

Synopsis no.: WP6-S6.7

Preliminary title: The cumulative and synergistic effect of environmental risk factors combined with familial risk on psychosis expression in a sibling-control analysis

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Publication category: WP6 GROUP Publication

Working and writing group: WP6 GROUP

Work Packages involved: WP6

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated:
GROUP investigators, WP3, WP8

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

Background:

According to the liability threshold model, if variation of liability is continuous in the population, phenotypic outcome can be determined quantitatively by the cumulative effect of the genetic load, and the cumulative amount of exposure to environmental factors (environmental load). Psychosis has been described as an all-or-none phenomenon distinguishing schizophrenia from non-ill states and also from other mental disorders; however, accumulating evidence suggests that psychosis expression is phenotypically continuous with subthreshold states. Recent genetic studies report that the risk for schizophrenia is increased by polygenic variation, and that up to 30% of the liability may be explained by the cumulative effect of common alleles with small effect. Exposure to, amongst others, urban environment, early childhood trauma, and cannabis use is consistently associated with psychotic outcomes in rigorously designed epidemiological studies, including prospective studies, in both clinical and general populations. Several studies have demonstrated that environmental risk factors may add to each other's effects in the causation of psychotic outcomes. Likewise, an additive effect across multiple environmental exposures was previously shown on the likelihood of persistence of psychotic experiences in the general population over time. Given the evidence, the liability-threshold model emerges as a valid theoretical groundwork to study gene-environment interplay (GxE and rGE) underlying psychosis.

In this analyses, we will focus on sibling status as an indirect measure of genetic risk for schizophrenia, and test for gene-environment interplay in sibling-control comparisons of subthreshold psychotic states, as well as indirect measures of psychosis proneness including experimental tasks of aberrant salience (white noise task), probabilistic reasoning bias (beads task) and cognition (social cognition, neurocognition).

Aim:

To examine synergistic effects of environmental load (urbanicity, ethnic group, bullying, discrimination, cannabis and other drug use, childhood trauma, life events) and genetic susceptibility on psychosis expression and expression of related phenotypes in genetically sensitive sibling-control comparison.

Hypotheses:

Each environmental risk factor (eg cannabis use, urbanicity, childhood trauma), both (i) separately and (ii) as a cumulative environmental loading variable, will combine, in a dose-response fashion with indirect measures of genetic susceptibility (sibling status) in a synergistic fashion to increase odds of psychosis expression and related phenotypes.

Methods

WP6 sample (sibling-control) will be used to test these hypotheses.

Data has been collected on

Expected results

See hypotheses

Data needed for the study:

MRC Sociodemographic Schedule Parts 1 and 2

Bullying

Discrimination

Childhood Experiences of Care and Abuse

Childhood Trauma Questionnaire

Cannabis Experiences Questionnaire

List/Impact of Events

Structured Interview for Schizotypy- Revised (SIS-R)

The Community Assessment of Psychic Experiences (CAPE)

IQ/composite neurocognitive score (endophenotype)

Beads Task ("jumper" status - endophenotype).

White Noise Task (presence of speech illusion; endophenotypes)

Plan for statistical analysis (overall strategy):

Tobit and multiple regression models will be applied to analyze whether the association between continuous psychosis expression (SIS-R, CAPE) and related phenotypes (speech illusion, jumping to conclusions, cognition) and genetic susceptibility (sibling status) is greater if there is also evidence of exposure to environmental risk factors (eg childhood trauma, urbanicity, cannabis use) or degree of continuous environmental load.

All analyses will be adjusted for age, sex, and educational level.

As observations are clustered within countries, hence not a simple random sample, country will be treated as a random effect with observation nested within the country in all regression models. Family will be included as an additional level as some families contributed more than one sibling.

Other analyses/methods:

Involvement of external Parties (non EU-GEI):

IPR check:

Timeframe: Data to be provided to the analysis team by . Analyses to begin, circulation of manuscript to authors, publication by.

Additional comments: