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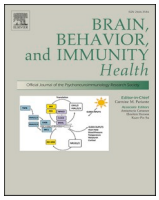

The eBRAIN study: The impact of early adversity on trajectories of brain maturation and mental health in young adolescents – A prospective cohort study

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A B S T R A C T

Introduction: More than 1 in 10 people are thought to experience a mental health problem during adolescence, with most adult psychopathology beginning during this time. Experiences of stress or adversity during childhood are important risk factors for poorer mental health outcomes and are also associated with alterations in neurodevelopment. There is evidence to suggest that this relationship is mediated by inflammation and the immune system. The eBRAIN study (The Impact of Early Adversity on Trajectories of Brain Maturation and Mental Health in Young Adolescents) will assess how early life adversity might affect trajectories of brain development throughout adolescence, whether these neurobiological changes are associated with psychopathology, and if they can potentially be explained by an activation of the immune system.

Methods: A cohort of 220 adolescents between the ages of 11–14 will be recruited into this study. Each participant will complete three study visits, each one year apart, at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, London (UK). At each study visit, they will be assessed with structural and functional MRI scans, biological sample collection as well as questionnaires and interviews to collect demographic information, assess experiences of adversity, and details of psychopathology. The study will also collect information about factors such as diet and nutrition, physical exercise, and cognition.

Ethics and dissemination: Ethical approval for this study has been received by King's College London Research Ethics Committee (REC reference: HR-18/19–9033). Findings from the study will be published in peer-reviewed journals and disseminated at national and international conferences. Patient and public involvement (PPI) is an important component of the study, 'Study Champions' recruited from participants, their parents and teachers at collaborating schools have been invited to take an active role in study governance and dissemination.

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1. Strengths and limitations

1.1. Strengths

- The study design will enable the collection of unique longitudinal data in a school-based adolescent population and will include a combination of psychosocial data and biological and neuroimaging data.
- The eBRAIN cohort does not consist of adolescents 'at risk' of mental health problems; instead, it consists of adolescents recruited from schools, and the results will therefore be widely generalisable to the general population.

1.2. Limitations

- Due to a pause in study assessment during the COVID-19 pandemic and subsequent government restrictions, some participants will have a longer follow-up interval. We have made every effort to minimise this delay and will employ growth-curve methods for data analysis which will account for variability in measurements.

2. Background

2.1. Mental health and neurodevelopment in young people

Adolescence is a key developmental period for the emergence of mental health problems. A 2017 survey by the UK Office for National Statistics found that 1 in 8 young people aged 5–19 had experienced at least one form of psychopathology (Mental Health of Children and, 2017). However, a recent publication by the Resilience, Ethnicity and AdolesCent Mental Health (REACH) study found the numbers to be higher and closer to 1 in 5 adolescents, and hypothesised that the prevalence of mental health problems is elevated in inner-city London compared to national samples (Knowles et al., 2021).

Furthermore, a large proportion of adult mental illnesses commence during adolescence, with 50% becoming apparent before the age of 15 (Kim-Cohen et al., 2003). During adolescence, the brain goes through a period of intense development, with a pre-pubertal increase in grey matter volume combined with neuronal growth, which is followed by a post-adolescent stage of dendritic pruning (JN et al., 1999). It is therefore crucial to investigate adolescent mental health and neurodevelopment at multiple time points over time rather than cross sectionally.

2.2. Adversity in young people can lead to mental health problems

Evidence suggests that the risk of developing mental health problems including anxiety, depression and psychoses is increased by exposure to early adversity and stress (Masten and Garmezy, 1985; Li et al., 2016). However, the definition of adversity in the literature is heterogeneous and includes area-level and socioeconomic adversity, such as deprivation, pollution, over-crowding, and individual experiences of adversity such as maltreatment, experiences of bullying and familial separation. These experiences have all been shown to be associated with an increased risk of psychopathology and of poorer functional and social outcomes (Dube et al., 2003). Of note, the presence of factors such as better cognitive abilities or positive interpersonal relationships, can help mitigate the association between early adversity and psychopathology and can lead to improved outcomes (E V- and DS, 2008). This study will capture information on a wide range of different forms of adversity and protective factors in order to explore their potentially different associations with adolescent development and psychopathology.

2.3. Early adversity is related to neurobiological changes

Several studies have shown that experiences of early life adversity are associated with brain morphological changes in adulthood, particularly in brain regions like anterior cingulate cortex, hippocampus, amygdala, dorsolateral prefrontal cortex, and dorsolateral orbitofrontal cortex (Gollier-Briant et al., 2016; CM et al., 2013; Mondelli et al., 2011; Teicher et al., 2016)'. The anterior cingulate cortex plays an important role in emotion regulation and is the area most frequently reported as being altered by experiences of childhood adversity (MH et al., 2016). Furthermore, this region is thought to attenuate the response of the amygdala, which is involved with emotion regulation and threat response (MH et al., 2016). Similarly, the orbitofrontal cortex is thought to regulate emotional responses through modulation of the amygdala (MH et al., 2016). The hippocampus is a stress-sensitive structure that has long been associated with learning and memory but which also plays an important role in mood regulation (McEwen et al., 2016). With their role in emotion and mood regulation, these structures are thought to be highly relevant to the development of psychopathology. From animal models, limbic system structures such as the amygdala and the hippocampus have also been found to be susceptible to stress, making them key areas to study in relation to childhood adversity (Morey et al., 2016).

More recently, morphological changes in these areas have also been found in adolescents and young adults who had experienced various forms of early life adversity or stress (KG et al., 2015; Jensen et al., 2015). However, previous studies that have reported this relationship have been mostly cross-sectional, with most longitudinal studies usually limited to acquiring only two MRI scans (McLaughlin et al., 2019). As adolescence is a key developmental period with a non-linear trajectory of neuronal growth, it is essential to study the development of these brain areas at multiple time points and over a longer period in this demographic group.

2.4. Inflammation can play a role in the relationship between early adversity and brain development and psychopathology

Many studies have demonstrated that early life adversity is associated with chronic activation of the immune system. In particular, higher levels of inflammatory biomarkers such as Interleukin-1 (IL-1) and C-reactive protein (CRP) have been reported in the blood of adults with a history of early adversity, as confirmed by a recent meta-analysis (Danese et al., 2007). In one study, higher levels of IL-6 and of the main stress hormone cortisol, together with low levels of the brain-derived neurotrophic factor (BDNF), were found to explain more than 70% of the variance in hippocampal volume found at illness onset in patients with first episode psychosis (Mondelli et al., 2011). Previous research has identified a molecular link between an increase in immune system activation and different trajectories of neuronal development through a reduction of neurotrophic factors and the initiation of neurogenesis (Zunszain et al., 2011). Taken together, these findings suggest that the activation of the immune system could be an important factor in the relationship between adversity and changes in neurodevelopment.

2.5. Diet can contribute to immune system activation

There is evidence to suggest that diet could contribute to immune system activation and could therefore play a part in the mediation of the relationship between early life adversity and alterations in neurodevelopment. Certain diets which are rich in fruits, fibre and vegetables, like the Mediterranean diet, have an anti-inflammatory effect and are associated with lower blood levels of inflammatory cytokines such as IL-6 and TNF alpha (R, 2010). It has been proposed that the anti-inflammatory effect of these diets is due to the high level of polyphenols contained in these foods. Polyphenols have been shown to downregulate different elements of the inflammatory system, including the synthesis of proinflammatory cytokines (Capiralla et al., 2012) and immune cell regulation (González et al., 2011). We will be able to validate participants' self-reported dietary patterns with measurements

of polyphenol and other food-related metabolites present in urine. This study will enable the analysis of longitudinal changes in both food-derived metabolites and levels of inflamatory cytokines, providing a unique opportunity to assess the relationship between dietary patterns, the immune system, brain development and psychopathology in the context of early adversity.

2.6. Aims and objectives

Our primary aims are to establish: 1) How and when individual and area-level early adversity affect brain development and function (i.e., longitudinal growth trajectory of brain areas involved in psychiatric disorders, built on three longitudinal brain MRI scans); 2) Whether growth trajectories are associated with the onset of specific psychopathology domains; 3) If alterations in growth trajectory are explained by persistent alterations in the levels of inflammatory markers; and finally 4) Whether dietary factors associated with immune activation are also associated with trajectories of immune function, brain development and psychopathology.

2.7. Primary objective

Objective 1. Do experiences of childhood adversity impact neurodevelopmental trajectories during adolescence?

2.8. Secondary objectives

Objective 2. Does altered neurodevelopment following childhood adversity underlie the onset of psychopathology?

Objective 3. Does increased inflammation mediate the relationship between childhood adversity and altered neurodevelopment?

Objective 4. Are diet and its metabolites associated with increased immune activation and psychopathology in adolescents with and without adversity?

3. Methods and analysis

3.1. Data collection plan

Participants will be assessed on three separate occasions, one year apart. At each study visit, data will be collected on socio-demographic characteristics, and an interview will be conducted to assess experiences of adverse events and psychopathology. Participants will also undergo biological sample collection and an MRI scan.

3.2. Questionnaires and interviews

Adverse experiences during childhood will be measured using questions from a number of validated questionnaires, including for example the Olweus Bully/Victim Questionnaire (Solberg and Olweus, 2003), the Threatening Life Events Questionnaire (Heubeck and O'Sullivan, 2007), the Childhood Experience of Care and Abuse Questionnaire (Brown and Harris, 1994) as well as from data on area-level disadvantage and population density. These will assess participants' experiences during childhood of several different harmful events including bullying, physical and emotional abuse, injury or illness and familial separation.

Participants will complete the Development and Wellbeing Assessment (DAWBA) which assesses several different symptoms of psychopathology including depression, anxiety, attention deficit as well as social competencies. The first section of the DAWBA comprises the Strengths and Difficulties questionnaire (SDQ). The SDQ comprises five subsets scores which can be combined to estimate the presence and severity of internalising and externalising symptoms (Goodman and Goodman, 2009). We will also administer the Child and Adolescent Psychotic Experiences Questionnaire (CAPE) which assesses the presence of psychotic experiences. Finally, at all three time points we will administer the Weschler Abbreviated Scale of Intelligence (WASI-II), which consists of verbal and matrix reasoning subscales, to obtain an estimate of general cognitive ability.

At each study visit participants will complete the Food Frequency Questionnaire (Lietz et al., 2002) and the Intake 24 (24-h food diary) (Simpson et al., 2017) that provide details of diet quality and an estimate of diet nutrients.

3.3. Neuroimaging

Participants will undergo an MRI scan with both structural and functional sequences at three time points (one year apart). Scans will be acquired on a 3.0 T MR scanner (General Electrics) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience. We will acquire a conventional volumetric MRI sequence (MP-RAGE) based on the ADNI protocol (http://adni.loni.ucla.edu/research/protocols/mri-protocols/). We will also acquire a resting state functional MRI as well as functional data during an in-scanner emotion recognition task. Finally, we will use multiparametric MRI techniques to create quantitative brain maps consisting of proton density, MTsat, R1 and R2 relaxometry measurements.

3.4. Biological samples

At each study visit participants will be asked to donate samples of saliva, blood, and urine. All samples will be stored according to Human Tissue Act (HTA) regulations. Blood will be analysed to measure inflammatory markers, such as for example CRP, IL-2, IL-6, IL-8, IFN-gamma, and TNF-alpha, using ELISA methods. Saliva will be analysed for cortisol levels also using ELISA. We will collect urine samples from participants and use ultra-high-performance liquid chromatography coupled to mass spectrometry to quantify diet metabolites in the urine.

3.5. Safeguarding and ethical considerations

All biological samples collected in this study will be handled and stored according to Human Tissue Act (HTA) guidelines and all data will be stored in accordance with General Data Protection Regulation (GDPR). All participants taking part in the study will be asked to provide informed assent and their parent/guardian will be asked to provide informed consent, before data are collected. All research activities will be in line with good clinical practice (GCP).

Rigorous safeguarding protocols will be applied to all aspects of the study. During each interview two researchers from the study team will always be present. If a disclosure is made which poses a safeguarding concern, stringent protocols will be followed to ensure this information is discussed with the Principal Investigator and passed on to appropriate individuals such as the participants' parents or guardians, or staff at their school.

3.6. Setting

This study will be conducted at the Institute for Psychiatry, Psychology and Neuroscience, King's College London, in London (UK). We will recruit participants primarily within South London boroughs: Lambeth, Southwark, Croydon, and Lewisham. These Boroughs have high levels of both ethnic and socioeconomic diversity and include some of the most deprived areas in the country (Lambeth Council, 2016; Southwark Council, 2021; Lewisham Council, 2019; Observatory, 2021).

3.7. Participants

Participants will be 220 adolescents aged 11–14. The only exclusion criteria will be unwillingness or contraindication to having an MRI scan.

3.8. Recruitment

Participants will be recruited through local schools which will be identified and approached by the study team. Working with the school, researchers will advertise the study at a student assembly (or similar). This presentation will explain the nature and design of the study and provide information for young people to take away and discuss with their parents/guardians. The study team will also advertise the study through other means including social media and in the local community. We will only include adolescents able to fully understand the aims and objectives of the study.

3.9. Informed consent

When recruiting participants, all young people and their parents will be given a detailed description of the study and of what participation will involve, and they will have the opportunity to ask questions. All individuals approached will be given details of the study website (www.ebrainstudy.com) which includes all information about the study and includes full participant and parent information sheets. Prior to the first study visit, young people and their parent/guardian will be asked to provide signed informed assent and consent forms respectively and be given an additional opportunity to ask questions.

3.10. Follow-up and minimising sample attrition

After the initial study visit there are two follow up visits, one year apart. At follow up, we will first attempt to contact participants making use of the contact details they provided at baseline, and if this approach fails, we will contact the school to request updated contact information. For all participants we will offer free transport to the study visit. To optimise the experience of participation and therefore improve levels of study retention, we will provide feedback forms to participants at each study visit and evaluate their experience.

3.11. Public involvement

We will work closely with schools for the duration of the study. The study team will offer a range of engagement activities and workshops to collaborating schools including content on mental health, wellbeing, and careers. The study team will work closely with the schools to provide content that is tailored to each school's needs.

The study will involve participants, parents and teachers with a particular interest in the topic of the study to act as 'Study Champions'. These individuals will be invited to be members of the study Steering Committee and to provide feedback on study conduct, interpretation, and dissemination of findings.

We will also deliver a regular Newsletter to all participants and teachers who have been involved with the study. This Newsletter will be co-edited with a pupil Champion and include updates about the progress of the study as well as insights from the study Champions, and information about neuroscience and mental health. This will also be published on our website (www.ebrainstudy.com).

4. Data analyses

In the first stage of analysis, we will complete a descriptive analysis of the demographics of our participant sample and assess the data for completeness. Depending on the analysis, extent, and nature of the missingness, appropriate missing data techniques (complete cases analysis, maximum likelihood, multiple imputation) will be employed.

Our overall approach, in addition to cross-sectional analyses and univariate analyses, involves fitting regional brain growth curves to structural neuroimaging data (see below), assessing the impact of early adversity on such curves, and using curves as predictors of outcome (e.g. development of specific psychopathology domains). Further to this, similar trajectories of change in immune biomarkers will be evaluated and integrated in these multivariable models. In addition, exploratory analyses will extend the above approach to test how protective factors, cognitive function, and social outcomes affect these relationships.

Specifically, we plan to develop multivariable statistical models from repeated measurements of subjects over time that will be used to test our hypotheses. The aims are two-fold: (a) to develop flexible statistical models that capture key features observed in repeated measurements of time-varying multivariable MRI data and so infer the hidden growth trajectories (or curves) within a population, using for example but not exclusively tensor-based morphometry; and (b) to develop statistical tests for comparing growth patterns between two or more populations of interests, and for the identification of regional brain patterns showing significant differences. We plan to develop functional linear mixed-effect models for this purpose (Montana et al., 2011; Berk et al., 2011). These will explicitly model the multiple types of variation at different levels that are present in the data: from voxel-level, individual-level, and cohort level. Each level of variability will be characterised by their effects on the growth patterns, which are modelled as smooth functions of time. The functions will be represented using smoothing splines initially, but other parametrisations will also be investigated. These mixed-effect models provide the flexibility required to handle relatively short time-series from unbalanced repeated measurements with missing data (Montana et al., 2011; Berk et al., 2011).

4.1. Number of participants and power analysis

We will aim to recruit a total of 220 participants at baseline which we will follow up for 3 years. As the study is conducted in London, we expect the sample to have rich ethnic diversity. We anticipate an attrition rate of 30% at each follow up point, which will result in a sample of $n = 154$ at the first follow up and of $n = 108$ at second follow up. The presence and severity of adversity will be investigated with a categorical and an ordinal approach, depending on the analyses. Mixed-model functional data analysis techniques do not have closed-form power calculations and instead rely on simulation. We report here a simplified conventional sensitivity analysis of power conducted in G*Power 3.1.9.7 (Faul et al., 2007). We anticipate this as a reasonable lower bound for detection of group differences in trajectory with more sophisticated techniques. For the neuroimaging data, a repeated measures ANOVA (2 groups of $n = 50$, 3 measurements, power $= 0.90$, alpha $= 0.05$, non-sphericity correction $= 0.75$), assuming a conservative rho of 0.35, would have sensitivity to detect a standardised interaction effect of $f = 0.185$ with 90% power. This detectable effect size is small-medium by Cohen and lower than standardised effect estimates of 0.21–0.3 derived from pre-term birth data (Karolis et al., 2017).

5. Conclusion

This study will deliver a unique dataset that includes data on early adversity, early brain developmental trajectories, immune and diet biomarkers, and psychopathology in a school-based adolescent cohort. The combination of these modalities in a single cohort will present a unique opportunity to explore the impact of adversity on adolescent brain development and psychopathology and relate this to a wide range of contributing factors. Finally, by recruiting our participant sample from healthy adolescents in the local community our findings are likely to be more generalisable to the UK population than those from studies on individuals at-risk.

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Declaration of competing interest

All authors declare that they have no conflicts of interest.

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