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 II: Development of functional connectivity related to 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 (8–10) and functional connectivity (11, 12), already in youth (7). 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 (7).

However, 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, little is known about how the functional interactions between these large-scale functional networks relate to individual differences in the maturation of behavioral control. Given the great impact that behavioral control has on mental health and behavior (17), more insight into the factors that drive the development of behavioral control is necessary.

While there is a large body of literature on the development of behavioral control (for overview, see: (1, 18, 20, 22)), studies have been limited in terms of sample size and have used traditional statistical methods that may not fully capture individual differences in behavioral control and neurobiology. 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) is a promising tool that allows the investigation of the complex relationships between two large sets of variables (19, 21). In the current study we propose to use CCA to investigate whole-brain resting-state functional connectivity 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, and behavioral control ability as measured through parent-report and behavioral performance on the SSRT task, with the goal of understanding the relation between resting-state functional connectivity and behavioral control, and investigating whether specific 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 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 to behavioral control development.

References (optional)

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3. Jolles DD, van Buchem MA, Crone EA, Rombouts SARB (2011): A comprehensive study of whole-brain functional connectivity in children and young adults. *Cereb Cortex*. 21: 385–91.
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6. Supekar K, Musen M, Menon V (2009): Development of large-scale functional brain networks in children. *PLOS Biol*. 7.
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12. Mueller S, Wang D, Fox MD, Yeo BTT, Sepulcre J, Sabuncu MR, *et al.* (2013): Individual variability in functional connectivity architecture of the human brain. *Neuron*. 77: 586–95.
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22. Somerville LH, Casey BJ (2010): Developmental neurobiology of cognitive control and motivational systems. *Curr Opin Neurobiol*. 20: 236–41.

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 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 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 data is currently available. Data-driven PCA-like methods like sCCA and LCA require large sample sizes, which is why we request all the available data.

General processing steps to prepare the data for analysis
Resting-state fMRI data will be preprocessed using a state-of-the-art pipeline, with rigorous quality control regarding subject motion. In short, rs-fMRI data will first be despiked to remove large intensity outliers (Patel et al., 2014). The images will then subsequently be registered to each other, to the anatomical image and to a template brain in standard space. After registration the images will be smoothed using a 6 FWHM kernel. Finally, the images will be highpass filtered (> 0.008 Hz) to filter out high frequency noise. To account for motion and physiological artefacts, ICA-AROMA (Pruim et al., 2015) will be used to identify sources of noise (e.g. CSF, white matter, motion), that will subsequently be regressed out of the data. Image quality will be 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). 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 sCCA, we will use raw item scores, recoding of data intro T-scores or subscales is not necessary. However, composite/T-scores of all questionnaires will be needed for demographic description of the sample.

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).

Resting-state fMRI analyses

Resting-state fMRI and behavioral data will be analyzed using sparse Canonical Correlation Analysis (sCCA). CCA is a multivariate statistical method that can simultaneously assess two different, high dimensional sets of variables, for instance brain measurements (i.e. resting-state connectivity between any two brain regions) and behavioral measures (SSRT task performance and child-/parent-rated questionnaires). CCA maximizes linear correspondence between variables, thereby seeking dimensions of shared variation in brain and behavioral measures. In other words, CCA is an optimal data-driven method to investigate brain-behavior correlations in datasets with a large number of variables (Xia et al. 2018, 2020).

First, whole-brain rs-fMRI timeseries will be extracted from 264 20mm spherical nodes (Power et al., 2011). Functional connectivity between any two of these 264 nodes is defined as the Pearson correlation between the mean timeseries from these two regions, creating an n × n weighted adjacency matrix, where n represents the total number of nodes in the parcellation. Given that this matrix will contain >34k connectivity features, dimensionality reduction will be performed by selecting the top 10% of edges (~3.4k) that show most variation. Between subject variability of the correlation between any two nodes will computed by calculating the median absolute deviation (MAD, median($|X_i$ – median(X)$|$), or the median of the absolute deviations from the vectors median (connections where correlations show higher individual differences have higher MAD).

The behavioral features to be included in the sCCA analyses will be included at item-level, and will be all items from the SDQ, SWAN, EATQ-R (parent and child), IRI, BIS, and the three SSRT performance measures (SSRT, SSD and MRT).

sCCA will then be performed in R, combining the behavioral and connectivity features. In short, given two matrices, $X_{n \times p}$ and $Y_{n \times q}$, where n is the number of observations (e.g., participants), p and q are the number of variables (e.g., behavioral and connectivity features, respectively), sCCA involves finding u and v, which are loading vectors, that maximize cor(Xu,Yv) (i.e. the correlation between connectivity and behavioral features, further details in Xia et al, 2018). Permutation testing will be applied to test for the significance of the canonical variates, and a resampling procedure will be applied to select the behavioral and connectivity features that contribute to each canonical variate.

Finally, network module analysis will be performed to assess within- and between module loadings of the connectivity features found in the sCCA analysis. Modules (the somatosensory/motor network (SMT), cingulo-opercular network (CON), auditory network (AUD), default mode network (DMN), visual network (VIS), fronto-parietal network (FPT), salience network (SAL), subcortical network (SCN), ventral attention network (VAN), dorsal attention network (DAN)) will be defined by a priori community assignment based on the Power et al. (2011) parcellation.

The relation between participant characteristics (age, gender, pubertal stage, IQ, psychiatric symptoms as measured by the CBCL), environmental factors (SES) and sCCA connectivity loadings will be analyzed using General Additive Modelling in R. FDR-correction for multiple comparisons will be applied to all statistical 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 propose to include all children from the Rondom-9 cohort with available resting-state fMRI data in this cross-sectional study. Specifically, we request the following data:

- Resting-state fMRI data, incl. T1 anatomical scan for registration
- 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