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Preliminary title:

G x E: Cannabis

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Publication category: 1 - integrated work from several Work Packages (1-11)

Working and writing group:

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Work Packages involved:

WP2, WP3, WP6, WP8

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated:

Objectives (scientific background, hypothesis, methods, and expected results):

Importance

Schizophrenia and related psychoses are a major cause of morbidity and mortality, with an annual cost in England of £11.8 billion. The aetiology of these disorders involves different combinations of risk factors, none of which are necessary or sufficient for illness onset . Cannabis use is among the best replicated risk factors .Therefore, it is important to establish the patterns of cannabis use that are especially likely to provoke psychosis and to worsen its outcome, and to examine how such patterns interact with a measure of genetic predisposition. This could then be used to inform lifestyle changes and improve prevention. For instance, if we had better understanding of who is at greatest risk because of their pattern of use and their genetic vulnerability, the number of people needed to be “treated” to prevent one case of schizophrenia would be significantly lower than previously suggested.

Background

Prospective studies have consistently demonstrated that cannabis use is associated with an increased risk of subsequent psychotic disorders . In the UK, cannabis use is a major problem both in provoking onset, and relapse, of psychosis . The potency of cannabis influences the magnitude of risk . This is of public health importance as high potency cannabis, termed “skunk” in UK, is increasingly available . In 2008 samples of resin (termed “hash”) seized by the London Police contained 2–4% Delta-9-THC compared to 12–18% in “skunk”. While the hash had similar proportions of D9-THC and CBD, the latter was almost absent in skunk . CBD is known to ameliorate the effects of THC , and its absence in skunk likely contributes to the higher risk of psychosis associated with skunk . Unfortunately, the quality of information about cannabis consumption in many studies is poor. There is a need to obtain detailed information on cannabis use to identify those patterns of use that most accurately predict risk of

cannabis-associated psychotic disorders.

Genetics

Individuals vary in their susceptibility to the effects of cannabis. Van Winkel et al demonstrated an interaction between the AKT1 rs2494732 genotype and cannabis use in provoking psychosis which we recently replicated . Nevertheless, it is likely that multiple genes will influence susceptibility to cannabis-associated psychosis and to its poor outcome. The Psychiatric Genomic Consortium (PGC) Schizophrenia Genome Wide Association Study (GWAS) identified 108 distinct genetic loci, including strong candidates such as the Dopamine Receptor gene DRD2 and genes in the AKT pathway. This opens the way to constructing an overall Polygenic Score as well as Pathway Scores to predict disease risk and outcome; an approach which demonstrated significant predictive power in several medical conditions.

Aim

The overall aims of these analyses are to examine synergistic (combined) effects of genes (using family history and polygenic risk scores (overall and pathway based)) and cannabis use on odds of psychosis (i.e. case status).

Hypotheses

1) Cannabis use (see below) will combine synergistically to increase odds of psychosis (i.e., case status), on an additive scale, with:

a) family history (morbid risk) of psychosis;

b) PGC2 schizophrenia informed overall polygenic risk score (derived from latest PGC schizophrenia study);

c) PGC2 schizophrenia informed AKT, endocannabinoid and dopamine pathway polygenic risk scores

d) overall CNV burden

e) rare variant burden in genes of the AKT, endocannabinoid and dopamine pathways

2) Assuming that subsets of SNPs related to particular pathways (i.e., AKT, endocannabinoid; dopamine) confer differential genetic sensitivity to specific environmental exposures (i.e., cannabis use), the strongest synergistic effects will be observed for pathway related polygenic risk scores + cannabis use

Methods

WP2 case-control data will be used to test these hypotheses.

Sample

WP2: approx. 1,200 incident cases, 1,200 controls

Data

In addition to DNA, detailed information has been collected across WP2, using the CEQ, on use of cannabis (e.g., age, frequency, type, etc.).

In addition, data has been collected on the following a priori confounders: age, gender, ethnicity, social class, cannabis use, premorbid function, IQ and family history of mental disorder (or psychosis).

Expected Results

See hypotheses

Data needed for the study:

- Family Interview for Genetic Studies (which will be used to calculate morbid risk for psychosis)
- Overall psychosis polygenic score
- AKT pathway polygenic score
- Endocannabinoid pathway polygenic score
- Dopamine pathway polygenic score
- Ancestry data for ethnicity (PCA), even within EU Caucasian groups
- Cannabis Experiences Questionnaire
- MRC Sociodemographic Schedule Parts 1 and 2
- Premorbid Adjustment Scale
- WAIS (IQ)

Plan for statistical analysis (overall strategy):

Main effects for childhood adversity(s) will be reported in other core papers.

1) Summary variables, derived following analyses for papers reporting main effects for cannabis use, will be used in these analyses. We will first summarise these main effects (adjusted odds ratios, derived from main effects analyses) in an online supplementary table.

2) In collaboration with WP3, polygenic risk scores (overall and pathway specific) will be constructed for common variants in the incidence sample using the results from the latest well powered (N>60,000) PGC schizophrenia study (pgc.unc.edu). To generate pathway specific scores, SNPs within the relevant pathways will be extracted and pruned for linkage disequilibrium. Polygenic scores will be calculated for each case and control from the number of risk alleles carried at each SNP, weighted by the log(OR).

3) In collaboration with WP3, the role of rare exome variations will be assessed using recent gene-based tests of association. Such methods calculate summary measures of the number of rare variants within a gene or locus, and test whether the burden of rare variants differs between cases and controls.

3) We will test for synergistic effects on an additive scale using Interaction Contrast Ratios. This allows use of odds ratios derived from logistic models to estimate the relative excess risk due to synergy for combinations of dichotomous, ordinal and continuous exposures (i.e., ICR = ORexposure A & exposure B - ORexposure A only - ORexposure B only + 1). In this model, positive deviation from additivity is indexed by an ICR greater than 0. Therefore, to test our hypotheses on synergistic effects we will first enter the relevant genetic variable, the relevant cannabis use variable, and the product of gene x cannabis use as independent variables in logistic regression models, with case-control status as the dependent variable and age, gender, ethnicity, premorbid function, education, and social class as potential confounders. Using the ORs derived from these models, we will calculate ICRs (i.e., ICR = OR g & cannabis use - OR g - OR cannabis use + 1). Confidence intervals and p-values for ICRs will be generated using the nlcom procedure in STATA.

4) Power calculations: To follow (in progress).

Preliminary replication plan: The findings from the discovery GxE analyses will be replicated in the EU-GEI 2000 prevalence cases and additional 1800 controls.

Other analyses/methods: None
Involvement of external Parties (non EU-GEI): Professor Cathryn Lewis, IoP
IPR check:
Timeframe: 6 months from completion of core papers on main effects of cannabis use and delivery of GWAS polygenic risk score data
Additional comments: