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Association of extent of cannabis use and psychotic like intoxication experiences in a multi-national sample of First Episode Psychosis patients and controls

Running Title:

Cannabis Intoxication in First Episode Psychosis

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Abstract:

Background: First Episode Psychosis (FEP) patients who use cannabis experience more frequent psychotic and euphoric intoxication experiences compared to controls. It is not clear whether this is consequent to patients being more vulnerable to the effects of cannabis use or to their heavier pattern of use. We aimed to determine whether extent of use predicted psychotic-like and euphoric intoxication experiences in patients and controls and whether this differs between groups.

Methods: We analysed data on patients who had ever used cannabis (n=655) and controls who had ever used cannabis (n=654) across 15 sites from six countries in the EU-GEI study (2010-2015). We used multiple regression to model predictors of cannabis-induced experiences and to determine if there was an interaction between caseness and extent of use.

Results: Caseness, frequency of cannabis use and money spent on cannabis predicted psychotic-like and euphoric experiences ($p \leq 0.001$). For psychotic-like experiences there was a significant interaction for caseness x frequency of use ($p<0.001$) and caseness x money spent on cannabis ($p=0.001$) such that FEP patients had increased experiences at increased levels of use compared to controls. There was no significant interaction for euphoric experiences ($p>0.5$).

Conclusions: FEP patients are particularly sensitive to increased psychotic-like, but not euphoric experiences, at higher levels of cannabis use compared to controls. This suggests a specific psychotomimetic response in FEP patients related to heavy cannabis use. Clinicians should enquire regarding cannabis related psychotic-like experiences and advise that lower levels of cannabis use are associated with less frequent psychotic-like experiences.

Keywords: schizophrenia, psychotic-like experiences, psychotomimetic, substance abuse

Association of extent of cannabis use and psychotic like intoxication experiences in a multi-national sample of First Episode Psychosis patients and controls

Introduction

There is consistent evidence supporting an association between cannabis use and later psychosis(Myles, Myles, & Large, 2015). Further, patterns of cannabis use in first episode psychosis (FEP) patients are greater in terms of quantity, frequency and potency of cannabis used compared to controls from the same population(Di Forti et al., 2015; Hasan et al., 2019; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016). There is converging evidence that cannabis is a component cause of psychotic disorder with well-replicated evidence of dose-response effects on psychotic outcomes(Marconi et al., 2016; Moore et al., 2007; Murray & Di Forti, 2016; Ortiz-Medina et al., 2018; Schoeler et al., 2016).

When discussing psychosis and cannabis use, it is important to differentiate between psychotic-like experiences (PEs) and clinical psychotic disorder. Clinical psychotic disorder is relatively rare (incidence 21.4-26.6 per 100,000 person years(Jongsma et al., 2018; Jongsma, Turner, Kirkbride, & Jones, 2019)) whereas PEs are common and self-limiting (incidence 3,000 per 100,000 person-years(J van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009)) but can be a harbinger of more serious disorder(Werbeloff et al., 2012). However, the usual instruments for measuring PEs, such as the Peter's Delusions Inventory (PDI) or the Community Assessment of Psychic Experience (CAPE), either do not specifically index drug-induced experiences as part of the intoxication state(Stefanis et al., 2002) or specifically exclude them(E. Peters, Joseph, Day, & Garety, 2004; E. R. Peters, Joseph, & Garety, 1999).

Recreational drugs such as cannabis are used primarily for their immediate psychoactive effects. Factor analytic approaches have clustered cannabis intoxication experiences into psychotic-like experiences (cPLEs) and euphoric experiences (cEEs)(E. J. Barkus, Stirling, Hopkins, & Lewis, 2006a; Quinn, Wilson, Cockshaw, Barkus, & Hides, 2016). cPLEs (sometimes called psychotomimetic experiences) are worthy of study in their own right as a model for psychotic disorder. cPLEs are increased in patients versus controls(Bianconi et al., 2016; D'Souza et al., 2005); increased in those with schizotypy and those at risk of schizophrenia(E. J. Barkus et al., 2006a; Stirling et al., 2008; Vadhan, Corcoran, Bedi, Keilp, & Haney, 2017). cPLEs may predict cessation of use in a non-clinical sample(Sami, Notley, Kouimtsidis, Lynskey, & Bhattacharyya, 2018) whereas patients with psychotic disorders report using cannabis for affect regulation and socialization, despite awareness that cannabis has a detrimental effect on positive symptoms of psychosis(Dekker, Linszen, & De Haan, 2009).

One study to date has reported that patients experience both cPLEs and cEEs more frequently than controls but this did not take into account increased use in patients(Bianconi et al., 2016). Given that both increased rates of cannabis use and increased cannabis experiences are seen in FEP, it is not yet clear how these relate to each other and whether this differs from that of controls. No study to date has examined specifically the relationship between extent of use, cannabis experiences and psychotic disorder.

We therefore studied cannabis experiences in a large international sample of FEP patients and control lifetime cannabis users. To index these experiences we used the Cannabis Experiences Questionnaire an instrument specifically developed to assess retrospective cannabis experiences(E. J. Barkus et al., 2006a; Stirling et al., 2008). We hypothesised that: (a) we would replicate the finding of increased cPLEs and cEEs in FEP patients versus controls; (b) extent of use (as indexed by frequency of use, money spent on cannabis, and potency) would be associated with more frequent cannabis-induced experiences when adjusted for confounders; and (c) this effect would differ between cases and controls: specifically that both cPLEs and cEEs would be more affected by heavy use in FEP patients versus controls. We included THC potency as a proxy of the dose of Δ^9-tetrahydrocannabinol the primary psychomimetic constituent in cannabis(Morrison et al., 2009).

Methods:

The European network of national networks studying gene environment interactions in schizophrenia (EU-GEI) study is a multi-centre study comprising several workpackages(Jim Van Os et al., 2014). Workpackage 2 comprises a 17 centre study across six countries (United Kingdom, Holland, Spain, France, Italy, Brazil) on first episode psychosis. Local Research Ethics Committee approval was obtained from each area.

Sample selection: Patients and controls were recruited between May 2010 and May 2015. Patients were identified by trained EUGEI researchers across the 17 sites and invited by clinical teams to participate. For patients inclusion criteria were: (i) age 18-64; (ii) presentation with First Episode psychosis (ICD-10 F20-33); and (iii) residence within each defined locality. Exclusion Criteria were: (i) organic psychosis (ICD-10: F09); (ii) psychosis due to acute intoxication (ICD-10: F1X.5) and (iii) previous contact with mental health services for psychosis. For full diagnostic data see sTable 1 (Supplement).

Controls were recruited using a quota strategy derived from local demographic data to be representative for age, sex and ethnicity of the population at risk for each site. In order to sample controls in the first instance we undertook random sampling a) from lists of all postal addresses and b) from GP lists from randomly selected surgeries. The EUGEI study aimed to over-sample certain groups (e.g. young men) using direct approaches such as local avertismenets and leaflets at local shops and community centers. Controls were excluded if they had received a diagnosis or treatment for psychotic disorder.

Further details of the EUGEI study have previously been described(Jongsma et al., 2018). For the purpose of this study, analysing cannabis experiences, we only analysed data from participants (both patients and controls) who reported having ever used cannabis (lifetime use).

We did not use data from two centres: Maison-Blanche (France) as this centre did not collect controls and Verona (Italy) as cannabis use data were not complete. We excluded 12 cases (1.8%) who were classified as having non-psychotic illness from the *Diagnosis and Statistical Manual IV* (DSM-IV) Operational Criteria Checklist (OPCRIT) screening of medical records.

Measures:

Demographics: data were collected on age, sex, ethnicity, site, country and years of education.

Cannabis use: A modified version of the Cannabis Experiences Questionnaire was used to collect cannabis use variables and cannabis experiences data(E. J. Barkus, Stirling, Hopkins, & Lewis, 2006b). This is a researcher administrated measure which collects self-reported data on: age of first use, frequency of use (categories: every day; more than once a week; a few times a month; a few times each year; only once or twice), average money spent in a week (categories: less than €2.50; €2.50-€5.00; €5.00-€10.00, €11.00-€15.00; €16.00-€20.00; and 6 above €20).

Potency: Since there is geographical variation in type of cannabis used we used an approach to determine users of low potency and high potency cannabis as has been reported before in the EUGEI study. Breifly participants were asked to name the strain they most often used in their own language. Strains were compared to mean reported THC concentration from published data from European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)(European Monitoring Centre for Drugs and Drug Addiction, 2016). High potency cannabis was categorized as THC>=10%: including UK home-grown skunk/sensimilla UK Super Skunk, Italian home-grown skunk/sensimilla , Italian Super Skunk, the Dutch Nederwiet, Nederhasj and geimporteerde hasj, the Spanish and French Hashish (from Morocco); or '*low potency*' with mean THC<10% including: hash/resin from UK and Italy, imported herbal cannabis from UK, Italy, Spain and France, Brazilian marijuana and hash and the Dutch Geimporteerde Wiet . For further details see (Di Forti et al., 2019)

Other drug use: We collected data on number of other drugs used, number of cigarettes smoked per day and units of alcohol consumed daily.

Cannabis Experiences: Frequency of nine intoxication experiences - six cPLEs (feeling fearful; feeling crazy or mad; feeling nervy; feeling suspicious; hearing voices; seeing visions); and three cEEs (feeling happy; understanding the world better; being full of plans or ideas) were rated on a 5 point Likert scale: (0 rarely or never, 1 from time to time, 2 sometimes 3 more often than not, 4 almost always). These experiences were chosen as previous factor analytic approaches in development of the Cannabis Experiences Questionnaire showed that these experiences load significantly onto respective subscales to index psychotic-like experiences and pleasurable effects(E. Barkus & Lewis, 2008; Stirling et al., 2008).

Statistical Analysis: Scores were obtained for cPLEs and cEEs by simple summation, as previously undertaken(E. J. Barkus et al., 2006b; Sami et al., 2018). As there were half as many euphoric experiences items as psychotic like experiences items, the scores for euphoric experiences were doubled rendering a scale of between 0 and 24 for both cPLEs and cEEs. Since such experiences can be conceptualised to index an underlying continuum both cPLEs and cEES were treated as continuous variables.

Extent of use was indexed primarily by frequency of cannabis use and by potency. In further sensitivity analysis we replaced these with money spent on cannabis use. We calculated Pearson's Correlation coefficients to test whether the extent of use variables were correlated.

Demographics and substance use: We ascertained differences between demographic (age at assessment, sex, ethnicity, years in education, site) and cannabis use parameters (age of first use, frequency of use, money spent per week, potency, duration of use, lifetime and 12 month dependence) and other drug use parameters (cigarettes per day, units of alcohol in a day, and other drugs ever used (excluding cannabis, alcohol, tobacco and caffeine)) using t-tests for continuous variables and chi-squared for categorical variables.

Main Analysis:

We undertook to test the three hypotheses in a regression analyses framework. To test hypothesis (a) that caseness predicts experience: we regressed cannabis experiences (cPLEs and cEEs) as the dependent variables and caseness as the independent variables. To test hypothesis (b) that extent of use predicts experiences: we regressed cannabis experiences as the dependent variables and the extent of use variables as the independent variables. As the extent of use variables we entered frequency of cannabis use, and THC potency into separate models. These two variables (frequency of use and potency) were chosen to primarily index extent of use as they are both related to the extent of cannabis exposure but are distinct behaviours (for example one can use very frequently but at low potency). To test hypothesis (c): that there is an interaction between caseness and extent of use on cannabis experiences: we regressed cannabis experiences as the dependent variables and caseness and the extent of use variables alongside the interaction of caseness x extent of use. In all models we entered cPLEs as a regressor when the dependent variable was cEEs and cEEs as a regressor when the dependent variable was cPLEs to ensure that the predictors identified for relationships were independent of the other experience.

In sensitivity analyses for hypothesis (b) and (c) we ran the same regressions models using money spent on cannabis use rather than the frequency or potency variables.

We undertook a further sensitivity analysis to adjust for confounders. Psychotic like experiences may be explained by a number of putative other confounders other than caseness or extent of use. We hence adjusted for firstly demographic variables (age, sex, ethnicity) in secondary models and further to this substance misuse confounders in tertiary models (number of other drugs ever used, tobacco use and alcohol use) as other substance misuse may arguably be related to cannabis induced experiences to see if interaction effects survived putative confounders.

Finally we undertook a supplementary analysis to see if interactions for other classes of drugs were present on cPLEs. This analysis did not change the main findings reported in the manuscript and is reported in full in the Supplement.

cPLEs and cEEs demonstrated positive skew (cEEs 0.612, cPLEs 2.231). Because of violations of homoscedasticity in regression models we undertook all analyses using the robust regression option in STATA. For the purpose of estimation of 95% Confidence Intervals (see Figure 1) we applied bootstrapping to inferential tests using 1000 samples and bias corrected and accelerated confidence intervals.

Missing data: Missing data rates are shown in Supplementary Table 4. cPLEs were available for 598/655 (91.3%) cases and 615/654 (94.0%) controls whereas cEEs scores were available for 602/655 (91.9%) cases and 616/654 (94.2%) controls.To ensure that results were not the result of systematic missing data, missing data was imputed using imputation analysis with chained equations(Azur, Stuart, Frangakis, & Leaf, 2012) for cPLEs and and cEEs as outcome variables, independent and auxillary variables. 29 variables were included in the imputation model, including cannabis use variables (age of first use, social use, frequency, money spent, diagnosis of misuse), other drug use variables (tobacco use, alcohol use, number of other drugs used), and demographic variables (sex, age, ethnicity, site, psychosis diagnosis). Fifty datasets were imputed with 10 cycles.

Regression and main analyses were run using the imputed dataset to account for missing data. Exploratory pairwise correlation between the extent of use variables was undertaken listwise since pairwise correlation is not available using the *mi estimate* command in STATA. Data was analysed using STATA version 15.

Results

Data were available for 1035 cases patients and 1382 controls. 655 cases (63.3% of all cases) and 654 controls (47.3% of all controls) reported ever use of cannabis and data analysis was restricted to them.

Baseline demographics:

Cases were significantly more likely than controls to be male, younger and have had fewer years of education (see Table 1a). As expected, cases were more likely to have started using cannabis younger, more likely to have used more frequently, to have used more other drugs, and smoked more cigarettes per day (see Table 1b). Detailed diagnostic, ethnicity and site data are presented in Supplementary Tables 1-3.

Extent of use:

As expected the variables indexing extent of use were significantly correlated. Frequency of use weakly correlated with dichotomised potency ($r=0.121$, $p=0.001$). Frequency of use strongly correlated with with money spent on cannabis per week ($r=0.703$, $p<0.001$) whereas potency moderately correlated with money spent on cannabis ($r=0.211$, $p<0.001$).

Caseness by frequency of use on cPLEs and cEEs (hypothesis a):

As hypothesised caseness predicted cPLEs independent of cEEs ($b=0.826$, $t=7.86$, $p<0.001$) and predicted cEEs independent of cPLEs ($b=0.840$, $t=4.40, p<0.001$) such that patients had both more frequent psychotic-like and euphoric experiences than controls.

Extent of use as a predictor of cPLEs and cEEs (hypothesis b):

As hypothesised extent of use predicted cPLEs independent of cEEs whether the extent of use variable was frequency of use ($b=0.502$, $t=6.18$, $p<0.001$), or potency ($b=0.543$, $t=2.36$, $p=0.019$) such that increased extent of use predicted increased psychotic-like experiences. Similarly frequency of use predicted cEEs independent of cPLEs ($b=2.17$, $t=21.46$, $p<0.001$) but this was not the case with potency ($b=0.210$, $t=0.55$, $p=0.58$).

Sensitivity analysis (hypothesis b):

For cPLEs results were the same when extent of use was indexed by money spent on cannabis per week ($b=0.397$, $t=6.17$, $p<0.001$) such that money spent predicted increased psychotic-like experiences. Similarly for cEEs increased money spent on cannabis predicted cEEs independent of cPLEs ($b=1.24$, $t=13.64$, $p<0.001$).

Interaction Effects (hypothesis c):

Model parameters for caseness by extent of use and their interaction on predicting cannabis psychotic-like experiences can be seen in Table 2 and caseness x extent of use scores for mean experiences are shown in Figure 1.

Caseness x frequency of use on cPLEs:

There was a significant caseness effect ($b=1.354$, $t=6.20$, $p=0.001$); a significant effect for increased frequency of cannabis use ($b=0.794$, $t=4.74$, $p<0.001$); and a significant interaction between group and frequency such that increasing frequency was associated with increased difference in cPLEs between cases and controls (b=0.229, t=3.49, p=0.001).

Caseness x potency on cPLEs:

There was no significant effect of caseness (p=0.676); but an effect for potency such that increased potency was associated with increased cPLEs (b=1.241, t=2.28, p=0.023); and a significant interaction for caseness by potency (b=0.438, t=2.04, p=0.042).

Caseness x extent of use variables on cEEs:

There was evidence for increased euphoric experiences as cannabis use increased frequency (b=2.152, t=9.44, p<0.001) but not for potency (p=0.935). There was no significant interaction for either frequency or potency of cannabis use x caseness for cEEs as the dependent variable.

Sensitivity analysis (hypothesis c):

Caseness x money spent on cPLEs: There was no significant effect of caseness (p=0.112); but there was a significant effect for money spent such that cPLEs increased with more money spent (b=0.591, t=4.56, p=0.001); and a significant interaction between caseness and money spent such that more money spent was associated with increased difference in cPLEs between cases and controls (b=0.177, t=3.29, p=0.001).

Caseness x extent of use variables on cEEs: There was evidence for increased euphoric experiences as cannabis use increased for money spent (b=1.109, t=5.75, p<0.001). There was no significant interaction for any of the extent of use variables x caseness for cEEs as the dependent variable.

Sensitivity analysis: Adjustment for demographic and substance use covariates:

In secondary models we adjusted models for cPLEs as the dependent variables for demographic covariates: the interaction terms remained significant for caseness x frequency of use (b=0.207, t=3.19, p=0.001); caseness x money spent on cannabis (b=0.163, t=3.07, p=0.002); caseness x potency (b=0.446, t=2.08, p=0.038). In tertiary models we additionally adjusted for substance misuse covariates: the interaction terms remained significant for caseness x frequency of use (b=0.208, t=3.23, p=0.001) and caseness x money spent on cannabis (b=0.176, t=3.30, p=0.001); caseness x potency (b=0.441, t=2.08, p=0.038). We conclude that the caseness x extent of use interaction for increased cPLEs for patients versus controls is robust to a number of demographic and substance use confounders.

Discussion:

To our knowledge, this represents the largest case-control study with extensive cannabis data in First Episode Psychosis ever undertaken. We (a) replicate the finding that cannabis intoxication experiences are more frequent in patients compared to controls; (b) show that extent of use as indexed by frequency of use and money spent on cannabis per week predict these experiences and (c) show that there is an interaction between caseness x frequency and caseness x money spent such that increasing levels of use are associated with more frequent psychotic-like experiences (but not euphoric experiences) in patients compared with controls. Importantly our findings are robust to a number of putative confounders including age, sex, gender and other substance use which would not explain any of these. Additionally we observe that these findings remains after accounting for various comorbid substance use parameters.

Importantly, these findings indicate that cannabis related experiences change as a function of extent of use. The Cannabis Experiences Questionnaire provides a measure of experiences as a proportion of total cannabis use, rather than a simple count of total experiences. A maximal score for cPLEs indicates that all six psychotic like experiences were experienced every time cannabis was used whereas a minimal score indicates that these experiences were never or rarely experienced, irrespective of total number of times used. Hence higher scores indicate that the experience changes rather than simply indicating an increased total number of experiences due to increased number of times that cannabis is used.

Although not the main purpose of this analysis we also found of interest that a history of crack cocaine and inhalant abuse are associated with an increase in cannabis induced psychotic experiences whereas such experiences appear less frequent in the context of opiate abuse (see Supplement for full details). This may indicate that there is a cross sensation of drugs of abuse and is consistant with with previous literature in which whereas cannabis and cocaine use are synergistic for psychosis experiences(C. Roncero et al., 2013) whereas opiate withdrawal is associated with psychosis experiences(Casado-Espada et al., 2019; Weibel, Mallaret, Bennouna-Greene, & Bertschy, 2012), but this does not influence our main results.

This study extends previous work(Bianconi et al., 2016) by showing that extent of use is a key predictor of psychotic-like experiences and that FEP patients and controls have divergent experiences with increasing extent of use. Interestingly, the same relationship does not hold for euphoric experiences as cEEs scores, when stratified by extent of use, are well-matched between cases and controls. This suggests that specific mechanisms underlie the cannabis-related increases of psychotic-like experiences which may be related to genetic predisposition and may further support a GxE interaction as has been demonstrated on cannabis use with the risk of schizophrenia spectrum disorder(Guloksuz et al., 2019). One putative mechanism to be examined is that variation in the DRD2 and possibly AKT1 genes may render cases more likely to develop postsynaptic supersensitivity(Colizzi et al., 2015; Morgan, Freeman, Powell, & Curran, 2016). Further work is needed to identify the specific genetic mechanisms which interact with increased extent of use.

Perhaps somewhat surprisingly we do not find the increased levels of use are associated with reduced euphoric experiences which would have been consistant with tolerance at heavier levels of use. Rather we find the relationship to indicate the opposite direction. There could be two possible explanations to this: either that repeated cannabis use is associated with increased sensitisation rather than tolerance to such experiences, or conversely that the association exists because individuals who have more euphoric experiences are more likely to use heavier amounts of cannabis. Further work is required to disentangle these two possibilities.

Strengths and Limitations:

The particular strengths of this study are (i) the sample size and (ii) the international sample. The limitations include: (i) the cross-sectional design, (ii) the use of self report measures and (iii) the lack of laboratory tests of potency.

The cross-sectional design precludes interpretation about temporal sequence of associations, which means it is difficult to disentangle whether extent of use causes enhanced experience or vice-versa. Euphoric experiences (cEEs) are likely to drive use whereas this is not the case for psychotic-like experiences (cPLEs) which have previously been shown to be associated with subsequent discontinuing use(Sami et al., 2018; Valmaggia et al., 2014). Furthermore in the case of cPLEs we included cEEs as a covariate in the model to regress out the association with euphoria. This may tentatively suggest a role for sensatisation to increasing levels of cannabis use for cPLEs in FEP.

Both exposure and outcome measures were based on self-report. It is possible that because cannabis can be amnestic in nature exposure to cannabis may be misreported. However the relationships we report were similar for both frequency of cannabis use and money spent on cannabis per week (and it is arguable whether money spent is a more salient indicator of use than frequency of use) which increase our confidence in reporting these relationships. There are limited methods to determine extent of use over a longer period. Hair samples can provide an estimate of use over three months, but have been shown to be unreliable in a major observational study(Taylor, Sullivan, Ring, Macleod, & Hickman, 2017). Moreover, self-report (but not hair) measures of cannabis use were found to predict acute psychotomimetic responses to cannabis(Curran et al., 2018). Additionally, self-reported data on cannabis potency is associated with its concentration of THC measured in the laboratory(Freeman et al., 2014) The outcome measures, although self-reported, were based on a considerable body of work validating cannabis experiences in non-clinical, although not in clinical populations(E. J. Barkus et al., 2006b; Quinn et al., 2016). Another limitation is that the psychotic-like experiences were rated retrospectively rather than as state measures (e.g. in an experimental design administering THC).

On the other hand, a strength of utilising retrospective self-report measures is that these are the experiences patients report to their clinicians during routine consultations. There were several differences between cases and controls, but the results persisted after adjusting for a wide variety of confounders. Perhaps most importantly cEEs were the same between patients and controls when accounted for extent of use: this indicates differences in cPLEs between FEP and controls to be specific to intrinsic biological differences between groups rather than to other confounders. One further limitation is that we did not account for non-psychosis comorbidities such as ADHD which may be synergestic with substance use for a psychotic outcome, as has been shown in the context of cocaine dependence(Carlos Roncero et al., 2013). This could be undertaken in future studies.

Clinical implications:

We consider this study to have a number of important findings in the clinical context. Although easily elicitable, clinicians do not routinely inquire about cPLEs in the clinical context. Our study suggests there are important differences between FEP patients and controls. Firstly our study adds to previous work(Bianconi et al., 2016), that patients experience cPLEs more frequently than controls. Secondly our work indicates that lower extent of use is associated with decreased cPLEs. This is in line with evidence suggesting that FEP who continue to use cannabis, especially daily high potency experience more relapses and worse clinical outcome than those who stop after illness onset(Schoeler et al., 2016). Thirdly we show that FEP patients are unlikely to derive greater euphoric effects compared to controls at increased levels of use, despite more frequent psychotic-like effects. In the absence of longtitudinal data we are unable to definitively determine whether change in use effects experiences. However in the interim patients and particularly those with profound cPLEs should be advised that lower levels of use are associated with fewer psychotic-like experiences; and be advised that for high-potency cannabis there is limited evidence of added euphoric effect.

Taken together we have shown that extent of cannabis use is associated with enhanced psychotic-like but not euphoric experiences in First Episode Psychosis patients compared to controls. This may suggest a Gene x Evidence interaction for extent of use and genetic risk for psychosis on cannabis experiences. Further research should aim to determine the biological mechanism underpinning differences between patients and controls.

Conflicts of Interest:

The authors have no conflicts of interest to declare in relation to the work presented in this paper.

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Table 1a: Baseline characteristics between cases and controls

	Case	Controls	p-Value
Male	475 (72.5%)	355 (54.3%)	**<0.001**
Missing	*nil*	*nil*	
White	415 (63.6%)	547 (83.8%)	**<0.001**
Missing	*nil*	*1 (0.2%)*	
Age at first contact (x̄)	28.07		
Missing	*nil*		
Age at assessment (x̄)	28.51	34.30	**<0.001**
Missing	*nil*	*1 (0.2%)*	
Years in Education	13.31	15.69	**<0.001**
*Missing**	*12 (1.8%)*	*2 (0.3%)*	

Table 1b: Comparison of Cannabis use patterns between cases and controls

	Case	Controls	p-Value
Age first tried cbs (x̄)	16.91	17.90	**<0.001**
*Missing**	*15 (2.2%)*	*nil*	
Frequency of cbs use			
Once or twice	108 (16.9%)	240 (36.8%)	
Few times year	65 (10.2%)	120 (18.4%)	
Few times month	63 (9.8%)	100 (15.3%)	
>Once a week	110 (17.2%)	100 (15.3%)	**<0.001**
Every day	294 (45.9%)	93 (14.2%)	
*Missing**	*15 (2.3%)*	*1 (0.2%)*	
Money Spent per week on cbs			
< €2.50	217 (37.0%)	415 (68.4%)	
€2.50-€5.00	52 (8.8%)	58 (9.6%)	
€6-€10	80 (13.5%)	42 (6.9%)	
€11-€15	36 (6.1%)	25 (4.1%)	
€16-€20	39 (6.6%)	24 (4.0%)	
>€20	170 (28.6%)	43 (7.1%)	**<0.001**
Missing	*61 (9.3%)*	*47 (7.2%)*	
Use of high potency cbs	291 (55.5%)	223 (43.1%)	**<0.001**
Missing	*131 (20.0%)*	*136 (20.8%)*	
Mean Duration of cbs use (years)	9.41	9.82	0.418
Missing	18 (2.7%)	28 (4.3%)	
Current cbs use	223 (34.2%)	151 (23.1%)	**<0.001**
Missing	*2 (0.3%)*	*1 (0.2%)*	
Lifetime DSM IV cbs Dependence	247 (39.3%)	58 (8.9%)	**<0.001**
*Missing**	*26 (4.0%)*	*3/654 (0.5%)*	
Last 12 month DSM IV cbs	96 (15.0%)	12 (1.8%)	

Dependence *Missing**	*26 (5.2%)*	*3 (0.5%)*	**<0.001**
Number of other drugs tried *Missing*	1.47 *nil*	0.97 *nil*	**<0.001**
Cigarettes/Roll-ups per day† *Missing**	10.83 *19 (2.9%)*	4.42 *8 (1.2%)*	**<0.001**
Units of alcohol per day† *Missing*	5.14 *143 (21.8%)*	5.65 *88 (13.4%)*	0.251

Legend: cbs: cannabis**;** Mean numbers ($\bar{x}$)are given unless specified as a proportion. Significance testing undertaken via 2-tailed independent t-tests for continuous variables and chi-squared tests for categorical variables. Missing data rates are italicised.

* indicates significant difference ($p<0.05$) in missing data between cases and controls (chi squared test or Fisher's exact test where any single value <=5).
† Data was cleaned to remove outliers to max 40 cigarettes/day. Units of alcohol data cleaned to max of 30 units day

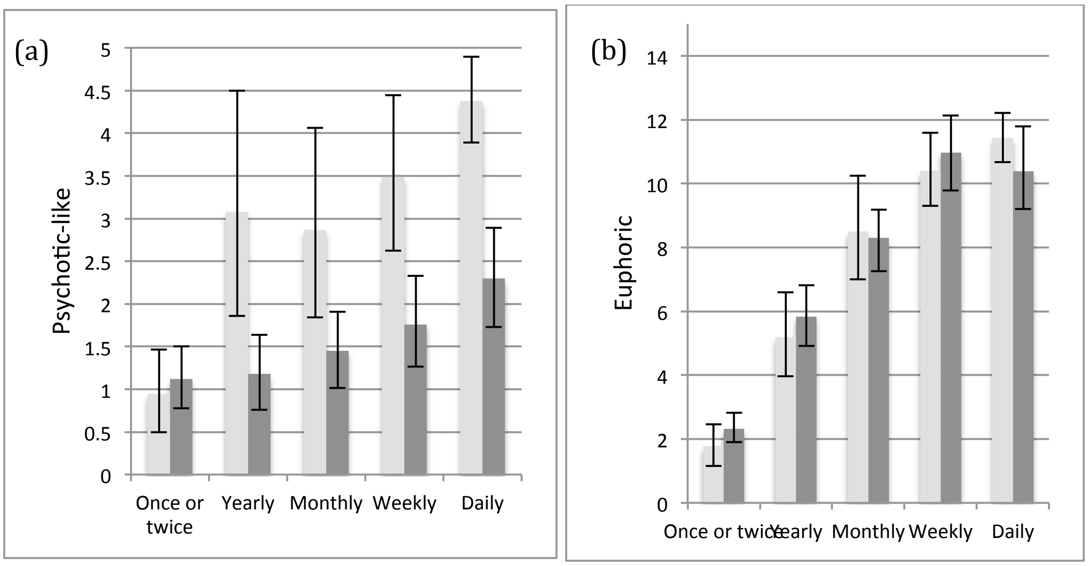
Table 2 Primary Models for cannabis-induced Psychotic-Like Experiences caseness x extent of use interaction

(i) Model 1 – Frequency of cannabis use as a predictor *F(4,1239.3)=33.65, p<0.001*			
	b	**t**	**p**
Frequency of cannabis use*	0.794	4.74	0.001
Caseness†	1.354	6.20	<0.001
Caseness x Frequency of use‡	0.229	3.49	<0.001
Cannabis-induced Euphoric Experiences	0.719	3.35	<0.001
(ii) Model 2 – Potency of cannabis as a predictor *F(4,1141.9)=27.02, p<0.001*			
	b	**t**	**p**
Potency of cannabis*	1.241	2.28	0.023
Caseness	0.142	0.42	0.676
Caseness x Potency‡	0.438	2.04	0.042
Cannabis-induced Euphoric Experiences	0.114	6.43	0.016
(iii) Model 3 – Money spent on cannabis as a predictor *F(4,1235.8)=33.35, p<0.001*			
	b	**t**	**p**
Money spent on cannabis*	0.591	4.56	<0.001
Caseness	0.267	1.59	0.112
Caseness x Money spent on cannabis‡	0.177	3.29	0.001
Cannabis-induced Euphoric Experiences	0.084	4.35	<0.001

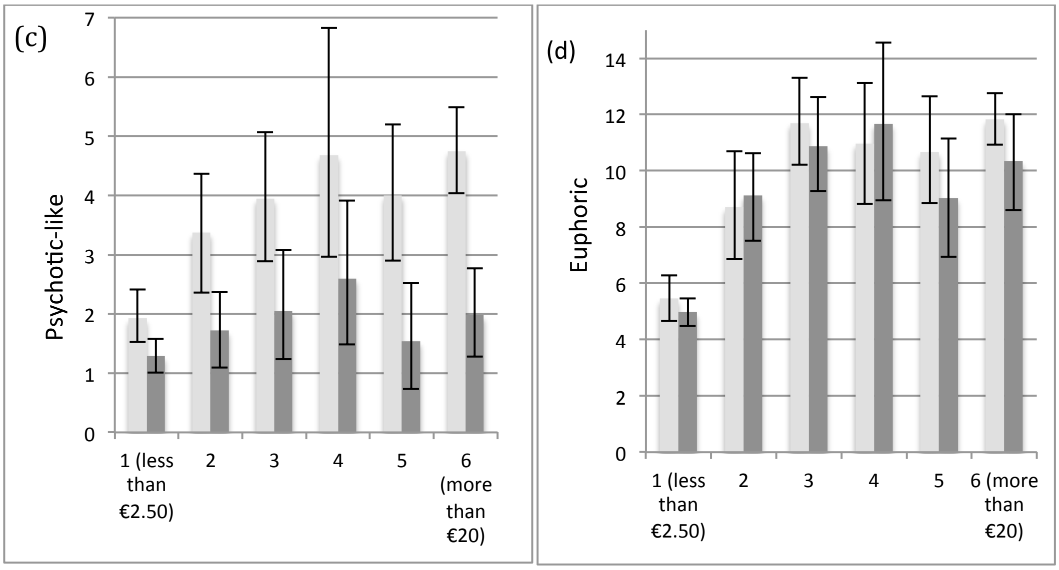
Legend:
Directions of effect as follows: *Increased extent predicts increased cPLEs; †First Episode Psychosis predicts increased cPLEs; ‡Significant caseness x extent interaction

Figure 1: Mean cannabis-induced Psychotic-like Experiences and Euphoric Experiences scores by case and control[1]

(a-b) Caseness x Frequency of cannabis use interaction on cannabis-induced experiences:

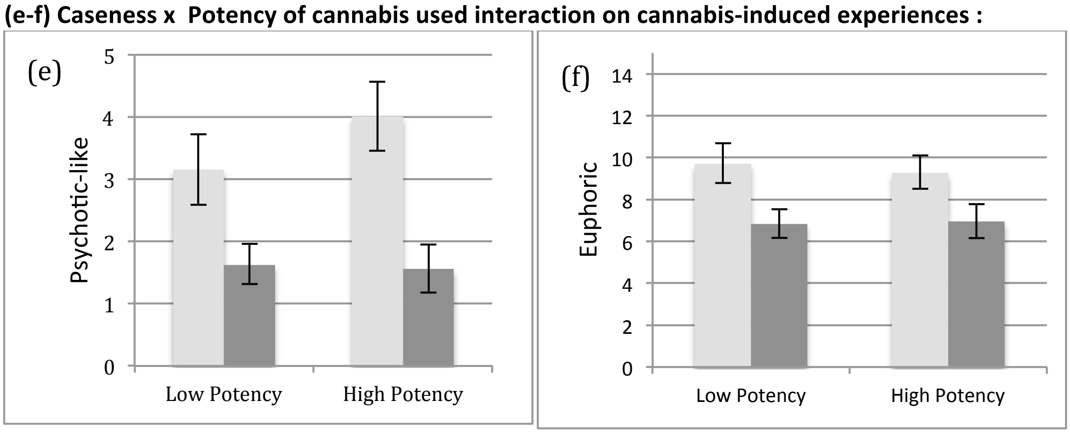


(c-d) Caseness x Money spent on cannabis per week interaction on cannabis-induced experiences:



-

(e-f) Caseness x Potency of cannabis used interaction on cannabis-induced experiences :



Legend: Light grey bars indicate First Episode Psychosis cases, dark grey bars for controls. Data drawn from complete case data. Y axis represents mean Psychotic Like Experiences and Euphoric Experiences scores +/- 95% Bootstrapped Confidence Interval.

Online supplement:

sTable 1 DSM IV diagnosis of cases* (Operational Criteria Checklist (OPCRIT):

	n	*%*
No diagnosis	69	10.3
Major depressive disorder with psychosis	56	8.4
Manic episode with psychosis	58	8.7
Schizophrenia	179	26.8
Schizophreniform disorder	115	17.2
Schizoaffective disorder, depressive type	13	1.9
Schizoaffective disorder, bipolar type	19	2.8
Delusional disorder	23	3.4
Psychosis not otherwise specified (atypical psychosis)	95	14.2
Bipolar I disorder	20	3.0
Missing	8	1.2
Total	**655***†	**98.2***†

*Ever cannabis using patients with FEP
† Cases excluded from analysis (not shown in table above) were those with diagnosis of non psychotic disorders (n=12; 1.8%): Moderate Major depressive disorder; Major depressive disorder severe; hypomanic episode; Manic episode without psychosis

sTable 2: Cases & Controls by site:

	Case	Control	Total
Brazil			
Ribeirão Preto	89 (13.6%)	60 (9.2%)	149 (11.4%)
France			
Val-de-Marne (Paris)	31 (4.7%)	38 (5.8%)	69 (5.3%)
Puy-de-Dôme (Clermont-Ferrand)	8 (1.2%)	23 (3.5%)	31 (2.4%)
Holland			
Amsterdam	86 (13.1%)	64 (9.8%)	150 (11.5%)
Gouda and Voorhout	69 (10.5%)	57 (8.7%)	126 (9.6%)
Italy			
Bologna	35 (5.3%)	39 (6.0%)	74 (5.7%)
Palermo	37 (5.6%)	59 (9.0%)	96 (7.3%)
Spain			
Barcelona	22 (3.4%)	23 (3.5%)	45 (3.4%)
Cuenca	13 (2.0%)	19 (2.9%)	32 (2.4%)
Galicia	19 (2.9%)	24 (3.7%)	43 (3.3%)
Madrid	29 (4.4%)	19 (2.9%)	48 (3.7%)
Oviedo	21 (3.2%)	21 (3.2%)	42 (3.2%)
Valencia	29 (4.4%)	16 (2.4%)	45 (3.4%)
United Kingdom			
Cambridge	29 (4.4%)	51 (7.8%)	80 (6.1%)
London	138 (21.1%)	141 (21.6%)	279 (21.3%)
Total	**655 (100.0%)**	**654 (100.0%)**	**1321 (100.0%)**

sTable 3: Cases & Controls by ethnicity

	Case	Control	Total
White	415 (63.4%)	547 (83.8%)	962 (73.5%)
Black	105 (16.0%)	46 (7.0%)	151 (11.5%)
Mixed	60 (9.2%)	31 (4.7%)	91 (7.0%)
Asian	22 (3.4%)	12 (4.7%)	34 (2.6%)
North African	31 (4.7%)	7 (1.1%)	38 (2.9%)
Other	22 (3.4%)	10 (1.5%)	32 (2.4%)
Total	**655 (100.0%)**	**653 (99.8%)***	**1308 (99.9%)**

*Ethnicity data for one control was missing.

sTable 4: Within item and between subscales correlations for Cannabis Experiences Questionnaire

	Fearful	*Crazy, mad*	*Nervy*	*Suspicious*	*Hearing voices*	*Seeing visions*	*Feeling Happy*	*Full of plans, ideas*	*Undertanding the world better*	*cPLEs*	*cEEs*
Fearful	1										
Crazy, mad	0.5073	1									
Nervy	0.4791	0.4349	1								
Suspicious	0.5485	0.4574	0.4862	1							
Hearing voices	0.2535	0.4047	0.2388	0.321	1						
Seeing visions	0.2642	0.3829	0.1965	0.2619	0.4496	1					
Feeling Happy	-0.0201	0.0236	0.0454	0.1065	0.063	0.0532	1				
Full of plans, ideas	0.0914	0.0984	0.1717	0.2809	0.1779	0.1639	0.4094	1			
Undertanding the world better	0.1553	0.1084	0.1757	0.2709	0.1656	0.1655	0.3162	0.4857	1		
cPLEs	0.7662	0.7558	0.7161	0.7848	0.5804	0.5397	0.0678	0.2379	0.2545	1	
cEEs	0.0923	0.0972	0.1656	0.2747	0.1728	0.1619	0.7611	0.814	0.7516	0.2343	1

sTable 5: Missing data rates

	Case	**Controls**
Male	*nil*	*nil*
White	*nil*	*1 (0.2%)*
Age at first contact	*nil*	
Age at assessment	*nil*	*1 (0.2%)*
Years in Education	***12 (1.8%)***	***2 (0.3%)***
Age first tried cbs	***15 (2.2%)***	***nil***
Frequency of cbs use	***15 (2.3%)***	***1 (0.2%)***
Money Spent per week on cbs	*61 (9.3%)*	*47 (7.2%)*
Use of high potency cbs	*131 (20.0%)*	*136 (20.8%)*
Mean Duration of cbs use (years)	18 (2.7%)	28 (4.3%)
Current cbs use	*2 (0.3%)*	*1 (0.2%)*
Lifetime DSM IV cbs Dependence	***26 (4.0%)***	***3/654 (0.5%)***
Last 12 month DSM IV cbs Dependence	**26 (5.2%)**	**3 (0.5%)**
Number of other drugs tried	*nil*	*nil*
Cigarettes/Roll-ups per day	***19 (2.9%)***	***8 (1.2%)***
Units of alcohol per day	*143 (21.8%)*	*88 (13.4%)*
cPLEs	57 (8.7%)	39 (6.0%)
cEEs	53 (8.1%)	38 (5.8%)

Legend: cbs: cannabis**;** Bold typeface indicates significant difference (p<0.05) in mi data between cases and controls (chi squared test or Fisher's exact test where any s value <=5).

sTable 6: Supplementary Analyses – cannabis frequency x status interaction regressing for substance type

In the main analyses we had used '*number of illicit substances ever tried'* as in order to control for illicit substance misuse. Reviewers had requested further analyses to control for different drug types as these may conceivable have different effects on cPLEs. We have therefore run a supplementary complete case analysis controlling for different drug types collected in the EU-GEI study: Inhalents, Crack, Cocaine, other Stimulants (such as amphetamines), Sedatives, Opioids, Hallucinogens, Ketamine and Novel Psychoactive Stubstances. We have run two analyses – firstly controlling for ever use of these substances (coded 1 – ever having used and 0 – never having used) and secondly controlling for lifetime misuse (coded 1 – meeting DSM IV abuse or dependence criteria and 0 – not meeting criteria).

sTable 6a: Prevelance of everuse and lifetime misuse by cases and controls

	Ever Use			**Lifetime misuse**		
	Case	Control	p-value	Case	Control	p-value
Inhalents	92 (14.0%)	50 (7.7%)	**<0.001**	9 (1.4%)	2 (0.3%)	0.064
Crack	56 (8.6%)	24 (3.7%)	**<0.001**	21 (3.2%)	9 (1.4%)	**0.0404**
Cocaine	279 (42.6%)	184 (28.1%)	**<0.001**	87 (13.3%)	39 (6.0%)	**<0.001**
Stimulants	203 (31.0%)	150 (22.9%)	**0.001**	41 (6.3%)	23 (3.5%)	**0.029**
Sedatives	51 (7.8%)	27 (4.1%)	**<0.001**	14 (2.1%)	2 (0.3%)	**0.004**
Opioids	46 (7.0%)	19 (2.9%)	**<0.001**	19 (2.9%)	5 (0.8%)	**0.006**
Hallucinogens	142 (21.7%)	118 (18.0%)	0.111	9 (1.4%)	6 (0.9%)	0.605
Ketamine	61 (9.3%)	36 (5.5%)	**0.011**	5 (0.8%)	1 (0.2%)	0.217
Novel Psychoactive Substances	36 (5.5%)	29 (4.4%)	0.446	9 (1.4%)	3 (0.5%)	0.144

sTable 6b: Interaction of cannabis frequency x caseness on cPLEs regressing for illicit substance use

		Coefficient	Standard Error	t	P>|t|
	Caseness	1.362	0.222	6.14	**<0.001**
	Frequency	0.798	0.172	4.63	**<0.001**
	Casenesss x Frequency	0.246	0.065	3.75	**<0.001**
	cEEs	0.134	0.044	3.04	**0.002**
Lifetime use	Inhalents	0.713	0.454	1.57	0.116
	Crack	0.993	0.605	1.64	0.101
	Cocaine	0.123	0.276	0.45	0.654
	Stimulants	0.366	0.336	1.09	0.277
	Sedatives	1.034	0.578	1.79	0.074
	Opioids	-0.545	0.595	-0.92	0.36
	Hallucinogens	-0.370	0.311	-1.19	0.235
	Ketamine	-0.423	0.412	-1.03	0.305
	Novel Psychoactive Substances	-0.048	0.493	-0.1	0.922
	Constant	5.165	0.641	8.05	**<0.001**

sTable 6c: Interaction of cannabis frequency x caseness on cPLEs regressing for illicit substance misuse

		Coefficient	Standard Error	t	P>|t|
	Caseness	1.381	0.229	6.03	**<0.001**
	Frequency	0.809	0.164	4.95	**<0.001**
	Casenesss x Frequency	0.250	0.070	3.58	**<0.001**
	cEEs	0.141	0.038	3.72	**<0.001**
Lifetime Misuse	Inhalents	3.226	1.179	2.74	**0.006**
	Crack	2.160	0.745	2.9	**0.004**
	Cocaine	0.139	0.402	0.35	0.729
	Stimulants	0.245	0.546	0.45	0.654
	Sedatives	2.399	0.974	2.46	0.014
	Opioids	-1.619	0.840	-1.93	**0.054**
	Hallucinogens	0.627	1.001	0.63	0.531
	Ketamine	-0.189	1.511	-0.13	0.9
	Novel Psychoactive Substances	1.361	1.175	1.16	0.247
	Constant	5.276	0.531	9.94	**<0.001**

Consequently we observe that the findings of the main analysis remain the same when adjusting for other illicit substance confounders. Additionally we observe that a history of inhalents misuse, crack cocaine misuse are associated with increased cPLEs whereas opioid misuse appears associated with diminished cPLEs. This is broadly in keeping with previous literature in which whereas cannabis and cocaine use are synergistic for psychosis experiences[1] whereas opiate withdrawal is associated with psychosis experiences[2,3]. However we note that overall numbers in the misuse groups for these substances are small (n<=30, see Table 6a) and such findings should be interpreted with caution.

References:

1. Roncero C, Daigre C, Gonzalvo B, et al. Risk factors for cocaine-induced psychosis in cocaine-dependent patients. *Eur. Psychiatr* 2013;28(3):141-146. doi:10.1016/j.eurpsy.2011.06.012.
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