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 the 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)

Contact person for the proposed study:	
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Contact person within YOUth (if any)	
Name:	
Institution:	
Department:	
Address:	
Email:	
Phone:	

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 moderating effect of parenting on the association between structural and functional brain development and parent-reported externalizing behavior in late childhood and early adolescence

Background of the topic of your research plan, rationale, relevance (max. 500 words)
Externalizing behaviors, such as aggression, delinquency, and antisocial behavior, are considered a problem to society as they may result in damages to property and harm to self and others. Twin and family studies have reported a heritable component for externalizing behaviors across the lifespan [1,2]. Large-scale genome-wide association studies have begun to uncover the genetic loci on human DNA associated with externalizing behaviors [3,4]. Externalizing behaviors have been associated with alterations in brain structures and brain function, focused primarily in the frontal-, temporal-, and striatal cortex, and the limbic system [5–7]. Recently, we have reported on the genetic association between brain structures and parent-reported externalizing behavior in a longitudinal adolescent twin cohort [8], and we have analyzed the unique contributions of brain structures and polygenic risk for externalizing behaviors to parent-reported externalizing behavior in independent cohort of children, suggesting the possibility of two separate, largely independent, pathways in the development of parent-reported externalizing behavior in late childhood (in preparation). Despite the moderately high heritability of externalizing behavior and its associations with brain structures, we had to conclude that a majority of the individual variation in externalizing behavior remained unresolved. We hypothesize that brain function can offer an additional unique contribution to individual variation in externalizing behavior that can aid in building better predictive models of externalizing behavior. E.g., hypoactivity in the amygdala scales with the severity of antisocial behavior, and externalizing behavior has a distinct pattern of altered network functional connectivity compared to other psychopathological symptoms [9,10]. In addition, it has been hypothesized that the presence of callous unemotional traits moderates the association between brain structures and externalizing behavior [11], with several successful applications reported in literature [12–14]. We hypothesize that environmental factors, such as the family and the social environment of the child, may also moderate the association between brain characteristics and externalizing behavior; i.e., negative parenting can aggravate externalizing behavior of the child beyond the intrinsic neurobiological determinants of the child, whereas positive parenting may act as a protective factor toward externalizing behavior. Parenting has an influence on externalizing behavior in children and adolescents [15], it plays a role in the transmission of externalizing behavior from parents to their children [16], and is an active target for intervention and therapies [17]. Parenting behavior has also been reported to have an effect on the developing brain of their children [18,19]. With this study, we want to validate our previous findings in the YOUth cohort and to expand the analysis by incorporating brain function to better predict externalizing behavior. In addition, we want to investigate the complex interactions between

brain development and environmental factors that play a role in the development of externalizing behavior during childhood and adolescence. Findings from this study could aid in the identification of children at risk of externalizing behavior and suggest potential targets for intervention and therapy.

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

We aim to (1) replicate our previous finding on the association between brain structures and parent-reported externalizing behavior; (2) assess to which extent brain function can aid in predicting externalizing behavior; (3) assess to which extent family and social environment moderate the association between brain characteristics and externalizing behavior.

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

We propose the include data from all participants of the first wave of the Child & Adolescent cohort "around age 9 years" for cross-sectional analysis, and, when available, from the second wave "around age 12 years" for longitudinal analysis. We request the MRI scans from which we want to extract global characteristics of the brain and characteristics for brain regions that have previously been identified in association with externalizing behaviors, including the brain regions activated in the task-based fMRI inhibition experiment. In regard to behavioral measures, we request data from the Child Behavior Checklist (CBCL), the Strengths and Difficulties Questionnaire (SDQ), the Child-Reported Parental Behavior Inventory (CRPBI), the Parental Control Scale (PCS), and Adult Self Report (ASR). We request basic demographics information on the families, pubertal developmental status (PDS), and full-scale IQ on the WISC, to be used as covariates in the statistical analysis. We request data from the physical and mental health questionnaires for child and parents/caretaker (including ASR) for possible classification of participants into at-risk groups if the data permits such classification to be made.

References (optional)

[1] Hicks et al., JAMA Psychiatry 2013; https://doi.org/10.1001/jamapsychiatry.2013.258
[2] Luningham et al., The Journal of Child Psychology and Psychiatry 2020; https://doi.org/10.1111/jcpp.13188
[3] Ip et al., Translational Psychiatry 2021; https://doi.org/10.1038/s41398-021-01480-x
[4] Tielbeek et al., JAMA Psychiatry 2017; https://doi.org/10.1001/jamapsychiatry.2017.3069
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[6] Noordermeer et al., Neuropsychology Review 2016; https://doi.org/10.1007/s11065-015-9315-8
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[9] Xia et al., Nature Communications 2018; https://doi.org/10.1038/s41467-018-05317-y
[10] Dugré et al., Neuroscience and Biobehavioral Reviews 2020; https://doi.org/10.1016/j.neubiorev.2020.09.013
[11] Viding et al., Journal of the Royal Society of Medicine 2012; https://doi.org/10.1258/jrsm.2011.110223
[12] Waller et al., Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2020; https://doi.org/10.1016/j.bpsc.2020.01.002
[13] Dotterer et al., NeuroImage: Clinical 2019; https://doi.org/10.1016/j.nicl.2019.101836
[14] Umbach and Tottenham, Development and Psychopathology 2020; https://doi.org/10.1017/S0954579420000401
[15] Pinquart et al., Marriage and Family Review 2017; https://doi.org/10.1080/01494929.2016.1247761
[16] Branje et al., Developmental Cognitive Neuroscience 2020; https://doi.org/10.1016/j.dcn.2020.100835
[17] Mingebach et al., PLoS ONE 2018; https://doi.org/10.1371/journal.pone.0202855
[18] Whittle et al., Developmental Cognitive Neuroscience 2014; https://doi.org/10.1016/j.dcn.2013.10.006
[19] Pozzi et al., Developmental Cognitive Neuroscience 2021; https://doi.org/10.1016/j.dcn.2021.100946

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
We expect (1) to replicate our previous findings on the association between brain structures and parent-reported externalizing behavior; (2) to find that brain function contributes equally or more in explaining individual variation in externalizing behavior compared to brain structure; (3) that parenting moderate the association between brain characteristics and externalizing behavior similar to callous unemotional trait; and (4) that, when all combined, brain structure and function both contribute uniquely to explaining individual variation in externalizing behavior, and better predict externalizing behavior than a single modality.

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 analyzed 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)
We will initially perform a cross-sectional analysis on all participants from the Child & Adolescent cohort "around age 9 years", and, when available, data from the Child & Adolescent cohort "around age 12 years" for longitudinal analysis. Data from all participants is requested because of the low prevalence of externalizing behavior in a typically developing cohort conform the general population and the anticipated small effect sizes.

General processing steps to prepare the data for analysis
Demographics: the demographics data will be summarized (means, standard deviation, range) for description of the sample, and will be used as covariates in the statistical analysis. *Brain imaging:* gray matter volumes and task-activation patterns of relevant brain regions (including global brain volumes), and structural and functional connectivity between those regions (including global topological brain network metrics), will be computed from the MRI scans with tools and processing pipelines both available to the public (e.g., FreeSurfer, FSL, CONN toolbox) and developed in-house. Relevant brain regions are on the frontal-, temporal-, cingulate cortex and limbic system in previously publications and peak activation clusters from the task-based fMRI data. Most of this data has already been processed by colleagues and could be re-used in this analysis. *Behavioral data:* (normalized) summary scores will be computed for the broad externalizing scale and its two subdomains on the parent-reported Child Behavior Checklist (CBCL), same for

the Adult Self Report (ASR). Three items on the Strengths and Difficulties Questionnaire (SDQ) and one item on the CBCL will be combined to compute a score for the callous unemotional trait scale. Summary scores will be computed for the domains on the parenting questionnaires (CRPBI, PCS); additional data reduction techniques will be applied to derive a latent factor for positive and negative parenting.

Risk classification: items on the child's physical health and psychiatric family history questionnaires and the summary scores on the CBCL and ASR will be used to classify participants into currently high-externalizing, and potentially "high" risk (family history of externalizing behavior or related disorders but currently low-externalizing) group, matched to "low" risk (no family history, physically sound, and currently low-externalizing) control group.

Specific processing and analysis steps to address the hypotheses

We will perform linear regression analysis to determine the effects of the covariates and the parenting behavior on parent-reported externalizing behavior of the children. Within this model, we will test if the brain structures that have previously been implicated in externalizing behavior will replicate in this large cohort of children in late childhood (hypothesis #1). Similarly, we will test to which extent brain function is associated with externalizing behavior (hypothesis #2). In addition, we will test if parenting moderates the association between brain characteristics and externalizing behavior within these models (hypothesis #3). A correction for multiple testing will be applied to the analysis of regional brain characteristics. We will test if the combined effect of brain structure and function better predicts externalizing behavior than a single modality (hypothesis #4); for the regional brain characteristics, predictive models will be constructed using machine learning methods (e.g., support vector machine) or a latent variable model with a latent factor specific to each modality and a general "brain" factor will be constructed, depending on the collinearity of the regional brain characteristics.

Additional methodological aspects (optional)

If necessary, and the data permits, we will run a post-hoc analysis to address potential concerns of an unbalanced design (i.e., only a small proportion of the participants are expected to exhibit externalizing behavior at "clinical" level conform the prevalence of disruptive behaviors in the general population). This post-hoc analysis will be run on a subset of the participants divided into the risk categories and is expected to show a staircase effect of the groups on the brain characteristics.

When sufficient data from the second wave of the Child & Adolescent cohort "around age 12 years" is made available, we would like to expand the analysis with longitudinal models to determine if changes in brain structures and function are predictive of changes in levels of externalizing behavior, or if brain characteristics at baseline assessment are predictive of externalizing behavior at follow-up assessment, and vice versa.

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 the following data from all participants of the Child & Adolescence cohort of the first wave "around age 9 years", and, when available, data from all participants of the Child & Adolescent cohort of the second wave "around age 12 years":

- Basic demographics of child and parents/caretaker (to be used as covariates in the analyses):
    - Sex & Age
    - Socioeconomic status
    - Parental education levels
    - Parental marital status
    - WISC full-scale IQ score
    - Pubertal development scale (PDS)
- Physical and mental health of child and parents/caretaker (for purpose of screening and classification of participants into risk groups for externalizing behavior):
    - Medical questionnaire of child's health (parent-reported)
    - Psychiatric family history questionnaire (parent-reported)
    - Adult Self Report (ASR; parents/caretaker)
- Magnetic resonance imaging scans:
    - Structural T_1-weighted MRI scans
    - Diffusion-weighted MRI scans
    - Resting-state functional MRI scans
    - Task-based functional MRI scans: Inhibition Experiment (including task performance data)
- Questionnaires related to externalizing behavior and parenting
    - Child Behavior Checklist (CBCL; parent-reported)
    - Strength and Difficulties Questionnaire (SDQ; parent-reported)
    - Child-reported Parental Behavior Inventory (CRPBI; child-reported)
    - Parental control scale (PCS; child-reported)

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