	Cannabinoid-positive (mean $\pm$ SD)	Unadjusted <i>p</i> -value	Adjusted <i>p</i> -value	<i>p</i> -value comparison
Log(CRP)	0.741 $\pm$ 0.650	0.515 $\pm$ 0.669	0.080	0.065	0.014
Log(IL-21)	0.664 $\pm$ 0.390	0.580 $\pm$ 0.345	0.241	0.074	0.033
Log(IFN- γ)	0.997 $\pm$ 0.340	0.869 $\pm$ 0.310	0.046	0.079	0.050
Log(IL-12)	0.411 $\pm$ 0.301	0.331 $\pm$ 0.275	0.155	0.085	0.067
Log(IL-2)	0.302 $\pm$ 0.292	0.235 $\pm$ 0.272	0.219	0.087	0.083
Log(IL-1 β)	0.024 $\pm$ 0.212	-0.018 $\pm$ 0.234	0.338	0.125	0.100
Log(IL-6)	0.520 $\pm$ 0.398	0.407 $\pm$ 0.454	0.174	0.231	0.117
Log(TNF- α)	1.148 $\pm$ 0.218	1.155 $\pm$ 0.171	0.871	0.324	0.133
Log(sIL-2Ra)	2.966 $\pm$ 0.199	2.911 $\pm$ 0.207	0.166	0.418	0.150
Log(IL-8)	0.529 $\pm$ 0.280	0.553 $\pm$ 0.307	0.680	0.436	0.167
Log(IL-10)	1.033 $\pm$ 0.299	0.997 $\pm$ 0.304	0.533	0.886	0.183

All models include body mass index (BMI), presence of an inflammatory disorder, and age as these variables differed between groups ($p < 0.1$). Additional covariates included in each model are as follows: log(CRP): sex and group x BMI interaction term; log(IL-21): sex; log(IFN- γ): none; log(IL-12): sex; log(IL-2): smoking status and sex; log(IL-1 β): sex; log; (IL-6): antipsychotic administration; log(TNF- α): none; log(sIL-2Ra): smoking status; log(IL-8): smoking status and temperature; log(IL-10): sex, antipsychotic administration, and benzodiazepine administration; *p*-values cut-off determined using the Benjamini–Hochberg procedure.

Table 3.

Estimated effects of log(IL-6) levels on total PANSS scores and subscales by group

PANSS TOTAL SCORE	Cannabinoid-negative		Cannabinoid-positive	
	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>
	−0.047 (−12.212, 8.858)	0.751	−0.283 (−20.816, −0.533)	0.040
PANSS POSITIVE SUBSCALE	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>
	0.036 (−3.620, 4.728)	0.791	−0.277 (−8.468, −0.326)	0.035
PANSS NEGATIVE SUBSCALE	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>
	−0.064 (−5.504, 3.461)	0.649	−0.303 (−8.885, −0.667)	0.024
PANSS GENERAL SUBSCALE	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>	<i>Estimated Effect (95% CI)</i>	<i>p-value</i>
	−0.071 (−7.514, 4.522)	0.620	−0.126 (−7.463, 2.955)	0.388

All models include body mass index (BMI), presence of an inflammatory disorder, and age as these variables differed between groups ($p < 0.1$). Antipsychotic administration during hospitalization before the blood draw covaried significantly with IL-6 levels and was included in every model ($p < 0.1$). Additional covariates included in each model are as follows: PANSS total, cannabinoid-negative: none; cannabinoid-positive: none; PANSS positive, cannabinoid-negative: benzodiazepine administration and hours slept; cannabinoid-positive: benzodiazepine administration; PANSS negative, cannabinoid-negative: hours slept, temperature; cannabinoid-positive: none; PANSS general, cannabinoid-negative: sex; cannabinoid-positive: none