HUMAN
Connectome
PROJECT for Early Psychosis

HCP Early Psychosis 1.1 Data Release: Reference Manual

19 August 2021

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1.0 Background and Rationale

The primary goal of the "Human Connectome Project for Early Psychosis" is to acquire high quality data consistent with the data acquired as part of the original Young Adult HCP, focused on a cohort of young adults with early phase psychosis (both affective and non-affective psychosis), within the first 5 years of the onset of psychotic symptoms.

The significance of this protocol is fourfold:
1) We address an important problem, early phase affective and non-affective psychoses, within 5 years of the initial onset of psychotic symptoms. This is an important cohort to study given that this is a time period early in the course of illness when there are fewer confounds such as prolonged medication exposure and the effects of chronicity, and it is also a time period when treatment intervention strategies may be most effective. Moreover, there is strong evidence that there are both common and distinct brain processes underlying these cohorts (e.g., Berrettini 2003; Murray et al., 2004; Baker et al., 2014). Accordingly, we have acquired a large volume of high quality data on these cohorts using the HCP Lifespan acquisition protocols for imaging, behavior, and cognition.

2) High quality data is maintained by performing data analysis and quality control procedures consistent with the original HCP. Here, we have used the HCP Lifespan imaging sequences at Brigham and Women's Hospital (BWH), McLean Hospital, and at Indiana University (IU).

3) We are also providing novel and modified tools that can be used in any HCP study, which can be downloaded from a public github repository for general use by the scientific community (https://github.com/pnlbwh). These tools include a new signal drop detection algorithm to facilitate data quality check, a multi-tensor tractography algorithm (Malcolm et al., 2010) essential to extract accurate connectomes from high angular resolution HCP data, a harmonization algorithm for diffusion magnetic resonance imaging (dMRI) data acquired across sites (Mirzaalian et al., 2015), and an algorithm that estimates free water from dMRI (Pasternak et al., 2009).

4) Lastly, as part of a separate project (R01MH117012), participants are evaluated at two follow-up timepoints in order to map brain, cognitive and clinical trajectories during this early course of illness compared to controls. **Note HCP-EP Release 1.0 and 1.1 have included only baseline measures.** Longitudinal follow-up data are included under a separate NDA collection (Collection Title: Neuroprogression across the Psychosis Spectrum in the Early Course of Illness; Collection ID: 3179).

2.0 Dataset Overview and Changes since Last Release

The **August 2021 HCP-EP Release 1.1 on NDA** contains behavioral data for **251** subjects (69 subjects added since the 1.0 release). Cohort assignment is as follows: **57** affective and **126** non-affective psychotic patients and **68** matched healthy controls. Updated MRI data is provided for **183** (unprocessed, all modalities) and **169** (minimally processed structural MRI) of these subjects (the same group of subjects as in HCP-EP Release 1.0). Updates were made to the processed structural MRI data such that CIFTI brain maps (e.g., *.dlabel.nii and *.dscalar.nii files) that were inadvertently excluded were reinstated.

See Table 1 for enrollment by site for subjects in this data release.

In addition to the added subjects for the Clinical Assessments and Procedures, corrections were made to some individual subject's values for variables in the following NDA structures:

- scid_v01 (Structure Clinical Interview (SCID-5-RV))
- ndar_subject01 (Research Subject and Pedigree)
- cains01 (Clinical Assessment Interview for Negative Symptoms (CAINS))
- psychosocial01 (Diagnosis Form)

The specific changes made can be found in **Appendix 3: HCP-EP Release 1.1 Change Log**.

3.0 Clinical Research Sites

Below we describe the 4 clinical recruitment sites:
Indiana University (IU) Psychotic Disorders Program, Prevention and Recovery for Early Psychosis (PARC). Eskenazi Midtown Community Mental Health PARC is a specialty program for early psychosis located in Indianapolis, Indiana and is an affiliate of Indiana University. PARC is the only comprehensive early psychosis specialty program in central Indiana and serves a population of over 1 million. Founded in 2009 by the study Multiple-PI Dr. Breier, and currently directed by him, PARC is a comprehensive treatment clinic, training program, and research center. PARCs recruitment program is funded by federal and state grants. PARC averages 7 new intakes per month (84 annually).

Beth Israel Deaconess Medical Center – Massachusetts Mental Health Center (BIDMC-MMHC), Prevention of and Recovery from Early Psychosis (PREP) Program. The early psychosis program at BIDMC-MMHC, directed by Dr. Keshavan (BIDMC Site-PI), began in the 1990's as a clinical psychopharmacology program and includes the PREP clinical outpatient program, the CEDAR (Center for Early Detection, Assessment and Response to Risk) High Risk ("prodromal") outpatient program, and an inpatient psychiatry unit. Referrals to the CEDAR clinical and research program are approximately 75/year and many of these putatively prodromal individuals have

had a first episode of psychosis and are referred into first episode programs. PREP receives approximately 100 referrals annually, and usually maintains a census of 50 patients.

McLean Hospital, McLean On Track. McLean On Track is a specialty first episode psychosis program within the Psychotic Disorders Division at McLean Hospital, where Dr. Öngür (McLean Hospitla Site-PI) is Chief. McLean on Track usually maintains a census of about 100 patients. Patients meeting study criteria will also be referred by treating physicians from the McLean Psychotic Disorders inpatient units where Dr. Ongur is also Chief.

Massachusetts General Hospital (MGH), First Episode and Early Psychosis Program (FEPP). FEPP is a specialty research and clinical program within the Schizophrenia Clinical and Research Program (SCRP), Department of Psychiatry of MGH. It is located in the outpatient department of MGH. Patients meeting study criteria will also be referred by treating physicians on the MGH Wang 8 inpatient unit. The majority of FEPP patients participate in research. The FEPP program usually maintains a census of about 80 patients. Dr. Holt is the Site-PI.

Table 1. Current Status of Subject Completion

	June 2021		
Sites	**Patient**	**Control**	**Total**
IU	90	26	116
BIDMC	25	11	36
MGH	10	13	23
McLean	58	18	76
TOTAL	**183**	**68**	**251**

4.0 Study Population (Inclusion/Exclusion Criteria)

Medically stable male and female subjects with a confirmed psychiatric diagnosis and healthy control subjects were enrolled in the study.

Inclusion Criteria (all three subject cohorts):

- 16 to 35 years of age at study entry
- Male or female
- Ability to provide informed consent or have a legal authorized representative or guardian
- Outpatient
- Fluent in English.
- Female subjects of childbearing age report that they are not pregnant and must test negative on a urine pregnancy test at the MRI visit.*
- Willing to share de-identified data with the Connectome database
- Meets additional inclusion criteria for one of the three subject cohorts described below

Cohort 1: Non-Affective Inclusion Criteria:

- DSM V** diagnosis of schizophrenia, schizophreniform, schizoaffective, psychosis NOS, delusional disorder, or brief psychotic disorder with onset within the past five years prior to study entry

Cohort 2: Affective Inclusion Criteria:

- DSM V** diagnosis of major depression with psychosis (single and recurrent episodes) or bipolar disorder with psychosis (including most recent episode depressed and manic types) with onset within five years prior to study entry

Cohort 3: Healthy Control Inclusion Criteria:***

- Does not meet the criteria for meet criteria for bipolar and related disorders, major depressive disorder (recurrent) or schizophrenia and other psychotic disorders
- Does not meet criteria for current anxiety disorder
- Anxiety disorders are allowable if the total duration of the illness was less than 12 months; has been in remission for at least 12 months; and did not require the use of medication to treat anxiety
- Does not have a first-degree family member diagnosed with a schizophrenia spectrum disorder
- Free of psychiatric medications at the time of study entry
- No history of psychiatric hospitalization

Exclusion Criteria (all three subject cohorts):

- Substance-induced psychosis or psychotic disorder due to a medical
- Known IQ less than 70 based on medical history**
- Subjects with known medical history of Human Immunodeficiency Virus positive (HIV+) status
- Subjects with an active medical condition that affects brain or cognitive functioning (eg. seizure disorder, epilepsy, head trauma, stroke, traumatic brain injury, significant loss of consciousness, or other neurological disorder) in the site principal investigator's opinion
- Subjects with implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, ventriculoperitoneal shunt, or other contraindication to undergoing an MRI scan
- Current severe substance use disorder in past 90 days (excluding caffeine and nicotine)
- ECT treatment in past 12 months
- Subjects considered a high risk for suicidal acts – active suicidal ideation as determined by clinical interview OR any suicide attempt in 30 days prior to screening
- Subjects who demonstrate overtly aggressive behavior or who are deemed to pose a substantial risk of danger in the Investigator's opinion

* Female subjects, including minors, who tested positive for pregnancy were informed at the time of testing. Site PI's were informed and addressed this issue with subjects on an individualized case by case basis.

** Inclusion/Exclusion criteria related to diagnosis and IQ are based on history and the patient phone screen and were confirmed during the screening assessments by the SCID-5-RV and the WASI-II, respectively.

*** Healthy control inclusion criteria are based on reported history and the healthy control phone screen but were confirmed during the SCID-5_RV screening assessment.

5.0 Study Procedures

The following assessments and procedures were completed by study personnel trained to administer the instruments and were based on interviews with the subject or questionnaires completed by the subject.

5.1 Clinical Assessments and Procedures

Whenever possible, all clinical assessments and procedures were administered to all subjects regardless of subject cohort unless otherwise specified. Clinical Assessments and procedures, including NIH Toolbox measures and additional cognitive assessments, for Boston area subjects occurred at BIDMC-MMHC, McLean Hospital, and MGH. MRI scans for Boston area subjects occurred at BWH, BIDMC, or McLean Hospital. Clinical and cognitive assessments and MR scans for IU subjects occurred at the IU School of Medicine.

Timing of Measures: The NIH Toolbox measures were completed in approximately 1.5 to 2 hours; the non-toolbox HCP Lifespan measures, and the additional HCP early psychosis measures took, on average, 2 to 2.5 hours to complete. All subjects were given breaks as needed. Testing occurred over two or more days, but within days of the imaging.

Screening Assessments: In addition to the measures listed below, all subjects completed a screening interview where demographics, family psychiatric history, screening for history of traumatic brain injury and contraindication to MRI testing were assessed.

Medical History: The subject's lifetime medical history were assessed during the screening period. Medical history included previous and current diseases and lifetime and current substance use. All concomitant medications were recorded in the source documentation. In order to address the potential effects of antipsychotic drugs on structural and functional indices lifetime antipsychotic medication dosage as CPZ equivalents using the Gardner approach (Gardner et al., 2010) were calculated for non-affective and affective subject cohorts.

Structured Clinical Interview (SCID-5-RV) (First et al., 2015), in conjunction with medical records and/or clinical interviews, was administered to all subjects, both patients and healthy controls, to rule out patient subjects who were not psychotic or who had a psychosis that was related to substance abuse or to an organic disease. The SCID-5-RV was also used to confirm that healthy control subjects did not meet criteria for bipolar and related disorders, major depressive disorder (recurrent) or schizophrenia and other psychotic disorders.

NIH Toolbox Measures

The following battery was included in the NIH Toolbox Measures (NIH Toolbox, 2013; Toolbox-CB, 2013; McDonald, 2014; Hodes et al., 2013).

- *Cognition* (Picture Sequence, Dimensional Change, Flanker, Picture Vocabulary, Pattern Completion, List Scoring, and Oral Reading)
- *Emotion* (Self-report emotion)
- *Sensation* (Words in Noise, Odor Identification, and Dynamic Visual Acuity)
- *Motor* (9-Hole Pegboard, and Grip Strength)

Additional Cognitive Assessments

- *HCP Lifespan Measures* (Gur et a., 2001; Gur et al., 2009).
  - Delay Discounting
  - Penn Emotion Recognition
- *WASI-II* (Wechsler, 2011)
- *Seidman Auditory Continuous Performance Test* (CPT; Seidman et al., 1998; Seidman et al., 2012)

Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is an assessment instrument for general psychopathology and positive symptoms. The PANSS contains 30 items that assess symptoms of psychotic disorders including positive, negative and general psychopathology. The PANSS was chosen because of its widespread use in clinical studies of psychosis, and its demonstrated reliability in assessing psychopathology across diverse patient populations.

Hollingshead Two-Factor Parental Socioeconomic Status Scale (Hollingshead, 1957) Parental SES is a standard matching variable in psychosis imaging studies because of the downward socio-economic drift associated with these illnesses.

Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013; Forbes et al., 2010; Horan et al., 2011). This is a 13-item negative symptom scale developed and endorsed by the NIMH's Consensus Development Conference on Negative Symptoms. We selected it because of its high reliability and the validation of two key factors - affect and avolition/motivation – that may be used for domain specific analyses.

Young Mania Rating Scale (YMRS) (Young et al., 1978). This is an 11-item clinician administered assessment scale for mania and one of the most commonly used scales to assess severity of mania.

Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). This is a 10-item clinician administered depression rating scale that has established reliability in both schizophrenia and mood populations.

MIRECC Global Assessment of Functioning (GAF) (Niv et al., 2007) provides global assessments of symptoms, work/school and social functioning. The GAF is commonly used in early stage psychosis studies.

5.2 MRI Procedures

MRI Data Acquisition Protocol (duration = approximately 70 minutes)

This project used three Siemens MAGNETOM Prisma 3T scanners at BWH, McLean, and IU. BWH and IU used a 32-channel head coil. The McLean used a 64-channel head & neck coil, with the neck channels turned off. All protocols were based on the 2016 CCF template protocol. Detailed imaging protocols for the three imaging sites are in **Appendix 1**.

In short, the protocol scan sequences were:

- T1w (MPRAGE) and T2w (SPACE) structural scans of 0.8mm isotropic resolution.
- Resting state fMRI (rfMRI) of 2mm isotropic resolution, multiband (MB) acceleration factor of 8, TR 720ms, acquired twice: once with AP and once with PA phase encoding.
- Diffusion MRI (dMRI) 1.5mm isotropic, MB acceleration factor of 4, 92 directions in each shell (b=1500 and 3000) acquired twice: once with AP and once with PA phase encoding. The first two acquisitions include 3 additional directions at b=200 and 6 directions at b=500 to improve modeling of fast diffusion processes such as free water.
- In addition, field maps were acquired to correct for intensity and geometric distortions.

Positioning and motion: Subjects were instructed to remain still during scanning and deformable foam cushioning was used to stabilize the head. Real time image reconstruction and processing were used for quality assurance at the time of scanning. If there was any detectable problem, the scan was repeated. Noise: Noise-attenuating headphones and ear stopples were used and provided excellent noise reduction while still permitting adequate auditory perception.

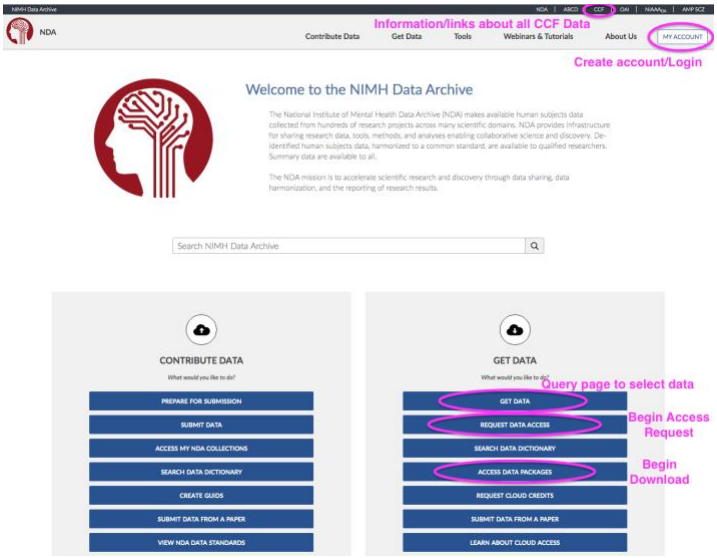
6.0 HCP-EP Release 1.1 Data

6.1 Requesting Access to NDA

Connectomes Related to Human Disease (CRHD) projects like HCP-EP and Lifespan HCP (Aging & Development) data managed and processed by the Connectome Coordination Facility (CCF) are being released through the NIMH Data Archive (NDA), a data repository funded by the National Institutes of Health (NIH).

HCP-Aging, HCP-Development, and CRHD imaging and behavioral data are currently only being shared through NDA.

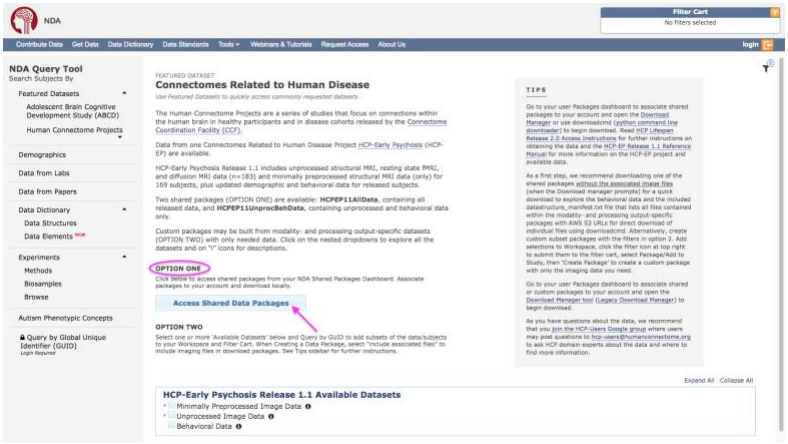
Gaining approval for a new request for NDA access is a multistep process that may take some time, possibly a few weeks, to gather the necessary information and signatures, especially if you are at an institution that must establish the eligibility requirements. Full instructions for obtaining access on NDA, including screenshots of the process, are available in the Lifespan HCP 2.0 Release Data Access & Download Instructions.



Once approved, access is valid for one full year. To maintain access, a renewal request should be submitted through the same process.

6.2 Selecting Data for Download

To obtain data from the HCP-EP Release 1.1, go to the Connectomes Related to Human Disease Featured Datasets query page. You can also get to this page by selecting "**Get Data**" from the NDA home page (pictured above), then selecting "Human Connectome Projects > Connectomes Related to Human Disease" at the top left of the query page.



On the Connectomes Related to Human Disease Featured Datasets query page, the user has two options for accessing the HCP-Early Psychosis data.

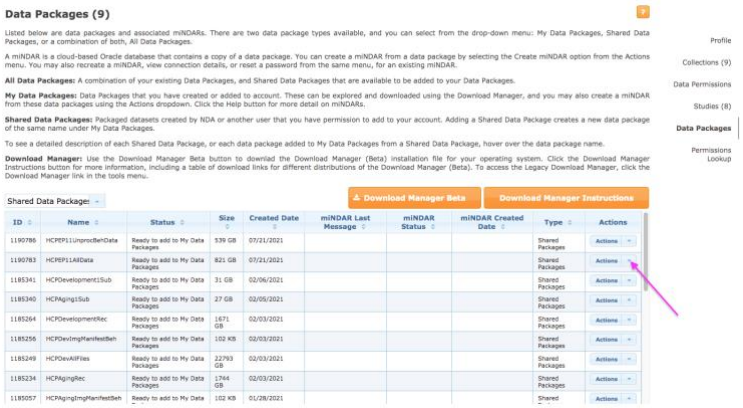
OPTION ONE

OPTION ONE accesses 2 premade, HCP-EP Release 1.1 shared data packages that we recommend as a starting point for download for many users. The **HCPEP11AllData** package contains all released data, and **HCPEP11UnprocBehData** contains unprocessed imaging data. Both packages contain the full released clinical and behavioral data.

Click on the "Access Shared Data Packages" button.

On the Data Packages page, in the Actions column in the row of the package you are interested in, select "Add to My Data Packages" (pink arrow). It will take some time (seconds to several

minutes depending on size) to add the package to your account and there should be a notification at the top of the page when it is complete.

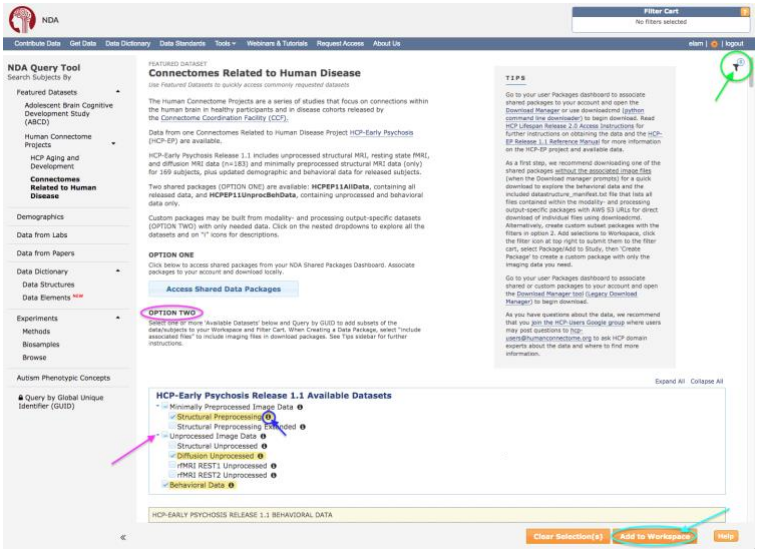


In the meantime, you can proceed with downloading and setting up the Java Download Manager or nda-tools for downloading on the command line. Full instructions for using these download options are available in the Lifespan HCP 2.0 Release Data Access & Download Instructions.

Note: We do not recommend using NDA's "Download Manager Beta" (button on the Data Packages page) at this time due to performance issues and long download times.

OPTION TWO

OPTION TWO allows the user to select modality- and processing output-specific "HCP-style package" filters to access part of the released data by clicking the nested dropdown options under **HCP-Early Psychosis Release 1.1 Available Datasets**.



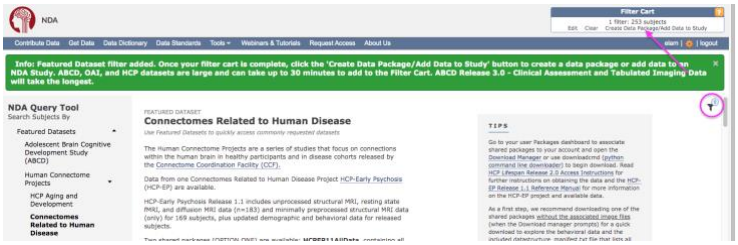
On the Connectomes Related to Human Disease Featured Datasets query page, under OPTION TWO, click the triangles next to the data types to reveal all the subset options (pink arrow). Click the black "i" information buttons (blue arrow) to see a description of the subset package.

Select the checkboxes of the subsets of the data you are interested in and click the "Add to Workspace" button at the bottom of the page (cyan arrow).

Note: The OPTION TWO subset package filters filter for data from all released subjects and are additive (if you make more than one selection), so total data sizes may become large. If you are interested in downloading one or a few subjects, see Filtering by Subjects in the Lifespan HCP 2.0 Release Data Access & Download Instructions.

Click on the Filter funnel icon at the top right (green arrow) showing the number of filters you added. This will show your Workspace, click "Submit to Filter Cart" at the bottom. It can take several minutes to update the Filter Cart at the top right.

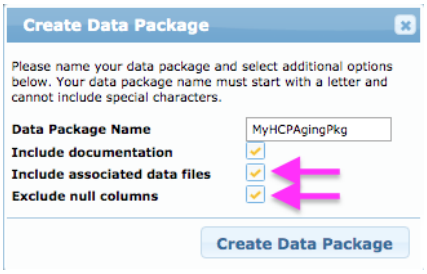
When finished, click on "Create Data Package/Add to Study" (pink arrow) at the bottom of the Filter Cart box at the top right.



On the Data Packaging page, you'll see the data you selected listed in NDA Data Structure categories (mostly useful for Behavioral data, click on the "i" buttons to see a tabular preview of the data).

Click the "Create Data Package" button to create your custom package.

Enter a Package Name, **be sure to click the "Include associated data files" checkbox** (MRI data are considered associated data files), and "Exclude null columns" (pink arrows), so the behavioral data will not have extraneous columns for unused variables.



Click "Create Data Package". The process of creating the package will take several minutes and can be tracked from your Packages Dashboard, with "My Packages" selected at the top left. You may need to refresh the page to see the status change.

While you are waiting, follow the instructions in the Lifespan HCP 2.0 Release Data Access & Download Instructions to download the Java Download Manager or command line download tools. You can also track package creation within the Java Download Manager GUI by clicking the Refresh Queue button until your package is listed as ready to download.

6.3 Files and Directory Structure

The user may choose to download the MRI unprocessed data, preprocessed structural data and the behavioral data by selecting prepackaged data or choose to create their own custom package as described above.

Note: The age of each subject recorded in the imaging, general demographics, and behavioral instruments may be inconsistent, because the time interval between subject consenting, MR scanning, and behavioral assessments was sometimes large (in the order of a few months).

The data package will download to the Save To: location on your file system with the top directory name matching the package name (<YourPkgName>, or, e.g., HCPEP).

If your package contains Minimally Preprocessed Image Data, and Unprocessed Image Data, the high-level <YourPkgName> directory will contain:

<YourPkgName>/

fmriresults01/	Preprocessed data (currently only Structural MRI)
fmriresults01.txt	Info on preprocessing pipelines run (per subject)
imagingcollection01/	Unprocessed data
imagingcollection01.txt	Listing of per subject data (by modality) in collection
md5_values.txt	md5 checksums for download verification
package_info.txt	Info on NDA filters used to create package
README.pdf	automatic README from NDA

We are using the NDA data structures fmriresults01 and imagingcollection01 (full directory structure described in **Appendix 2**) to organize the preprocessed and unprocessed, respectively, per subject data into the same directory structure as that of previously released HCP Young Adult data, so that it is compatible with the expected inputs and outputs of processing through the HCP Pipelines.

The fmriresults01/ directory contains the preprocessed data, currently structural preprocessing outputs only, for the subjects available.
The imagingcollection01/ directory contains unprocessed data of all modalities

Under these two directories, are high level <SubjectID_01_MR>, directories and a manifests directory. Manifests are JSON files (*.json) that organize related data (e.g. unprocessed REST1 data) into a structured set of files to be downloaded according to the directory structure specified. In this case, we have used the manifests to organize the data into per subject, unprocessed and processed "packages" as we did for the HCP Young Adult Study in the directory structure output by and required for input to the HCP pipelines.

6.4 Behavioral Data Structures

Behavioral and clinical measures listed in section 5.1 were mapped to the NDA behavioral data structures listed below. If you include Behavioral data in your download package, tab-delimited text files for all behavioral structures you choose to include will be included in the <YourPkgName>/ directory (e.g. er4001.txt).

Notes:

- The **ndar_subject01** structure has 1 duplicate subject, NDARGK424RPR src_subject (project ID) 4098. That is why NDA counts 252 subjects, when there are only 251 subjects. The other NDA structures do not have duplicate information for this subject. This will be corrected in a future release.

- The following NIH Toolbox instruments were inadvertently not included in HCP-EP Release 1.0, but are now available as part of the behavioral dataset for HCP-EP Release 1.1:

cogcomp01	Cognition Composite Scores
psm01	Picture Sequence Memory Test Age 8+ Form A v2.1
pcps01	Pattern Comparison Processing Speed Test Age 7+ v2.1

Released behavioral data structures

NDA Structure	Measure Name
er4001	Penn Emotion Recognition Task-40
ndar_subject01	Research Subject and Pedigree, includes Phenotype
acpt01	Auditory CPT
madrs01	Montgomery-Asberg Depression Rating Scale
deldisk01	Delay Discounting Task
tbi01	Traumatic Brain Injury
cains01	Clinical Assessment Interview for Negative Symptoms
predd01	NIH Toolbox Sadness CAT Age 18+ v2.0
cgi01	MIRECC GAF Score Sheet
socdem01	Demographics Form
psychosocial01	Diagnosis Form
scid_v01	SCID-5-RV Score Sheet
ses01	Parental SES Hollingshead-Rendlich
mhx01	Lifetime Antipsychotic Drug Exposure
presio01	Nicotine Tracking
panss01	PANSS QuickScore
olfact01	Olfactory Questionnaire
wasi201	WASI II
fmhx01	FIGS Data Screen
cogcomp01	Cognition Composite Scores
dccs01	NIH Toolbox Dimensional Change Card Sort Test v2.1
flanker01	NIH Toolbox Flanker Inhibitory Control and Attention Test v2.1
lswmt01	NIH Toolbox List Sorting Working Memory Test v2.1
orrt01	NIH Toolbox Oral Reading Recognition Test Age 3+ v2.1
pcps01	Pattern Comparison Processing Speed Test Ages 3-6 v2.1
prang01	PROMIS Anger
promisgl01	Social Satisfaction Summary
prsi01	NIH Toolbox Loneliness FF v2.0
psm01	NIH Toolbox Picture Sequence Memory Test v2.1
pss01	NIH Toolbox Perceived Stress Scale
self_effic01	NIH Toolbox Self-Efficacy CAT v2.0
tlbx_emsup01	NIH Toolbox Emotion Domain – Emotional Support Survey

tlbx_fearanx01	NIH Toolbox Emotion Domain - Fear Surveys
tlbx_friend01	NIH Toolbox Emotion Domain - Friendship Survey
tlbx_motor01	NIH Toolbox Motor Domain
tlbx_perhost01	NIH Toolbox Emotion Domain - Perceived Hostility Surveys
tlbx_rej01	NIH Toolbox Emotion Domain - Peer Rejection and Perceived Rejection Surveys
tlbx_sadness01	NIH Toolbox Emotion Domain - Sadness Surveys
tlbx_socwit01	NIH Toolbox Emotion Domain - Social Withdrawal and Positive Peer Interaction Surveys
tlbx_sensation01	NIH Toolbox Sensation Domain
tlbx_wellbeing01	NIH Toolbox Emotion Domain - Psychological Well-Being
tpvt01	NIH Toolbox Picture Vocabulary Test

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