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ORIGINAL PAPER

Cannabis use influence on peripheral brain-derived neurotrophic factor levels in antipsychotic-naïve first-episode psychosis

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Abstract

The objective of this study is to determine whether cannabis influences BDNF levels in patients with psychosis (FEP) and healthy volunteers (HV) to help understand the role of BDNF in psychosis. We assessed the association between BDNF and cannabis in a cohort of FEP antipsychotic-naïve patients and HV, whilst controlling for other potential confounding factors. 70 FEP drug-naive patients and 57 HV were recruited. A sociodemographic variable collection, structured clinical interview, weight and height measurement, substance use determination, and blood collection to determine BDNF levels by ELISA analysis were done. In FEP patients, cannabis use was associated with BDNF levels (high cannabis use was associated with lower BDNF levels). Moreover, cannabis use was statistically significantly associated with age (high use of cannabis was associated with younger age). In HV, no relationship between cannabis use and BDNF levels was observed. Otherwise, cannabis use was significantly associated with tobacco use, so that high cannabis users were also high tobacco users. This study showed a different association between cannabis use and BDNF levels in FEP patients compared with HV, particularly, with high doses of cannabis. These findings may help understand the deleterious effects of cannabis in some vulnerable individuals, as well as discrepancies in the literature.

Keywords Psychosis · Schizophrenia · BNDF · Biomarkers · Cannabis

Introduction

Schizophrenia, a heterogeneous and severe mental illness, is among the leading causes of disability worldwide [1]. Despite much research, its aetiology remains unclear; robust neurobiological markers of psychosis are essential to advance understanding [2, 3]. Brain-derived neurotrophic factor (BDNF) is a replicated biomarker associated with psychosis but the understanding of factors that might modulate BDNF levels remains limited [4, 5].

BDNF is a neurotrophin distributed throughout the central nervous system, with an especially high concentration in the hippocampus [6]. BDNF plays an important role in brain development and it has also been described for its implications in neurogenesis, neurite outgrowth, neuronal survival, and normal maturation of neurodevelopmental pathways. BDNF also plays a significant role in the adult brain, helping to regulate neuronal integrity, promote synaptic plasticity, and modulate synthesis, metabolism, and the release of neurotransmitters (dopamine, γ-aminobutyric acid, serotonin, and glutamate) [7]. All these functions make BDNF a key

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neurobiological marker in psychosis. Interestingly, peripheral BDNF levels strongly correlate with brain BDNF levels, which allow its use as a peripheral biomarker [8].

One meta-analysis [9] showed that patients with schizophrenia present moderately lower levels of peripheral BDNF, and that BDNF levels decrease at an accelerated pace with age. However, BDNF levels across the various studies included in that meta-analysis were highly heterogeneous, for reasons that remain unclear. The results of that meta-analysis showed that neither gender nor antipsychotic use had any influence on BDNF levels, in contrast to previous reports [10, 11]. Indeed, another meta-analysis showed that plasma BDNF levels increased with antipsychotic treatment, while BDNF levels decreased substantially as a function of illness duration [12].

We previously conducted a systematic review of studies comparing peripheral BDNF levels in patients with first-episode psychosis (FEP) versus healthy controls. In that review, we only included patients with FEP to avoid potential confounders such as illness duration, prolonged treatment, or comorbidities. Importantly, our findings revealed that most of the studies had observed lower peripheral BDNF levels in patients—including drug-naïve individuals—versus controls. However, most studies excluded patients who used cannabis [13]. Cannabis use is highly frequent among FEP patients, with prevalences ranging from one to two-thirds of FEP patients [14, 15], is associated with psychosis development and prognosis [16–18], and may be responsible for modifications in BDNF levels [19, 20]. Therefore, we consider assessing cannabis use essential in studies of peripheral BDNF levels in FEP. Other factors, such as body mass index (BMI) and tobacco use, have also been associated with BDNF levels [21, 22]. However, these factors have generally been neglected in studies that compare peripheral BDNF levels in patients with FEP versus controls.

Study aims

We aimed to determine whether cannabis influences peripheral BDNF levels in patients with psychosis and healthy volunteers (HV) to help understand the role of BDNF in psychosis. We assessed the association between BDNF and cannabis in a cohort of FEP antipsychotic-naïve patients and HV, whilst controlling for other potential confounding factors such as BMI, tobacco use, gender, and age.

Material and methods

Study population

A total of 70 drug-naive patients with FEP, treated between April 2013 and July 2017 at the Hospital del Mar (ETEP, Barcelona, Spain), were included in this study. Inclusion criteria for patients were: (1) age 18–35 years; (2) DSM-IV-TR criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia with less than 1 year of symptoms, or unspecified psychosis; (3) no previous history of severe neurological medical conditions or severe traumatic brain injury; (4) presumed IQ level above 80 based on clinical records (evidence from past IQ assessments or suggested by the patient's educational or employment level; and (5) no substance abuse or dependence disorder except for cannabis and/or nicotine use. None of the patients included had previously received antipsychotic medications. However, treatment with benzodiazepines was allowed.

A total of 57 HV were recruited using the same inclusion criteria for nicotine and/or cannabis abuse/dependence as for patients. HV who screened positive for any psychiatric disorder was excluded from the study.

Assessments

All participants (patients and HV) underwent a comprehensive assessment that included sociodemographic variables, a structured clinical interview for DSM-IV-TR axis I disorders for diagnosis, weight and height measurement to calculate BMI, and substance use assessment including tobacco (cigarettes per day) and cannabis use. Cannabis use frequency was recorded and grouped into one of three categories (none, low use, or high use) established in the Cannabis Experience Questionnaire (none = no use; at weekends or less frequently = low use; everyday = high use), following the procedures used in similar studies [23–25]. We also recorded the age at first cannabis use and the duration of cannabis use. The Positive and Negative Syndrome Scale (PANSS) for symptoms related to psychosis [26] and the Global Assessment of Functioning (GAF) [27] for functionality were administered in the patient group.

All subjects gave written informed consent in accordance with protocols established by the local ethics committee. This study met the ethics criteria established in the Declaration of Helsinki and fully complied with all local laws governing patient confidentiality and data protection.

Collection of blood samples and determination of BDNF levels

Fasting blood samples were obtained in the morning, upon arrival at the health center, prior to the administration of any medication. Blood samples were collected into glass K3–EDTA blood-drawing tubes for whole blood. Serum was isolated by centrifugation at 300 g for 15 min, removed and stored frozen at − 80 ºC until the analysis. All blood samples from patients and controls were obtained between 8 a.m. and 12 a.m. to avoid circadian fluctuations in BDNF

levels, which have been reported to occur in men but not in women [28]. BDNF levels were measured using a sandwich enzyme-linked immunoabsorbent assay kit according to the manufacturer's instructions (Chemikine™). Absorbencies were determined using the Wallac Victor 2 microplate reader with the wavelength set at 450 nm. BDNF concentrations were detected according to the standard curve, which was constructed from duplicate samples containing appropriate concentrations. All the samples were analyzed in duplicate. The calculated overall intra-assay variation coefficient was 3.7% and the calculated overall inter-assay variation coefficient was 8.5%; the detection limit of the BDNF assay was 15 pg/mL.

It should be noted that blood analysis of patients and controls was carried out in two different laboratories (Core Biochemical Assay Laboratory, Clinical Biochemistry, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge, UK; and Laboratory of Pharmacology Unit, Department of Medicine, Barcelona University, Barcelona, Spain). Thus, although both laboratories used the same methodology, we decided to not include the direct comparison of BDNF serum levels between patients and HV in this study.

Statistical analysis

The normality of the variables was assessed with Kolmogorov–Smirnov tests. Differences between patients and HV to assess the comparability of groups and differences in patients and HV regarding cannabis use were assessed with univariate analysis with Mann–Whitney *U* test, Chi Squared, *t* test and Kruskal–Wallis test when appropriate. We also carried out Spearman correlations between BDNF levels and cannabis age at first use and duration of use. As BDNF levels were not normally distributed, we used two robust regressions models to determine the association between cannabis and BDNF in FEP and HV. BDNF was the dependent variable and age, gender, BMI, and cannabis were the independent variables. We used STATA, v.15 (StataCorp, College Station, TX, USA) to perform statistical analyses. *P* values ≤ 0.05 were considered statistically significant.

Results

FEP patients

A total of 70 patients were included in this study. Most (60%) of the patients were males. The median age was 23.5 years (interquartile range (IQR) = 23.68–26.29). The mean (SD) duration of untreated psychosis (DUP) was 124.8 days (198.1). Median BNDF levels were 39.58 pg/mL (IQR = 39.42–51.69). In relation to cannabis use, the mean duration of use was 3.32 years (1.67) and the mean age at first use was 17.67 years (3.02). The other clinical characteristics of the sample are displayed in Tables 1 and 2.

The univariate analysis showed that cannabis use was associated with BDNF levels in FEP patients. High cannabis use was associated with lower BDNF levels ($x^2 = 9.24$; $p = 0.01$) (post hoc: *no vs. low* $U = 153$, $Z = -1.734$, $p = 0.083$; *no vs. high* $U = 199$, $Z = -2.975$, $p = 0.003$; *low vs. high* $U = 161$, $Z = -0.74$, $p = 0.472$) (Table 3). Cannabis use was also statistically significantly associated with age. High use of cannabis was associated with younger age ($x^2 = 6.32$; $p = 0.042$) (post hoc: *no vs. low* $U = 167.5$, $Z = -1.388$, $p = 0.165$; *no vs. high* $U = 230.5$, $Z = -2.45$ $p = 0.014$; *low vs. high* $U = 160$, $Z = -0.773$, $p = 0.455$). We found no other clinical characteristics associated with cannabis use in patients. Neither cannabis age at first use ($r = 0.06$, $p = 0.98$) nor duration of use ($r = 0.157$, $p = 0.498$) were associated with BDNF levels in patients.

The robust regression analysis (Table 4) showed that high cannabis use was associated with lower BDNF levels in patients (B = 31.4; 95% CI −60.1 to −2.7; $p = 0.006$). A trend was also found between low cannabis use and lower BDNF levels in patients (B = −16.5; 95% CI −33.34 to 0.24; $p = 0.055$).

Healthy volunteers

A total of 57 HV were included in this study. Most (75.44%) of them were males and the median age was 22 years (IQR = 21.91–24.37). Median BDNF levels were 216 pg/mL (IQR = 220.35–318.46). In relation to cannabis use, the mean duration of use was 4.58 years (2.53) and the mean age at first use was 15.76 years (3.11). The other clinical characteristics of the sample are displayed in Table 2.

The univariate analysis showed no relationship between cannabis use and BDNF levels ($p = 0.501$). The analysis showed that cannabis use was significantly associated with tobacco use, so that high cannabis users were also high tobacco users ($x^2 = 23.92$; $p < 0.005$) (post hoc*:* *no vs. low* $U = 156$, $Z = -2.923$, $p = 0.003$; *no vs. high* $U = 36$,

Table 1 Clinical characteristics of first-episode patients (FEP)

DUP (m, sd)	124.74 (198.07)
PANSS total (m, sd)	91.71 (18.1)
PANSS positive (m, sd)	28 (6.72)
PANSS negative (m, sd)	21.37 (15.72)
PANSS general pathology (m, sd)	45.56 (9.21)
GAF (m, sd)	31.42 (11.89)

DUP duration untreated psychosis, *PANSS* positive and negative symptom scale, *GAF* general assessment functioning, *m* mean, *sd* standard deviation

Table 2 Characteristics of first-episode patients (FEP) and healthy volunteers (HV)

	Patients (*N*=70)	Healthy volunteers (*N*=57)	Chi squared	Mann–Whitney *U* test	*p*
Age, years (Me, IQR)	23.5 (23.68–26.29)	22 (21.91–24.37)		1619.5	0.068
Sex (%)			3383		0.066
Male	42 (60.00)	43 (75.44)			
Female	28 (40.00)	14 (24.56)			
BMI (Me, IQR)	21.43 (21.61–23.16)	22.37 (22.42–25.05)		1680.5	0.127
Tobacco use, cig/day (Me, IQR)	2,83 (1.01–4.64)	2.26 (1.09–3.44)		1816.5	0.245
Cannabis use (%)			2.94		0.23
No use	30 (42.86)	24 (42.11)			
Low use	15 (21.43)	19 (33.33)			
High use	25 (35.71)	14 (24.56)			

N sample size, *p* significance level, *Me* median, *IQR* interquartile range, *BMI* body mass index

$Z = -4.988$, $p < 0.005$; *low vs. high* $U = 75.5$, $Z = -2.228$, $p = 0.035$).

We also did not find any association between BDNF levels and cannabis age at first use ($r = 0.224$, $p = 0.21$) or duration of use ($r = 0.002$, $p = 0.992$).

The robust regression analysis (Table 4) showed no statistically significant association between serum BDNF levels and the variables in the healthy volunteer group.

Discussion

The present study aimed to determine the association between cannabis use and BDNF levels in antipsychotic-naïve FEP patients and HV. We found that low BDNF levels were significantly associated with high cannabis use, and marginally associated with low cannabis use in patients with FEP. None of the other variables were associated with BDNF, neither in patients, nor in healthy volunteers.

Few studies have investigated the relationship between cannabis use and peripheral BDNF levels in HV and FEP. Animal studies have shown that BDNF is elevated in multiple brain areas following THC exposure [29], particularly in the hippocampus [30]. Interestingly, a study [31] that compared adolescent wild-type mice and disrupted-in-schizophrenia-1 (DISC-1) dominant-negative (DN) mice (a mouse model for mental illness induced by environmental insults during brain development), showed that robust subchronic administration of THC during adolescence increased hippocampal BDNF expression in healthy mice but not in DISC-1–DN mice. This increase in BDNF was associated with a reversal of the deleterious effects of cannabis on memory impairment and synaptic plasticity [31]. Those authors concluded that—in genetically vulnerable animals—an inability to increase BDNF levels to compensate for the effects THC after robust, chronic administration of that substance during adolescence, could lead to deleterious THC-related effects. Our results reveal some similarities with that study: we also found a differential association between cannabis use and BDNF levels in patients and HV. This differential expression of BDNF in patients—or genetically susceptible individuals—versus healthy volunteers in response to THC doses, especially high doses, could explain the harmful effects of THC, especially in susceptible individuals, potentially leading to cognitive deficits, mental dysfunction, and even psychosis. A different study conducted in humans [17] showed that acute, but not chronic, exposure to THC was associated with an increase in BDNF levels. These results could also be in line with ours. One could interpret that the increase in BDNF levels is a homeostatic response to cannabis exposure, and that chronic users, and especially vulnerable individuals would have had an exhaustion effect, although this is just and speculation. The finding that especially high cannabis use is associated with lower BDNF levels is also consistent with data showing that cannabis-associated psychosis has been linked to high doses of that drug [17, 23]. Nevertheless, it is important to highlight that with the present design it remains unclear whether the association between changes in BDNF levels and cannabis is causal or represents an epiphenomenon.

In contrast to our findings, Jockers et al. [20] found higher serum BDNF levels in cannabis-using FEP patients when compared to both non-using patients and matched healthy volunteers. The reason for the discrepancy between their findings and ours remains unclear. However, differences in the genetic characteristics of the sample [32] and methodological procedures (e.g., fasting conditions or variations in time of day of extraction) may have contributed to this discrepancy [33].

We found no association between tobacco use and peripheral BDNF levels. In rats, an increase in BDNF levels with chronic nicotine administration [34], and a decrease in

Table 3 First-episode patients (FEP) and healthy volunteers (HV) characteristics regarding cannabis use

	Healthy volunteers					Patients				
	No user (*N*=24)	Low user (*N*=19)	High user (*N*=14)	Chi Squared	*p*	No user (*N*=30)	Low user (*N*=15)	High user (*N*=25)	Chi Squared	*p*
Age, years (Me, IC)	23.5 (22.52–26.31)	22 (20.79–24.58)	20 (18.44–24.71)	5.32	0.07	26 (24.5–29.03)	23 (21.69–26.93)	22 (21.4–25.16)	6.32	0.042
BMI (Me, IC)	22.29 (22.15–27.56)	22 (20.89–24.45)	23.56 (21.45–24.06)	1.45	0.483	21.22 (20.92–23.63)	22.92 (20.9–24.6)	21.6 (21.14–23.45)	0.45	0.799
Tobacco use, cig/day (Me, IC)	0 (0)	2.58 (0.34–4.82)	4.5 (2.43-9)	23.92	< 0.005	1.87 (0.13-3.87)	4.33 (0.83–9.49)	3.08 (0.58–6.74)	1.22	0.543
BDNF serum levels, pg/mL (Me, IC)	308 (216.39–369.52)	174 (172.21–326.64)	186 (124.84–387.45)	1.38	0.501	48.66 (46.41–67.53)	39.29 (29.59–50.33)	34.38 (26.58–43.88)	9.24	0.01
DUP (m, sd)						100 (182.25)	106.13 (197.39)	126.68 (196.29)	0.71	0.701
PANSSP (m, sd)						26.5 (6.1)	22.2 (7.02)	25.92 (6.95)	4.01	0.135
PANSSN (m, sd)						20.57 (10.54)	15.53 (7.32)	17.68 (7.07)	3.14	0.208
PANSSGP (m, sd)						45.13 (7.25)	42.47 (10.39)	44.28 (10.82)	3.65	0.161
PANSST (m, sd)						91.87 (19.18)	80.27 (21.11)	87.88 (18.85)	1.64	0.44
GAF (m, sd)						32.3 (10.76)	31.67 (12.05)	29.84 (10.32)	1.3	0.522

N sample size, *p* significance level, *Me* median, *IQR* interquartile range, *m* mean, *sd* standard deviation, *BMI* body mass index, *BDNF* brain-derived neurotrophic factor, *DUP* duration untreated psychosis, *PANSS* positive and negative symptom scale (*P* positive, *N* negative, *GP* general pathology, *T* total), *GAF* general assessment functioning

Table 4 Robust regression in first-episode patients (FEP) and healthy volunteers (HV)

	Patients		Healthy volunteers	
	(Adjusted B)	*p*	(Adjusted B)	*p*
Age, years (m, sd)	−0.27 (−1.48 to 0.93)	0.654	−0.66 (−13.31 to 11.99)	0.917
Sex (%)				
Male	0		0	
Female	−3.33 (−16.15 to 9.49)	0.606	−2.54 (−133.56 to 128.47)	0.969
BMI (m, sd)	0.53 (−1.45 to 2.51)	0.594	0.7 (−10.97 to −12.37)	0.904
Tobacco use, cig/day (m, sd)	0.7 (−0.14 to 1.55)	0.102	0.4 (−14.19 to 14.99)	0.956
Cannabis use (%)				
No use	0		0	
Low use	−16.5 (−33.34 to 0.24)	0.055	−45.64 (−182.33 to 91.05)	0.506
High use	−21.13 (-35.92 to −6.35)	0.006	−63.14 (−230.2 to 103.97)	0.451

B regression coefficient, *p* significance level, *m* mean, *sd* standard deviation, *BMI* body mass index

BDNF mRNA levels in rat hippocampus after acute nicotine administration have been reported [35]. Other studies conducted in humans have observed that heavy smokers had higher BDNF levels compared to non-smokers, whereas no difference was observed in light smokers [36]. The differences with our results could be explained by total smoking years, as it has been related as a significant predictor of serum BDNF levels in healthy controls [37]. Our patients were young adults, and they probably have not been smoking for a long time, although we do not have exact data on this matter. Finally, one study in patients with schizophrenia has reported higher peripheral BDNF levels in tobacco-using patients [21]. Several factors could explain the discrepancies between our findings and those reported by Zhang et al. [21]. In addition to the smoking years, Zhang and colleagues included chronic patients on antipsychotic treatment whereas we did not. In this sense, we have to take into account that although the meta-analysis performed by Green et al. [9] was unable to find any effect of antipsychotic treatment on BDNF levels, another meta-analysis did find such an effect [12].

We found no association between peripheral BDNF levels and BMI in either patients with FEP or HV. However, a study conducted in rats reported lower body weight and appetite suppression with BDNF infusion into the rat brain [38]. Another study with healthy human participants found a negative correlation between BDNF levels and body weight, BMI, and cholesterol levels [39]. Moreover, Yang et al. [22], in a study involving chronic schizophrenia patients, reported a significant inverse correlation between BMI and peripheral BDNF levels, but only in female patients. Another study [40] found that lower serum BDNF levels were associated with antipsychotic-induced weight gain in schizophrenia patients.

Again, the lack of significant association between these factors in our study versus other studies could be explained by different factors. First, in healthy volunteers, the lack of differences could be explained by their young age and low BMI. Moreover, there are more males than females, and it has been shown that the association between BNDF levels and BMI is more powerful in females, especially during the menstrual cycle [22, 39]. Second, in patients, it is important to remark that other studies included chronic schizophrenia patients under long-term antipsychotic treatment [41–43].

Strengths and limitations

The present study has several strengths: we included a large number of first-episode antipsychotic-naïve patients, a sample particularly difficult to recruit, because once psychosis is identified, medication is generally given quite rapidly. In addition, our methodology was original, in the sense that we assessed BDNF levels in patients and HV, whilst adjusting their determinants for several confounding factors (e.g., cannabis, tobacco use, and BMI). Indeed, these factors have generally been neglected in current research.

However, we acknowledge some limitations to this study. First, we did not assess the composition of the cannabis used, which could have affected our results. Cannabis contains a variety of cannabinoids, which can be found in different ratios and have different biological actions; while tetrahydrocannabinol (THC) is the main intoxicating component, associated with its psychogenic effects, cannabidiol seems to counteract THC's effects [44]. In addition, physical exercise may influence BDNF levels [45]. Although this has not been demonstrated yet [46, 47], a recent study described lower BDNF levels in physically active chronic cannabis users compared to non-users [48]. Nevertheless, we did not assess this variable in our study and it could have affected our results. Besides, we did not account menstrual cycle in relation to blood collection in females, and it has been shown that this could influence also in BDNF levels [22, 39]. Furthermore, different laboratories were used for FEP and HV, so although we used the same methodology, we could not directly compare BDNF levels between them. Moreover, we only have measured mature BDNF levels, without

its precursor, proBDNF. It is known that both forms have differential effects in the CNS though different receptors [49–52], so this fact could influence our results too. As well, we acknowledge multiple testing but note that our largest and statistically significant effects have biological plausibility in that they involved the highest cannabis use category. Finally, our results warrant replication using larger samples.

Conclusions

The present study showed a different association between cannabis use and BDNF levels in first-episode patients compared with healthy volunteers, particularly, with high doses of cannabis. These findings may help understand the deleterious effects of cannabis in some vulnerable individuals. Physicians should advise their patients about the risks of cannabis use.

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Compliance with ethical standards

Conflict of interest Dr. Mané and Dr. Bergé have received financial support to attend meetings, travel support, and served as a speaker from Otsuka and Janssen Cilag. Dr. Fernandez-Egea has received consultant fees from Recordati and Angelini. The other authors of this manuscript do not have any conflicts of interest.

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