Synopsis no.: S2.42

Preliminary title: Polygenic risk and adverse environmental factors in Affective Psychosis.

Contact info for the person(s) proposing the synopsis

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Publication category:

Working and writing group:
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Others interested to contact Victoria

Work Packages involved:
WP2

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: Cathryn Lewis and Paul O'Reilly (SGDP, IOPPN)

Objectives (scientific background, hypothesis, methods, and expected results):
The importance of inherited factors for bipolar disorder and major depression is widely accepted. The Kraepelinian dichotomy distinguishing these disorders from schizophrenia has been questioned in the light of evidence showing shared genetic and environmental factors with schizophrenia, suggesting a continuum model instead of the current categorical one. Efforts are being focussed on delineating the genetic basis underlying the different psychiatry disorders, in particular through the development of polygenic risk scores for schizophrenia, bipolar disorder and depression.

Moreover, genetics is not the end of the story. A recent systematic review points as possible risk factors for affective psychotic illnesses, the exposure to viral infection, substance abuse and trauma; while another recent review found that early trauma was more often noted in bipolar adult patients than the general population. Nonetheless, it is still unclear to what extent environmental factors moderate the relationship between the genetic liability for affective psychosis disorders and the development of the illnesses.

Aims:

- To establish the clinical utility of different Polygenic Risk scores (PRS) for detecting and differentiating affective psychosis including Psychotic Depression and Bipolar Disorder from controls and from other psychotic patients;
- To examine the extent to which environmental factors and PRS have a synergic effect on phenotypic differences (affective/non-affective psychosis).

Methods:

Diagnoses from the OPCRIT system will be used to separate affective from non-affective psychosis as binary outcome and to construct symptom dimensions (mainly focusing on affective dimensions) as continuous outcomes. Polygenic scores for each individual will be calculated based on the latest PGC summary data for schizophrenia, bipolar and MDD. These will be combined with environmental exposures (cannabis, childhood trauma, urbanicity, migration) to predict the development of affective psychosis as binary outcome or the level of affective dimensions as continuous outcomes and among cases with affective psychosis to differentiate Bipolar disorder from major depression.

Hypothesis:

1. Respective PRSs will distinguish patients with affective psychosis from controls and from patients with non-affective psychoses. In particular, we expect that affective psychosis patients will have lower schizophrenia PRS and higher Bipolar and MDD PRS than non-affective psychosis.

2. Environmental data and PRS scores will explain significantly more variance in the different diagnoses under the umbrella of affective psychosis than using genetic data only.

Data needed for the study:

- Basic sociodemographic from MRC1 & 2
- OPCRIT (items)
- WP2 GWAS data
- Overall psychosis polygenic score (for schizophrenia, bipolar disorder and MDD)
- Environmental variables: CEQ (cannabis and other drugs), TAL (tobacco), CECA (Childhood Experiences of Care and Abuse), LEDS (Life Events and Difficulties Schedule), Urban environment during development, Migration.

Plan for statistical analysis (overall strategy):

1) To investigate how differences in the distribution of each PRS can predict diagnosis of affective psychosis, we will run models based on logistic regression for the different comparisons (bipolar vs controls, depression vs controls, bipolar vs depression and affective vs non-affective psychotic disorders). Basic demographics, country, site and Principal Components will be used as covariates in the analysis.

2) To investigate the role of Bipolar and MDD PRS in affective dimensions, we will perform factor analysis to construct the relevant dimensions (in collaboration with Diego Quattrone)

3) To study the potential relationship of the adverse environmental factors noted above to genetic load we will test for gene-environmental correlation or interaction. Models including environmental factors and their interaction with PRS will be compared to simpler models with likelihood ratio tests. Analyses will be conducted for each environmental factor separately and for a combined polyenvironmental risk score that we will calculate.

Other analyses/methods:

Involvement of external Parties (non EU-GEI):

IPR check:

Timeframe:
For project 1 (PRS prediction of affective/non-affective psychosis and dimensions): October 2017 to complete the analyses and December 2017 to prepare 1st draft of paper.
For project 2 (testing genetic and environmental prediction of affective psychosis): March 2018 to complete the analyses and June 2018 to prepare 1st draft of paper.

Additional comments: