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The Lifespan Human Connectome Project in Development: A large-scale study of brain connectivity development in 5–21 year olds

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ABSTRACT

Recent technological and analytical progress in brain imaging has enabled the examination of brain organization and connectivity at unprecedented levels of detail. The Human Connectome Project in Development (HCP-D) is exploiting these tools to chart developmental changes in brain connectivity. When complete, the HCP-D will comprise approximately ~1750 open access datasets from 1300 + healthy human participants, ages 5–21 years, acquired at four sites across the USA. The participants are from diverse geographical, ethnic, and socioeconomic backgrounds. While most participants are tested once, others take part in a three-wave longitudinal component focused on the pubertal period (ages 9–17 years). Brain imaging sessions are acquired on a 3 T Siemens Prisma platform and include structural, functional (resting state and task-based), diffusion, and perfusion imaging, physiological monitoring, and a battery of cognitive tasks and self-reports. For minors, parents additionally complete a battery of instruments to characterize cognitive and emotional development, and environmental variables relevant to development. Participants provide biological samples of blood, saliva, and hair, enabling assays of pubertal hormones, health markers, and banked DNA samples. This paper outlines the overarching aims of the project, the approach taken to acquire maximally informative data while minimizing participant burden, preliminary analyses, and discussion of the intended uses and limitations of the dataset.

The transformation from childhood to mature adulthood is a period of dramatic change in brain and body. Major physical and hormonal events transform the body, and foundational maturational processes shape brain and behavior, with widespread impact on cognition, health, and daily

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functioning. Despite the centrality of childhood and adolescent neurodevelopmental processes, our understanding of how human brain networks change over development remains fragmentary.

Technical advances in noninvasive human neuroimaging have provided powerful tools to probe fundamental questions about neurodevelopmental processes at the macroscopic scale. This includes successful efforts of the Human Connectome Project (HCP), a pair of NIH-funded consortia providing analytic tools and foundational data on brain circuitry in young adults (Fan et al., 2016; Glasser et al., 2016a; Setsompop et al., 2013; Smith et al., 2013; Van Essen et al., 2013). The Lifespan Human Connectome Project in Development (HCP-D) is taking advantage of these technical advances to generate a foundational dataset that advances our understanding of the development of brain organization and connectivity in 5–21 year olds. The HCP-D consortium includes four imaging sites – Harvard University, University of California-Los Angeles (UCLA), University of Minnesota (UMinn), and Washington University in St. Louis (WUSTL) – with Oxford University contributing to acquisition and data analytic approaches. Here, we provide an overview of the HCP-D, including project aims, the data being acquired, key decisions that led to the final HCP-D protocol, and preliminary results. Details on the brain imaging acquisition protocol can be found in a companion paper by Harms et al. (under review).

1. Overview OF HCP-D

1.1. Aims

The HCP-D has four interrelated scientific aims:

Aim 1: Adapt existing HCP protocols to the practical challenges of studying developmental populations. The magnetic resonance imaging (MRI) scanning protocols used by all four acquisition sites balance two constraints – to harmonize with data from the original HCP but also to adapt data acquisition to specific challenges of developmental imaging. This includes the need to reduce participant burden and to cope with an anticipated greater head and body motion that is common in children.

Aim 2: Acquire high quality multimodal imaging data to characterize age-related changes in brain network organization and connectivity. HCP-D is generating brain imaging data from 1300 + healthy volunteers, ages 5–21 years, emphasizing connectivity in tandem with rich characterization of behavior, health, and environmental factors. A longitudinal component focuses on within-subject changes in brain connectivity within the active pubertal phase.

Aim 3: Prioritize inflection points of health-relevant behavioral changes within specific developmental phases. HCP-D will enable the study of links between pubertal and brain network development, aiming to distinguish between age-related versus pubertal-related changes in brain connectivity. Another focus is on reward and cognitive control interactions, a set of processes that have important health-related implications for adolescents.

Aim 4: Optimize data processing schemes for developmental data and make the data and analytic tools publicly available for the scientific community. The HCP-D analysis pipelines will be adapted to accommodate unique features of developmental MRI data, and the data will be made freely available to the scientific community.

1.2. Relation to other brain imaging projects

The HCP-D builds on the success of the HCP Young Adult (HCP-YA) Project, which studied 1100 22–35 year olds from 2010 to 2016 (Van Essen et al., 2013). Continuity across the lifespan is provided by two additional projects: the Human Connectome Project in Aging (HCP-A) spans ages 36–100 + years (Bookheimer et al., under review) and the "Baby Connectome" project spans ages 0–5 years using methods customized for very young children [http://babyconnectomeproject.org]. Although the HCP-D and HCP-A are distinct projects with dissociable goals and methods, the consortia overlap extensively in institutions, investigators, staff, and leadership. This facilitates coordination across many commonalities between the two projects, as detailed in a companion paper (Harms et al., under review). That said, there are important differences in imaging protocols reflecting the need to customize the project to the scientific and pragmatic needs associated with a developmental population.

HCP-D also aims for synergy with other larger-scale imaging studies on developmental populations, while retaining a unique focus. For example, recent publicly available datasets including the Philadelphia Neurodevelopmental Cohort (Satterthwaite et al., 2014a; age 8–21 years), the Pediatric Imaging, Neurocognition, and Genetics study (Brown et al., 2012; age 3–20 years), Imagen (Schumann et al., 2010; age 14–16 years), and Generation R (Kooijman et al., 2016, White et al., 2018; age 6–11 years) have yielded numerous publications that enhance our understanding of neurodevelopment. We anticipate that HCP-D data will be useful not only for replication studies but also for many additional analyses that capitalize on high data quality, diverse modalities, preprocessing via "HCP-style" pipelines and analysis strategies (Glasser et al., 2016a; b), a focus on brain connectivity development, and the availability of hormonal assessments.

HCP-D is also complementary to the ongoing Adolescent Brain and Cognitive Development (ABCD) project (Volkow et al., 2017; Casey et al., 2018). The HCP-D is mainly a cross-sectional project spanning ages 5–21 years, with embedded longitudinal cohorts around puberty, whereas ABCD is a fully longitudinal study starting at ages 9 and 10. The studies assess many of the same imaging modalities, with conceptual overlap on the fMRI tasks. Further, many out-of-scanner assessments are intentionally matched across projects. Results from the HCP-D cross-sectional component will enable hypothesis generation that can be tested for replication on ABCD data once children have passed from puberty into young adulthood. The potential for data-driven analyses in the HCP-D that can be replicated in the ABCD data is a crucial step to validate the results of more exploratory analyses.

2. Population of study

2.1. What is "typical development"?

HCP-D aims to characterize changes in brain networks over typical development, yet there is no agreed-on or precise definition of "typical development". We therefore set participant inclusion and exclusion criteria to represent a broad range of typical human traits and behavioral patterns, but to exclude individuals: *a)* who could not feasibly complete the study in a way that is comparable to other participants (e.g., those with learning disabilities or insufficient English fluency), *b)* who have health problems that would compromise their inclusion within the broader dataset or jeopardize their anonymity when the data are publicly released, and *c)* who have disorders that may have altered the course of typical development. It is also necessary to exclude any participants with contraindications for MRI (due to safety and/or data quality), which entails excluding many children having orthodontic treatment. Our approach to inclusion/exclusion largely parallels that used for HCP-YA and HCP-A.

Aside from these constraints, the inclusion and exclusion criteria preserve substantial heterogeneity in many domains. For instance, participants remain in the study irrespective of whether they test positive or negative on a urine drug screen, whether they have elevated symptoms of psychiatric illness (as long as they have not been diagnosed and treated for 12 months or longer), and whether they are using prescription medications such as oral contraceptives. Detailed data are acquired on these heterogeneous facets of the sample so that analyses will be able to statistically control for them, or examine effects dependent on them, as desired. In addition, there are no restrictions on enrolling multiple members of the same family, which could include siblings in HCP-D, or children whose parents or grandparents are participating in HCP-A. We are making a good-faith effort to collect information about relatedness

based on participant report. This information will be included in future data releases, although its access will be restricted. Table 1 provides a broad overview of HCP-D inclusion and exclusion criteria, with the complete inclusion and exclusion screening provided in Supplementary Table 1.

2.2. Sample

The HCP-D aims to enroll N = 1300 + children, adolescents, and young adults ranging in age from 5 to 21 years. The total number of participants was selected to maximize the quantity of data acquired within the constraints of the project duration, available funding, and balancing between cross-sectional and longitudinal sessions. The upper and lower bounds of the age distribution were set for programmatic reasons to conform to the NIH Funding Opportunity Announcement (FOA. This age range provides continuity but not overlap with the neighboring HCP-YA and HCP Baby projects. Recruitment for the finalized protocol began in the spring of 2017 and has proceeded on a pace that should enable meeting our recruitment objectives. As of July 2018, 665 HCP-D subjects have been recruited of the total of 1344 participants targeted for initial sessions by the end of 2019. We anticipate that the remaining stages of recruitment will be more challenging in order to meet our multiple demographic targets (age bins, sex, race/ethnicity, and SES).

The intended number of total datasets varies by age to oversample the ages for which rapid development in brain networks is expected (see Fig. 1 for sample targets by age). These recruitment goals reflect logging based on the number of participants who undergo an MRI scan, anticipating that a small proportion of participants will be entirely unusable, and that some data components may be missing or unusable for included participants. The minimum data necessary to qualify a dataset for inclusion is the successful consent, intake, and acquisition of a T1w and T2w scan; fortunately, the vast majority of participants to date have completed the assessments in their entirety.

Most participants (n = ~1060+) complete the study once as cross-sectional-only participants (Fig. 1, red). Approximately n = 240 participants participate in a three wave longitudinal acquisition, returning for repeat testing two additional times 15 months apart (Fig. 1, green and blue). The longitudinal component focuses on early-middle (green) and middle-late (blue) phases of active pubertal development. Sampling goals, inclusion criteria, and exclusion criteria are identical between the cross-sectional and longitudinal samples. Section 2.3 below provides additional information on the longitudinal component.

Participants under 18 years are accompanied by a parent or legal guardian who provides informed, written permission for their child's participation. Parents of minors also complete a battery of tasks and assessments (see Section 5.2), reporting about themselves, the family environment, and about their child's traits. Both parents and children are remunerated for their time spent participating in the study.

We aim for balanced numbers of male and female participants at each age (except where noted below for the longitudinal component). For tracking and balancing recruitment goals, we rely on biological sex but we also acquire data on self-perceived gender including non-binary options. Our sampling aims to match the ethnic and racial diversity of the United States according to 2016 Census data (www.census.gov/quickfacts/fact/table/US/PST045216). We also aim for diversity across socioeconomic status (SES) with a good faith effort to distribute SES over sex and race. We exploit the different demographics of the four acquisition locations (Boston, Los Angeles, Minneapolis, St. Louis) to achieve an appropriately diverse sample on ethnicity, race, and SES). In HCP-D, SES is computed using income-to-poverty ratio which is based on family income relative to poverty thresholds, adjusted for family size (Diemer et al., 2013). We aim to acquire approximately one third of the participants with income-to-poverty ratio in the 0–2.5 range, one third in the 2.5–5 range, and one third above 5. Achieving sampling diversity is very challenging for neuroscientific research, and no entirely normative developmental neuroimaging samples have been reported despite evidence that sampling biases exert a substantial impact on neurodevelopmental measurements (LeWinn et al., 2017). These recruitment targets should provide more ethnic, racial, and SES diversity than most previous developmental neuroimaging samples.

Table 1
Overview of inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Age 5–21 years	Premature birth
Speaks English well	Serious medical conditions (e.g., stroke, cerebral palsy)
Safe to enter MRI	Serious endocrine condition (e.g., precocious puberty, untreated growth hormone deficiency)
	Long term use of immunosuppressants or steroids
	Any history of serious head injury
	Hospitalization >2 days for certain physical or psychiatric conditions or substance use
	Treatment >12 months for psychiatric conditions
	Receiving certain special services at school
	Claustrophobia
	Pregnancy

Note: See Supplementary Table 1 for exhaustive list of inclusion and exclusion criteria.

2.3. Longitudinal component

When originally designing the study, we were motivated to include a large longitudinal component within the HCP-D, given the inferential strengths of longitudinal approaches for making claims about the trajectories of developmental processes. Given the resources and size constraints specified by the FOA, the consortium elected to focus the longitudinal component on pubertal hormone-related changes from late childhood through late adolescence.

The focus on pubertal mechanisms reflects its role as a major biological event that propels developmental change. Despite the importance of hormones in neurodevelopmental processes (Giedd et al., 2006; Goddings et al., 2014; Romeo, 2003; Sisk and Foster, 2004; Spear, 2000), the relationship between puberty and brain connectivity changes remains poorly understood. This is, in part, due to the pragmatic challenges associated with characterizing pubertal development, especially hormonal components of puberty (Dorn et al., 2006; Shirtcliff et al., 2009). Methodological difficulties of measuring puberty have resulted in inconsistencies across studies (Granger et al., 2004), a problem exacerbated by a paucity of reference datasets to validate interrelationships across multiple measures of pubertal change (e.g., self-report, saliva and hair hormone concentrations) (Gao et al., 2013). Further, because hormonal effects occur within specified age windows but with great individual differences (Sizonenko, 1978), comprehensive mapping of hormone-brain relationships requires a wide enough age span to capture transitions into and out of the active windows of change.

The longitudinal component is a four-cohort design including equal proportions of 9-year-old females (tracked until 11–12 years), 13-year-old females (tracked until 15–16 years), 10-year-old males (tracked until 12–13 years), and 14-year-old males (tracked until 16–17 years) with approximately 60 participants in each group. These ~240 participants return to complete the HCP-D battery two additional times 15 months apart, totaling three measurements across 2.5 years. Longitudinal sampling begins earlier for females than males because of differences in pubertal onset by sex (females initiating ~1 year earlier than males, on average) (Kaplowitz et al., 2001; Sizonenko, 1978).

The study procedures are nearly identical for every testing session, regardless of whether the participant belongs to the cross-sectional or longitudinal sample, and regardless of wave for the longitudinal study. The key exception is that for certain tasks and tests it is advantageous for

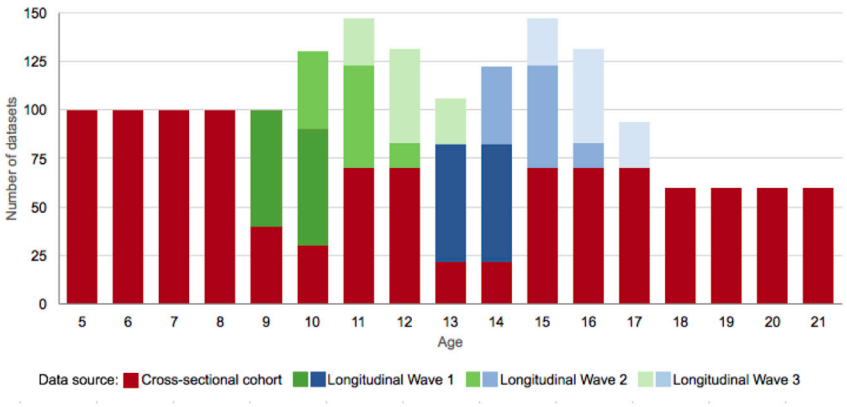

Fig. 1. HCP-D recruitment targets by age. HCP-D will enroll N = 1300 + participants. Most participants will be tested once (cross-sectional cohort; red). A subset of participants in the pubertal range are a part of the longitudinal component. There are two longitudinal cohorts, encompassing early puberty (green, starting at age 9 years for females and 10 years for males) and later puberty (blue, starting at 13 years for females and 14 years for males). The longitudinal participants return for two additional waves of testing (Wave 2 and 3, middle and lighter colors) approximately 15 months apart. X-axis: Age (in years) at testing; Y-axis: Number of datasets.

stimuli not to be repeated, to avoid habituation or practice-related confounds across visits. These exceptions are noted where applicable.

3. Study flow

Fig. 2 presents an overview of a typical study timeline for participants who are 5–17 years old (i.e., with parental involvement); Supplementary Fig. 1 details the timeline for participants 18 and above. For all participants, the second session is typically administered within two weeks of the first, with a maximum lag between sessions of 1 month.

4. Brain imaging

4.1. Overview of imaging

The HCP-D brain imaging protocol includes high-resolution scans for structural, resting-state, task-based, diffusion, and cerebral blood flow (CBF) measures, acquired during two separate MRI sessions. Each modality is described briefly below and in detail in the companion paper

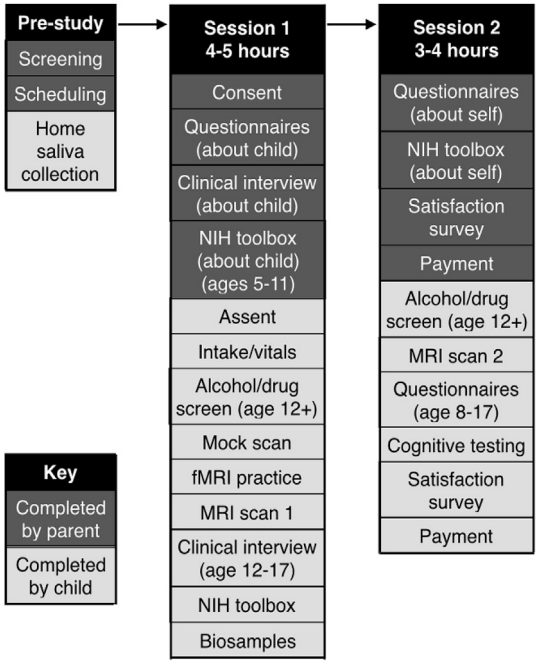

Fig. 2. Example study participation flow. This example represents typical participation for 5–17 year old participants. See Supplementary Fig. 1 for the participation flow for 18–21 year olds, whose parents do not take part.

(Harms et al. (under review)). Fig. 3 presents examples of unprocessed data in each modality from a child participant showing high compliance and stillness during MRI scanning.

All HCP-D (and HCP-A) brain imaging is conducted on a 3 T Siemens Prisma scanners (Siemens, Erlangen, Germany). Participants 8–21 years old are scanned using the Siemens 32-channel Prisma head coil; a pediatric 32-channel head coil developed by Ceresensa (www.ceresensa.com) is used for 5–7 year old participants (see Harms et al. (under review)).

Generally, the HCP-D uses an 'HCP-style' approach to data acquisition developed for the HCP-YA project (Glasser et al., 2016a) and adapted for youths. We train participants to remain still using mock scanning, offer prizes and praise, keep the participants busy while in the scanner with movies (for the structural and dMRI scans), constrain the head in space with pillows and tape, use FIRMM software to monitor head motion in real-time (Dosenbach et al., 2017), and conduct the MRI scanning toward the beginning of study visits whenever possible.

Structural T1 weighted (T1w) and T2 (T2w) scans provide the anatomical reference for analysis of all imaging modalities and must be of high quality in order to generate accurate cortical surface reconstructions (Glasser et al., 2013), and cortical "myelin maps" (Glasser and Van Essen, 2011). The structural T1w and T2w protocols include volumetric navigators for prospective motion correction (Tisdall et al., 2012) to reduce bias in age-related morphometric comparisons. Diffusion imaging is an of high interest because white matter pathways undergo a major neurodevelopmental progression through childhood, adolescence, and into young adulthood (Asato et al., 2010; Giedd et al., 1999; Paus, 2005). The HCP-D diffusion protocol samples 185 directions on 2 shells of b = 1500 and 3000 s/mm^2, along with 28 b = 0 s/mm^2 images. Arterial spin labeling (ASL) (Alsop et al., 2015; Detre et al., 1992) provides a quantitative measurement of CBF, a surrogate marker of brain metabolism and function. While previous studies indicate that CBF declines from childhood through adolescence (Biagi et al., 2007) at a pace that is linked to pubertal timing (Satterthwaite et al., 2014b), there is still much to learn about the basic changes in CBF in the developing brain.

Resting state functional MRI is widely used to infer the intrinsic organization and "functional connectivity" of large-scale brain networks (Buckner et al., 2013; Fox and Raichle, 2007). Maturation of functional connectivity can be examined by quantifying age-related changes in the strength and spatial distribution of intrinsic brain networks (Dosenbach et al., 2010; Fair et al., 2009). During HCP-D rfMRI scanning, participants are instructed to stay still, stay awake, and blink normally while looking at the fixation crosshair. For participants 8 years and older, we acquire 26 min of resting state scanning in four runs, consistent with recent findings and recommendations about obtaining robust connectivity estimates from rfMRI data (Glasser et al., 2016b; Laumann et al., 2017; Pannunzi et al., 2017). For the youngest ages (5–7 years) we reduced the duration of individual runs and the total duration of rfMRI scanning to 21 min.

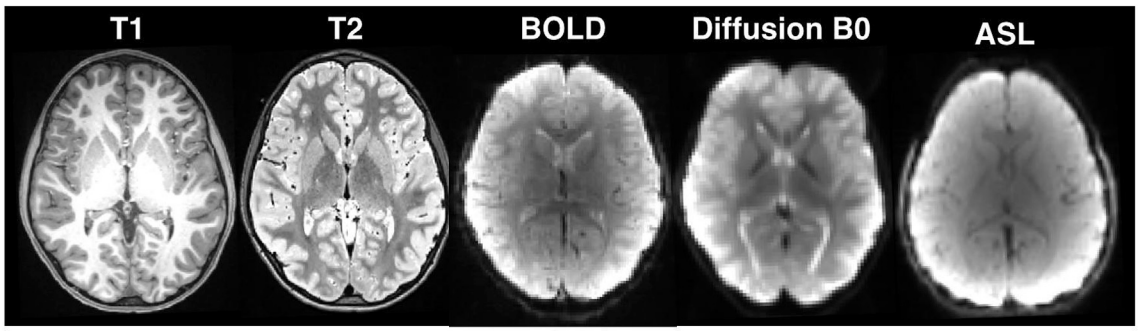

Fig. 3. Representative unprocessed images from each of the HCP-D scan modalities from a 10 year old male participant. Images have undergone affine registration but are otherwise unprocessed.

4.2. Task fMRI

The HCP-D includes three fMRI tasks focused on information processing domains that show prominent maturational changes and/or robust individual differences. Task fMRI analyses can target task-dependent functional connectivity (e.g. (Cole et al., 2014; Gratton et al., 2016; Insel et al., 2017; Krienen et al., 2014; Repovš and Barch, 2012),), which provides a collateral measure of brain network coordination that may overlap or differ in informatively from other measures of brain connectivity. Neurodevelopment from age 5–21 shapes a wide array of cognitive, emotional, and social processes, making it challenging to prioritize specific functional domains. Whereas the HCP-YA study devoted an hour to fMRI task scans and included seven distinct tasks in its data acquisition battery (see (Barch et al., 2013)), scan time was more limited in HCP-D. We prioritized functional domains that relate to emergent health risks during this age window, while also aiming to maintain some degree of harmonization with HCP-YA. We selected three distinct, but interrelated, information processing domains – emotion processing, reward/loss anticipation and consumption, and inhibitory control processes.

These processes were selected for several reasons. First, while prior work has shown normative age-related change in functional brain recruitment (e.g., Rubia, 2013; Casey, 2015), there is a relative dearth of data examining brain connectivity change during information processing in these domains. Second, these domains underpin crucial changes in health-relevant behaviors and experiences including affective reactivity, reward drive, impulsivity, and approach behaviors. Third, these functional processing domains are linked to common symptoms of internalizing and externalizing psychopathology (Hulvershorn et al., 2011; Zhang et al., 2013; Barch et al., 2018) that emerge at unprecedented frequency during the adolescent transition (Lee et al., 2014). We also designed the functional tasks for "multipurpose" use that could satisfy a range of additional scientific questions. For example, we omitted an explicit motor task because fundamental motor processes can be isolated in any task requiring button presses.

An additional goal was to include as many functional domains as possible within the available scanning time, which required prioritization of tasks that were well-powered to observe characteristic activation patterns at the group level, with even brief data acquisition. For each of the three selected tasks, we acquired pilot data and compared activation of brain networks of interest for different amounts of data analyzed. In addition, we have evaluated task activation maps for the early participants acquired in HCP-D (see below). Both the initial pilot analyses and the evaluation of early HCP-D participants demonstrated that the brain networks of interest could be observed at the group level with shortened acquisitions.

It is important to articulate the scope of the intended use of the HCP-D fMRI tasks for data analysis and statistical inference. We anticipate that neural responses in some brain regions will be weaker or stronger at different developmental stages but not necessarily observable at the individual level. The brevity of the tasks will further limit their ability to reliably detect activation in individual participants. Rather, these tasks are likely most suitable for group-based analyses that *a)* utilize the power of group average aggregation (e.g., across age bands comparing 8 year olds versus 9 year olds, etc.), and/or *b)* query brain function and functional connectivity that covaries with age or other individual differences such as pubertal development or behavioral traits.

4.2.1. Reward magnitude (i.e., "guessing") task

Adolescence is characterized by a remodeling of behaviors and neurobiological signals relevant to valuation and motivation (Hartley and Somerville, 2015; Davidow et al., 2018; Doremus-Fitzwater et al., 2010). While most human neuroimaging research in this area has focused on reactivity to rewarding outcomes, valuation-related processes also include anticipation, processing of loss, and representing the value of a given outcome relative to the available alternatives. The HCP-D uses a task that permits broader measurements of neural signals contributing to reward and loss processing and includes reward anticipation, consumption, and tracking of outcome magnitude.

The Reward Magnitude ("guessing") task was adapted from the well-validated reward processing task (Delgado et al., 2000) to measure neural responses to gains and losses of different magnitudes. It has been adapted in two key ways: to make it more child-friendly (Gaffrey et al., 2018), and to add a magnitude manipulation which allows comparison of small and large gain and loss outcomes (Insel et al., under revision, Insel & Somerville, in press). During the task (Fig. 4A), participants can win or lose bonus money by guessing between two response options whenever they view a question mark on the screen. For each trial, participants view a guess cue ("?"), a jittered interstimulus interval, and then view feedback indicating whether they are correct (winning money) or incorrect (losing money). A block of four trials begins with either a low stakes or high stakes cue screen, which indicates whether the subsequent trials would be played for "Low" magnitude outcomes ($0.20 for wins and -$0.10 for losses) or "High" magnitude outcomes ($1.00 for wins and -$0.50 for losses). The losses are half as large as gains in accordance with prior work indicating that losses are over-weighted in human valuation processes (Tversky and Kahneman, 1991).

In sum, the Reward Magnitude task isolates neural responses during the cue period indicating an upcoming block of high or low magnitude outcomes, the guessing period, and each of four feedback types (large win, large loss, small win, small loss). General linear modeling permits analyses of *a)* neural response to receipt of rewards and punishments, *b)* neural activity that tracks reward and punishment magnitude (small versus large quantities), and *c)* neural activity that responds in anticipation of high and low magnitude outcomes. See Supplementary Table 2 for specific task parameters.

4.2.1.1. Reward conditioning manipulation. A special design feature of this task allows for an additional manipulation – a reward conditioning induction that is probed in the Inhibitory Control task that immediately

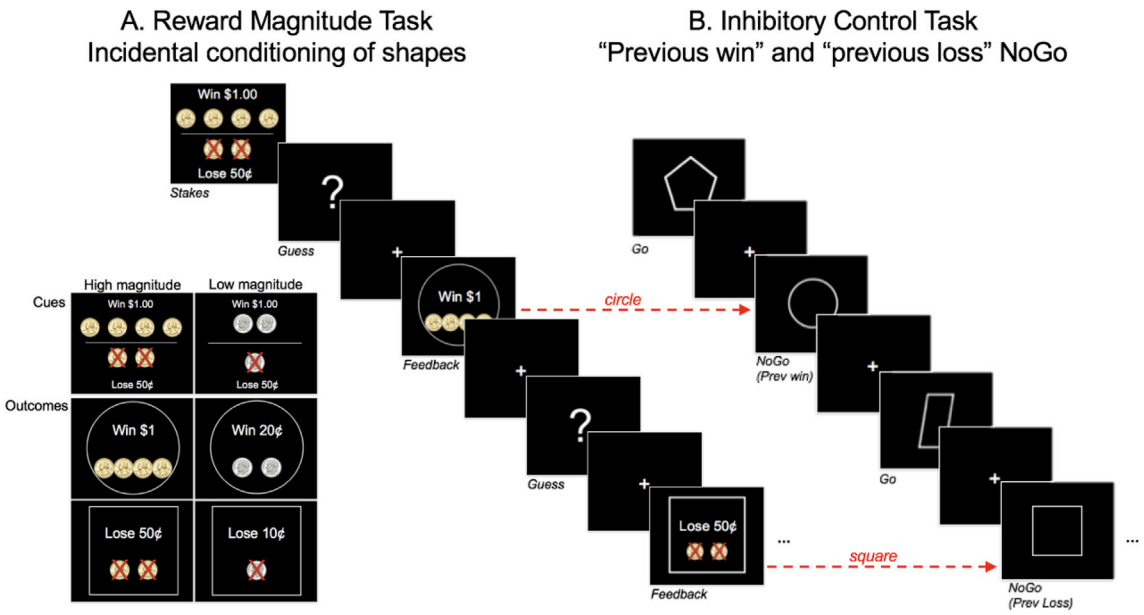

Fig. 4. Reward Magnitude ("Guessing") (A) and Inhibitory Control ("CARIT") (B) tasks. A) During the Reward Magnitude task, participants are cued that an upcoming series of trials will pay out either high or low stakes gains and losses. During a trial, participants press a button to an arbitrary guess (see text) and find out whether they were correct – resulting in monetary gain – or incorrect – resulting in monetary loss. B) During the Inhibitory Control task, participants view a series of shapes, and are instructed to press a button to all shapes (i.e., Go stimuli) except for circles and squares (i.e., NoGo stimuli). In the Reward Magnitude task, incidental shapes (circles and squares) surround the win or loss feedback and subsequently become the two shapes used in NoGo trials in the Inhibitory Control task, where participants are instructed to withhold button presses. In the example shown here, the circle was always paired with winning outcomes in the Reward Magnitude task, potentially facilitating the passive acquisition of a reward-conditioned association. A fixation crosshair is presented during the interstimulus intervals, and represents moments of rest during both tasks.

follows it (see Section 4.2.2.). On feedback screens that inform participants whether they won or lost, the win feedback is incidentally surrounded by a circle (or square, counterbalanced across subjects) whereas the loss feedback is incidentally surrounded by a square (or circle, counterbalanced; see Fig. 4B). Circles and squares are subsequently carried forward to become stimuli in the Inhibitory Control task in which participants are instructed to withhold button press responses to the shape stimuli that had been associated with receipt of reward or receipt of loss. Counterbalance assignment is maintained throughout longitudinal participation.

4.2.1.2. Preliminary data analysis. We evaluated the activity evoked by this task in an early set of HCP-D participants (N = 104, 44 female, mean age = 13.26 years, SD age = 3.58, min = 8, max = 21). Data were preprocessed using existing HCP pipelines (see Supplementary Materials for details). Following preprocessing, data were submitted to a GLM to estimate task effects. The seven regressors of interest described above (high cue, low cue, guess, high win, low win, high loss, low loss) were represented as predictive timeseries by specifying their temporal event onset, convolved with a double-gamma canonical hemodynamic response function. While several types of reward-related processing can be queried with this task, initial analyses focused on a simple *Win vs Loss* contrast (average of high & low win > average of high & low loss), which was carried forward to a group random effects analysis. We identified areas of differential functional activity in the group map using a threshold of Z = 5.01, which corresponds to a stringent grayordinate-wise Bonferroni correction of $p < 0.05$. For all analyses reported here, we chose not to examine age-related differences because the early sample available for analysis does not reflect a balanced sample with respect to age, sex, ethnicity, or SES.

Results indicated that, as expected, the task yielded significant modulation of the brain's canonical valuation network (Delgado et al., 2000; Haber and Knutson, 2010) including robust responses in the dorsal and ventral striatum, and ventromedial prefrontal cortex for monetary wins relative to monetary losses (Fig. 5). No brain regions were observed to be significantly more active to monetary losses than wins. Overall, this analysis builds confidence in the capability of this task to isolate valuation-related signals in the brain.

4.2.2. Inhibitory control (i.e., "CARIT") task

This task measures inhibitory control processes and the modulation of inhibitory control by reward history, otherwise known as the Conditioned Approach Response Inhibition Task (CARIT (Davidow et al., in press; Winter and Sheridan, 2014);). At its core, it is a classic Go/NoGo task which allows mapping of differential neural activity when response inhibition demands are high (NoGo trials) compared to freely executing a prepotent motor action (Go trials). In addition, as mentioned above, the NoGo targets have special "conditioned" qualities in this task. One of the two shapes that constitutes a NoGo stimulus had been paired with monetary gains and the other NoGo stimulus had been paired with monetary losses during the immediately preceding Reward Magnitude task. Therefore, this task has the simultaneous capability of eliciting robust engagement in neural systems involved in inhibitory control such as the lateral prefrontal cortex (Ridderinkhof et al., 2004) and motivation-by-cognition responses that draw on frontostriatal circuit function (Braver et al., 2014).

During this event-related task, participants view shape stimuli and are instructed to press a button as quickly as possible ("Go") to every shape except for the circle and the square. "Go" shapes are six different shapes that had not been seen previously (see Supplementary Table 2 for specific task parameters and behavioral scoring).

4.2.2.1. Preliminary data analysis. We evaluated the activity evoked by this task in an early set of participants in the HCP-D study (N = 86, 35 female, mean age = 12.51 years, SD age = 3.11, min = 8, max = 20). Data were preprocessed using existing HCP pipelines (see Supplementary Materials). Following preprocessing, data were submitted to a GLM to estimate task effects with six task regressors (correct Go, incorrect Go,

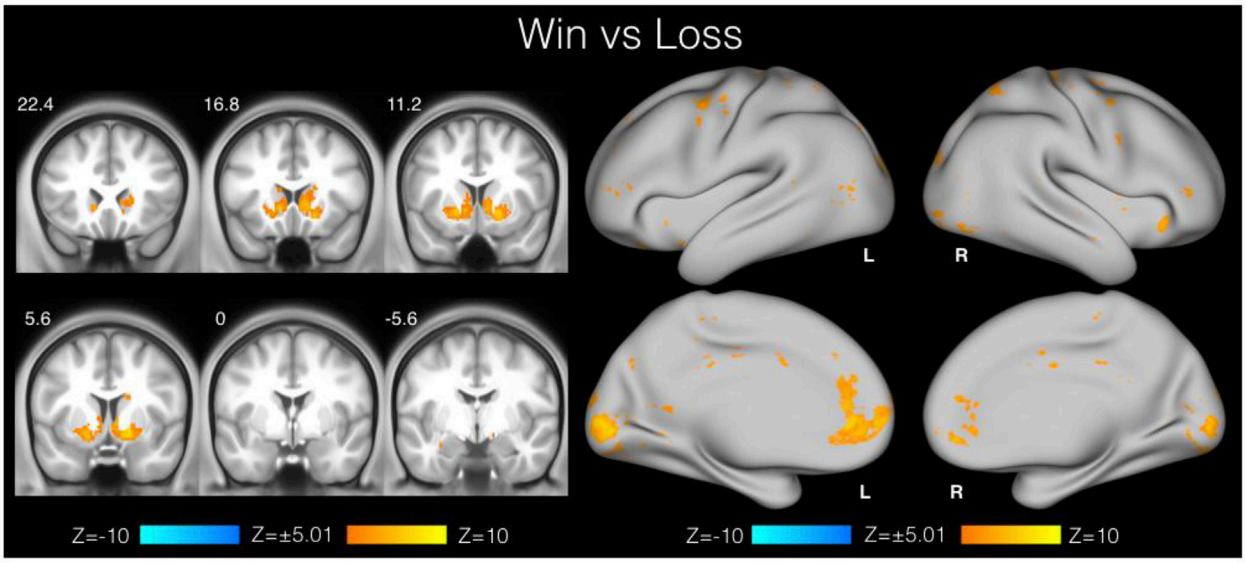

Fig. 5. Group activation maps for the primary contrast in the Reward Magnitude task in an early sample of HCP-D participants (N = 104). Positive activations (hot colors) depict Win > Loss activity, and no negative activations were observed. Analysis was grayordinate-based, so the volume view on the left is restricted to subcortical structures. Image threshold Z > 5.01, which corresponds to $p < 0.05$, Bonferroni-corrected across grayordinates. Coronal images in neurological convention (R = R). Numbers on left denote y-slice coordinates (mm) in MNI152 space. L = left, R = right. Data and maps available at https://balsa.wustl.edu/k1D2.

correct previously rewarded NoGo, incorrect previously rewarded NoGo, correct previously punished NoGo, incorrect previously punished NoGo), represented as a predictive timeseries by specifying their temporal event onset convolved with a double-gamma canonical hemodynamic response function. The participants included in this initial analysis had at least one instance of each trial type and thus no "empty regressors". Because the assignment of event to regressor partially depends on participants' performance accuracy, future work will need to implement analysis adaptations to accommodate those participants without instances of a given trial type (e.g., those who make no errors).

While several types of maps can be generated using this task, initial analyses focused on a simple *NoGo vs Go* contrast of correct trials (average of correct previously rewarded NoGo & correct previously punished NoGo > correct Go), which was carried forward to a group random effects analysis to isolate differential neural responding based on inhibitory control demands. We initially used the same threshold as the task analyses reported above (Z = 5.01, $p < 0.05$ Bonferroni corrected across grayordinates). However, because the observed activations were sparse in subcortical regions (a single grayordinate in the putamen exceeded this threshold), we present the subcortical activations at a relaxed threshold of Z = 2.32, which approximately corresponds to $p < 0.001$, uncorrected thresholding.

Results indicated that, as expected, we observed significant modulation of motor and cognitive control networks. For the *NoGo > Go*

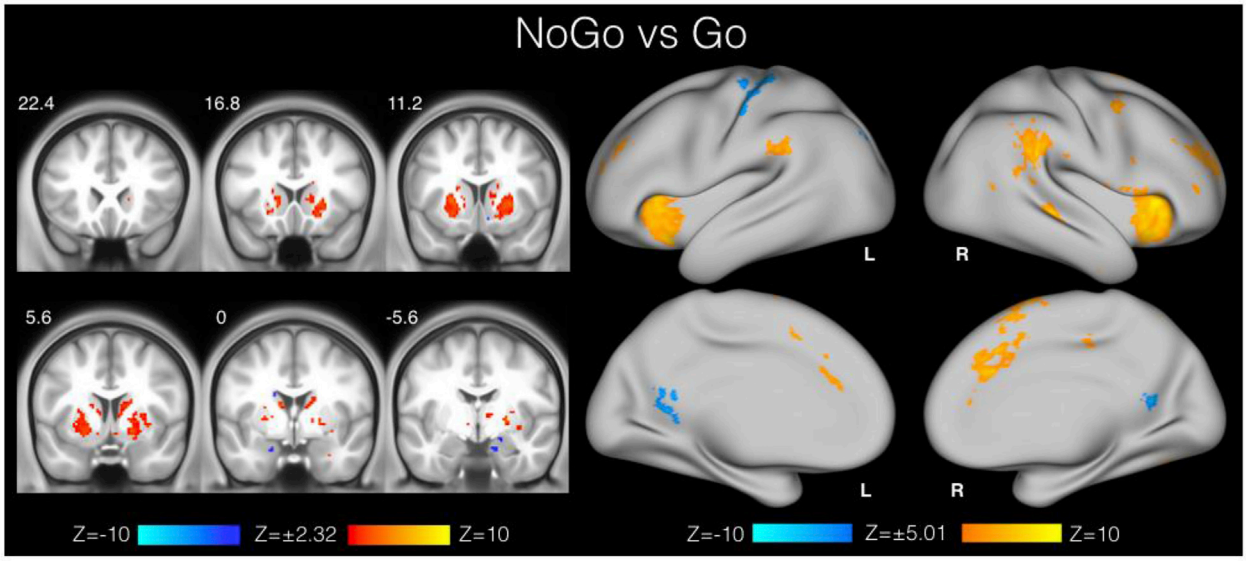

Fig. 6. Group activation maps for the primary contrast in the Inhibitory Control task in an early sample of HCP-D participants (N = 86). Positive activations (hot colors) depict NoGo > Go activity, negative activations (cool colors) depict Go > NoGo activity. Analysis was grayordinate-based, so activation in the volume view on the left is restricted to subcortical structures. Left: Subcortical data displayed at relaxed threshold of Z > 2.32, which corresponds to $p < 0.001$, uncorrected. Right: Cortical (surface) data thresholded at Z > 5.01, which corresponds to $p < 0.05$, Bonferroni-corrected across grayordinates. Coronal images in neurological convention (R = R). Numbers on left denote y-slice coordinates (mm) in MNI152 space. L = left, R = right. Data and maps available at https://balsa.wustl.edu/0KNl.

contrast, we observed significantly greater activity in the posterior striatum, ventrolateral and dorsolateral prefrontal cortex, and the dorsal anterior cingulate cortex (Fig. 6). For the *Go > NoGo* contrast, we observed significantly greater activity in the left motor cortex (participants used their right hand to make button presses). Overall, this analysis builds confidence in the capability of this task to isolate response inhibition-related signals in the brain.

4.2.3. Emotion task

The Emotion task probes emotion-relevant neural processes, and was successfully implemented in the HCP-YA. This task (modified from Hariri et al., 2000; Hariri et al., 2002) has moderate reliability (Manuck et al., 2007) for engaging the amygdala and other structures that detect and represent emotion and face-processing related processing. During the Emotion task, participants see three images (either emotional faces or shapes), one at the top and two at the bottom of the display. The face stimuli depict angry or fearful expressions. Face stimuli have been adapted from the original version of the task to include more ethnically diverse faces. Participants are instructed to press the left button if the left-hand image on the bottom of the screen matches the top image, and to press the right button if the right-hand image on the bottom of the screen matches the top image (Fig. 7). The bottom of the screen shows button mappings to reduce working memory demands for young children. See Supplementary Table 2 for detailed task parameters.

4.2.3.1. Preliminary data analysis. We evaluated the activity evoked by the Emotion task in an early set of participants in the HCP-D study (N = 105, 44 female, mean age = 13.23 years, SD age = 3.59, min = 8, max = 21). Data were preprocessed using existing HCP pipelines (see Supplementary Materials) then submitted to a GLM to estimate task effects. The two regressors of interest represented separate timeseries of stimulus presentation for face blocks and shape blocks, convolved with a double-gamma canonical hemodynamic response function. A contrast of interest representing *Faces vs Shapes* was carried forward to a group random effects analysis to isolate differential responding to faces relative to shapes. We identified areas of differential functional activity in the group map using a threshold of Z = 5.01, which corresponds to a stringent grayordinate-wise Bonferroni correction of $p < 0.05$.

Consistent with prior work, we observed a robust pattern of activity for *Faces > Shapes* that implicates a distributed set of brain regions including bilateral activation of the amygdala and the fusiform cortex (Fig. 8). Thus, we are confident that this task, despite its brevity, is serving its intended purpose as a provocation of emotion and face-related processing.

4.3. Mock scan and practice

Before MRI scanning, all HCP-D participants undergo Mock Scanning in a simulated MRI scanner. The specific mock scanner brand varies by site, but each is similar to the Prisma environment. During the mock scans, participants evaluate their comfort in the MRI environment and learn to remain still inside of the MRI scanner based on tailored feedback. The mock scanners are equipped with hardware and software [MoTrak and SimFx software (Psychology Software Tools, Inc.; WUSTL, UCLA, and UMinn) or similar functioning custom system (Harvard)] that tracks participant head motion in real-time via a small sensor placed on the participant's forehead. Within the mock scanner, participants first learn how head motion and various actions (e.g., wriggle your nose, cough, yawn, move your arms/legs/back, etc.) affect their head position using real-time feedback from the head motion tracking system. Participants then watch a video that pauses when the person's head movement exceeds a pre-specified threshold, providing real-time feedback which prompts participants to remain more still to keep the movie from pausing. Participants complete approximately 5 min of stillness training with simultaneous presentation of the scanner noise in the mock scanner bore. Some of the training is spent while viewing the video and some while viewing the fixation cross used in the rfMRI runs. The younger participants earn small prizes as incentives for staying still during the mock scan.

Participants also complete a structured, experimenter-guided orientation and practice session immediately prior to their first MRI scan. This practice session, coded in Psychopy (Peirce, 2007), includes general guidelines about the scanner environment, a preview of the resting state MRI scan instructions, and guided practice for each of the fMRI tasks.

5. Outside of scanner measures

5.1. Biological samples

Participants provide several biological samples for a range of purposes, as detailed below and in Table 2.

5.1.1. DNA

The HCP-D acquires blood or saliva samples for potential genotyping. However, budgetary constraints preclude genotyping under the purview of HCP-D, so samples are currently being acquired and banked for

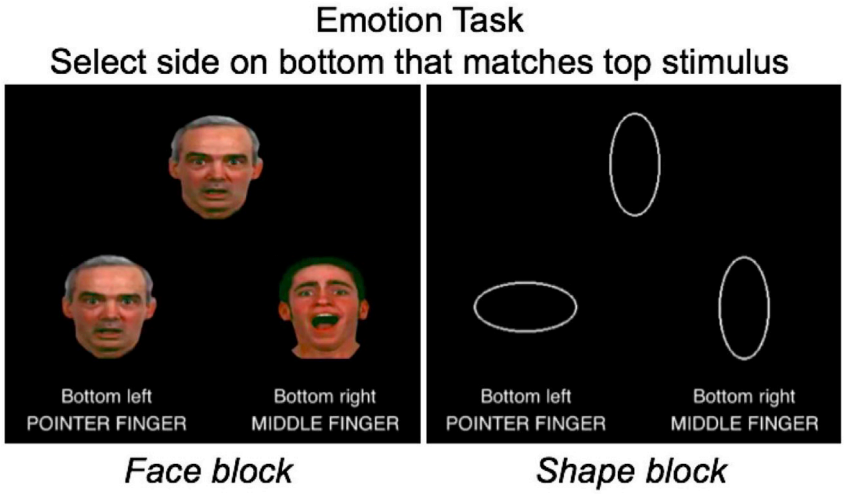

Fig. 7. Emotion task, adapted from Hariri et al. (2000, 2002). During alternating blocks, participants match the top image with the left or right bottom image. The timing and general structure of the task is highly similar to that used for the Emotion task in HCP-YA (Barch et al., 2013), but the specific sets of face stimuli differ, and only a single run is acquired (compared to 2 runs per subject in HCP-YA).

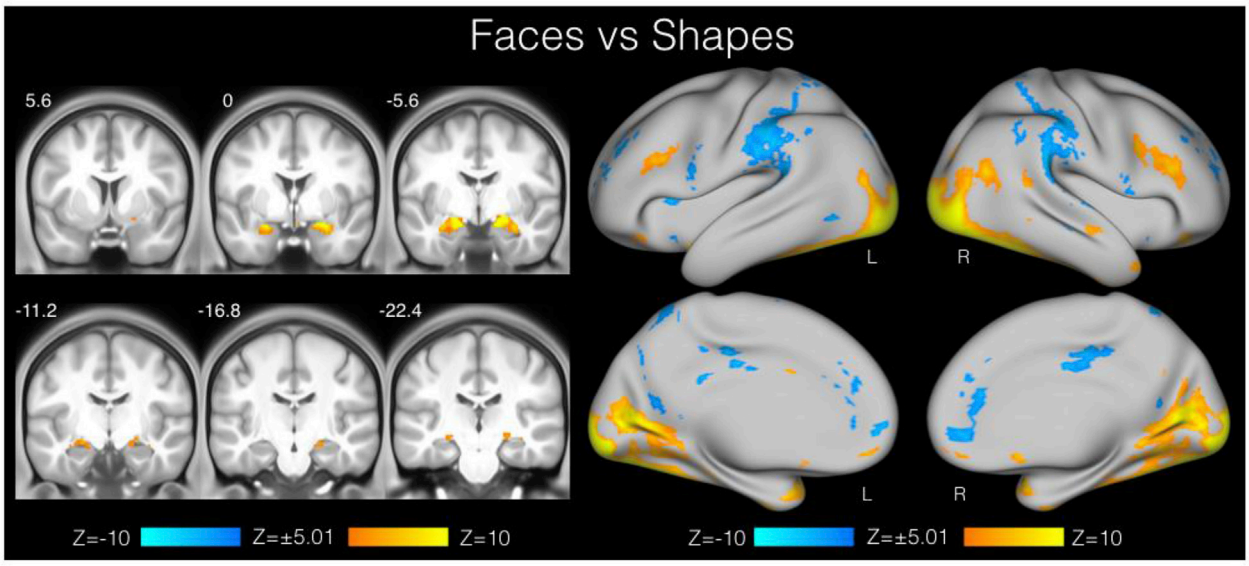

Fig. 8. Group activation maps for the primary contrast in the Emotion task in an early sample of HCP-D participants (N = 105). Positive activations (hot colors) depict Faces > Shapes activity, negative activations (cool colors) depict Shapes > Faces activity. Analysis was grayordinate-based, so activation in the volume view on the left is restricted to subcortical structures. Image threshold Z > 5.01, which corresponds to $p < 0.05$, Bonferroni-corrected across grayordinates. Coronal images in neurological convention (R = R). Numbers on left denote y-slice coordinates (mm) in MNI152 space. L = left, R = right. Data and maps available at https://balsa.wustl.edu/2KLG.

possible future analysis at the Rutgers University Cell & DNA Repository (RUCDR) (www.rucdr.org). Blood is acquired into custom RUCDR kits which are mailed to RUCDR within three days of collection. Participants may opt out of the blood draw if they strongly oppose having blood taken, in which case they provide a saliva sample for genotyping instead (2 mL sample, held at room temperature in Oragene DNA kits). All participants aged 5–8 years provide a saliva sample for genotyping by default.

5.1.2. Hemoglobin A1c

For participants providing blood, an additional sample is acquired for assaying Hemoglobin A1c, an indicator of metabolic function that provides information about an individual's risk for obesity and diabetes (American Diabetes Association, 2009; Bunn et al., 1978).

5.1.3. Drug testing

At every session, participants ages 12–21 years complete a Breathalyzer test (AlcoHawk Pro) to detect alcohol in the system and a urine screen for recent drug use (brand is site specific; e.g., Accutest MultiDrug Panel Test). Regardless of brand, all tests used have matched panels that assay for cocaine, opioids, amphetamines, methamphetamine, oxycontin, and THC. Participants may remain in the study if they test positive for drug use (so long as their behavior does not indicate they are under active influence of alcohol or drugs at the time of their study session).

Table 2
Summary of biological samples acquired in HCP-D.

Purpose	Assay	Sample	Ages Acquired
Genotyping	DNA (Banked for future analysis)	Blood, saliva (if blood not acquired)	Blood: 9–21 y.o. Saliva: 5–8 y.o., and if blood draw refused
Diabetes risk	Hemoglobin A1c	Blood	9-21 y.o.
Drug use	Cocaine, THC, Opiates, Amphetamine, Methamphetamine, OxyContin	Urine	12-21 y.o.
Active alcohol use	Breathalyzer	Breath	12-21 y.o.
Pubertal hormones	Testosterone, progesterone, estradiol, DHEA	Hair, saliva	5-21 y.o.

5.1.4. Pubertal hormones

The HCP-D includes an extensive protocol to measure sex steroid hormonal concentrations. The hormonal dataset doubles as a methodological study that can be used to evaluate the correspondence of a range of hormonal and pubertal measures in the same participants, and can serve as a benchmark dataset for other studies aiming to capture age windows of hormonal transition.

The HCP-D acquires self- and parent-reported pubertal stage based on self-reported markers of physical development and secondary sex characteristics (Morris and Udry, 1980; Petersen et al., 1988; Shirtcliff et al., 2009). In addition, the study measures dehydroepiandrosterone (DHEA), testosterone, progesterone, and estradiol from participants using two complementary methods – saliva (Braams et al., 2015; Shirtcliff et al., 2009) and hair. For saliva, participants fill a tube (Salimetrics *SalivaBio* passive drool kits) at home when they wake up, before eating, drinking, and brushing their teeth. Samples are kept frozen at home until their study appointment, when they are transported in a freezer pack and deep frozen on arrival at the study site (−70 °C or colder). All saliva samples are processed in batches with standard ELISA assays for the four sex steroid hormones listed above.

The timing of hormone collection was guided by existing standards of the field (Granger et al., 2003; Khairullah et al., 2014; Mihm et al., 2011; Shirtcliff et al., 2009). Males, premenarcheal females, and menarcheal females who do not have regular cycles are instructed to collect saliva on the morning of their first study session. For postmenarcheal females who have regular cycles, participants are instructed to generate the saliva sample during the early follicular phase (cycle day 7). We also aim to schedule participants' first study session on cycle day 7, but it is not always possible and in these cases, participants store their cycle day 7 saliva samples in their home freezers until their study visit.

The HCP-D also capitalizes on recent advancements in the bioassay of steroid hormones which have broadened to include hair (Sauvé et al., 2007; Stalder and Kirschbaum, 2012). We are acquiring hair samples on all willing participants. Hair assays are particularly valuable as an index

of cumulative steroid exposure (Dettenborn et al., 2012; Kalra et al., 2007) from clippings of the ~1 cm closest to the scalp (Li et al., 2012), and they correlate well with the individual's environment over a relatively long duration (Russell et al., 2012; Sharpley et al., 2012) as 1 cm of hair reflects sex steroid hormone levels over the past ~1 month. This represents a key advantage over saliva assays that show extraneous fluctuation based on menstrual and diurnal rhythms (Dorn et al., 2006; Shirtcliff et al., 2009). Sex steroids can be assayed from hair using an extraction step and a simple enzyme-immunoassay with a commercially available kit (Gao et al., 2013; Wheeler, 2006).

To acquire hair, we clip a small sample of hair (circumference of a pencil eraser) at the scalp on the back of the head. All samples are further cut to approximately 1 cm of hair from the scalp end during analysis. Hair is stored at room temperature until batched assay. We also administer a brief questionnaire about factors that can influence measure of sex steroids in hair, such as the frequency of washing and the use of permanents or dyes. While hair is being acquired from all willing participants, funding constraints will restrict assays to a subsample of 400 participants aged 6–18, including all samples from the longitudinal cohort.

5.2. Assessment of behaviors, abilities, traits, and environments

The HCP-D obtains an extensive account of the traits, behaviors, and abilities of each participant for several purposes. This information may be used to evaluate the relationship between individual differences in these characteristics and brain network connectivity (e.g. (Finn et al., 2015; Smith et al., 2015),). It can also be used to select subsets of participants for analysis based on a special interest in participants with particular experiences, environments, or traits. Finally, these data can be used as covariates of non-interest (such as IQ) to statistically control for individual variability in relevant traits.

Participants and/or their parents (depending on participant age) complete a series of questions to obtain information about medical history and demographic data about the participant and their family. Participants also complete a battery of assessments summarized in Table 3 and described extensively in Supplementary Table 3. In addition, participation eligibility is confirmed on the day of the study through an intake interview with participants aged 18–21 years, and parents of minor participants (Supplementary Table 4).

The assessments include a combination of self-report questionnaires and task-based measures including segments of the NIH Toolbox (Gershon et al., 2010), the PhenX toolkit (Hamilton et al., 2011), and the PNC (Satterthwaite et al., 2016) among others. These were selected with multiple objectives in mind. First, we chose assessments that are validated for direct comparison across the entire age range whenever possible. Second, we aimed to cover a range of traits and functional domains to render the dataset as useful as possible to a broad variety of questions the field may be interested in examining within HCP-D data. Finally, we were constrained by time limitations and thus aimed to use assessments that were as brief as possible. In addition, parents of minor participants complete several additional assessments about themselves.

5.3. Clinical assessments

Although HCP-D is a study of healthy development and those with severe and chronic psychopathology are excluded (see Supplementary Table 1), we anticipate that a sizable proportion of participants will experience at least some symptoms of psychopathology. To assess for current and past history of psychopathology, participants complete the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), a diagnostic interview assessing current and past episodes of psychopathology according to DSM-V criteria (Kaufman et al., 1997). The HCP-D is acquiring K-SADS data from the parent only for 5–11 year olds, from parent and child for 12–17 year olds, and from the participant only for 18 + year olds. Data acquisition is on a computerized platform recently developed by the creators of the original K-SADS (KSADS-COMP; Center for Telepsychology, Madison WI; clinicaltrials.gov/ct2/show/NCT01866956).

Table 3
Summary of experiential and functional domains assessed in HCP-D.

Domain	Assessments
Cognitive	Estimated IQ
	Languages learned
	Vocabulary and reading
	Inhibitory control
	Episodic and working memory
	Processing speed
	Impulsivity
	Delay discounting
Emotional	Emotion recognition
	Positive and negative emotion
	Psychopathology symptoms and family history
	Loneliness
	Hostility
	Self-efficacy
	Temperament
	Personality
	Behavioral Inhibition and activation
Sensorimotor and physical	Vision
	Olfaction
	Auditory word recognition
	Physical strength
	Physical endurance
	Manual dexterity
	Pubertal development
Experiential and behavioral	Adverse life events
	Perceived stress
	Friendships and social support
	Family structure
	Screen time
	Sleep
	Social rejection
	Sports and activities
	Substance abuse
	Risk taking behavior

See Supplementary Table 3 for full listing of tasks and instruments used.

For children under 18, parents complete the Achenbach Child Behavior Checklist (Achenbach, 2009), a dimensional assessment of current psychopathology. In addition, children ages 11 to 17 complete the Achenbach Youth Self Report and participants 18 + complete the Achenbach Adult Self Report, which also provide dimensional assessments of psychopathology. Parents also complete the Achenbach Adult Self Report (Achenbach, 1997) about themselves, as well as a short self-report of current and past psychiatric diagnosis.

For substance use and abuse, we are acquiring the NIDA Substance Abuse and Alcohol Core: Tier 1 assessments of Tobacco, Alcohol and Substance Use. Participants aged 12 and older and co-participating parents both complete this assessment.

5.4. Fifteen-month follow-up

All participants are re-contacted 15 months after their initial participation in the study. Members of the longitudinal cohort are re-contacted to schedule a follow-up in-lab session, and all cross-sectional participants are contacted for an online-only follow-up (with phone or paper backup for families without reliable internet) where several of the original self-report measures are reacquired. This includes assessments of puberty, affect, psychopathology, substance use, and general health. See Supplementary Table 3 for details of the assessments used.

The purpose of this follow-up is to characterize each participant's developmental change on a subset of the functional domains just described. These data can be used on their own or in tandem with the previously-acquired brain imaging measures to identify predictors of subsequent growth in behaviors, abilities, and traits.

6. Intended use and limitations

We believe the HCP-D is well suited to address a host of novel questions concerning the nature of brain connectivity development and factors that influence it. While great strides have been made in understanding human brain development, much research is limited by constraints of the available acquisition and analysis techniques, incomplete sampling of the developmental periods in question, and/or limited collateral data to gain a clear picture of factors that could shape individual differences in neurodevelopmental outcomes. The HCP-D pairs multimodal examination of brain connectivity with a richly characterized sample including cross-sectional coverage of the age range from 5 to 21 years, and longitudinal coverage of the transition to adolescence – a key period of change in both behavior and mental health. Further, the multimodal nature of HCP-D imaging permits examination of the interrelations among structural and functional brain organization development, a key question that has received relatively little attention in the literature.

We are also eager to gain further insight into brain connectivity development that is linked to puberty. Puberty is thought to represent a second wave of plasticity whereby hormones *organize* brain structure and function, and exert *activational* effects in which neural circuits are especially reactive to particular environmental inputs. For example, rises in testosterone during puberty predict male-specific increases in white matter across the brain (e.g., Paus et al., 2010), and heightened striatal response to rewards (e.g., Op de Macks et al., 2011). Dopaminergic signaling (e.g., Sato et al., 2008) during adolescence is also moderated by testosterone levels, which predict connectivity within thalamo-striato-cortical networks (Asato et al., 2010). In addition, active pubertal hormone shifts are thought to contribute to adolescent-unique behavioral tendencies such as rises in sensation seeking, sexual behavior, and risky decision making (Spear, 2000). Understanding the hormonal contributions to these behaviors and their intermediate neurobiological mechanisms is of critical importance to age-specific shifts in health risks.

While we believe this project has many strengths, it also has important limitations that constrain the scope and strength of the inferences that are possible from the project. For one, we are not asserting that the upper age of 21 marks the conclusion of active development. Indeed, neurodevelopment is thought to continue well beyond the age of age 21 on nearly every measure of brain structure and brain function (see Somerville, 2016 for commentary on this point). The HCP-D is therefore more optimized toward informing middle childhood and adolescent neurodevelopmental windows, compared to the final waves of neurodevelopment and stabilization that occur in the third decade of life and beyond.

In addition, it is important to recognize that there are substantial technical challenges in merging data from the HCP-D project with those of the HCP-YA project, which acquired brain imaging data on a different model of scanner and with some important differences in the scanning protocol. The associated technical challenges are detailed in Harms et al. (under review). Further, it is well known that data quality tends to co-vary with age (with younger participants producing data that tend to have greater motion and overall poorer quality). Accordingly, data quality confounds can compromise the inference that age-related structural and neurobiological changes are truly attributable to age (see Smith and Nichols, 2018 for discussion). We believe that datasets like HCP-D serve as crucial test-beds for analytic techniques to manage these confounds to the extent it is possible, but also recognize the need to exercise interpretive caution and close scrutiny of these nuisance confounds.

7. Conclusion

The major technological and analytical advances in adult human brain imaging achieved as part of the Human Connectome Project (HCP-YA) have allowed examination of structural and functional brain connectivity at unprecedented levels of spatial and temporal resolution. The HCP-D builds on these strengths to push understanding of normative brain development to new levels – knowledge that will critically inform prevention and intervention efforts targeting well-known public health concerns of children and adolescents. The rich, multimodal data acquired in HCP-D will inform the neurodevelopmental processes associated with biological and cognitive constructs that are of critical importance to health and well-being in the 5–21 year age range. We are eager for a wide range of investigators in the community to use these data to test their own hypothesis about brain development, connectivity, and health.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.08.050.

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