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
Connected and in control: The morphology of large-scale functional networks supporting behavioral control

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

Behavioral control, or the ability to plan and adapt behavior flexibly in the face of changing circumstances, is in continuous development from infancy to adulthood (1). Neurobiological models suggest that the development of behavioral control is associated with changes in connectivity in frontostriatal and frontoparietal circuitry (2,3), where functional integration and segregation lead to the development of coherent and efficient control networks (4–6). Notably, as compared to e.g. primary visual or motor functional networks, association regions show most inter-individual variability in topography (7–9) and functional connectivity (10,11), already in youth (12). Specifically, the large inter-individual variation in topography and functional connectivity of the association regions has been related to individual differences in executive function in youth (12).

The ability to exert behavioral control relies on more than the maturation of frontostriatal and frontoparietal executive networks alone: dynamic cross-network interactions between the Central Executive Network (CEN), the Salience Network (SN) and Default Mode Network (DMN), are thought to underlie individual differences in cognitive functioning (13). Changes in the flexible interactions between the CEN, SN and DMN have been related to developmental psychiatric disorders associated with behavioral control problems, such as Attention Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD) (14–16).

Yet, development of large-scale functional networks and their functioning is constrained by brain structure (17). During childhood and adolescence, the brain regions involved in behavioral control undergo dramatic structural change (18,19), and even though brain function is thought to be highly related to brain structure, there is no clear one-to-one relationship (20–22). However, the relation between structure and function does strengthen and become more stable with development (23,24). Also, fast, perhaps experience-dependent, changes in functional connectivity may precede slower changes in brain structure (21). Nevertheless, the degree to which individual differences in brain

structure contribute to the development of integrated functional networks and how this relates to cognitive abilities is relatively unclear.

In the current study, we plan to use a multimodal approach combining questionnaires and task-performance measures associated with behavioral control and MRI-based techniques for studying connectivity between large-scale cognitive networks and the morphological properties of these networks. Large and rich datasets such as the YOUth cohort allow for advanced analysis methods that capitalize on the high dimensionality of the data to investigate the relation between behavior and related neural circuitry. Specifically, Canonical Correlation Analysis (CCA), which we are currently also using in the YOUth studies of Dienke Bos and Bram Gooskens, is a promising tool that allows the investigation of the complex relationships between two large sets of variables (25,26). In the current study we propose to apply a two-step procedure of multimodal CCA (mCCA) and joint Independent Component Analysis (jICA) (27,28) to investigate the relation between whole-brain resting-state functional connectivity, cortical morphology and behavioral control as measured by a large number of questionnaires and behavioral task performance on a Stop-Signal Reaction Time (SSRT) task.

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

The aim of this project is to use data-driven methods to investigate the relation between whole-brain resting-state functional connectivity within and between large-scale resting-state networks, particularly CEN, SN and DMN, the morphological properties of those networks, and behavioral control ability as measured through parent-report and behavioral performance on the SSRT task, with the goal of understanding the relation between brain morphology and function and behavioral control, and investigating whether specific morphological and/or functional connectivity patterns are associated with behavioral control problems.

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

We propose to include all children from the Rondom-9 cohort with resting-state fMRI and anatomical T1 data available in this cross-sectional study. In addition, we request the behavioral data from the fMRI SSRT paradigm and a set of (psychometric) questionnaires that cover behavioral control and a wide range of related behaviors, such as social interaction and communication, anxiety, and impulsivity in order to relate resting-state functional connectivity and brain morphology to behavioral control development.

References (optional)

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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 hypothesize that individual differences in behavioral control are associated with individual differences in the relation between dynamic cross-network interactions of large-scale functional networks and the morphological features of these networks. Based on our previous work with this sample, we expect to find linked dimensions of resting-state functional connectivity and behavioral control in a large developmental sample that includes a wide spectrum of behavioral control abilities. We hypothesize that children with poor behavioral control will show a relative delay in development of underlying neural circuitry compared to children with better behavioral control. In addition, we hypothesize that the specific patterns of behavioral control and associated resting-state functional connectivity will be associated with behavioral control problems that are related to child characteristics such as increased impulsivity on the one hand, or increased rigidity or anxiety on the other.

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)
We propose to include all children from the Rondom 9 cohort for whom resting-state fMRI and anatomical T1 data is currently available and preprocessed. Resting-state fMRI has already been preprocessed by Dienke Bos, and anatomical T1 data has been processed by Elizabeth Buimer. Data-driven PCA-like methods like CCA require large sample sizes, which is why we request all the available data.

General processing steps to prepare the data for analysis
Behavioral data Behavioral data from the SSRT task has already been processed. Questionnaire data has already been processed to the level that it can be distributed to researchers. For the CCA, we will use raw item scores, recoding of data into T-scores or subscales is not necessary. However, composite/T-scores of all questionnaires will be needed for demographic description of the sample. *Resting-state fMRI data* Resting-state fMRI data has already been preprocessed using a state-of-the-art pipeline, with rigorous quality control regarding subject motion. In short, rs-fMRI data has been despiked to remove large intensity outliers (Patel et al., 2014). The images were subsequently registered to each other, to the anatomical image and to a template brain in standard space. After registration the images were smoothed using a 6 FWHM kernel. Finally, the images were highpass filtered (> 0.008 Hz) to filter out high frequency noise.

To account for motion and physiological artefacts, ICA-AROMA (Pruim et al., 2015) was used to identify sources of noise (e.g. CSF, white matter, motion) that were subsequently regressed out of the data. Image quality was assessed using the FreeSurfer anatomical segmentation to plot BOLD intensity change over time per voxel in a way that is instinctively visually assessable (Power et al., 2017).

Anatomical data

Anatomical T1-weighted scans have been processed using Freesurfer version 6 for automatic brain segmentation and cortical parcellation (Fischl, 2012). In short, brain segmentation consisted of registering the brain into Talaraich space (Talairach and Tournoux 1988), removing non-brain tissue using a deformable template model (skull stripping), and neuroanatomical labeling, based on both voxel intensity values and a probabilistic atlas (Fischl et al. 2002). The reconstruction of cortical surfaces involved the segmentation of white matter, used to derive a surface representing the gray-white matter boundary (white surface). The white was is then refined and deformed to locate the pial surface (gray matter/cerebrospinal fluid boundary) (Dale et al. 1999). Finally, by incorporating both geometric information derived from the cortical model and standard neuroanatomical conventions from cortical atlases, the procedure automatically assigned a neuroanatomical label to each location on the cortical surface (cortical parcellation). In the current study, the cortical regions from the Desikan-Killiany atlas will be used.

Prior studies suggested that the distinct dimensions of cortical morphology (i.e. cortical thickness and cortical surface area) are regulated through partially different developmental processes. According to the radial unit hypothesis (Rakic 1995), cortical thickness is determined by the number of neurons within each radial unit, whereas cortical surface area is largely driven by the number of units. Therefore, in our analysis we will incorporate both independent markers of cortical morphology. For each cortical area, surface area will be measured along the white surface, whereas cortical thickness will be estimated as the average distance between parcellated portions of pial surface and white surfaces (Fischl and Dale 2000).

Specific processing and analysis steps to address the hypotheses

Behavioral data analysis

Demographic information (age, gender, IQ, presence of psychiatric symptoms (CBCL subscales), socio-economic status (SES) and pubertal development) will be used for sample description (means and standard deviations).

Joint resting-state fMRI, anatomical T1, and behavioral analysis

In this study study we will be using a two-step analysis procedure, multiset CCA (mCCA) and joint Independent Component Analysis (jICA), to analyse resting-state fMRI, cortical morphology (thickness and surface area), and behavioral data simultaneously (see Lerman-Sinkoff et al., 2017).

mCCA (Correa et al., 2008; Li et al., 2009) is a data-driven multivariate statistical method that can simultaneously assess multiple, multi-modal, high dimensional sets of variables, for instance brain morphometric measures (i.e. cortical thickness and surface area at specific regions of interests), functional measures (i.e. resting-state connectivity between any two brain regions), and behavioral measures (SSRT task performance and child-/parent-rated questionnaires). In other words, mCCA is an optimal data-driven method to investigate brain-behavior correlations in datasets with a large number of variables (Xia et al. 2018, 2020). Similarly, jICA is an extension of traditional ICA methods (Calhoun et al., 2006) that identifies latent sources of variance in multimodal data.

The combination of these two analysis methods (mCCA + jICA) will enable us to overcome the intrinsic limitations of each method alone. For example, mCCA may fail to achieve complete separation of sources of variation in the data due to strong inter-dependencies within the data. On the other hand, jICA may be less able to detect weakly-linked relationships when the individual modalities are less correlated. Therefore, mCCA and jICA together will improve our ability to detect both strong and weak data-dependencies, maximizing the chance of identifying maximally independent, cross-modality sources of variance.

In this study, we will extract cortical thickness and surface area measures from 34 regions per hemisphere according to the Desikan-Killiany (DK) cortical atlas in FreeSurfer (Desikan et al. 2006).

Second, we will extract whole-brain rs-fMRI timeseries from the same cortical parcellation scheme (DK), with the addition of several subcortical regions defined by FreeSurfer. Functional connectivity matrices will be then computed as the Pearson correlation between the mean timeseries from all these brain regions.

Third, we will collect behavioral measures from a set of questionnaires, namely items from the SDQ, SWAN, EATQ-R (parent and child), IRI, BIS. Furthermore, we will extract the three performance measures from the SSRT task (SSRT, SSD and MRT).

All data features (cortical thickness and surface area measures, resting state functional connectivity correlations, questionnaires and task-performance behavioral data) will then be analysed using mCCA. Next, we will apply jICA to further decompose the data into maximally spatially independent sources of variance (components). All analyses will be performed in MATLAB, R and the Fusion ICA Toolbox (FIT: http://mialab.mrn.org/software/fit/). Permutation testing will be applied to test for the significance of the jICA analyses, and a resampling procedure will be applied to select the brain and behavioral features that contribute to each component.

The relation between participant characteristics (age, gender, pubertal stage, IQ, psychiatric symptoms as measured by the CBCL, socio-economic status) and mCCA+jICA loadings will be analyzed using General Additive Modelling in R. FDR-correction for multiple comparisons will be applied to all statistical analyses.

Section 5: Data request

Additional methodological aspects (optional)

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

Data requested

We propose to include all children from the Rondom-9 cohort with available resting-state fMRI and T1 data in this cross-sectional study. Specifically, we request the following data:

- Resting-state fMRI data
- T1 anatomical scan (specifically processed Freesurfer data)
- Performance data from the fMRI SSRT task
  - Stop-Signal Reaction Time (SSRT)
  - Stop-Signal Delay (SSD)
  - Mean reaction time (MRT)
- A set of (psychometric) questionnaires on behavioral control and related behaviors
  - CBCL
  - SDQ
  - SWAN
  - EATQ-R (parent & child)
  - IRI
  - BIS
- Demographic information

- Age
- Gender
- Pubertal development
- Full-scale IQ
- Socio-economic status

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