Synopsis for EU-GEI WP5 Publication

Synopsis no.: S5.3

Preliminary title: Genetic and environmental factors moderating sensitivity to stress in daily life: an experience sampling study.

Contact info for the person(s) proposing the synopsis

Name: Uli Reininghaus
Partner no: 1 MUMC, 2 IoP
e-mail address: ulrich.reininghaus@kcl.ac.uk

Publication category: 3
Publications from a single work package involving only some parties (or in some cases only one party) in the Work Package

Working and writing group: Uli Reininghaus, ESM group and WP5 author group. We also expect to add additional appropriate authors.

Work Packages involved: WP5

EU-GEI Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated:
MUMC, IoP, AMC, UOM

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

Scientific background
Understanding how genes and adverse social environments combine with each other and impact on individuals in the development of psychotic experiences (such as odd beliefs or unusual perceptual experiences) to increase risk of disorder is no doubt complex. One possibility that has been repeatedly suggested is that individuals who i) have a greater genetic risk for psychosis, ii) encountered problematic social environments in their life, iii) used cannabis (and other illicit drug) over long periods, or iv) have altered DNA methylation profiles may experience stronger emotional reactions in response to minor daily hassles or, in short, may be more sensitive to stress. For individuals with such elevated stress sensitivity, psychotic experiences may, in turn, be v) more likely to persist and, ultimately, result in vi) a transition to psychotic disorder.

Hypotheses
The overall aim of this publication is to investigate whether stress sensitivity, characterised by a) intense emotional reactions and b) psychotic experiences in response to daily life stress, is an important mechanism underlying the interplay of genes and adverse environments in childhood and adulthood in the development of psychosis.

To this end, we will address the following hypotheses:

1. whether daily life stress (i.e. daily hassles, defined as distinctive unpleasant events in daily life, as well as thought-related, activity-related, and social stress) is associated with a) intense emotional reactions and b) psychotic experiences (as indicator of elevated stress sensitivity) in an ARMS sample;
2. whether these associations are modified by i) higher polygenic scores, ii) exposure to adverse social contexts and experiences (i.e. childhood adversity, neighbourhood-level social environment), iii) long-term cannabis (and other illicit drug) use, iv) altered DNA methylation profiles, v) persistence of attenuated psychotic symptoms (without transition), and vi) transition to psychotic disorder.

These hypotheses are related to the following aims of WP5:

- To prospectively identify genetic, clinical, momentary assessment and environmental factors associated with the development of persistent psychotic symptoms and the onset of schizophrenia.
- To demonstrate how these outcomes depend on the interaction of genetic, epigenetic and environmental factors
- To develop a translational tool that uses Risk Assessment Charts and Momentary Assessment Technology to predict which individuals will later develop schizophrenia

Methods and expected results

Experience sampling data collected to assess stress sensitivity in the daily life of individuals with an at-risk mental state for psychosis in Amsterdam, London, and Melbourne will be used and combined with data on genetic risk and adverse environments. Linear mixed models will be used to test whether individuals with i) greater genetic risk (i.e. higher polygenic scores), ii) exposure to adverse social contexts and experiences (i.e. childhood adversity, neighbourhood-level social environment), iii) long-term cannabis (and other illicit drug) use, or iv) altered DNA methylation profiles experience stronger emotional reactions in response to minor daily hassles. These analyses will be probed further to investigate whether, in individuals with elevated stress sensitivity, psychotic experiences are more intense, more likely to persist and result in a transition to psychotic disorder. These analyses will generate evidence on stress sensitivity as a potential mechanism underlying the interplay of genes and adverse environments in the development of psychosis.

Data needed for the study: (please list the EU-GEI WP5 instruments)

- Experience sampling data on stress sensitivity
- Schedules for the assessment of social contexts and experiences: Childhood Experiences of Care and Abuse, Bullying, Social Environment Assessment Tool.
- Childhood Trauma Questionnaire (CTQ)
- Cannabis Questionnaire (+alcohol and drugs)
- Polygenic scores (i.e. generic and biologically-coherent/pathway scores) and DNA methylation profiles
- Family Interview for Genetic Studies (FIGS)
- CAARMS+
- Clinical Global Impression (CGI)

Plan for statistical analysis (overall strategy):

ESM data have a multilevel structure, such that multiple observations are nested within subjects. Linear mixed models will therefore be used to control for within-subject clustering of multiple observations. In a two-level model, multiple observations (level-1) will be treated as nested within subjects (level-2). First, models will be fitted with daily hassles as the independent variable and a) emotional reactivity or b) intensity of psychotic experiences as dependent variables, adjusting for potential confounding factors. Interaction terms for daily hassles and i) higher polygenic scores, ii) exposure to adverse social contexts and experiences (i.e. childhood adversity, neighbourhood-level social environment), iii) long-term cannabis (and other illicit drug) use, iv) altered DNA methylation profiles, v) persistence of attenuated psychotic symptoms (without transition), and vi) transition to psychotic disorder will then be added to this model. Exploratory analyses will be performed using moderated multilevel mediation analysis to test whether the impact of daily hassles as independent variable (level-1) on psychotic experiences as outcome variable (level-1) is mediated by emotional reactivity as mediator (level-1), with stronger indirect effects in individuals with i) higher polygenic scores, ii) exposure to adverse social contexts and experiences (i.e. childhood adversity, neighbourhood-level social environment), iii) long-term cannabis (and other illicit drug) use, iv) altered DNA methylation profiles, v) persistence of attenuated psychotic symptoms (without transition), and vi) transition to psychotic disorder.

Other analyses/methods: N/A
Involvement of external Parties (non EU-GEI): N/A
IPR check (Intellectual property rights): N/A
Timeframe: Start date: Date of completion of ESM data collection in Amsterdam, London, and Melbourne Month 2: Literature search; obtaining, merging, checking, cleaning of data (Milestone 1) Month 4: Completion of statistical analysis and first draft of manuscript (Milestone 2) Month 6: Manuscript submission (Milestone 3)
Additional comments: N/A