

## Synopsis for EU-GEI WP5 Publication

<b>Synopsis no.: S5.10</b>
<b>Preliminary title:</b> Structural MRI of Childhood Adversity in the At-Risk Mental State for Psychosis (PhD of Maria Calem)
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<b>Publication category: 3</b> Publications from a single work package involving only some parties (or in some cases only one party) in the Work Package
<b>Working and writing group:</b> Maria Calem, Matthew Kempton, Craig Morgan, Philip McGuire and other interested individuals within WP5
<b>Work Packages involved:</b> WP5
<b>EU-GEI Partners involved from whom candidate co-authors (<i>additional to working and writing group</i>) should be nominated:</b> IoP and other interested centres within WP5
<b>Objectives (scientific background, hypothesis, methods, and expected results):</b>  This projects aims to clarify the neuroanatomical changes associated with childhood adversity in the At-Risk Mental State (ARMS) using structural magnetic resonance imaging (MRI) scans. This study will focus on region-of-interest analysis of brains structures that either form the HPA-axis (the hypothalamus and pituitary gland) or affect its activity, such as the hippocampus and amygdala. Research into the neuroanatomy of childhood adversity has been criticised for restricting itself purely to region-of-interest analysis (Hart and Rubia, 2012), in that there may be regions that are relevant to childhood adversity that are not been identified in more targeted analysis. This study will also therefore include a voxel-based morphometry approach, which will allow for a whole-brain, unbiased analysis, and may identify other brain regions relevant to childhood adversity in ARMS.  A second aim of the project is to investigate whether in ARMS a history of childhood adversity increases sensitivity to stress later in life. Participants are followed up over two years, and re-scanned up to three times at follow-up: at 6, 12 and 24 months. This will allow for the investigation of: what changes in brain structure over time are associated with the number of stressful life events experienced, and whether within an ARMS sample, people with a history of childhood adversity show greater structural changes in response to stressful life events, suggesting a greater sensitivity to stress.  Lastly, the study will investigate whether childhood adversity is associated with poorer functional outcomes and greater symptom severity in the ARMS, and whether structural brain changes mediate these associations.  This project will aim to investigate the following hypotheses:  1. Childhood adversity will be associated with altered volume of HPA-axis-related brain structures in the

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At-Risk Mental State, namely: reduced hippocampal, hypothalamic and amygdala volume and increased pituitary volume. VBM analysis will identify associations between childhood adversity and reduction in the frontal lobe regions in ARMS

2. Recent stressful events will be associated with volumetric changes of HPA-axis-related brain structures over time in the At-Risk Mental State, and that those with a history of childhood adversity display greater stress sensitivity, as suggested by greater volumetric changes in response to recent stressful events.

3. Childhood adversity will be associated with worse functioning at baseline, and a greater decline in function over time. Altered volume of HPA-axis related brain structures will mediate this association between childhood adversity and functional decline.

### **Data needed for the study: (please list the EU-GEI WP5 instruments)**

- Baseline Structural MRI data (longitudinal MRI data will come from Matthew Kempton's MRC Fellowship)
- Childhood Experiences of Care and Abuse Questionnaire (CECA-Q)
- Childhood Trauma Questionnaire (CTQ) and
- Bullying Questionnaire. List Of Threatening Experiences.
- CAARMS
- SCID
- Global Assessment of Functioning

### **Plan for statistical analysis (overall strategy):**

I will compare the volume of regions of interest (ROI) in cases with and without a history of childhood adversity using a general linear model. I will repeat this process using the VBM data, to compare individual differences in brain structure associated with childhood adversity in cases.

To examine the impact of recent stressful life events on brain structure, I will run an analysis of covariance to assess associations between the number of recent stressful events and changes in ROI volumes. Using data from the VBM analysis, I will run a voxel-wise correlation analysis between the number of recent stressful life events and the difference in grey matter volume between consecutive scans.

I will investigate whether a history of childhood adversity moderates the association between the number of recent stressful events and volumetric changes in relevant regions of interest by entering childhood adversity history and number of stressful life events as an interaction term.

In addition, I will test whether childhood adversity is associated with decline in function (as measured by the GAF) in cases using repeated measures analyses of variance to compare the mean GAF scores in cases with and without childhood adversity over time.

Finally, I will carry out a mediation analysis to study whether changes in brain structure mediate the relationship between childhood adversity and decline in function (as measured by the GAF) in cases.

Linear mixed effects regression models will be used to testing these hypotheses while accounting for correlation of participant characteristics within research centres and heterogeneity between research centres.

### **Other analyses/methods:**

N/A

### **Involvement of external Parties (non EU-GEI):**

N/A

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**IPR check (Intellectual property rights):**

**N/A**

**Timeframe:**

Start date: Once WP5 data has been collected and initial data cleaning is complete

Analysis: 4 months

Write up: 2 months

**Additional comments:**

**N/A**