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## The Philadelphia Neurodevelopmental Cohort: A Publicly Available Resource for the Study of Normal and Abnormal Brain Development in Youth

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### Abstract

The Philadelphia Neurodevelopmental Cohort (PNC) is a large-scale study of child development that combines neuroimaging, diverse clinical and cognitive phenotypes, and genomics. Data from this rich resource is now publicly available through the database of Genotypes and Phenotypes (dbGaP). Here we focus on the data from the PNC that is available through dbGaP and describe how users can access this data, which is evolving to be a significant resource for the broader neuroscience community for studies of normal and abnormal neurodevelopment.

### Keywords

neuroimaging; development; adolescence; MRI; data-sharing

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## INTRODUCTION

The Philadelphia Neurodevelopmental Cohort (PNC) is a large-scale study of child development that incorporates rich multi-modal neuroimaging, genetics, and detailed clinical and cognitive phenotyping (1). The PNC is a resource that responds to a paradigm shift in the field of psychiatric neuroscience, where major mental illnesses are increasingly conceptualized as disorders of development (2–5). Together, the multi-level data of the PNC provides a resource to delineate patterns of normal brain development, describe how abnormal patterns of brain development are related to cognitive dysfunction and psychiatric symptomatology, and most ambitiously explore how genetics impacts brain and behavioral development and predisposes individuals to risk of psychiatric symptoms.

While a collaborative team in Philadelphia collected the data, comprehensive analysis that leverages this broad research agenda is best accomplished by sharing the data with the scientific community. As previously emphasized (6–12), large publicly available datasets are a prerequisite for the collaboration necessary to gain traction towards understanding complex phenomena such as the neurodevelopmental origins of psychiatric illness. Furthermore, the unique data of PNC is certain to outstrip the expertise of any single research group; appropriate utilization of the PNC as a resource will require the perspectives of many investigators with complementary skill sets. Accordingly, when the PNC was designed it was explicitly conceptualized as a publicly available resource, to be shared through the Database of Genotypes and Phenotypes (dbGaP; 13). While we have previously described the design of the PNC in detail (1), here we focus on the publicly available PNC datasets in dbGaP and associated data access procedures.

## STUDY OVERVIEW

The PNC was funded by the National Institutes of Mental Health through the American Reinvestment and Reconstruction Act of 2009 as a two-year collaborative study between the Center for Applied Genomics (CAG) at the Children’s Hospital of Philadelphia (CHOP; PI: Hakon Hakonarson) and the Brain Behavior Laboratory at the University of Pennsylvania (Penn, PI: Raquel E. Gur). Importantly, the study capitalized on the resources available through CAG, including a subject pool of (at that time) approximately 50,000 genotyped youths. Critically, approximately 78% of the genotyped youths in the CAG database had provided consent to be re-contacted for future research, allowing for subjects to be approached for recruitment to the PNC. The participants were from the greater Philadelphia area and contacted after stratification by sex, age, and ethnicity. The institutional review boards of the University of Pennsylvania and the Children’s Hospital of Philadelphia approved all study procedures.

Overall, the PNC data in dbGaP includes information from 9,498 children ages 8–21, who were evaluated with a detailed neuropsychiatric evaluation. The psychiatric and neurocognitive assessment was conducted at home (68.8% of participants) or in the laboratory (31.2%), according to participant preference and suitability of the home environment for assessment. Assessment was administered by trained assessors, who recorded information regarding the quality of the testing environment and subject

engagement. A sub-sample received multi-modal neuroimaging performed on a separate study visit at Penn. The average interval between imaging and assessment was 3.3 months. All clinical, neurocognitive and genetic data was placed in dbGaP; the multi-modal neuroimaging data currently available in dbGaP consists of cross-sectional data from 1,000 subjects.

To participate in the PNC, minimal inclusion criteria were required. These included the ability to provide signed informed consent (for participants under age 18, assent and parental consent were required), English proficiency, and the physical and cognitive ability to engage in psychiatric and cognitive phenotyping procedures. Most PNC participants came for primary care in one of the CHOP-affiliated pediatric clinics throughout the Delaware Valley, but the overall sample also included children with more complicated illnesses who received care at CHOP. However, on screening for participation in the neuroimaging component, subjects with medical problems that could impact brain function were excluded. These included major medical problems that could affect brain function, including major severe medical problems (malignancy, immunological disorders, renal / hepatic compromise), neurological conditions (stroke, meningitis, epilepsy, brain tumor, traumatic brain injury), or endocrine disorders (including thyroid or adrenal abnormalities). Additionally, participants with impaired vision or hearing, implanted ferrous metal, unverified metal exposure, claustrophobia, or other contraindications to MRI were also excluded.

## PNC DATA AVAILABLE IN dbGaP

PNC data available in dbGaP is composed of a) a super-set of 9,498 subjects with medical, psychiatric, neurocognitive, and genomic data and b) a sub-set of 1,000 subjects who received multi-modal neuroimaging. The super-set of subjects grew to 9,498 in early 2015 from the original 8,741 subjects released in January 2014. At present, this constitutes a static archive of data collected in the initial cross-sectional acquisition phase of the PNC. However, as described in further detail below (see Future Directions) the PNC is an ongoing study and dbGaP archive will be updated annually. Below, we briefly describe the clinical, neurocognitive, and imaging phenotypes available. Genotyping procedures are not discussed here, but the genotyping pipeline used at CAG has been previously described in detail (14,15) and further information can be accessed at [www.caglab.org](http://www.caglab.org). The vast majority of the samples were genotyped on the 550HH and 610Q SNP arrays from Illumina that overlap in over 500,000 SNPs and are readily imputable to multi-million variants. Further information regarding clinical assessment, cognitive testing, and imaging procedures is provided in PNC manuscripts that have used these data types (16–28), as well as in the data manifest, data dictionary, and phenotype description files available in dbGaP. The compressed size of a single subject's data is approximately 250 MB.

## Demographic, medical, and psychopathology assessment

Demographic, medical, and psychopathology history were assessed using a structured computerized instrument, called GOASSESS (25). GOASSESS was developed from a modified version of the Kiddie-Schedule for Affective Disorders and Schizophrenia (29). In addition to standard demographic data, the psychopathology screener allows symptom and criterion-related assessment of mood, anxiety, behavioral, eating disorders, psychosis

spectrum symptoms, and substance use history. Both subject and collateral informant data was acquired for children ages 11–17; for children under age 11 only collateral data was acquired, whereas for young adults older than age 18 only subject report was acquired. As described in detail elsewhere (30), Bachelor's and Master's level assessors underwent a common 25-hour training protocol that included didactic sessions, assigned readings, and supervised pair-wise practice. They were certified for independent assessments through a standardized procedure requiring observation by a certified clinical observer who rated the proficiency of the assessor on a 60-item checklist of interview procedures (30).

Psychopathology data from GOASSESS is represented in dbGaP as nearly 600 individual item-level responses. To assure the quality of interview data, each assessment underwent a computerized error-checking algorithm that identified areas requiring assessor's attention, and a standardized post-administration review process by certified clinical reviewers. Results were reported to assessors and supervisors. A computerized chart review module provided management tools for the comprehensive review process for supervisors, reviewers, and assessors, as well as an automated check to ensure that all steps were completed successfully. Data were checked, cleaned, and corrected prior upload to dbGaP.

In addition to data on psychopathology, GOASSESS included over 150 self-report items regarding medical history, including specific review of systems questions regarding major organ systems (neurologic, cardiac, pulmonary gastrointestinal, endocrine, etc; see (31)). Although neuroimaging screening sought to exclude individuals with a history of major medical problems, subsequent analysis of this medical inventory revealed that a small percentage of the imaged sample did indeed have a history of medical disorders that could impact brain function, or had a clinical abnormality of brain structure that was encountered incidentally (32). Thus, in published studies from our group, medical items from GOASSESS (in concert with data from the electronic medical record, see below) was used to perform a second round of medical exclusions.

### **Computerized neurocognitive battery**

The Penn computerized neurocognitive battery (Penn CNB) has been widely used in large-scale studies of psychiatric illness and collaborative genomics studies (33,34). As part of the PNC, the Penn CNB was simplified for the pediatric population and shortened to a one-hour administration time (23,26,35). Shorter administration time was achieved without increased measurement error through combination of classical psychometric as well as item response theory methods (21,23,26,27). The CNB used as part of the PNC consisted of 14 tests that were adapted from tasks applied in functional neuroimaging studies to evaluate a broad range of cognitive domains. These domains include executive control (abstraction and mental flexibility, attention, working memory), episodic memory (verbal, facial, spatial), complex cognition (verbal reasoning, nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion intensity differentiation, age differentiation) and sensorimotor and motor speed. Except for the latter two tests that only measure speed, data in dbGaP includes both accuracy and speed information for each trial type in each test. This information, along with normative performance metrics, was used to generate validation codes for each test and the CNB as a whole. Clinical, cognitive, and demographic data is

available for all subjects with neuroimaging data, and can be downloaded from dbGaP as a comma-separated values (.csv) file.

### Multi-modal neuroimaging

All imaging data from the PNC was acquired at Penn, on a single scanner, in a short period of time that did not span any software or hardware upgrades. All MRI scans were acquired on a single 3T Siemens TIM Trio whole-body scanner using the VB17 revision of the Siemens software. Signal excitation and reception was obtained using a quadrature body coil for transmit and a 32-channel head coil for receive. Gradient performance was 45mT/m, with a maximum slew rate of 200 T/m/s. Due to the short study timeline and lack of a development phase, with the exception of perfusion imaging sequence, product sequences were used. The MRI protocol was comprised of scans designed to obtain information on brain structure, perfusion, structural connectivity, resting state functional connectivity, working memory function, and emotion identification. All scans were acquired with a straight magnet axial orientation (i.e. non-oblique). The total scanning time of the entire protocol was 50 minutes, 32 seconds.

Sequence parameters and the number of subjects available for each scan type in dbGaP are displayed in Table 1. The scanning protocol used a fixed order of sequence acquisition, so while 1000 scans are available for the first sequence (the T1 structural image), fewer subjects are available for subsequent runs due to incomplete scanning sessions (e.g., lack of time or subject withdrawal). The two fMRI tasks (the fractal n-back task and the emotion identification task) were administered in a counter-balanced order across the course of the study. Log files for in-scanner task responses for the fMRI tasks are present in dbGaP as well.

As displayed in Table 1, the T1 and BOLD runs used standard product sequences. However, as described in more detail in our prior paper on the design of the PNC, several details regarding the diffusion weighted and perfusion imaging sequence should be noted. In pediatric and clinical populations, the diffusion sequence is typically less well tolerated due to the gradient induced table vibrations. In order to reduce the continuous duration for which the subject was required to tolerate the scan, the DWI sequence was broken into two separate imaging runs. Consequently, a 64-direction set (36) was divided into two independent sets, each with 32 diffusion-weighted directions. Each sub-set was chosen to be maximally independent, such that they separately sampled the surface of a sphere. The first direction set contained 3 b=0 acquisitions, and the second direction set contained 4 b=0 acquisitions.

Perfusion imaging in the PNC used a custom written pseudo-continuous arterial spin labeling (pCASL) sequence (37). The sequence used a single-shot spin-echo EPI readout. The arterial spin labeling parameters were: label duration = 1500 ms, post label delay = 1200 ms, labeling plane = 90 mm inferior to the center slice. The sequence alternated between label and control acquisitions for a total of 80 acquired volumes (40 label and 40 control), with the first acquired volume being a label. The slices were acquired in ascending, non-interleaved order to avoid slice ordering confounds associated with interleaved schemes. In order to ensure that all slices had a similar post-label delay, slices were acquired

in a compressed scheme immediately following the post-label delay, as opposed to distributing the slice acquisitions evenly throughout the TR period. While spin-echo pCASL has the advantage of a higher SNR than gradient-echo pCASL, due to the large chemical shift of fat in the phase-encoding direction, it was observed that residual fat signal resulted in erroneous CBF quantitation, primarily in inferior occipital regions. While we currently are investigating methods to mitigate this effect, we have found that removal of four image pairs substantially reduces this frequency-dependent artifact (20).

Scans from the first 1000 subjects scanned as part of the PNC are available from dbGaP in dicom format. No quality control criteria were applied to uploaded images. As extensively discussed elsewhere (38,39), image quality assurance and de-noising procedures remain a major area of active research in developmental and psychiatric neuroimaging. Thus, by including the full range of acquired images, we expect that the PNC may become a valuable resource for methodological studies. Indeed, prior and ongoing work using PNC data has focused on the confounding influence of motion artifact in studies of resting state functional connectivity (40–42) and diffusion weighted imaging. Accordingly, all runs with a complete acquisition were uploaded to dbGaP.

### Data de-identification procedures

Genetic and phenotypic (clinical, cognitive and neuroimaging) data underwent a multi-step process with multiple encrypted identifiers as part of an anonymization process in order to de-identify participant data. The data anonymization process was setup such that no individual was allowed access to both identifiable phenotype data and clinical data. The encryption system is made up of 3 steps; two of the steps are in the form of a RSA encryption and the third step is in the form of a lookup table in a database connecting a second level encrypted ID to a 10 digit human readable subject ID. For the raw neuroimaging data, all identifying information was stripped from the image headers; demographic information including age (in months), sex, self-reported race, and the new final encrypted ID were written into this anonymized header.

## DATA ACCESS PROCEDURES

Unlike many other neuroimaging data repositories, genetic data is available for all PNC subjects. Due to resulting concerns regarding confidentiality, in collaboration with funding agencies it was decided that imaging, genetic, and phenotypic data would be shared jointly in dbGaP. The PNC is listed under the original project name: “Neurodevelopmental Genomics: Trajectories of Complex Phenotypes.” The full URL is [http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000607.v1.p1](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v1.p1). As described in detail elsewhere (13), dbGaP was created to be a general repository for sharing genetic and phenotypic data from large-scale studies in a secure manner. Accordingly, most of the access and sharing procedures for the PNC are governed by dbGaP policies; these are summarized briefly here. However, further detail can be found both in published manuscripts (13,43) and also in extensive online guidance on the dbGaP website.

The dbGaP is designed to be a repository for both genotypic and phenotypic data. Each study receives a unique identifier within dbGaP (data type prefix: “phs”); the study

accession ID for the PNC is phs000607.v1.p1. Within dbGaP there are specific data types for study documents (“phd”) including data dictionaries and protocol documents. Tables of phenotypic traits (“pht”) include individual phenotypic variables (“phv”), which are linked to study documents and data dictionaries via XML formatting. Genetic data (“phg”) is represented in matrix format. Version suffixes are supplied for each data type. Errors detected will be updated upon detection and annual updates. Large phenotypes such as the neuroimaging files in dicom format are compressed in .tar format. The data manifest for the PNC provides an orientation of data accessible via dbGaP.

The PNC data in dbGaP is accessible to qualified investigators, defined as an individual with PI credentials in eRA Commons. Individuals who do not have PI credentials can collaborate with PIs who may apply on their behalf. All users must complete a brief Data Access Request, which includes a Research Use Statement (2,200 characters maximum) that summarizes project goals. Following access approval, the submitted Research Use Statement is made publicly available on the dbGaP project page for the PNC. A non-technical summary for the lay public is also required (1,100 characters maximum). Data access requests must designate the appropriate institutional signing official as well as the local information technology director, who has the authority to vouch for the capability to conform to the data security policies of the dbGaP Data Use Certification. This Data Use Certification details that users will only use data in accordance with the proposal outlined in the Data Access Request; other research requires a separate Data Access Request. The term of use is 1 year, and can be renewed. Furthermore, approved users must pledge to not attempt to identify any individuals in the dataset, nor transfer the data to any individual not included in the initial Data Access Request; any inadvertent data release or security breach should be reported. While dbGaP does allow for a one-year publication embargo period, this embargo expired January 31<sup>st</sup>, 2015.

Once users are granted access to the PNC data in dbGaP, they may download the data using the Aspera Connect utility, which is publicly available (<http://downloads.asperasoft.com/downloads>). Aspera connect allows very large datasets to be downloaded from dbGaP through a FASP protocol that uses UDP, providing download rates of up to 1 gigabit per second. Furthermore, the utility has automatic checksum and bandwidth dialing capability to ensure transfer completion and minimize interruptions.

## FUTURE DIRECTIONS

The first 1000 subjects imaged as part of the PNC were released to dbGaP for public use. However, both cross-sectional (current n=1,601) and longitudinal (current n=404) data acquisition is ongoing. Given this expanded sample, it is likely that the public PNC neuroimaging datasets may be expanded in the future. However, it is possible that certain data may not be made public, but reserved for use in analysis challenges as a test/validation dataset. Additionally, certain data from PNC participants was not placed in dbGaP for public use. This includes data from the electronic medical records and other potentially identifying information.

PNC data in dbGaP is a relatively static resource comprised of raw imaging data. While presently there are no resources to provide active ongoing support for all users of the repository, moving forward we hope to extend current data to include processed data, quality assurance information, and support for data management. Currently, such resources are available only for collaborative research. To facilitate such research, we have developed an internal system for managing, tracking, and servicing collaborations, with links to both REDCAP (subject variable) and XNAT (neuroimaging data) databases at UPenn.

Public interest in the PNC has been rapidly accelerating. The PNC data was placed in dbGaP in January 2014; as of January 2015 there have been 62 approved data use requests to access the PNC data. Many of these requests were related to RFA MH-15-400 (“Leveraging a Recovery Act Resource to Accelerate Research on Neurodevelopment”), which will provide three years of R01-level funding to several groups to perform integrative data analysis on publically available PNC data. The goal of this mechanism is to both accelerate discoveries regarding the neurodevelopmental origin of psychopathology and to stimulate the use of the PNC data within the wider neuroscience community. Through this mechanism and other ongoing research, the publicly available PNC data in dbGaP is therefore likely to become a major resource for neurodevelopmental research.

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### Highlights

- The PNC is a large-scale study of neurodevelopment.
- Data includes imaging, rich cognitive and clinical phenotyping, and genomics.
- Investigators can access data through dbGaP.

Table 1

Sequence	TR/TE/TI (ms)	FOV RL/AP (mm)	Matrix RL/AP/ slices	Slice thick/gap (mm)	Flip angle (deg)	Reps	GRA PPA factor	BW/pixel	PE direction	Acq time	# Subjects in dbGaP
MPRAGE	1810/3.5/1100	180/240	192/256/160	1 / 0	9	-	2	130	RL	3:28	1000
PCASL	4000/15/-	220/220	96/96/20	5 / 1	90/180	80	2	2604	AP	5:32	942
BOMap	1000/2.69+5.27/-	240/240	64/64/44	4 / 0	60	-	-	500	AP	1:04	
Emotion ID	3000/32/-	192/192	64/64/46	3 / 0	90	210	-	2056	AP	10:36	934
N-Back	3000/32/-	192/192	64/64/46	3 / 0	90	231	-	2056	AP	11:39	913
DTI	8100/82	240/240	128/128/70	2 / 0	90/180/180	35	3	2170	AP	5:24	
DTI	8100/82	240/240	128/128/70	2 / 0	90/180/180	36	3	2170	AP	5:32	885
Resting FC	3000/32/-	192/192	64/64/46	3 / 0	90	124	-	2056	AP	6:18	883