Synopsis no.: S2.8

Preliminary title:

Childhood Adversity and Psychosis: Synergistic Effects and Mediators

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Publication category: 2

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Work Packages involved: WP2

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

There are two parts to the background for this proposed set of analyses and paper:

First, 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 exposure to adversity and abuse in childhood may confer an enduring vulnerability to psychosis (and indeed other disorders) via deleterious effects on biological (e.g., HPA axis function) and psychological (e.g., affect and emotion) processes. This vulnerability may then become manifest as (initially) low level psychotic experiences and, more rarely, psychotic disorder, in the event of exposure to further risk factors over time, such as other significant life events and cannabis use, for which there is some limited emerging evidence. This evidence, however, relates mainly to psychotic experiences in adolescent or general population samples.

Second, there is developing evidence that some pathways from early adversity to psychosis may be via affective dysregulation and negative cognitive schema about the self and others. One interpretation of this is that traumatic experiences have long-term effects on affect and social cognition, fostering tendencies toward disturbances of affect and distorted cognitive schema that, in time and in the presence of further risk factors, may develop into, for example, perceptual distortions and negative false beliefs about the intentions of others (i.e., psychotic experiences) and ultimately psychotic disorder. However, research on putative mediators in relation to childhood adversity and psychosis remains under developed.

The perspective sketched above suggests psychotic experiences and symptoms may sometimes emerge from a confluence of causal factors that combine over time in a largely sociodevelopmental trajectory to disorder. Modelling such interrelationships is complex and this is made more so by the fact that some factors may both lie on a causal path from childhood adversity to psychosis and interact with childhood adversity to increase risk (i.e., mediated synergy).

Aim

The overall aims of these analyses are to examine synergistic (combined) effects of environmental factors (specifically life events and cannabis use) and psychological (cognitive and affective) mediators.

Hypotheses

1) Each childhood adversity (see below) will combine synergistically, on an additive scale, with a) life events (total number) and b) cannabis use (high frequency; high potency) to increase odds of psychosis (i.e., case-control status)

2) The impact of each childhood adversity will be modified by protective factors (e.g., social support, IQ)

3) Associations between each childhood adversity and psychosis will be mediated via:

a) negative beliefs about the self and others

b) affective (depression, anxiety) symptoms

c) life events

d) cannabis use

Methods

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

Detailed information has been collected, using the CECA and CTQ, from samples of first-episode cases of psychosis and population-based controls on the duration, frequency, timing and severity of exposure to a wide range of childhood adversities, from separation from a parent to sexual abuse.

Data has been collected on each modifier/mediator: Life events, using the LTE; Cannabis use, using the CEQ; depression and anxiety, using the Hamilton Depression Scale and the Hamilton Anxiety Scale; and negative cognitive schema, using the Brief Core Schema Scales.

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

Expected Results

See hypotheses

Data needed for the study:

- Case-control status
- MRC Sociodemographic Schedule Parts 1 and 2
- Childhood Experiences of Care and Abuse

- Childhood Trauma Questionnaire
- List of Threatening Experiences
- Cannabis Experiences Questionnaire
- Hamilton Depression Scale
- Hamilton Anxiety Scale
- Brief Core Schema Scales
- Premorbid Adjustment Scale
- WAIS (IQ)
- Family Interview for Genetic Studies

Plan for statistical analysis (overall strategy):

Main effects for childhood adversity(s), life events and cannabis use will be reported in other core papers.

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

2) 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 childhood adversity variable, life events (or cannabis use) and the product of abuse and life events (or cannabis use) as independent variables in logistic regression models, with case-control status as the dependent variable and age, gender, ethnicity, premorbid function, education, social class, family history of mental disorder (psychosis) and, as appropriate, cannabis use as potential confounders. Using the ORs derived from these models, we will calculate ICRs (i.e., ICR = OR abuse & life events [or cannabis use] - OR abuse - OR life events (or cannabis use) + 1). Confidence intervals and p-values for ICRs will be generated using the nlcom procedure in STATA.

3) We will use multiple mediation analyses to examine whether there is evidence that the effect of each childhood adversity is mediated through cognitive schema, affective symptoms, life events and cannabis use. The total effect of each childhood adversity on psychotic experiences will be parsed into direct and indirect (mediated) effects. Probit coefficients for total and specific indirect effects will be estimated using the robust weighted least squares means and variance adjusted estimator in MPLus (Version 6.1), which allows for use of bias-corrected bootstrapping. The total indirect effect will calculated as the sum of the specific indirect effects.

Evidence for both synergistic and mediation effects of life events and/or cannabis use will be suggestive of mediated synergy.

Other analyses/methods:

None

Involvement of external Parties (non EU-GEI):

None

Synopsis for EU-GEI Publication

IPR check:

Timeframe:

3 months from completion of core papers on main effects of childhood adversity(s), life events and cannabis use

Additional comments:

1) The approach adopted here could provide a template for similar analyses using other effect modifiers (e.g., resilience and support – synopsis being prepared) and mediators.

2) A further approach to examining how different environmental risk factors combine or cluster in individuals to increase risk of psychosis is to use latent class analyses to identify groups or classes of individuals with particular sets of exposures. We plan to propose a synopsis on this.

In all the above, careful consideration will need to be given to any suggestion of variations in effects by site.