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Interaction between cannabis consumption and childhood abuse in psychotic disorders: preliminary findings on the role of different patterns of cannabis use

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Interaction between cannabis consumption and childhood abuse in psychotic disorders: preliminary findings on the role of different patterns of cannabis use

Abstract

Aim: Several studies have suggested that lifetime cannabis consumption and childhood abuse synergistically contribute to the risk for psychotic disorders. This study aimed to extend existing findings regarding an additive interaction between childhood abuse and lifetime cannabis use, by investigating the moderating role of type and frequency of cannabis use.

Methods: 231 individuals presenting for the first time to mental health services with psychotic disorders and 214 unaffected population controls from South London, United Kingdom, were recruited as part of the Genetics and Psychosis study. Information about history of cannabis use was collected using the Cannabis Experiences Questionnaire. Childhood physical and sexual abuse were assessed using the Childhood Experience of Care and Abuse Questionnaire.

Results: Neither lifetime cannabis use nor reported exposure to childhood abuse were associated with psychotic disorder when the other environmental variable was taken into account. Although the combination of the two risk factors raised the odds for psychosis by nearly three times (adjusted OR=2.94, 95% CI: 1.44-6.02, p=0.003), no evidence of interaction was found (adjusted OR=1.46, 95% CI: -0.54-3.46, p=0.152). Furthermore, the association of high potency cannabis and daily consumption with psychosis was at least partially independent of the effect of childhood abuse.

Conclusions: The heavy use of high potency cannabis increases the risk of psychosis but, in addition, smoking of traditional resin (hash) and **less than daily** cannabis use may increase the risk for psychosis when combined with exposure to severe childhood abuse.

Key words: Cannabis; Childhood trauma; First-episode psychosis; Interaction; Marijuana smoking.

Introduction

Both childhood maltreatment and cannabis abuse are considered to play a role in the pathogenesis of psychosis.[1,2] Recent studies indicate that their effect on psychosis is neither fully confounded by other risk factors,[3,4] nor a simple effect of gene–environment correlation.[5] Moreover, there are suggestions that the risk for psychosis is greater in subjects exposed to both risk factors compared to those who experienced only either of them.[6-8] For instance, a preliminary investigation using the US National Comorbidity Survey found that when cannabis use and sexual molestation/rape before 16 years of age were entered into the same model neither of them was associated with psychosis, but it was only the combination of the two that increased the risk in a more than multiplicative way (OR=11.96, 95% CI 2.10-68.22).[6]

Subsequent studies have confirmed the interaction between cannabis and trauma, though at an additive level. In a small sample of adolescents aged 12-15 years, the odds of reporting psychotic symptoms was 20.9 among subjects exposed to both child abuse and lifetime cannabis use, compared to 1.9 among those exposed only to cannabis, and 2.6 in those exposed only to trauma.[7] Konings and colleagues replicated this additive interaction in a birth cohort study (the Greek National Perinatal Study) and a longitudinal population study (the Netherlands Mental Health Survey and Incidence Study, NEMESIS). It was found that the strength of interaction between lifetime cannabis use and childhood trauma increased with the frequency of maltreatment suggesting a dose-dependent, extra-linear relationship.[8] Contrasting with these promising findings, in another Dutch study (the Early Developmental Stage of Psychopathology, EDSP) there was no evidence that broadly defined traumatic experiences before 18 years of age (including, among others, wars, natural disasters, and serious accidents in addition to physical and sexual abuse) moderated the effect of smoking cannabis (five times or more) on psychotic symptoms.[9] One possible reason for the discrepancies in the findings is that previous studies used fairly crude measures of cannabis use, which often did not consider frequency of consumption, and may have

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included participants using different strengths of cannabis – higher concentrations of delta9-tetrahydrocannabinol (Δ9-THC) have been associated with greater odds of developing psychosis.[10]

Therefore, the aim of the present study was to replicate existing findings regarding an additive interaction between childhood abuse and lifetime cannabis use in a sample of individuals presenting for the first time to mental health services with psychotic disorders and to extend these findings by investigating the moderating role of type and frequency of cannabis use on the association between childhood abuse and psychosis.

Methods

Participants

Psychosis cases and unaffected controls were recruited as part of the Genetics and Psychosis Study (NIHR-BRC GAP), approved by the South London & Maudsley National Health Service (NHS) Trust and the Institute of Psychiatry ethical committees.[10,11] All the participants were informed about the study aims and provided written informed consent. Cases were individuals aged 18 to 65 with a first episode of psychosis who presented to the Lambeth, Southwark and Croydon adult in-patient units of the South London and Maudsley Mental Health NHS Foundation Trust between December 2005 and October 2010. Cases had to fulfil International Classification of Diseases (ICD-10)[12] criteria for psychosis (codes F20-29 or F30-34); cases with a known organic cause for psychosis were excluded. Diagnoses were formulated by trained psychiatrists according to DSM-IV[13] and ICD 10[12] criteria using the Operational Criteria system, OPCRIT[14], on the basis of clinical notes collected for each patient during the first month after admission. Controls were recruited from the same catchment area as cases through leaflet distributions and internet and newspaper advertisements. Potential controls were screened for current or past psychotic disorders using the Psychosis Screening Questionnaire (PSQ),[15] and those who met criteria for a psychotic disorder, or reported a previous diagnosis of psychosis, were excluded. Subjects with IQ<70 or poor English fluency were also excluded.

The data analysed in this paper was limited to the participants who provided full information about the two exposures of interest, by completing both the cannabis and the childhood abuse assessments. Therefore, it includes only 231/489 (47%) of the patients and 214/278 (77%) of the controls recruited into the study.[11] Reasons for dropout included the lack of interest in the research, the length of the assessment, and their view of their mental health.[16,17] There were no significant demographic differences between this subsample and the full GAP sample, except in the age of the control group (27.6 ± 9.0 vs. 30.2 ± 9.5, t=3.120, p=0.002), though this only differed on average by 3 years.

Measures

Socio-demographic information (age, gender, self-rated ethnicity, level of education achieved) and family history of psychiatric disorder (psychotic disorders, mood disorders, or substance/alcohol use disorders) were collected on both cases and controls using respectively the Medical Research Council Sociodemographic Schedule[18] and the Family Interview for Genetic Studies (FIGS).[19] Childhood physical and sexual abuse were assessed using the Childhood Experience of Care and Abuse Questionnaire (CECA.Q).[20] In order to reduce the possibility of recall bias and maximise likely effect on psychosis, analyses were limited to physical abuse resulting in injuries and to penetrative sexual abuse reported as occurring prior to 17 years of age. Reports of either of these forms of severe abuse were considered to indicate exposure to childhood abuse.

Lifetime cannabis use (i.e., having ever smoked cannabis, one time or more), type of cannabis most often used, and lifetime frequency of cannabis consumption (i.e., the frequency that characterized the subject's most consistent pattern of use) were investigated using the Cannabis Experiences Questionnaire modified version (CEQmv).[10] The types of cannabis used by the participants were classified as mainly resin (hash) vs. mainly sinsemilla (skunk), according to the different concentrations of delta9-tetrahydrocannabinol (Δ9-THC). Δ9-THC is the active principle component responsible for the psychogenic effect and cognitive impairments associated with

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cannabis,[21] and is estimated as being 2–4% concentrated in cannabis resin but 12-18% in

sinsemilla/skunk.[22] The lifetime frequency of cannabis consumption was classified as less than

daily vs. daily.

Statistical analyses

Analyses were carried out using Stata version 12.0 (Stata Corporation, USA). Logistic regression

was used to assess the effect of the independent variables on the dependent variable (presence of

psychotic disorder). Analyses were repeated adjusting for the potentially confounding effects of

gender, self-rated ethnicity, current level of education, and family psychiatric history because in the

study sample these variables were associated either with psychotic disorders or with either of the

two exposures (lifetime cannabis use or childhood abuse). Statistical interaction is a model-

dependent estimation of biological synergism and refers to a situation in which the combined effect

of two or more exposures exceeds the sum (additive model) or the product (multiplicative model) of

their solitary effects.[23,24] Additive interaction between cannabis use and childhood abuse was

assessed using the Interaction Contrast Ratio (ICR), which estimates the relative excess due to

interaction using odds ratios (OR) derived from logistic regressions. In the presence of statistical

interaction, the ICR shows that the odds of being psychotic in those exposed to both risk factors is

greater than the sum of the odds conveyed by each risk factor (departure from additivity).[25,26]

Although the ICR was originally designed to assess additive interaction in cohort studies, it can be

used in the context of case-control studies under the rare-disease assumption that, when the

outcome is rare in the source population, odds ratios approximate risk ratios. Therefore, we

stratified our independent variable into four levels: those exposed to both cannabis and child abuse

(AB), those exposed only to cannabis (A), those exposed only to child abuse (B), and those exposed

to neither cannabis nor child abuse (reference category). The Stata nlcom command was used to

calculate the ICRs and the related 95% confidence intervals (CI) and p values.

One issue in interaction studies is that the "true" effect of the interaction may be confounded by correlation, meaning the extent to which one risk factor can drive the exposure to another risk factor.[27] In this study Environment by Environment correlation (rEE) refers to the probability that childhood trauma *per se* alters the probability that an individual will use cannabis. To test rEE we analysed the effect of childhood trauma on cannabis use in the control group using logistic regression. Because of a small percentage of missing data concerning family psychiatric history, a sensitivity analysis was carried out to investigate the effect of missingness on the interaction between cannabis use and childhood abuse, using an imputation method. *Post-hoc* power analysis was conducted using GPower 3.1.5.

Results

Socio-demographic characteristics of the sample are reported in Table 1. There was some evidence of a difference between the psychosis cases and unaffected controls in terms of ethnicity, education level, and family psychiatric history. Furthermore, cases included a higher proportion of men although there was no strong evidence of a gender difference between the groups.

[Insert Table 1 here]

Cannabis use by childhood abuse interaction

There was no evidence of an association between childhood abuse and cannabis use in the control group (OR=0.98, 95% CI 0.46-2.08, p=0.963), suggesting no evidence of environment-environment correlation. Table 2 presents unadjusted and adjusted ORs for the four combinations of the environmental exposures and their associations with psychotic disorder.

[Insert Table 2 here]

While lifetime cannabis use alone (i.e., in those without exposure to childhood abuse) and childhood abuse alone (i.e., in those with no lifetime cannabis use) were not associated with psychotic disorders, the combination of the two exposures raised the odds for the disease by nearly

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three times (adj. OR=2.94, 95% CI 1.44-6.02, p=0.003). The ICR (2.18, 95% CI 0.01-4.36, p=0.049) was greater than 0 and showed some evidence of an effect, suggesting that the joint effect of cannabis use and childhood abuse on the additive scale was greater than the sum of their effects alone. However, after adjusting for confounders, the interaction effect was attenuated and became non-significant (ICR=1.46, 95% CI -0.54-3.46, p=0.152).

Sensitivity analyses

Family psychiatric history was the only variable to account for a small percentage of missingness in this sample (51/445, 11.5%). Missing data were equally distributed across levels of gender, education level, ethnicity, cannabis use, and child abuse but were more frequent in cases than controls (40 (17.3%) vs. 11 (5.1%), χ^2=16.2, p<0.001). All missing values were replaced first by positive family history and then by negative family history and analyses were repeated using these new variables. There was no evidence of an interaction after imputation either of a positive (ICR=1.23, 95% CI -0.35-2.81, p=0.127) or negative (ICR=1.53, 95% CI -0.33-3.39, p=0.107) family history.

Effect of type and frequency of cannabis use

Associations with psychotic disorders for potency of cannabis consumed (hash-like vs. skunk-like) and frequency of cannabis use (daily vs. less than daily) in conjunction with reported exposure to childhood abuse are presented in Tables 3 and 4, respectively. Looking at the effect of cannabis alone or combined with childhood abuse (Tables 3 and 4), there is a suggestion that high-potency and daily cannabis users might develop psychotic disorders at least partially independently of the occurrence of severe childhood adversities. However, due to the small sample size, the interaction between childhood abuse and specific patterns of cannabis use could not be formally tested.

[Insert Tables 3 & 4 here]

Discussions

Cannabis use by childhood abuse interaction

This study found that neither lifetime cannabis use nor reported exposure to childhood abuse were associated with psychotic disorder when the other environmental variable was taken into account. By contrast, the combination of the two exposures appeared to exert a significantly greater effect than the sum of their individual effects suggesting an additive interaction. Nevertheless, after controlling for several covariates, this study found no evidence of interaction between lifetime cannabis use and childhood abuse. This result is consistent with the findings of Kuepper et al.,[9] who reported that the effect of smoking cannabis on psychotic symptoms was not affected by exposure to traumatic events in childhood or adolescence.

Effect of type and frequency of cannabis use

To our knowledge, this is the first study to investigate the different effects of type and frequency of cannabis smoking in relation to the association between childhood abuse and psychosis. Our results suggest that hash-type cannabis and less than daily frequency of use are more likely to combine with childhood abuse in increasing the odds for psychosis. **It could be speculated that the interaction between cannabis use and childhood abuse in psychosis is mostly driven by low potency and less than daily cannabis use.** This might explain why our findings did not replicate the additive interaction described by Harley et al.[7] and Konings et al.[8]

On the other hand, high potency, skunk-like, cannabis and daily smoking seemed to influence the pathway to psychosis both alone as well as in association with childhood abuse in this sample. This confirms the existing literature demonstrating that individuals affected by psychotic disorders are over six times more likely to smoke cannabis every day and to use high-potency cannabis.[10,28,29] Furthermore, previous studies have suggested that the effect of cannabis on psychosis was not confounded by childhood trauma.[28,29] In fact, this is consistent with the view that in complex multifactorial disorders, such as psychotic disorders, individuals who are exposed to a

variety of risk factors might develop the disease either because of the specific effect of a particular

risk factor (biological parallelism) or because of a combination of them (biological synergism).[23,30]

Potential mechanisms

According to the sensitization hypothesis, genetically vulnerable individuals exposed early to

environmental risk factors – including childhood adversities and certain illicit drugs – might show a

progressive increase in the dopaminergic response to psycho-social stress that, in turn, might result

in stable changes in dopaminergic reactivity and the development of psychotic symptoms.[31,32]

While preliminary animal studies have suggested that housing stress moderates rats' response to

delta-tetrahydrocannabinol (THC),[33] recent evidence suggests that the sensitization process was

bidirectional, so that environmental stress may affect sensitivity to THC but also that THC

administration alters the endo-cannabinoid transmission.[34] Despite these promising findings, the

cross-sensitization between environmental stress and THC has not been fully supported by human

studies.[35-37]

Limitations

Compared with previous studies that reported an additive interaction between cannabis and

trauma,[7,8] our findings are based on a smaller sample and might have been affected by inadequate

power. In fact, *post-hoc* power analysis based on the results of the NEMESIS study[8] suggests that

we had over 95% power to replicate the difference in the prevalence of psychosis amongst cannabis

consumers who were also exposed to child abuse (62.5% vs. 26.5%), but only 44% power to

replicate the analogous difference in the unexposed group (9.2% vs. 4.8%). This could explain why

our study resulted in weaker findings. To our knowledge, the only other study reporting trauma by

cannabis interaction with a similar sample size (N=211) is the one by Harley et al.[7]: the authors

reported an ICR of 17.4 which was suggestive of additive interaction, but the lack of confidence

intervals did not allow evaluation of the significance of their results. Thus, further studies of the interaction between cannabis and trauma are warranted.

This study relied on self-reported retrospective information and, thus, results might have been affected by recall bias regarding traumatic experiences and use of illicit substances. Despite the fact that the reliability of psychosis patients' reports of earlier abuse has been questioned in the past, a recent study demonstrated that such reports are stable over time, consistent between measures, and not affected by current symptomatology.[38] In our sample the prevalence of either physical or sexual abuse among subjects affected by psychotic disorders was 28% which is higher than rates estimated for the general population[39] but lower than those reported by literature reviews of prevalence rates in psychosis patients (50%).[40] This might be related to the very conservative definition of physical and sexual abuse used in this study, the difficulty in disclosure some individuals experience during face-to-face interviews, or the tendency to under-report childhood abuse, especially when involving family members. Reassuringly, though, another first-episode psychosis sample obtained from an overlapping geographical area and using the same measurement tool – **but a less conservative threshold** – found almost identical rates of physical and sexual abuse (31%).[41] **Previous studies on cannabis by trauma interaction have used less conservative definitions of child abuse but still found elevated rates of psychotic phenomena in those reporting exposure to child abuse.[7,8] As pointed out by several reviews,[40,42] studies on childhood adversities and psychosis have employed a wide range of measures and definitions of early traumas, some of which did not account for severity. While broader definitions might be more sensitive to minor events and contribute to greater generalizability of results, use of narrow definitions of child abuse may be preferable as more severe events are postulated to be more accurately remembered thus reducing recall bias.[43]** Similarly to childhood abuse, cannabis use was assessed using a semi-structured interview, and was not supported by any biological measure such as a urine or blood test. However, given that we were interested in lifetime cannabis use and preferred type of cannabis used, these biological measures would not have

improved our study, because they are informative only about current consumption. Indeed, the strength of the association between cannabis and psychosis was consistent with those reported by existing literature reviews[2,3] and the prevalence of lifetime cannabis consumption among cases and controls (69.7% vs. 57.9%) was fairly similar to the rates reported in a partially overlapping sample (62.5% vs. 56.9%).[10]

Furthermore, it is possible that our findings were affected by selection bias, since our sample included only 231/489 (47%) of the patients and 214/278 (77%) of the controls recruited into the GAP study.[11] This is because we included only participants who provided exhaustive information about both their frequency and type of cannabis use as well as the type and severity of childhood abuse. In addition, there was a small proportion of missing data in one of the covariates (family psychiatric history), an issue that was addressed by sensitivity analysis. However, our cases and controls appear similar to those included by Di Forti et al.[11] in terms of the main demographic variables suggesting their representativeness of the full study sample.

Conclusions

This study did not replicate previous findings regarding the synergistic effect of cannabis consumption and childhood abuse on the onset of psychotic disorders. Our findings suggest that, besides the obvious risk conveyed by heavy use of high potency cannabis, smoking resin (hash) and less than daily smoking are likely to increase the odds for psychosis when combined with severe childhood abuse. For that reason, children and adolescents exposed to physical or sexual abuse might benefit from psycho-social interventions aimed at promoting adaptive coping strategies and informing them about the health-related risks of substance misuse. Clearly replication of these results is required before clinical trials to test this proposition could be initiated.

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TABLE 1. Demographic characteristics for psychosis cases and unaffected controls

	Controls n (%) N=214	Cases n (%) N=231	Chi square/ Student's t test	p value
Gender Male	116 (54.2)	146 (63.2)	3.71	0.054
Ethnicity Non-Caucasian	104 (48.6)	153 (66.2)	**14.16**	**<0.001**
Level of education Lower than Degree	111 (52.1)	183 (79.9)	**38.29**	**<0.001**
Age mean (sd)	27.6 (9.0)	28.1 (9.1)	-0.59	0.554
Diagnosis Non-affective psychoses Affective psychoses		140 (60.6) 44 (19.0)		
	Controls n (%) N=203	Cases n (%) N=191		
Family psychiatric history	75 (37.0)	92 (48.2)	**5.07**	**0.024**

sd, standard deviation.

TABLE 2. Cannabis use by childhood abuse interaction for psychotic disorders

	Controls n (%) N=214	Cases n (%) N=231	OR	95% CI (p value)	Adj OR[†]	95% CI (p value)
No child abuse and no cannabis use	76 (35.5)	58 (25.1)	1		1	
Cannabis use without child abuse	105 (49.1)	108 (46.8)	1.35	0.87-2.08 (0.178)	1.43	0.86-2.38 (0.164)
Child abuse without cannabis use	14 (6.5)	12 (5.2)	1.12	0.48-2.61 (0.787)	1.05	0.40-2.74 (0.919)
Child abuse and cannabis use	19 (8.9)	53 (22.9)	**3.66**	**1.96-6.83** (<0.001)	**2.94**	**1.44-6.02** (0.003)

[†]adjusted for gender, ethnicity, education level, and family psychiatric history.

Adj, adjusted. CI, confidence interval. OR, odds ratio.

TABLE 3. Cannabis potency by childhood abuse interaction for psychotic disorders

	Hash-like cannabis						Skunk-like cannabis					
	Controls n (%) n=167	Cases n (%) n=143	OR	95% CI (p value)	Adj OR[†]	95% CI (p value)	Controls n (%) n=137	Cases n (%) n=158	OR	95% CI (p value)	Adj OR[†]	95% CI (p value)
No child abuse and no cannabis use	76 (45.5)	58 (40.6)	1	-	1	-	76 (55.5)	58 (36.7)	1	-	1	-
Child abuse without cannabis use	14 (8.4)	12 (8.4)	1.12	0.48-2.61 (0.787)	0.96	0.37- 2.51 (0.938)	14 (10.2)	12 (7.6)	1.12	0.48- 2.61 (0.787)	1.15	0.44- 3.04 (0.776)
Cannabis use without child abuse	68 (40.7)	48 (33.6)	0.92	0.56-1.53 (0.761)	1.04	0.57- 1.88 (0.908)	37 (27.0)	60 (38.0)	**2.12**	**1.25- 3.62 (0.006)**	**2.16**	**1.15- 4.06 (0.016)**
Cannabis use and child abuse	9 (5.4)	25 (17.5)	**3.64**	**1.58-8.39 (0.002)**	**2.82**	**1.12- 7.11 (0.028)**	10 (7.3)	28 (17.7)	**3.67**	**1.65- 8.16 (0.001)**	**3.46**	**1.34- 8.97 (0.011)**

[†]adjusted for gender, ethnicity, education level, and family psychiatric history.
Adj, adjusted. CI, confidence interval. OR, odds ratio.

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TABLE 4. Frequency of cannabis use by childhood abuse interaction for psychotic disorders

	Less than daily use						Daily use					
	Controls n (%) n=197	Cases n (%) n=166	OR	95% CI (p value)	Adj OR[†]	95% CI (p value)	Controls n (%) n=107	Cases n (%) n=135	OR	95% CI (p value)	Adj OR[†]	95% CI (p value)
No child abuse and no cannabis use	76 (38.6)	58 (34.9)	1		1		76 (71.0)	58 (43.0)	1		1	
Child abuse without cannabis use	14 (7.1)	12 (7.2)	1.12	0.48- 2.61 (0.787)	0.97	0.37- 2.52 (0.944)	14 (13.1)	12 (8.9)	1.12	0.48- 2.61 (0.787)	1.19	0.45- 3.16 (0.732)
Cannabis use without child abuse	92 (46.7)	59 (35.5)	0.84	0.52- 1.35 (0.471)	0.97	0.56- 1.68 (0.919)	13 (12.2)	49 (36.3)	4.94	2.45- 9.95 (<0.001)	5.37	2.33- 12.34 (<0.001)
Cannabis use and child abuse	15 (7.6)	37 (22.3)	3.23	1.62- 6.45 (0.001)	2.51	1.13- 5.56 (0.023)	4 (3.7)	16 (11.9)	5.24	1.66- 16.52 (0.005)	5.31	1.45- 19.47 (0.012)

[†]adjusted for gender, ethnicity, education level, and family psychiatric history.
Adj, adjusted. CI, confidence interval. OR, odds ratio.