Synopsis no.: S5.5

Preliminary title: Social withdrawal, daily life stressors and psychotic experiences in patients with an At Risk Mental State for developing a psychotic disorder

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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:

ESM group (Inez Myin Germeys, Eva Velthorst, Barnaby Nelson, Uli Reininghaus, Jim van Os), Lieuwe de Haan, Carin Meijer, Abraham (Avi) Reichenberg and WP5 author group.

Work Packages involved: WP5

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

Several longitudinal studies have underscored social withdrawal as one of the most important risk factors of transition to a psychotic disorder in ARMS samples (e.g. Velthorst et al., 2009; Yung et al., 2006; Cannon et al., 2008). More recently, in a cohort of more than half a million male Israeli adolescents, we found social engagement to be already impaired up to 15 years prior to first hospitalization, with a sudden decline in the years prior to illness onset. Again, social withdrawal appeared to contribute most to the prediction of psychosis; more than other social constructs and established risk factors such as SES, IQ and migration status (Velthorst, Reichenberg et al., in preparation). While these results clearly indicate that social withdrawal can no longer be ignored in the pathway to schizophrenia, research to date largely overlooked factors that could account for this phenomenon. As a consequence, it is still unclear whether social withdrawal is indicative of genetic liability, a marker of the illness, or a social risk factor (independent of, or modified by, genetic risk).

One possibility is that people tend to withdraw in reaction to psychotic experiences (or daily stressors), which, because thoughts are no longer tested among peers, eventually accelerate into e.g. clear paranoid delusion. It may, however, be that individuals report more intense psychotic experiences in response to social withdrawal instead of primarily the other way around. Alternatively, those with a greater genetic risk for developing schizophrenia possibly have a greater tendency to withdraw in response to psychotic experiences (and/or daily hassles) than others. Also, genes predisposing to

psychosis may, among other symptoms, also predispose to social withdrawal. In this case, social withdrawal would occur alongside psychotic symptoms but they would have no direct relationship to each other.

Key questions

Using ESM data, with the present proposal we aim to investigate social withdrawal behaviour in ARMS and healthy control subjects in daily life. We will investigate the associations between the amount and quality of social contact, psychotic experiences and daily life-stressors (defined as distinctive unpleasant events in daily life) in the development of a psychotic disorder by examining the moment-to-moment and daily variation in social withdrawal patterns in response to psychotic symptoms and daily stressors and vice versa. In addition, we aim to examine whether social withdrawal in high-risk samples is associated with worse outcomes.

We will address the following hypotheses:

1. Social withdrawal (i.e. being alone) is (temporarily) associated with psychotic experiences and daily life stressors in an ARMS sample;
2. These associations are modified by higher polygenic scores, and;
3. Higher levels of social withdrawal are associated with poorer functional outcome, persistence of attenuated psychotic symptoms (without transition) and transition to psychotic disorder.

Methods and expected results

Experience sampling data collected to assess psychotic experiences, the frequency and quality of social contact, and 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 functional outcome.

- **(Baseline and follow-up) ARMS and control data needed for the study:**
- Experience sampling data on psychotic experiences, daily stressors and social contact
- Polygenic scores
- Family Interview for Genetic Studies (FIGS)
- CAARMS+
- Clinical Global Impression (CGI)
- GAF scores

NB: all measurements requested will solely be used in relation to ESM data.

Plan for statistical analysis (overall strategy):

Following the core ESM paper, we will make use of linear mixed models to control for within-subject clustering of multiple observations. First, models will be fitted with psychotic experiences (or daily stressors) as the independent variable(s) social withdrawal as dependent variable, adjusting for potential confounding factors. Second, two-way interaction terms for psychotic experiences (or daily stressors) x higher polygenic scores will be added to these models. Third, a separate analysis will be conducted to examine whether higher levels of social withdrawal are associated with poorer functional outcome, persistence of attenuated psychotic symptoms (without transition) and transition to psychotic

disorder. Finally, time-lag analysis will be used to explore whether psychotic experiences (or daily stressors) precede social withdrawal, or vice versa.
Other analyses/methods: N/A
Involvement of external Parties (non EU-GEI): Icahn School of Medicine at Mount Sinai (Eva Velthorst, Avi Reichenberg)
IPR check: 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 Month 4: Completion of statistical analysis and first draft of manuscript Month 6: Manuscript submission
Additional comments: N/A