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1. Title:

Neurodevelopmental influences in youth at high risk for psychosis: a multimodal diagnostic and prognostic model integrating genetic, environmental and neuroimaging data.

2. Scientific abstract:

Background: Schizophrenia (SZ) and Bipolar Disorder (BD) are considered nosologically distinct but they co-segregate in families and are characterised by extensive genetic sharing. Cognitive and brain imaging abnormalities could lie on a continuum of severity across the two disorders, possibly reflecting a gradient of neurodevelopmental load associated with vulnerability for psychotic disorders.

Aims: The study will examine children and adolescents who are at high risk (HR) of developing SZ or BD because they have an affected parent. It will employ data-driven approaches in order to cluster participants based on cognitive function rather than parental diagnosis. Such approach aims to dissect the cognitive heterogeneity observed in both SZ and BD offspring and address questions related to neurodevelopmental mechanisms. The study will employ cognitive function as a proxy measure of neurodevelopmental load and a) assess its effect on brain structure and connectivity, b) examine longitudinal trajectories of brain development across childhood and teenage years, c) examine the relationship between cluster membership and accumulated genetic risk for SZ and BD d) predict clinical symptoms across the psychotic spectrum and between categories identified based on neurodevelopmental load.

Methods: The study will examine the largest cohort of genetic HR children and adolescents in Spain, with a total of 140 HR participants (90 BD offspring, 50 SCZ offspring) and 80 healthy controls. Participants have been assessed using clinical, cognitive, genetic, and MRI measures at baseline and at two and four-year follow-up.

Analyses: Participants will be clustered based on measures assessing multiple areas of cognitive function. Structural MRI data will be examined with a cross-sectional and a longitudinal approach in order to examine trajectories of brain development. Genetic risk will be examined computing the polygenic risk score for schizophrenia and for bipolar disorder. The above measures will be integrated in machine based learning models in order to discriminate between groups and also predict functioning at follow-up.

3. Keywords: Schizophrenia, Bipolar Disorder, High-risk, Neurodevelopmental, Clusters