Synopsis no.: *S2.44*

Preliminary title:

The influence of paternal age on dimensions of attenuated psychosis (psychotic experiences/ schizotypy) and on risk for psychosis

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WP2, WP3

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated:
All partners/sites involved in WP2 and WP3

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

1. Scientific Background/ objectives

1.a. Background

Advanced paternal age (APA) has been associated with an increased risk for schizophrenia (e.g. Wohl & Gorwood, 2007) and other neurodevelopmental disorders. Indeed, compared to offspring of fathers 25-30 years old, offspring of fathers in their mid 30s or older have an increased risk (RR=1.2 or more) to develop schizophrenia (Gratten et al, 2016). Given the worldwide trend of increasing parental age and the importance of understanding the aetiology of schizophrenia, it is not surprising that numerous studies and reviews examined the importance of this putative risk factor and attempted to unravel the mechanisms by which it increases the risk.

The fact that a similar increase in risk is not seen with mothers' age pointed to the possibility of de novo mutations in the germ lines as a potential explanation for these findings (contrary to ovum, number of cell divisions and the potential of de novo mutations in the sperm lines increase with age) (de Kluiver et al, 2016).

An alternative hypothesis states that the association between APA and increased risk of schizophrenia is not causal but the result of common (genetic) factors associated with both delayed fatherhood and risk for schizophrenia. This hypothesis is based on the observation of a stronger association between risk for schizophrenia and age of fatherhood (age of father at the birth of his first child) than between risk for schizophrenia and the father's age at birth of the index case (Petersen et al, 2011).

Along with these two principal hypotheses, two other alternative explanations have been suggested: the existence of epigenetic changes (age related DNA methylation in imprinted regions) and the existence of environmental factors associated with APA (e.g. risk of fathers' death during childhood, which increases the risk of schizophrenia, urbanicity, etc.) (Janecka et al, 2017).

To date, the exact mechanism (or mechanisms - as the above hypotheses are not mutually exclusive) is not known.

Schizotypy and/or psychotic experiences have been linked at the phenomenological (clinical picture) and aetiological level to schizophrenia. They have been conceptualized as categorical constructs or, echoing a growing body of evidence, as continuous or dimensional constructs (Bentall et al. 1989, Stefanis et al. 2002). Psychometric schizotypy (defined as continuously measurable traits of schizotypy/ attenuated psychosis) has been increasingly used to deepen our understanding of the aetiology, expression and development of the entire schizophrenia spectrum disorders as an alternative approach to case-control studies (Nelson et al. 2013; Barrantes-Vidal et al. 2015; Debbané et al. 2015). Research using the schizotypy/attenuated psychosis paradigm benefits from the stability of traits over time (Venables and Raine 2015) and from the absence of some of the confounding factors present in clinical populations of schizophrenic patients (e.g. the effect of pharmacological treatments and hospitalisation) (Schürhoff et al. 2005).

Beyond this theoretical interest, the study of risk factors associated with schizotypy/attenuated psychosis is worth in itself as schizotypy has been associated with psychiatric comorbidity (anxiety, depression – Lewandowski et al, 2006), handicap (Pulay et al, 2009) and altered quality of life (Cohen and Davis, 2009).

At our knowledge, only one study testing the hypothesis of an association between psychometric schizotypy and APA has been published (Grattan et al, 2015). In this study, the authors found that positive schizotypy has opposite associations with father's age (positive correlation) and mother's age (negative correlation) (No association with negative schizotypy or disorganisation has been observed). However, this study had several limitations: it is based on a sample limited in size and variation (only undergraduate students) and the authors had not the possibility of (directly) exploring the (genetic) mechanisms of the association.

In the EU-GEI study (WP2), there are large samples of cases with psychosis (either affective or non-affective), controls and relatives. In controls (and relatives) continuous measures of dimensions of attenuated psychosis (schizotypy and/or psychotic experiences) are available (CAPE, SIS)

Are also available fathers' age at birth of the subject and other detailed data on risk factors - genetic and environmental - that allow for testing the hypothesis of an association and the putative mechanism(s), taking into account the potential cofounders.

1.b. Objectives

The first objective is to test the association of APA with risk for affective and non-affective psychoses (case-control study) and, in controls (and sibs) with positive and negative dimensions of attenuated psychosis (psychotic experiences/ schizotypy).

The second objective is to test the role of the different mechanisms in this association by assessing the influence of selected variables on the link between case status (or attenuated psychosis measures) and APA. The characteristics compared have been linked to the different alternative hypotheses (see bellow).

2. Hypotheses

The main hypothesis is that psychosis risk and the positive dimension of attenuated psychosis are associated with increased APA.

Based on previous theoretical work (Gratten et al. 2016), we expect to find more arguments in favour of the hypothesis of increased APA associated with inherited vulnerability to the schizophrenia continuum.

3. Methods

3.1. Centres included

All centres participating in WP2

3.2. Subjects included

All subjects for which diagnosis (for cases) or measures of schizotypy/ psychotic experience (i.e. CAPE and SIS measures - for controls and sibs) are available along with paternal age at birth.

3.3. Dependent variables

Diagnosis (either affective or non-affective psychosis) will be used for analyses of increased risk.
For the association with quantitative (continuous) measures of attenuated psychosis the best variables to be used (derived from CAPE and/or SIS) will be selected based on the analyses from another synopsis (S.2.23).

3.4. Explanatory variables

Fathers' age at birth of the subject is the principal variable of interest.

In the first series of analyses (association with diagnosis or with dimensions of attenuated psychosis), several potentially confounding factors will be used including (but not necessarily limited to): age, sex, mothers' age at birth at the index subject, ethnic origin, socio-economic level of father/mother.

The second series of analyses will test arguments in favour of (and the part of the association explained by) the different mechanisms.
To this end, the influence of several variables (each of them in favour of a different mechanism) on the strenght of the association between the dependent variables and father's age will be tested. These variables include (but are not necessarily limited to):
- family history of schizophrenia and (when available from WP3) the Polygenic Risk Score (PGRS) for schizophrenia (contrasted results expected under the de novo mutation vs. common genetic factors hypotheses; absence of a significant influence in favour of the first hypothesis [i.e. de novo mutations]);
- age at fatherhood (age of fathers at birth of their first child) for fathers and also (when available) of index cases (to directly test an association of schizotypy with late fatherhood) - based on data from the FIGS (contrasted results expected under the de novo mutation vs. common genetic factors hypotheses; in favour of the second hypothesis - a greater influence of age at fatherhood than of age of father at birth);
- environmental factors potentially associated with APA (e.g. childhood trauma/ traumatic events - including fathers' death) - attenuation of the association between paternal age and the dependent variables being in favour of an explanatory role of these factors;
- epigenetic changes (methylation) in imprinted regions (as data are available from WP3) - same justification as above.

3.5. Statistical analyses

General linear modelling of the dependent variables (after, if needed, transformation of dependent and/or explanatory variables)

Data needed for the study:

For each subject (from partners): diagnosis and/or SIS and CAPE data, fathers age and data on other potentially explanatory variables (see above) or potential confounding factors, e.g. basic demographics (age/ gender etc.).
Part of the variables of interest will be the result of other, preceding, analyses (e.g. best measures for schizotypy, PGRS etc.).

Plan for statistical analysis (overall strategy):

As detailed above we will proceed using a two steps strategy: - first we will use confirmatory analyses (to ascertain the influence of APA on risk for psychosis or attenuated psychosis scores) - second exploratory analyses to test the arguments in favour of the different putative mechanisms
Other analyses/methods: none
Involvement of external Parties (non EU-GEI): No
IPR check:
Timeframe: - Studies for the first series of analyses could be started as soon as the results of the analyses on the best measures of schizotypy are available (and all other needed data availale) - Second series of study will depend on the availability of the data (e.g. from WP3) - Time to first draft of the study - 6 months from availability of data
Additional comments: The present proposal specifies a previous, more general, proposal (synopsis S2. 24) and expands it (mainly by including case-control analyses)

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