

Synopsis for EU-GEI Publication

Synopsis no.: S5.30
Preliminary title: Brain structure correlates of urban upbringing in individuals in the early stages of psychosis.
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Publication category: 3 Publications from one work packages involving only some parties in the Work Package
Working and writing group: Stefania Tognin, Matthew Kempton, Andrea Mechelli, James Kirkbride, Evangelos Vassos, Lucia Valmaggia, Philip McGuire and WP5 collaborators
Work Packages involved: WP5
Partners involved from whom candidate co-authors (<i>additional to working and writing group</i>) should be nominated:
Objectives (scientific background, hypothesis, methods, and expected results): Urban upbringing has been consistently associated with increased risk of psychosis and mental illness (March et al., 2008; Vassos et al., 2012) however the possible mechanisms that contribute to increased vulnerability are yet to be clarified. Previous studies have shown that urban upbringing has an effect on the brain structure (Haddad et al., 2014) and function (Lederbogen et al., 2011) of healthy individuals. The aim of this study is to investigate the effect of urban upbringing in a group of individuals at clinical high risk of psychosis (CHR) and in a group of matched healthy controls (HC). CHR and HC participants will be stratified along an urban-rural gradient (Haddad et al., 2014). Details about each participants' place(s) of residence from birth to age 18 (i.e. minimum age required to enter the study) will be converted into a Urbanicity Score. Specifically, for each place of residence a web-based search will be performed to establish i) the population size of place of residence and ii) the population density. Once this information is obtained 1 to 3 categories will be assigned depending on the number of inhabitants. Categories scores will be then multiplied by the number of years spent in that residence in order to obtain a final cumulative Urbanicity Score. A whole brain analysis as well as a region of interest (ROI) analysis will be carried out to identify those brain areas that are associated to urban upbringing. Specifically, regions that were found to be associated with social stress will be included in the ROI analysis: hippocampus, amygdala, and the perigenual anterior cingulate cortex (pACC). The following hypotheses will be tested: <ol style="list-style-type: none">1. Irrespective of the diagnosis, participants with a higher urbanicity score will show more pronounced total gray matter volume loss compared to those participants with a lower urbanicity score.2. Irrespective of the diagnosis, participants with a higher urbanicity score will show more pronounced total gray matter volume loss in the chosen regions of interest.3. The interaction diagnosis x Urbanicity Score will show that UHR individuals have consistently more pronounced structural abnormalities in the regions of interest than healthy controls.
References:

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- Haddad L, Schäfer A, Streit F, Lederbogen F, Grimm O, Wüst S, Deuschle M, Kirsch P, Tost H, Meyer-Lindenberg A. Brain structure correlates of urban upbringing, an environmental risk factor for schizophrenia. *Schizophr Bull.* 2015 Jan;41(1):115-22. doi: 10.1093/schbul/sbu072. Epub 2014 Jun 3
- Lederbogen F, Kirsch P, Haddad L, et al. City living and urban upbringing affect neural social stress processing in humans. *Nature.* 2011;474(7352):498–501.
- March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, Susser E. Psychosis and place. *Epidemiol Rev.* 2008;30:84–100. [PubMed]
- Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM. Meta-analysis of the association of urbanicity with schizophrenia. *Schizophr Bull.* 2012;38:1118–1123.

Data needed for the study:

Main analysis: data from CHR, and HC

- Baseline Structural MRI data
- Postcodes of places where UHR and HC have been living up till the date of study entry and current postcode.

Covariates: data from CHR and HC

- Baseline socio-demographic data (e.g. age, gender)
- CAARMS baseline and follow-up to establish diagnosis
- SCID baseline and follow-up to establish diagnosis
- Indicators of socioeconomic status (subject and parental)
- estimate of IQ
- -Mental illness in first degree relatives (FIGS)

Plan for statistical analysis (overall strategy):

Structural imaging data will be analyzed using a Voxel Based Morphometry approach.

Details about each participants' place(s) of residence from birth to age 18 will be converted into a Urbanicity Score as described above.

The effect of urbanicity on gray matter volume will be tested in a multiple regression analysis with the urbanicity score as covariate of interest.

The potential interaction between diagnosis and urbanicity score will be tested using an ANOVA with diagnosis and centre as factor and diagnosis by urbanicity score as covariate of interest.

To account for possible confounds, gender, age, IQ, socio-economic status of subject and parents, mental illness parents will be included as nuisance covariates.

Other analyses/methods:

Involvement of external Parties (non EU-GEI):

Dr Andrea Mechelli

IPR check:

Timeframe:

Determining Urbanicity Score (see below) = 6-9 months

Data analysis = 3 months

Writing up = 3 months

Additional comments:

-Calculating the Urbanicity Score for all the UHR and HC participants for each participating site will be completed within an estimated time of 6-9 months. This will involve establishing the population size and population density of each place of residence in which the participants have been living till the date of study entry.