Synopsis for EU-GEI Publication

Synopsis no.: *S2.58 /S6.9*

Preliminary title: The role of genetics of social withdrawal in the (environmental) pathway to psychosis

Contact info for the person(s) proposing the synopsis

Name: Eva Velthorst
Partner no: 8
e-mail address: eva.velthorst@mssm.edu/ e.velthorst@amsterdamumc.nl

Publication category:

Working and writing group:
Adam Socrates, Eva Velthorst, any members of WP2, 3 and 6 that would like to be involved.

Work Packages involved:
WP2, 3 and 6

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated:
P2, P3, P5, P7, P8, P21

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

Background
Social withdrawal is one of the primary negative symptoms of schizophrenia and related psychotic disorders (here forward: SCZ). In previous studies, we found that social withdrawal behaviour is already observable up to 15 years prior to first hospitalization for SCZ, and is one of the strongest risk factors of a clinical SCZ diagnosis in high risk samples (Velthorst et al., 2009; 2016).

The underlying mechanisms that drive the association between social withdrawal and SCZ are not yet understood. With advances in molecular genetic studies, we are now able to test several hypothesis that could help explain this association:

One possibility is that social withdrawal and psychosis have a shared genetic aetiology, but are not necessarily phenotypically connected (i.e. there is no causal path between social withdrawal and risk for SCZ). However, it not unlikely that a genetic vulnerability for social withdrawal may itself be on the causal pathway to psychosis development by increasing risk for social isolation and, as a result, from reality testing, ultimately leading to psychotic decompensation. Factors that determine whether individuals with an increased genetic vulnerability for social withdrawal do or do not express social withdrawal behaviour and go on to develop SCZ are not clear, but likely include environmental factors known to be associated with increased risk for SCZ. Specifically, it may be that individuals with an increased genetic vulnerability for social withdrawal that live in anonymous urban, or unsafe environments, or that recently migrated to an unknown area, are most prone to social isolation. In fact, this may help explain the well-established association between these factors and SCZ.

Recently, we performed a genome-wide association study (GWAS) on the behavioural aspects of social withdrawal in the UK Biobank and found 17 single-nucleotide polymorphisms at genome-wide significance, indicating a significant genetic component to behavioural traits of social withdrawal. In the Avon Longitudinal Study of Parents and Children (ALSPAC) and Philadelphia Neurodevelopmental Cohort (PNC), we found polygenic risk scores (PRS) derived from the social withdrawal GWAS predicted friendship scores, social anxiety, depression, avolition, and prodromal psychotic symptoms.

This suggests the genetic factors that drive behavioural aspects of social withdrawal may also have downstream effects on mental health outcomes and may possibly lie on the causal pathway between genetics, behaviour, and psychiatric disorders.

In order to map, in greater detail, the links between genetics, social withdrawal, and mental health outcomes, other factors associated with psychosis such as urbanicity, migration, and isolation should be explored with regards to the genetic factors involved in social withdrawal. Each of these is considered a risk factor for SCZ, but it is possible that behavioural genetics may at least partially drive the association. Further, as the cohort contains both controls and SCZ cases, it may be possible to ascertain whether or not the genetics of social withdrawal behaviour are associated with SCZ diagnosis, and if environmental traits linked to psychosis mediate this. In doing so, it will be possible to uncover a potential pathway from social withdrawal genetics to environmental factors to psychosis.

Aim

The overall aims of this project is to determine whether or not social withdrawal is genetically correlated with other risk factors for schizophrenia and related psychotic disorders (SCZ), with a specific focus on traits pertaining to urbanicity and migration. Further, we aim to determine whether or not there is pathway between social withdrawal genetics to SCZ diagnosis via environmental mediators such as the above traits.

Methods

1) Polygenic risk scores (PRS) will be derived for the EUGEI cohort using genotype data and the recent social withdrawal GWAS summary statistics.

2) These PRS will be used in regression analyses for the phenotypes of interest, including social environment and social demographic outcomes.

3) These PRS will also be used to predict schizophrenia (SCZ) case/control status in the cohort. Other mental health outcomes available will also be predicted.

4) If the PRS are able to predict SCZ case/control status, additional mediation analyses will be used to find environmental mediators between social withdrawal PRS and SCZ case/control status.

Hypothesis

1) Social withdrawal polygenic scores will predict traits associated with psychosis, as per our previous study, as a replication.

2) Social withdrawal polygenic scores will predict worse social environments e.g. isolation, lower SES, urbanicity and migration

3) Social withdrawal polygenic scores will predict SCZ case/control status in the cohort.

4) The relationship between social withdrawal polygenic scores and SCZ is likely mediated by urbanicity, isolation, lower SES and migration.

Expected results

As we have already ascertained that the social withdrawal polygenic scores are able to predict outcomes related to social behaviour and anxiety, it is expected that these relationships may also include urban factors, lower SES, and migration. This is because urban environments are often

considered isolating, and as such genetic factors contributing to social withdrawal behaviour may also influence behaviours that might lead to migration to urban environments. These are likely to have downstream effects on psychosis, so we may also see an association between social withdrawal genetics and SCZ diagnosis, mediated by these environmental factors.

References:

Velthorst E, Reichenberg A, Kapara O, Goldberg S, Fromer M, Fruchter E, et al. Developmental trajectories of impaired community functioning in schizophrenia, JAMA Psychiatry. 2016 Jan;73(1):48-55.

Velthorst E, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, Klaassen R, et al. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophrenia Research 2009; 109 (1-3): 60-5

Data needed for the study:

- WP2 & WP6 GWAS data
- basic CEQ information (cannabis and other drugs);
- GAF
- OPCRIT (items); TAL (tobacco);
- SIS-R;
- CAPE;
- Detailed sociodemographic from MRC1 & 2, including the social environment assessment tool & urbanicity information
- WAIS (IQ)
- Hamilton Depression Scale
- Hamilton Anxiety Scale

Plan for statistical analysis (overall strategy):

1) PRSice will be used to generate polygenic risk scores for social withdrawal using our existing genome wide association study.

2) Logistic and linear regressions will be used to regress the phenotypes of interest on these scores, controlled for age, sex, SES, and 10 principle components.

3) Mediation analysis to infer a pathway from polygenic scores to mental health outcomes including SCZ via significantly predicted traits of interest.

Other analyses/methods:

None

Involvement of external Parties (non EU-GEI):

IPR check:

Timeframe:

March 2022: Polygenic score analysis
March 2022: Mediation/MR analysis
April 2022: Paper write-up
May 2022: Paper write-up and submission

Additional comments:
None