Synopsis no.: S2.14

Preliminary title:

G x E: Childhood Adversity

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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):

Background

Only a small proportion of those who are exposed to childhood adversity in its various forms develops psychotic experiences and, even more rarely, psychotic disorders. Other intervening factors must modify risk, either amplifying or reducing the likelihood of psychosis following adversity (abuse). It is possible, for example, that the impact of exposure to childhood adversity on risk is dependent on, or combines with, underlying genetic vulnerability (g x e interaction).

There is increasing evidence for g x e for many disorders. In relation to schizophrenia and other psychoses, most evidence relates to g x cannabis use. Some studies have investigated g x childhood abuse, with mixed results so far (e.g., Tienari et al, in an adoption design, found evidence of g x family communication deviance in increasing risk of schizophrenia; Fisher et found no effect using family history as a proxy for genetic risk; and Collip et al found some evidence of interactions between childhood trauma and polymorphisms of FK506 binding protein 5 (FKBP5)). Further analyses in larger datasets are evidently needed.

In addition to using global markers of genetic risk (i.e., family history – morbid risk) and single nucleotide polymorphisms, advances in our understanding of the genetic architecture of schizophrenia through genome-wide association studies has opened the possibility of constructing polygenic risk scores that, in essence, sum the effects of multiple risk alleles, either overall or for specific biological pathways.

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 childhood adversity on odds of psychosis (i.e. case status).

Hypotheses

1) Childhood adversity (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 HPA axis and dopamine pathway polygenic risk scores

d) overall CNV burden

e) rare variant burden in genes of the HPA axis and dopamine pathways

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

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 CECA and CTQ, on exposure to a wide range of childhood adversities, from separation from a parent to sexual abuse.

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
- HPA axis pathway polygenic score
- Dopamine pathway polygenic score
- Ancestry data for ethnicity (PCA), even within EU Caucasian groups
- Childhood Experiences of Care and Abuse
- Childhood Trauma Questionnaire
- MRC Sociodemographic Schedule Parts 1 and 2

- Cannabis Experiences Questionnaire
- 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 childhood adversity(s), 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 childhood adversity variable, and the product of gene x adversity as independent variables in logistic regression models, with case-control status as the dependent variable and age, gender, ethnicity, premorbid function, education, social class, and cannabis use as potential confounders. Using the ORs derived from these models, we will calculate ICRs (i.e., ICR = OR g & adversity - OR g - OR adversity + 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 childhood adversity(s) and delivery of

GWAS polygenic risk score data
Additional comments: