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 combined neurobiological and behavioral stratification of self-regulation in childhood

Background of the topic of your research plan, rationale, relevance (max. 500 words)
Self-regulation is the ability to regulate one's emotions, behavior and social interactions in daily life, including in the face of changing circumstances. There are vast individual differences in the development of self-regulation. Recent work has shown that individual differences in behavior are associated with variability in brain activity[1,2,3,4]. Typically, in the pre-SMA, SMA[5,6], pre-motor cortex[7,8], parietal cortex[9,10], right inferior frontal cortex (IFC)[11,12,13,14], ventrolateral PFC and insula[15,16]. Others have shown that task-induced brain

activity during self-regulation may involve a more complex network of cortical and subcortical brain regions[17,18,19,20]. Studies using data-driven methods further showed separable behavioral and/or neurobiological subgroups related to self-regulation, and reward- or reinforcement-related behavior[21,22,23]. As yet, it remains unclear whether and how different manifestations of self-regulation are associated with separable neurobiological mechanisms.

In our previous paper[24], we reported different factors that drive the development of self-regulation and its neural circuitry at the group level. While environmental factors can play an important role in moderating the effectiveness of self-regulation processes[25], we found that none of the assessed individual child characteristics or environmental factors were associated with stop-signal reaction time (SSRT). However, we found associations between impulsivity and proactive inhibition, and between variability in basic response execution and an authoritarian parenting style, indicating that self-regulation styles may be affected in other ways. Our findings led us to the hypothesis that there may be separable self-regulation styles that are differentially affected by environmental factors, and each associated with a specific pattern of behaviors (e.g., externalizing, impulsive, anxious or withdrawn behavior) and their own pattern of neural activation.

Understanding the different manifestations of self-regulation and associated neurobiology may have implications for those who develop psychopathology. Self-regulation problems can be expressed in a variety of ways, e.g., through externalizing behaviors, inattention, or emotional problems[26]. When such problems impair daily life activities, they may even lead to psychiatric diagnoses such as depression, attention-deficit/hyperactivity disorder (ADHD), addiction, conduct disorder or psychosis[27,28]. While the core symptoms of these diagnoses are very different, there may be overlap in the self-regulation processes that are affected[29].

In the current study, we aim to characterize the relation between separable dimensions of self-regulatory behavior and functional activation during performance of the Stop-Signal Anticipation Task (SSAT) in the YOUth Rondom 9 cohort. We will build on the findings from the Exploratory Factor Analysis in our previous paper, and capitalize on the large sample size of the YOUth cohort by using Canonical Correlation Analysis (CCA) to identify sub-groups that show linked dimensions of behavior and functional activation during self-regulation. Ultimately, we will examine the similarities and differences in brain-behavior correlations in relation to self-regulation problems and environmental factors, in children with different characteristics, with the aim to understand how self-regulation problems contribute to the development of psychopathology.

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

The aim of this study is to investigate the relation between dimensions of self-regulatory behavior and task-specific brain activity patterns related to self-regulation. We will apply a weighted voxel co-activation network analysis (WVCNA)[23,30,31] to identify functional brain networks associated with self-regulation as measured during the Stop-Signal Anticipation Task (SSAT). Using Canonical Correlation Analysis (CCA), we will identify correlations between child characteristics (based on our Exploratory Factor Analysis from Gooskens et al. (*in preparation)*[25] and task-specific activation networks during performance of the

SSAT. Ultimately, we will examine the similarities and differences in brain-behavior correlations in relation to environmental factors, with the goal of understanding individual differences in the manifestation of self-regulation and how self-regulation problems contribute to the development of psychopathology.

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 stop-signal anticipation task (SSAT) fMRI data available in this cross-sectional study. In addition, we request the behavioral data from the fMRI SSAT and a set of questionnaires that cover a wide range of behaviors, related to internalizing and externalizing behavior, to relate task-specific brain activity patterns to features of behavior.

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
First, based on our earlier work with this sample, we expect to find frontostriatal and frontoparietal networks of co-activated brain regions, both cortical and subcortical, during reactive and proactive control. Second, we expect that distinct brain activation patterns during the Stop-Signal Anticipation Task (SSAT) performance will be associated with specific patterns of self-regulatory behavior. E.g., we hypothesize that the specific patterns of self-regulation and associated brain networks will be associated with child characteristics such as increased externalizing behavior on the one hand, or increased impulsivity or anxiety on the other. Last, we expect that the different dimensions of self-regulation will each be uniquely affected by environmental factors.

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 stop-signal anticipation task (SSAT) fMRI data are currently available. Data-driven PCA-like methods such as WVCNA and CCA require large sample sizes, which is why we request all the available data.

General processing steps to prepare the data for analysis
The fMRI data has been analyzed using Statistical Parametric Mapping 12 (SPM12) software. Preprocessing steps involved the standardized pipeline by Matthijs Vink to harmonize our analyses with other studies in the consortium. In short, the pipeline includes slice time correction, realignment, co-registration of the anatomic image to the mean functional image, spatial normalization to a Montreal Neurologic Institute (MNI) template brain and smoothing (using a 6 mm full-width at half maximum (FWHM) Gaussian kernel). We will define brain networks underlying the Stop Signal Anticipation Task (SSAT) by analyzing contrasts that are most relevant to self-regulation behavior: two contrasts will be generated for reactive and proactive control: (1) successful stops trials versus failed stops trials [StopSuccess versus StopFailure] and (2) successful go trials with a stop-signal probability of 20 and 33 percent pooled and weighted together versus baseline go trials with a stop-signal probability of 0% [Uncertain >0% versus Baseline 0%]. These analyses will produce three t-maps for each participant: (1) Successful stop [StopSuccess – StopFailure]; (2) Failed stop [StopFailure – StopSuccess]; and (3) Proactive control [Uncertain >0% – Baseline 0%]. Six realignment parameters will be added as regressors of no interest to correct for head motion. All data will be high-pass filtered with a cutoff of 128 seconds to control for low-frequency drifts. Behavioral data from the SSAT task has already been processed. Questionnaire data has already been processed to the level that it can be distributed to researchers. For the rCCA, 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.

Specific processing and analysis steps to address the hypotheses

Behavioral data analysis

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

fMRI analyses

To identify brain networks associated with the different contrasts of the Stop-Signal Anticipation Task (SSAT) task, we will apply weighted voxel co-activation network analysis (WVCNA)[23,30,31] by combining the scale-free network assumption with a dynamic cut of the dendrogram, to maximize the resolution of localized brain network features (further details in Jia et al., 2020[23]). To minimize the arbitrary choice of parameters, we will take the default and suggested settings of the R package WGCNA[32]. Adjacency matrices will be generated, which will be used to generate the topology overlapping matrices, which will capture both the direct and indirect connections among voxels. Further, we will remove redundant information by applying an additional hierarchical clustering on these nodes with a static cut at the 90th percentile, keeping the 10% most distinctive branches (representing clusters) in each dendrogram. Specifically, hierarchical clustering will be applied on the distance matrices as 1 minus the topology overlapping matrices and, together with the dynamic cut-tree function, the fMRI modules will be generated as functional ROIs. The first principal component of each module will be included in the following analysis to represent brain activation (or BOLD response). There will be no merge of modules conducted after the hierarchical clustering to avoid using an arbitrary threshold. This procedure will enable us to efficiently reduce dimensionality while still preserving localized network features from WVCNA[23]. Using this approach, we will identify clusters in the two contrasts (successful/failed stopping and proactive control), demonstrating self-regulation in the Stop-Signal Anticipation Task (SSAT).

Canonical Correlation Analysis (CCA) is a multivariate statistical method that can simultaneously assess two different, high dimensional sets of variables, for instance brain measurements (i.e., brain connectivity between any two brain regions) and behavioral measures (SSAT 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[23,33].

To find meaningful correlations between functional brain networks as derived through WVCNA and the child characteristics, we will use (ridge-regularized) canonical correlation analysis (rCCA)[34]. The rCCA method seeks to find subsets of variables in two datasets that best correlate with each other while stabilizing the result through penalization of correlations within each dataset. The child characteristics to be included in the rCCA analyses will be included at item-level, and will be all items from the CBCL, CBSA, EATQ-R (parent and child), IRI, SDQ, QBF. For each correlation, the *P*-value or significance level is determined using permutation tests, where the individual IDs of behavior items will be randomly shuffled at each iteration to generate the null distribution of statistics of interest. Particularly, we will use the eta square (η^2) to represent the proportion of mutually explained variance between the two sets of variables.

Ultimately, we will examine the similarities and differences in brain-behavior correlations in relation to self-regulation problems and environmental factors, in children

with different characteristics, with the goal of understanding how self-regulation problems contribute to the development of psychopathology. Based on the rCCA results, we will analyze the relation between participant characteristics (age, gender, pubertal stage, IQ), self-regulation performance (SSRT, SSD, MRT), environmental factors and rCCA brain activity loadings 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 task-fMRI data in this cross-sectional study. Specifically, we request the following data:
- Stop-Signal Anticipation Task (SSAT) fMRI data, incl. T1 anatomical scan for registration
- Performance data from the fMRI SSAT task
  - Stop-Signal Reaction Time (SSRT)
  - Stop-Signal Delay (SSD)
  - Mean reaction time (MRT)
- A set of questionnaires on related behaviors
  - CBCL
  - CBSA
  - SDQ
  - EATQ-R (parent & child)
  - IRI
  - QBF
- A set of questionnaires on environmental factors
  - Demographics questionnaire (Socio-economic status (SES))
  - List of long-term social events questionnaire
  - CRPBI
  - PCS
  - NOSI (COMP)
- Demographic information
  - Age
  - Gender
  - Pubertal development
  - Full-scale IQ

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