Data Request form YOUth (version 6.0, February 2020)

Introduction

The information you provide here will be used by the YOUth Executive Board, the Data Manager, and the Data Management Committee to evaluate your data request. Details regarding this evaluation procedure can be found in the Data Access Protocol.

All data requests will be published on the YOUth researcher's website in order to provide a searchable overview of past, current, and pending data requests. By default, the publication of submitted and pending data requests includes he names and institutions of the contact person and participating researchers as well as a broad description of the research context.

After approval of a data request, the complete request (including hypotheses and proposed analyses) will be published. If an applicant has reasons to object to the publication of their complete data request, they should notify the Project Manager, who will evaluate the objection with the other members of the Executive Board and the Data Management Committee. If the objection is rejected, the researcher may decide to withdraw their data request.

Section 1: Researchers

In this section, please provide information about the researchers involved with this data request.

- Name, affiliation and contact information of the contact person
- Name and details of participating researchers (e.g. intended co-authors)
- Name and details of the contact person within YOUth (if any)

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Section 2: Research context

In this section, please briefly describe the context for your research plans. This section should logically introduce the next section (hypotheses). As mentioned, please note that this section will be made publicly available on our researcher's website after submission of your request.
Please provide:

- The title of your research plan
- A very brief background for the topic of your research plan
- The rationale for and relevance of your specific research plan
- The specific research question(s) or aim(s) of your research (Please also provide a brief specification)
- A short description of the data you request

References can be added at the end of this section (optional).

Title of the study
The developing prenatal brain, family history of psychiatric illness, and postnatal functional outcome

Background of the topic of your research plan, rationale, relevance (max. 500 words)

Word count: 444

When a baby is born it has its whole life in front of it, and this includes major development of the brain. However, the blueprint of the brain has already been formed earlier in the womb, when the human brain undergoes major developmental changes and growth. This fetal period is essential for normal brain development. However, it poses also is a period of risk.

This period of complex developmental processes poses the brain vulnerable for (gene-by-) environmental factors which can have a permanent effect leading to developmental disorders later in life (Clifford et al., 2016; Davies et al., 2020; Gao et al., 2019; Hulshoff Pol et al., 2000). However, whether individual differences in brain structure precede problems later in life and at what point during development (i.e., prenatal or postnatal) these abnormalities arise remains largely unknown. Knowing which risk-factors are associated with early brain development, when deviations occur, and how they relate to functional outcome measures later in life is extremely important for the design of effective prevention strategies.

Normal fetal brain size and growth can inform functional outcome postnatally. Recently, a more pronounced fetal brain size and growth in early-mid gestation was positively associated with academic attainment in mid-childhood learning capacity in the area of mathematics, writing, reading, and logical thinking (Norris et al., 2018). Moreover, a faster growth from mid to late pregnancy predicted a lower risk of delayed infant development at 12 months of age (Henrichs et al., 2010).

A large and steadily accumulating body of evidence suggests that abnormal prenatal brain development is associated with several psychiatric disorders, such as in psychosis (Davies et al., 2020). Differences in brain structure and cognitive function have also been reported in relation to those at familial risk for psychiatric disorders (de Zwarte et al., 2019, 2020), even at a young age (van Haren et al., 2020). This suggests that the familial risk factors of psychiatric disorder already interact with neurodevelopment at an early age. However, when during development (i.e., pre- and/or postnatal) these deviations occur in children with a familial risk for psychiatric disorders, and if so, whether this differs for boys and girls, remains unclear.

In this study we will investigate if, and if so to which extent, familial influences of having a parent with a psychiatric disorder impact fetal brain development and subsequently postnatal functional and long-term outcome.

Since the current Covid-19 pandemic has led to increased levels of stress in the pregnant women that participate in the YOUth cohort, we will also investigate if interactions between familial risk for psychiatric disorder and environmental stress during the pregnancy related to Covid-19 impact fetal brain development and subsequently the developing child.

The specific research question(s) or aim(s) of your research

i) Is familial risk for psychiatric disorders related to prenatal brain development?
ii) Is familial risk for psychiatric disorders related to functional outcome at the age of 3 years,
iii) and if so, is this relationship explained (at least in part) by altered prenatal brain development?

i), ii) and iii) Is there an impact of the Covid-19 pandemic?

Summary of the data requested for your project: Please indicate which data you request to answer your research question.

We request all of the following data of the currently available "Baby & Child" group (~2000 subjects):

Ultrasounds
- 3D ultrasounds at 20 and 30 weeks
- Gestational age at time of scan

Sex

Birth information
- Head circumference at birth
- Height/weight at birth
- Gestational age at birth
- Obstetric complications

Familial risk for psychiatric disorders
- Psychiatric background parents and first-degree relatives

Functional outcome after birth
- Child Behavior Checklist Questionnaire (CBCL; 'Around 3')
- Ages and Stages Questionnaire: Social-Emotional Second Edition (ASQ-SE; 'Around 0 and 3')

Additional information
- Covid-19 questionnaire
- Educational attainment parents
- Socioeconomic status parents (SES)

References (optional)

Albers MEWA, Buisman ETIA, Kahn RS, Franx A, Onland-Moret NC, de Heus R (2018). Intra- and interobserver agreement for fetal cerebral measurements in 3D-ultrasonography. Hum Brain Mapp 39(8): 3277-3284. https://doi.org/10.1002/hbm.24076

Caspi Y, Brouwer RM, Schnack HG, van de Nieuwenhuijzen ME, Cahn W, Kahn RS, […], Hulshoff Pol HE (2020). Changes in the intracranial volume from early adulthood to the sixth decade of life: a longitudinal study. Neuroimage 220: 116842. https://doi.org/10.1016/j.neuroimage.2020.116842

Clifford A, Lang L, Chen R, Anstey KJ, Seaton A (2016). Exposure to air pollution and cognitive functioning across the life course - a systematic literature review. Environ Res 147: 383-398. https://doi.org/10.1016/j.envres.2016.01.018

Davies C, Segre G, Estradé A, Radua J, De Micheli A, Provenzani U, […], Fusar-Poli P (2020). Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. Lancet Psychiatry 7(5): 399-410. https://doi.org/10.1016/S2215-0366(20)30057-2

de Zwarte SMC, Brouwer RM, Agartz I, Alda M, Aleman A, Alpert KI, […], van Haren NEM (2019). The association between familial risk and brain abnormalities is disease-specific: an ENIGMA–Relatives study of schizophrenia and bipolar disorder. Biol Psychiatry 86(7): 545–556. https://doi.org/10.1016/j.biopsych.2019.03.985

de Zwarte SMC, Brouwer RM, Agartz I, Alda M, Alonso-Lana S, Bearden CE, […], van Haren NEM (2020). Intelligence, educational attainment, and brain structure in those at familial high-risk for schizophrenia or bipolar disorder. Hum Brain Mapp [Online ahead of print] https://doi.org/10.1002/hbm.25206

Gao W, Grewen K, Knickmeyer RC, Qiu A, Salzwedel A, Lin W, Gilmore JH (2019). A review on neuroimaging studies of genetic and environmental influences on early brain development. Neuroimage 185: 802-812. https://doi.org/10.1016/j.neuroimage.2018.04.032

Henrichs J, Schenk JJ, Barendregt CS, Schmidt HG, Steegers EA, Hofman A, […], Tiemeier H (2010). Fetal growth from mid- to late pregnancy is associated with infant development: the Generation R Study. Dev Med Child Neurol 52(7): 644-651. https://doi.org/10.1111/j.1469-8749.2009.03513.x

Hulshoff Pol HE, Hoek HW, Susser E, Brown AS, Dingemans A, Schnack HG, […], Kahn RS (2000). Prenatal exposure to famine and brain morphology in schizophrenia. Am J Psychiatry 157(7): 1170-1172. https://doi.org/10.1176/appi.ajp.157.7.1170

Norris T, Johnson W, Petherick E, Cameron N, Oddie S, Johnson S, […], Baker PN (2018). Investigating the relationship between fetal growth and academic attainment: Secondary analysis of the Born in Bradford (BiB) cohort. Int J Epidemiol 47(5): 1475-1484. https://doi.org/10.1093/ije/dyy157

van Haren NEM, Setiaman N, Koevoets MGJC, Baalbergen H, Kahn RS, Hillegers MHJ (2020). Brain structure, IQ, and psychopathology in young offspring of patients with schizophrenia or bipolar disorder. Eur Psychiatry 63(1): e5. https://doi.org/10.1192/j.eurpsy.2019.19

Section 3: Hypotheses

In this section, please provide your research hypotheses. For each hypothesis:

- Be as specific as possible
- Provide the anticipated outcomes for accepting and/or rejecting the hypothesis

Hypotheses
i) There is a relationship between risk for psychiatric illness and early brain development The effect of (risk for) psychiatric illness is known to have an impact on brain volume in adults, and data suggests that brain development is altered (at least in part maybe) very early in brain development in those at increased risk for the disorder. We hypothesize stunted prenatal brain development with increased familial risk for psychiatric disorders. **ii) There is a relationship between familial risk for psychiatric disorders and postnatal functional outcome** An increased familial risk for psychiatric disorders is related to lower functional outcome at age 3 years. **iii) The relationship between familial risk for psychiatric disorders and functional outcome is in part mediated by prenatal brain growth** The association between familial risk for psychiatric disorders and functional outcome at age 3 can in part be explained by deviating prenatal brain development and this effect is more pronounced in boys than in girls. **Environmental stress due to the Covid-19 pandemic increases the effects found in i) ii) and iii)**

Section 4: Methods

In this section, you should make clear how the hypotheses are tested. Be as specific as possible. Please describe:

- The study design and study population (Which data do you require from which subjects?)
- The general processing steps (to prepare the data for analysis)
- The analysis steps (How are the data analysed to address the hypotheses? If possible, link each description to a specific hypothesis)
- Any additional aspects that need to be described to clarify the methodological approach (optional)

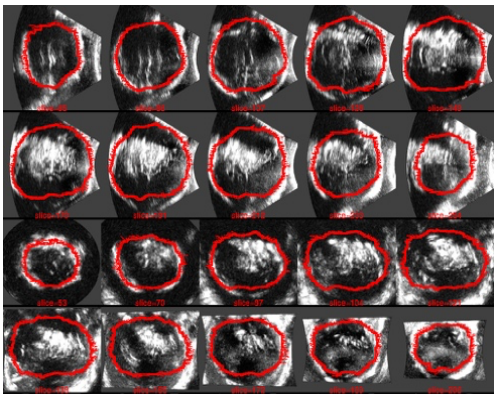
Study design, study population and sample size (e.g. cross-sectional or longitudinal; entire population or a subset; substantiate your choices)
The proposed study design is longitudinal with 2 prenatal measurements, and 1 postnatal measurement. Based on the literature we expect small effects and therefore we will need all available data to have sufficient power.

General processing steps to prepare the data for analysis
We have three options for the processing of the entire 3D ultrasound dataset: i) **Manual segmentation** Building on the work of Albers et al. (2018), we have continued to manually annotate fetal brain structure with Virtual Organ Computer Aided Analysis (VOCAL), using the GE Medical Systems 4D View software, version 14 Ext.4 (GE Healthcare, Zipf, Austria). We know from previous work that some brain structures are more robustly and consistently detected than others. In particular, intracranial volume, and cerebellar volume have high intra- and inter observer scores and are therefore reliable measures to investigate (Albers

et al., 2018). Major downsides of manual segmentation are however that it is very time consuming and requires a trained specialist.

ii) Inhouse developed pipeline for semi-automated ICV segmentation

In the meanwhile, as a first step to automize segmentation of fetal brain structures from 3D ultrasounds, we have started with the development of a semi-automated tool to segment intracranial volume. This more classical segmentation approach is based on affine and b-spline transformations building on our extensive inhouse MRI segmentation knowledge (Caspi et al., 2020). We already have successfully piloted this tool for fetal intracranial volume in 3D ultrasound images obtained at 30 weeks of gestational age (see figure).



iii) Fully automated deep learning tool in collaboration with TU/e

In the proposed project we will go significantly beyond these initial results via advanced probabilistic deep learning in collaboration with Dr Ruud van Sloun from the Signal Processing Systems group at the TU/e. The ultimate goal is to design advanced deep learning methods for automatic and rapid segmentation of the fetal brain and its substructures in 3D ultrasound.

Our deep learning approach will be fully dedicated to ultrasound-specific imaging characteristics such as spatially varying resolution, operator-dependent time-gain compensation, and changes in focal point across acquisitions. To that end, we will design deep networks that are inherently invariant to such changes, through novel architectures and ultrasound physics-based data augmentation. We will train our deep networks using a combination of supervised and unsupervised learning on (ideally) 1000 3D ultrasound acquisitions, benefiting from both expert-labeled ground truth well as large amounts of unlabeled 3D ultrasound data in the YOUth-cohort. Our unsupervised learning methods will complement the supervised learning strategy by extracting meaningful semantic image encodings and high-level course segmentations using recent developments in deep representation learning such as contrastive predictive coding. We will also use the unlabeled data to learn physically plausible morphological transformations that we can then use for realistic data augmentation.

Specific processing and analysis steps to address the hypotheses
Regression analyses will be performed with R software (https://www.r-project.org). Sex and (gestational) age will be modelled as independent variables. A dummy variable will be created to analyze familial risk for psychiatric disorder, i.e., having at least one first-degree family member with a DSM diagnosis (1=yes, 0=no). Linear mixed models will be used for longitudinal data analyses to assess brain development over time and its relationship with postnatal outcome and familial risk for psychiatric illnesses. We will correct our p-values using the false discovery rate (FDR) to correct for the multiple testing. Path analyses will used to explore directionally/causality, which is possible due the chronological order of the acquisition, i.e., *prenatal* brain structure/growth and *postnatal* functioning. Sex differences will be investigated post hoc by analyzing the boys and girls separately. Additional confounders including Covid-19 (stress related) exposure, obstetric complications at birth, parental educational attainment and SES will also be investigated post hoc by adding each variable separately as independent variable in the analyses.

Additional methodological aspects (optional)

Section 5: Data request

In this section, please specify as detailed as possible which data (and from which subjects) you request.

Data requested
We request all of the following data of the currently available "Baby & Child" group (~2000 subjects): **Ultrasounds** - 3D ultrasounds at 20 and 30 weeks - Gestational age at time of scan **Sex** **Birth information** - Head circumference at birth - Height/weight at birth - Gestational age at birth - Obstetric complications **Familial risk for psychiatric disorders**

- Psychiatric background parents and first-degree relatives

Functional outcome after birth
- Child Behavior Checklist Questionnaire (CBCL; 'Around 3')
- Ages and Stages Questionnaire: Social-Emotional Second Edition (ASQ-SE; 'Around 0 and 3')

Additional information
- Covid-19 questionnaire
- Educational attainment parents
- Socioeconomic status parents (SES)

Data request for the purpose of:
☒ Analyses in order to publish
☐ Analyses for data assessment only (results will not be published)

Publication type (in case of analyses in order to publish):
☒ Article or report
☐ PhD thesis
☐ Article that will also be part of a PhD thesis

Would you like to be notified when a new data lock is available?
☒ Yes
☐ No

Upon approval of a data request, the complete request will be made publicly available on our researcher's website by default.

Do you agree with publishing the complete request on our researcher's website after it is approved?
☒ Yes
☐ No. Please provide a rationale