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The psychosis human connectome project: An overview

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Abstract

Investigations within the Human Connectome Project have expanded to include studies focusing on brain disorders. This paper describes one of the investigations focused on psychotic psychopathology: The psychosis Human Connectome Project (P-HCP). The data collected as part of this project were multimodal and derived from clinical assessments of psychopathology, cognitive assessments, instrument-based motor assessments, blood specimens, and magnetic resonance imaging (MRI) data. The dataset will be made publicly available through the NIMH Data Archive. In this report we provide specific information on how the sample of participants was obtained and characterized and describe the experimental tasks and procedures used to probe neural functions involved in psychotic disorders that may also mark genetic liability for psychotic psychopathology. Our goal in this paper is to outline the data acquisition process so that researchers intending to use these publicly available data can plan their analyses. MRI data described in this paper are limited to data acquired at 3 Tesla. A companion paper describes the study's 7 Tesla image acquisition protocol in detail, which is focused on visual perceptual functions in psychotic psychopathology.

Keywords

Psychosis; Schizophrenia; Connectomics; Neuroimaging; Brain; MRI

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Supplementary materials

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1. Introduction

The psychosis Human Connectome Project (P-HCP) is part of the series of Connectomes Related to Human Disease funded by the National Institutes of Health. The original Human Connectome Project was an effort aimed at mapping normative brain structure and function and making the resulting data publicly available. This work was extended to apply similar measures to populations diagnosed with various disorders that affect the brain. The project described in this paper, titled, "Neural Disconnection & Errant Visual Perception in Psychotic Psychopathology" was focused on psychotic psychopathology in adults.

Psychosis is characterized by altered perceptual experiences (hallucinations) and delusional beliefs that distort one's sense of reality and, as a result, significantly impair a person's ability to function in their social and occupational roles (Raij et al., 2009). Neural abnormalities, including gray matter loss (De Peri et al., 2012), compromised white matter connectivity (Pettersson-Yeo et al., 2011; Wheeler and Voineskos, 2014), and aberrant functional connectivity (Baker et al., 2019; Calhoun et al., 2012) have been consistently documented in psychotic disorders by a large body of research. However few studies examine the relation between neural connectivity and symptom severity. Thus, the specific neural circuitry underlying symptoms is not yet known. Evidence suggests that the compromised neural connectivity in psychosis may be related to hallucinatory experiences (Ashtari et al., 2007; Whitford et al., 2012). In particular, connectivity between low-level sensory and high-level cognitive areas of the brain demonstrate abnormal interactions in people with psychosis (PwP) which may contribute to the experience of hallucinations (Allen et al., 2008; Pokorny et al., 2020). However, information is limited on neural connections that integrate low- and high-level perceptual processing. Further, psychotic illnesses may share common pathophysiology (Zwicker et al., 2018) and are characterized by cognitive deficits such as reward processing (Esslinger et al., 2012; Hanssen et al., 2015; Juckel et al., 2006a, 2006b; Murray et al., 2008; Nielsen et al., 2012; Schlagenhauf et al., 2009), cognitive control (Poppe et al., 2016; Smucny et al., 2020), and social cognition deficits (Das et al., 2012); Martin et al., 2016). A long history of twin and family studies reveal schizophrenia as a highly heritable condition (Gottesman, 1991). Finally, heritability estimates and evidence of subtle neural alterations among healthy biological relatives of people with psychotic disorders suggest a genetic predisposition towards abnormalities typically observed in psychotic disorders (de Zwarte et al., 2019, 2020). Together, this previous research provides the groundwork for transdiagnostic investigations aimed at studying brain connectivity in psychosis using a family study design. Thus, the current study was designed to measure neural mechanisms of aberrant perception, cognition, and other characteristics of psychosis by implementing Human Connectome Project imaging protocols with a sample of individuals affected by psychotic psychopathology and their first-degree biological relatives.

The goal of the psychosis Human Connectome Project (P-HCP) was to collect multimodal data that allows for testing of a wide range of hypotheses related to connectomics, genetics, and various cognitive processes relevant to psychosis. Specific hypotheses about visual function are described in our companion paper (Schallmo et al. (2021) in preparation). The

P-HCP is well poised to link connectivity measures to dimensional variation in perceptual anomalies and other psychotic symptomatology by collecting multimodal data from a transdiagnostic sample of people with a history of psychosis, who meet diagnostic criteria for one of several psychotic disorders (i.e., schizophrenia, schizoaffective disorder, bipolar I disorder with psychotic features). This approach is in line with the NIMH Research Domain Criteria (RDoC) framework and allows for examination of neurophysiological mechanisms involved in psychotic symptomatology across the psychosis spectrum. Data from the P-HCP study will be made publicly available, as is done with other Human Connectome Projects as well as similar psychosis-focused open source projects such as the Biomedical Informatics Research Network (BIRN; http://www.nbirn.net; Glover et al. 2012) or the Mind Research Network's Centers of Biomedical Research Excellence (COBRE) and MIND Clinical Imaging Consortium (MCIC; www.mrn.org; Gollub et al. 2013), among others. Further, because P-HCP was designed as a family study that included first-degree biological relatives of the participants with psychotic psychopathology, the neural abnormalities associated with aberrant perception could be tested as markers of genetic liability for psychotic psychopathology.

The P-HCP was designed to acquire multimodal data from three groups with the following recruitment goals: 150 PwP, 100 of their first-degree biological relatives, and 50 healthy control participants. Clinical, cognitive, motor, blood, and 3 Tesla neuroimaging data, including structural, diffusion weighted imaging (dMRI), resting state fMRI (rfMRI) and task fMRI (tfMRI) data were used to test study hypotheses related to psychotic psychopathology, cognitive function, genetic liability for psychosis, and neural connectivity and function. All data were collected at the University of Minnesota, with neuroimaging scans conducted at the Center for Magnetic Resonance Research in accordance with HCP protocols (Harms et al., 2018). Neuroimaging data were also collected on a Siemens 7 Tesla scanner, the specific goals and acquisition parameters of which are described in a companion paper (Schallmo et al. (2021) in preparation).

2. Objectives

The aim of this project was to use state-of-the-art brain imaging techniques from the Human Connectome Project in concert with cognitive tasks to develop and test neurophysiological models of aberrations in basic and complex functions of the brain related to psychotic psychopathology. The data contributed by the *P*-HCP informs our understanding of the neural circuitry related to distorted cognition and perception in psychosis. This information may facilitate interventions by uncovering neural mechanisms central to the development and maintenance of psychotic symptoms, which could serve as novel treatment targets. The goal of this paper is to describe how our data were collected such that other research groups can understand the nature of the dataset and plan their analyses.

3. Participants

The goal of the study is to enroll a total of 300 adult participants. Due to the Coronavirus Disease 2019 (COVID-19) pandemic, data collection was suspended in March 2020, with planned completion of data collection in the near future. To date, 247 participants completed

the study (see Table 1 for demographic characteristics). Of the 131 PwP, 79 met criteria for schizophrenia, 16 for schizoaffective disorder, and 36 for bipolar I disorder with psychotic features. Of the 74 relatives, 41 were relatives of a person with schizophrenia, 9 were relatives of someone with schizoaffective disorder, and 24 had a first-degree family member with bipolar disorder with psychotic features. The majority of relatives were siblings (58.1%) with the remaining relatives being either parents (32.4%) or offspring (9.5%) of someone with a psychotic disorder.

3.1. Recruitment

Potential participants with psychosis were recruited from the community through advertisements and in-person announcements at community mental health support agencies, referrals from other research studies conducted at the University of Minnesota or collaborating institutions, referrals from local mental health care providers, and informational mailings following medical record review. Additionally, participants from our group's previous studies who consented to being contacted for future research were also invited to participate. Once enrolled, participants with a history of psychotic symptomatology were asked to provide contact information for their first-degree relatives for recruitment outreach. This was not required and not doing so did not preclude people with a history of psychosis from participation. If the participant agreed, letters announcing the opportunity for participation were sent to first-degree relatives with follow-up by telephone if the letter went unanswered.

To enroll healthy control subjects, advertisements and postings announcing the study were placed in organizational newsletters and public places (e.g., hospital clinics, foyers and hallways of public and private institutions). Control participants from our group's previous studies who agreed to follow-up communication regarding additional studies were also contacted.

3.2. Inclusion/exclusion criteria

To be eligible for enrollment, all participants spoke English as their primary language and did not have: a legal guardian (or otherwise lack capacity to provide informed consent), alcohol/drug abuse in the past month or alcohol/drug dependence in the last 6 months, a diagnosed Learning Disability or estimated IQ lower than 70 (if either condition was diagnosed based on testing by a trained professional or the latter by research staff), a current or past central nervous system disease (including: seizures, epilepsy, encephalitis, MS, Parkinson's, stroke), history of head injury with skull fracture or loss of consciousness greater than 30 min, history of electro-convulsive therapy (ECT) in the last year, tardive dyskinesia (as evidenced by medical record), obstructed or compromised vision (e.g., lazy eye that is uncorrected or was corrected after age 17 / strabismus / cross eyes / permanent eye injury / abnormality in visual field / cataract), hearing problems (e.g., cannot hear without hearing aid / severe tinnitus), or a condition likely making it impossible to perform tasks (e.g., paralysis, severe arthritis). Additionally, PwP were between the ages of 18 and 65 years old with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar I disorder with a history of psychotic symptomatology (i.e., delusions or hallucinations) with no indication that symptoms were caused by substance use or a general medical condition.

While PwP were screened and excluded for current substance use issues, a history of such issues as well as current/lifetime comorbidities of any kind were permitted for enrollment in the study in order to have a sample representative of patients with psychosis in the general population while simultaneously limiting nuisance effects. Biological relatives were 18–69 years old with a first-degree biological relative with schizophrenia, schizoaffective disorder, or bipolar I disorder with psychosis, and living within one day's drive or planning to visit the vicinity of the University of Minnesota. Because relatives included parents of PwP, we expanded the age range of the relatives group to accommodate recruitment efforts. Relatives were enrolled regardless of psychopathology. Approximately half (45.95%) of the first-degree biological relatives in the study carried their own mental health diagnosis (e.g., major depression). Occasionally, relatives with substance dependence in partial remission (3 participants, 3.9%), current substance dependence (1 participant, 1.3%), or psychotic psychopathology (1 participant, 1.3%) were included in the study. Controls were aged 18–65 and had no history of schizophrenia, schizoaffective disorder, or bipolar I disorder with psychotic features, or other psychotic symptoms or history of major depressive disorder. Additionally, controls had no first-degree biological relative with a history of psychiatric hospitalization for a psychotic or affective disorder. Finally, as this was a family study, PwP and relatives were not adopted.

3.3. Screening

Eligibility screening began with a semi-structured telephone survey prior to any in-person visits. The 15-to-25 min interview obtained basic demographics and information on medical conditions and past episodes of mood dysregulation, psychosis, and drug or alcohol use. Additionally, potential participants were screened for whether they could be safely scanned via MRI.

3.4. Study visits

Procedures were approved by the Institutional Review Board at the University of Minnesota, and followed the guidelines for human subjects research set by the Declaration of Helsinki. All participants completed an informed consent process, provided written consent, and were assessed for their capacity to provide informed consent using the University of California Brief Assessment of Capacity to Consent (Jeste et al., 2007). Demographic information was then collected, including current (e.g., living arrangements, work status, income, marital status) and lifetime variables (e.g., participant education, parent educational achievement; usual work status of parents; see Table 1). Participants then completed a clinical interview and self-report questionnaires, followed by cognitive and motor assessments, and additional study tasks. Clinical and cognitive assessments were often completed on two separate days to alleviate participant fatigue. Participants also provided a blood or saliva sample and then completed neuroimaging scans. Participants whose 3 T imaging data met acceptable data quality thresholds were invited to return to complete an ultra-high field MRI at a 7 T scanner. Finally, a subset of PwP completed a second 7 T scan and brief clinical interview follow-up. Overall, participants were able to tolerate the schedule of visits and only in rare instances were unable to complete all assessments due to fatigue, claustrophobia, excessive motion in the scanner, or time constraints.

3.5. Retention

Retention in the study was high, though several factors reduced the sample of complete data sets (n = 247). As of March 2020, 355 participants were initially consented and enrolled in the study, of which 284 participants (80%) completed the clinical assessments (the remaining 20% of participants did not complete the study for the following reasons: 15.49% were ineligible based on information gathered during clinical interview, 1.69% withdrew from the study, and 2.82% had their participation interrupted due to COVID-19). The majority (90.49%) of the 284 participants who completed clinical assessments went on to complete the 3T neuroimaging protocol. Reasons for not completing the scanning included: 2.82% became unreachable or moved out of state, 2.82% were excluded (due to the presence of significant motion artifacts, unable to fit in the scanner, or new information about meeting study eligibility criteria such as MRI contraindications), 2.46% withdrew (felt uncomfortable or claustrophobic in the scanner environment), and 1.41% had their participation interrupted due to COVID-19. The majority of participants (97.67%) who completed both clinical and 3 T scanning had usable data (only 6 participants - 2.33% - either had an MRI abnormality or significant motion artifacts that interfered with data quality) and the majority of those had their diagnoses confirmed during consensus review (4 participants were excluded after chart review; see description of this procedure in Clinical Assessment section below), yielding the sample of 247 participants described in this paper. Participants were provided with support to facilitate completion of study tasks (e.g., meals, transportation, breaks). The time to complete all study visits varied due to participant availability and study-related scheduling challenges (e.g., scanner upgrades). While some participants were able to complete all study visits within a few weeks, others required longer follow-up. On average, participants completed clinical, cognitive, and 3 T visits over the course of one month (mean = 33.82, SD = 55.89 days) and then, if eligible, returned to participate in 7 T scanning (see Schallmo et al. (2021) in preparation). Occasionally, participants decided to withdraw from the study, typically due to hesitations about confinement in the MRI scanner.

4. Clinical assessment

Diagnostic information was collected using the Structured Clinical Interview for DSM-IV-TR disorders (SCID; First et al., 2002). In place of the SCID module focused on psychosis, the psychosis section of the NIMH Diagnostic Interview for Genetic Studies (DIGS) version 3.0 revised 7 (Nurnberger et al., 1994) was used because the DIGS psychosis items more closely resemble the items queried using the study's dimensional symptom measures (described below), which reduces participant burden. Staff training prior to independent administration of the diagnostic interview involved: reviewing the SCID user guide and DIGS manual, watching introductory videos provided by the SCID authors that describe the interview tool, engaging in a 9 session group training and (for trained staff) refresher meeting led by a PhD-level member of the team, completing practice ratings of interview videos provided by the SCID authors for the purpose of training, completing at least one mock interview with a fellow staff member, observing a trained rater administer at least two diagnostic interviews with study participants, and administering at least two diagnostic interviews with study participants while being observed

by a trained rater. Interviewers regularly consulted with a doctorate-level study staff member regarding symptom classification and diagnosis. Clinical interviews and supporting materials (e.g., dimensional symptom measures, personality inventories, medical and work histories, medical records, when available) were reviewed by a team of at least 2 clinical psychology graduate students and / or postdoctoral associates to determine which diagnostic criteria were met and reach consensus on the most appropriate DSM diagnoses. Current and lifetime diagnoses were recorded, along with information for each of the five axes of the DSM-IV multiaxial diagnostic system. In addition, age of onset was collected for all PwP so that duration of illness can easily be calculated and examined in future analyze.

Further clinical information was provided by medical record review with consent and a participant-identified informant who could report on the participant's current psychosocial functioning and symptomatology. Additional clinical measures are listed in Table 2 and described below. These include assessments of symptoms, functioning, personality, perception, physical health, and substance use. Behavioral measures, including assessments of cognition, handedness, emotion recognition, theory of mind, vision, and motor function, are listed in Table 3 and described below.

4.1. Dimensional assessment of symptoms

Symptoms of psychosis and mood dysregulation were measured with the Brief Psychiatric Rating Scale-24 Item Version (BPRS; Ventura et al., 2000) and the Scales for the Assessment of Negative/Positive Symptoms (SANS/SAPS; Andreasen 1981, 1983). Ratings on these measures reflect symptom severity over the previous 30 days. The BPRS and SANS/SAPS were repeated on the day of scanning if the initial assessment occurred over one month prior. Staff training on these measures involved a similar process as the training for diagnostic interview administration. The most recent inter-rater reliability check yielded intraclass correlations above 0.80 for all research staff administering the BPRS and SANS/SAPS measures. We will provide raw scores as well as summary scores for symptom domains or factors (e.g., see (Wilson and Sponheim, 2014) for BPRS factor solution). Preliminary examination of total BPRS symptoms shows an overall significant group difference as well as significant post-hoc comparisons such that, on average, relatives reported an intermediate level of symptoms in comparison to PwP and controls, as seen in Table 1 and Fig. 1 A. Following the diagnostic interview and symptom questionnaires, a further assessment of lifetime psychiatric symptoms, the Operational Criteria In Psychotic Illness (OPCRIT), was completed by research staff. The OPCRIT is a clinical rating form that uses semi-structured interview data to characterize a participant's lifetime occurrence of symptoms across three domains (psychotic, depressed, manic) as well as other aspects related to the course of psychopathology in order to apply operational diagnostic criteria (McGuffin et al., 1991). Finally, the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) was used to assess affective-hedonic experiences.

4.2. Functioning

Real-world functioning was measured using the Global Assessment of Functioning scale (Hall, 1995) as part of the SCID, the Global Functioning Social and Role Scales (Auther et al., 2006; Niendam et al., 2006), the Social Adjustment Scale-Self Report (SAS-SR

Short; Weissman and Bothwell, 1976), and the Quality of Life Scale (QOLS; Flanagan, 1978). Participants with psychosis additionally completed the Social Functioning Scale (SFS; Birchwood et al., 1990), which provides a thorough assessment of social adjustment over the past three months.

4.3. Personality

Personality and behavioral traits were assessed using the Personality Inventory for DSM-5 (PID-5; Krueger et al., 2012), the Behavioral Approach/Inhibition Scale (BIS/BAS; Carver and White, 1994), and the Schizotypal Personality Questionnaire (SPQ; Raine, 1991). The original 220-item PID-5 was slightly modified for the current study to include two validity items and 34 items from the absorption scale of the Multidimensional Personality Questionnaire (Tellegen, 1982). As with the BPRS, all study groups differed in SPQ total scores such that relatives had an intermediate level of symptoms compared to controls and PwP (see Table 1 and Fig. 1 B). Biological relatives and healthy control participants also completed the Modified Structured Interview for Schizotypy (SIS; Kendler et al., 1989; Nurnberger et al., 1994). These measures allow for dimensional variation on queried traits to be captured in this transdiagnostic sample of PwP and their biological relatives, who may themselves have some mental health concerns and/or mild to moderate levels of symptom expression.

4.4. Sensory/Perceptual phenomena

Perceptual aberrations were queried using the self-report Sensory Gating Inventory (SGI; Hetrick et al., 2012) and items from the Structured Interview for Assessing Perceptual Anomalies (SIAPA; Bunney et al., 1999) were administered in questionnaire format to assess everyday experiences with aberrant visual and auditory perception.

4.5. Physical health

To thoroughly characterize our sample, we obtained each participant's account of their medical history, their current medication list, and their self-reported sleep habits via the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), among other demographic and lifestyle information ascertained through the clinical interview.

4.6. Substance use

Problematic substance use was assessed during the diagnostic interview. In addition, participants completed the Drug Abuse Screening Test (DAST-10; Skinner, 1982) with study staff, as well as an in-house measure of lifetime cannabis use that allowed clinical evaluators to supplement the information gathered during the diagnostic interview, and an in-house questionnaire assessing recent use of alcohol and tobacco products (within the past 7 days prior to the clinical and MRI visits).

5. Cognitive assessment

General cognitive ability was estimated using the similarities and matrix reasoning subtests to calculate IQ (Denney, 2015) from the Wechsler Adult Intelligence Scale - fourth edition (Wechsler, 2008). The word reading subtest of the Wide Range Achievement Test, fourth

edition (WRAT-4) was used as an estimate of reading ability (Wilkinson and Robertson, 2006). A variety of cognitive domains implicated in psychotic disorders were assessed using the paper version of the Brief Assessment of Cognition in Schizophrenia (BACS; Atkins et al., 2016), the digit span subtest of the WAIS-IV (Wechsler, 2008), the Trail Making Test of visual attention and task switching (Reitan and Wolfson, 1993), and the visual perceptual Degraded Stimulus-Continuous Performance Task (DS-CPT; Nuechterlein et al., 1983) of sustained attention which was administered via computer. Handedness was measured using the 10-item Edinburgh Handedness Inventory (Oldfield, 1971). Ratings were made on a scale of handedness preference (1: left hand only, 2: left hand preferred, 3: either hand/no preference, 4: right hand preferred, 5: right hand only) for each of the 10 actions queried. An item was added to the handedness inventory to assess how the wrist and hand are positioned when writing.

Speed of processing was measured in multiple modalities, using the symbol coding subtest of the BACS as well as two computer-based tasks from the battery provided by the PositScience Corporation: “Visual Sweeps” and “Sound Sweeps” (see https://www.brainhq.com). In the visual sweeps task, participants watched parallel, vertical bars moving across a portion of the screen and were instructed to identify the direction of the bars’ movement, as the bars were either compressing (moving inward toward each other) or expanding (moving outward, away from each other). This measure of basic visual processing speed engages several neural functions by alternating stimuli luminance and spatial frequency. The sound sweeps task required participants to determine the direction in which sounds “sweep” (rise or fall in pitch). Sounds were presented at different frequencies (500–5000 Hz) and with varying inter-stimulus intervals to simulate human speech and elicit common errors. This auditory task measures basic skills necessary for speech comprehension and sound differentiation. Performance on the Sound Sweeps and Visual Sweeps tasks among PwP and relatives was examined in a recent study from our group (Ramsay et al., 2020).

6. Emotion recognition

Emotion recognition abilities were measured using the 40 item Penn Emotion Recognition Test (ER-40) (Pinkham et al., 2008; Gur et al., 2002; Kohler et al., 2003; Kohler et al., 2004) and the PROID test, which is a computer-based task provided by the PositScience Corporation (see https://www.brainhq.com). The ER-40 presents photographs of male and female faces expressing mild or extreme happiness, sadness, anger, or fear, as well as neutral faces. The ER-40 faces include Black, White, and Asian individuals, as well as individuals of Hispanic origin. Participants indicated which emotion each face was expressing in a forced choice format. The PROID test of emotion recognition presents 21 trials of male and female speakers reading aloud a neutral sentence with either no emotional valence or to convey 1 of 6 different emotions (happiness, sadness, anger, fear, surprise, disgust). Participants were instructed to identify the emotional valence and rate the intensity on a Likert scale. Together, these two tasks provide a measure of emotion recognition based on visual and auditory input.

7. Theory of mind assessment

Theory of Mind, or mentalizing, was assessed using an alternate form of the multiple-choice version of the Social Attribution Task (SAT-MC-II; Johannesen et al., 2013; Johannesen et al., 2018; Bell et al., 2010; Klin, 2000; Heider and Simmel, 1944). In the SAT-MC-II, participants first view a short (approximately 1 min) animated video depicting three shapes (i.e., oval, rectangle, triangle) acting out a social drama, which is then played for participants again. Next, the video is shown again in shorter segments, after which a multiple-choice question is asked regarding the clip that was just viewed (Johannesen et al., 2013).

8. Vision screening

Participants completed a vision-related self-report questionnaire from the NIH PhenX Toolkit (www.PhenXtoolkit.org; Hamilton et al., 2011) to document self-reported vision health and personal or family history of strabismus and corrective lens use. Vision was also screened using behavioral measures of visual acuity, contrast acuity, and color vision. The Snellen eye chart is a measure of visual acuity that involved participants reading letters that decreased in size (Snellen, 1862). The Mars Letter Contrast Sensitivity test is similar, but the letters decrease in contrast in order to measure processing of low retinal spatial frequencies (Arditi, 2005). The Farnsworth Dichotomous Color Vision test screens for subtle abnormalities in color perception and tests color grading and discrimination abilities by requiring participants to arrange colored caps in order based on hue (Farnsworth, 1947). These measures were used to determine eligibility for neuroimaging tasks targeting visual functions.

9. Motor function

Gross and fine motor functioning were assessed using a battery of tests from the NIH Toolbox (http://www.nihtoolbox.org/). These included an assessment of dexterity using the 9-Hole Pegboard Dexterity Test, a measure of strength using the Grip Strength Test, a test of endurance using the 2 Min Walk Endurance Test, and a test of locomotion using the 4 Meter Walk Gait Speed Test (Reuben et al., 2013). Additionally, participants completed the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976).

A subset of participants completed additional motor tasks including a force steadiness task (n = 240; 128 PwP, 69 relatives, 43 controls), a postural sway task (n = 212; 102 PwP, 66 relatives, 44 controls), and a handwriting task (n = 67; 31 PwP, 5 relatives, 31 controls).

The force steadiness task was similar to those used in previous studies (e.g., Mittal et al., 2011; Cortese et al., 2005; Caligiuri et al., 1997). In this task, participants attempt to apply constant pressure (approximately 300 centinewtons [cN] of force) to a load cell (visual feedback of both target force and force applied is provided) for two sets of three 15 s trials for both the dominant and non-dominant hand. Dyskinesia is reflected by increased variability in the force signal, which results from irregular muscle contractions (Mittal et al., 2011; Cortese et al., 2005; Caligiuri et al., 1997).

The postural sway task involves participants standing still on a Nintendo Wii Balance Board (Gilmore et al., 2015; Gilmore et al., 2017). Similar to Kent and colleagues (2012), participants were instructed to stand as still as possible for two minutes in each of four conditions that manipulated visual input and stance. Specifically, participants stood with their feet either together or shoulder-width apart and their eyes either closed or open (and looking straight ahead at an eye-level fixation cross).

For the handwriting task, participants used a Wacom Intuos Pro digitizing tablet (active area of 22.352 cm x 13.97 cm) (Wacom, Saitama, Japan) and a non-inking pen. Participants copied several patterns (e.g., overlaid circles, loops/repeated cursive letter "l") under various conditions specifying size, speed, and handedness, with 5 trials for each condition. Movement of the pen was sampled using MovAlyzeR software (Neuroscript, LLC http://www.neuroscriptsoftware.com/ Tempe, AZ, USA). This task allows for the interrogation of a variety of motor variables, including for example movement fluidity (e.g., Teulings et al., 1997; Caligiuri et al., 2010; Caligiuri et al., 2015; Kent et al., 2019; Dean et al., 2013) and velocity scaling (e.g., Caligiuri et al., 2006; Caligiuri et al., 2009; Dean and Mittal, 2015).

10. Blood specimen collection

In order to harmonize biological data with the larger HCP database, blood samples were acquired in accordance with the HCP protocol. Participants provided a total of 20 mL (4 teaspoons) of blood via intravenous puncture. In accordance with HCP procedures, DNA and RNA material were extracted from whole blood and frozen and stored in a −70 °C freezer for future analyze. Serological samples were also extracted from whole blood by centrifuge at 2400 rpm and 24 °C for 16 min. If a participant was unable to provide a blood sample (e.g., needle discomfort, anemia), a saliva sample was obtained instead to be used for DNA analysis. For the first 247 participants with complete clinical and 3 T imaging data: 79% provided blood samples, 14% provided saliva samples, 2% declined to provide either, and a further 2% provided both types of samples, whereas 3% plan to provide a sample at a future 7 T imaging visit. There were no significant group differences in whether, or what type of, a DNA sample was provided (χ^2 (8,247) = 11.16, p =.193).

11. MRI hardware

Imaging data were collected on a whole-body Siemens 3 T Prisma scanner (with the standard high gradient strength, 80 mT/m maximum amplitude and 200 T/m/s maximum slew rate) using a Siemens 32 channel head coil at the Center for Magnetic Resonance Research of the University of Minnesota.

12. Imaging data acquisition at 3 Tesla

We collected structural scans, diffusion weighted imaging, resting state fMRI, and task fMRI data across two scan sessions each of approximately 60–90 min duration. Typically, both scanning sessions were completed on the same day with a lunch intermission, but sessions occasionally occurred on separate days to accommodate participant fatigue and scheduling conflicts. The MRI sequence was split into two scan sessions to reduce

participant burden for this clinical population spanning a wide age range, as was done in the HCP Lifespan protocol. This approach is not uncommon and standard co-registration procedures and options (such as AFNI's align_epi_anat.py "-big_move" option; Cox 1996; Cox and Hyde 1997; Taylor et al. 2018) can be used in data processing to account for any participant placement differences between the two sessions, provided that gradient non-linearity correction is performed (Glasser et al., 2013). On the day of scanning, participants completed a brief questionnaire assessing current sleep and medications as well as recent use of caffeine, tobacco, alcohol, and other substances. Participants also completed the Positive Affect Negative Affect Scale (PANAS; Watson et al., 1988) to document their affective state prior to and after scanning. Finally, participants completed a MRI Debriefing Survey, in which participants reflected on the scanning experience. Preliminary analysis of this measure indicated that the imaging protocol was tolerable for this population and age range (average response agreeing with the statement, "I was comfortable while in the scanner" on a scale of 1–5 was 4.44, SD = 0.90; and 4.55, SD = 0.70 for the statement, "The length of time in the scanner was reasonable").

12.1. Imaging protocol consistent with previous HCP studies

The P-HCP scanning protocol matches that of the Lifespan Human Connectome Projects, (see Harms et al., 2018), which collected data on healthy individuals across development. Specifically, structural T_1- and T_2-weighted imaging, diffusion weighted imaging, and resting state functional imaging remained consistent. The rationale for matching our imaging protocol to that of the Lifespan HCPs was that the adaptations (e.g., reduced scan duration, real-time motion correction for T_1 and T_2 scans) that were made to accommodate the youngest and oldest participants in the Lifespan HCPs also apply to our sample of vulnerable adults who, similarly, are likely to experience fatigue and increased motion. Additionally, the use of consistent imaging protocols across study populations allows for data to be integrated across HCPs, which is directly in line with the goals of the NIH.

Structural imaging.—Structural scans included both a multi-echo T_1w MPRAGE sequence and a variable-flip-angle, turbo-spin-echo T2w scan with volumetric navigators to aid real-time motion correction and selective reacquisition. As in the Lifespan HCP (Harms et al., 2018), up to 30 k-space lines for the T1w scan and up to 25 *k*-space lines for the T2w scan were allotted for reacquisition. Protocol details are provided in Table 4 and Inline Supplementary Table 1.

Diffusion weighted imaging.—The diffusion weighted imaging (dMRI) protocol was identical to that of the HCP-development and HCP-aging projects (Harms et al., 2018). Briefly, we administered a total of 4 diffusion runs (186 b = 1500 s/mm^2, 184 b = 3000 s/mm^2 and 28 b = 0 s/mm^2 volumes across all runs) using the HCP 98 and 99 "direction" tables with both AP and PA phase encoding directions (see Table 4). We chose to use the same dMRI protocol as HCP-development/aging given the relatively short scan duration as compared to other HCP protocols. At the start of the study, we were concerned that the protocol might be burdensome enough on participants that we would suffer from a high attrition rate in the second session. For this reason and to improve the chances that we would collect some dMRI data, the 98-direction dMRI data was collected in session *A* while the

99-direction data was acquired in session *B*. Contrary to our concerns our completion rate was very high and after 32 participants were scanned we moved the 98 direction dMRI data to the session B acquisition, as was done in the HCP development and aging studies. Using the same dMRI protocol also allows investigators to combine datasets across these studies.

Resting state fMRI.—To remain consistent with the Lifespan HCP, four resting state scans in total were administered, each lasting 6.5 min (488 volumes), in pairs of two runs with opposite phase encoding directions. Matching the Lifespan HCP approach, for each resting pair the scans were always administered with the anterior-to-posterior acquisition first followed by the posterior-to-anterior phase encoding). This decision may have introduced an order effect into the resting state data. Participants were instructed to keep their eyes open and fixated on a cross, to not think about anything in particular, and to try to stay awake. Real time evaluation of subject motion was performed using the Framewise Integrated Real-time MRI Monitoring (FIRMM) software (Dosenbach et al., 2017). When a resting state fMRI scan had excessive motion based on objective criteria (> 20% of data with framewise displacement > 0.4mm) from FIRMM, and/or visual monitoring of participant motion, we reran the scan if time allowed. A monitoring camera was trained on the participant's eyes to ensure that their eyes were kept open and fixated on the cross. If subjects closed their eyes for prolonged periods we verbally prompted them between scans. Notes of subject compliance with task instructions were saved in the database and will be shared along with the data. Respiration and heart rate data were also collected.

12.2. Imaging protocol unique to P-HCP

Task fMRI.—Our imaging protocol differs from that of the Lifespan HCP in the tasks we selected for functional scans. The tasks we included were selected to probe processes specifically implicated in psychosis: reward processing, cognitive control, social cognition. The acquisition parameters (other than number of runs and volumes per run) for tfMRI are identical to those of the resting state fMRI scans (see Table 4). For all resting state and task fMRI runs, each scan begins with the acquisition of a single-band reference that is used for calibration and is reconstructed as a separate series. Each fMRI run then has 4 "dummy" volumes that the scanner runs through but does not reconstruct in order to allow steady-state magnetization to be reached before image reconstruction and saving occurs. For task fMRI, the task was triggered at the start of the first reconstructed volume. Participants practiced all tasks outside the scanner until performance reached a minimum standard to demonstrate their full comprehension of task instructions. Once inside the magnet, staff reviewed the task instructions with participants before each task scan was run. Task images were displayed to participants in the scanner via a mirror mounted to the head-coil that reflected a screen just at the edge of the bore of the magnet onto which images were projected. During task fMRI data acquisition, study staff monitored participants' button presses to identify and correct technological issues (e.g., finger mis-alignment) or participant somnolence. The same, four-button, curve-right fiber optic response pad (Current Designs Inc. https://www.curdes.com/ Philadelphia, PA, USA) was used across tasks.

12.3. Task fMRI: monetary incentive delay (MID) task

The cued reinforcement reaction time task (CRRT) is a monetary incentive delay task that was developed to measure motivated actions in response to varying reinforcement likelihoods, while accounting for individual differences in reaction time by using adaptive learning technology (Cools et al., 2005). The CRRT allows researchers to evaluate responsiveness to rewards above and beyond the confound of processing speed deficits that are common in psychotic disorders.

Participants completed 25 practice trials outside of the scanner until a passing score of 20/25 was obtained. Only participants who successfully achieved this threshold in the practice session went on to complete the task in the scanner. The task practice was repeated one time inside the scanner. The CRRT consists of two types of cues (gain or loss), a 2.5–3 s delay, a target stimulus of three circles arranged in a row containing an outlier (odd-one-out), and feedback regarding the outcome of the trial (whether money was gained or lost; see Fig. 2 for stimuli). The CRRT was administered using Presentation (version 18.3, Neurobehavioral Systems, 2016, Inc., Berkeley, CA, www.neurobs.com). Two runs, each lasting 13 min (up to 1040 volumes) and containing 80 trials, were administered. Participants made responses with the response pad turned sideways and using their left thumb to press button 1 and their right thumb to press button 4. Participants were instructed to respond quickly and accurately. The amount earned on each trial depended on the participant's reaction time (see Simon et al., 2015). Participants received payment commensurate with the amount of money they won in the task (up to $60). For the current study, the CRRT was revised slightly to include different colors for the types of reward stimuli (win = green; lose = red; see Fig. 2) and to display reward quantities in United States dollar currency (rather than Euros, as in Simon et al. 2015). Participants were instructed to respond quickly and accurately.

Behavioral variables include total amount of money won, number of errors and response time for each condition. Further, "reinforcement-related speeding" can be calculated to give an estimate of whether participants respond faster to reward-relevant versus neutral stimuli and to cues indicating higher versus lower reward amounts (see Fig. 2 A). This is done by subtracting the response time to neutral trials from gain or loss trials, or extending this concept further by subtracting lower reward amounts from the higher amount of corresponding valence.

The literature on monetary incentive delay task activation shows reduced activation in the ventral striatum during anticipation of monetary rewards across the schizophrenia spectrum, including: people with chronic schizophrenia (Juckel et al., 2006a, 2006b), first-episode psychosis (Esslinger et al., 2012; Hanssen et al., 2015; Nielsen et al., 2012; Schlagenhauf et al., 2009), unaffected first-degree relatives (de Leeuw et al., 2015; Grimm et al., 2014) and individuals at ultrahigh risk for schizophrenia (Juckel et al., 2012). Other first-degree relative studies have identified hypoactivation of the dorsal striatum during reward anticipation (Li et al., 2018) and hyperactivation of the default mode network (Hanssen et al., 2015). In bipolar disorder, monetary incentive delay task studies have shown mood-congruent reward processing bias in the left lateral orbitofrontal cortex during anticipation of gains and losses in people in a state of mania despite intact task performance (Bermpohl et al., 2010). When utilizing the CRRT version, people with first-episode schizophrenia exhibit deficits in

reward-related speeding (Murray et al., 2008), though this was not observed in people with schizophrenia or schizoaffective disorder of any illness duration (Simon et al., 2015). Taken together, these findings suggest reward-related activation and performance abnormalities across different phases of psychotic illness, positioning the CRRT well within the aims of the current project.

12.4. Task fMRI: dot pattern expectancy (DPX) task

The Dot Pattern Expectancy (DPX) Task serves as a measure of cognitive control and context processing deficits, which are implicated in schizophrenia (Poppe et al., 2016). Recent research suggests that cognitive control deficits are not specific to schizophrenia but also occur in schizoaffective disorder and bipolar I disorder (Smucny et al., 2020). Cognitive control involves both proactive and reactive control mechanisms to regulate thoughts and behaviors (Braver, 2012). Proactive control requires that information is actively maintained in memory in order to carry out goal-directed behavior. Reactive control requires recall of information when triggered by a stimulus that is relevant to the intended goal-directed behavior. The DPX task used in this study is a variant of the expectancy AX continuous performance task created by Cohen and colleagues (Cohen et al., 1999; MacDonald, 2008; Servan-Schreiber et al., 1996). The version used in the current study displays stimuli of dot patterns instead of Latin alphabet letters in an effort to prevent participants from forming verbal rules to complete the task. For a detailed examination of psychometric properties of the DPX task, see Jones et al. (2010).

The task consists of three runs each lasting 6 min (450 v) and containing 40 trials. Each trial displays a cue and a probe, both of which are dots arranged in varying Braille letters (see Fig. 3). Prior to scanning, participants were familiarized with the task stimuli and were provided the opportunity to practice making responses. During this orientation, participants were told that the white and blue dot patterns form pairs and that they were to respond to each pair but indicate the “special” (correct) pair with a different button press. Participants then practiced until they reached 80% accuracy for both cue and probe responses. Participants were instructed to fixate their gaze on a cross in between each trial. Participants were asked to respond to the target probe (X) only when it is preceded by the appropriate cue (A) such that only AX pairs are valid. The majority of trials are AX trials. Participants also performed button presses to the cue, indicating that it is not a target, which increases the prepotency of the motor response. The response pad was positioned lengthwise such that the buttons faced away from the participant and the cord ran towards the participant’s feet; the participant pressed button 4 with the index finger of their dominant hand to make a target response and button 3 with the middle finger of their dominant hand for non target responses. Invalid cues (B) and probes (Y) are incorporated into the task to elicit participant cognitive control responses. Proactive control is engaged when a participant must maintain in memory an invalid cue (B) that precedes the valid probe (X) in order to inhibit their response to the otherwise valid probe. Reactive control is engaged when a valid cue (A) is followed by an invalid probe (Y) and the participant successfully inhibits their response. The DPX task was administered using E-Prime version 2.0 (Psychology Software Tools, 2015, Pittsburgh, PA). Output variables include the error rates for each trial type (i.e.g, AX, AY, BX, BY) and response times.

12.5. Task fMRI: social cognition task

To measure theory of mind, a component of social cognition, the current study adapted the theory of mind task described in Barch et al. (2013) account of the Human Connectome Project task-fMRI battery. Our task used the Frith-Happé animations (see Fig. 4), wherein the movement of two triangles corresponds to one of three conditions: (1) theory of mind (the shapes were interacting socially, appearing to take each other's mental states into account); (2) goal directed (movement of the shapes seemed related to each other, but they did not appear to be aware of each other's thoughts and feelings); and (3) random (Abell et al., 2000; Castelli et al., 2000; White et al., 2011). Participants were familiarized with the task outside the scanner prior to scanning, and practiced viewing and responding to videos from each of the three conditions.

The task was administered using *E*-Prime version 2.0 (Psychology Software Tools, 2015, Pittsburgh, PA) and conducted across three runs, each run containing 295 v. Each run presented two videos from each condition in pseudorandom order. Participants watched a 20 s video, followed by a response screen and then 15 s of rest/fixation. At the end of each video, participants chose what type of interaction they believed was going on using their dominant hand and same response pad placement as during the DPX task: mental interaction (index finger), non-mental interaction (middle finger), or no interaction (ring finger; similar to White et al. 2011). Participants were instructed that there was no "right" or "wrong" answer, and to select the type of interaction they thought had occurred. Additionally, participants were instructed to press any of the three buttons during the video as soon as they thought they knew which type of interaction was occurring.

This task was selected for inclusion in the *P*-HCP protocol because of its focus on social cognition, and in particular theory of mind, which is an area of great interest in schizophrenia spectrum research. For example, people with schizophrenia have demonstrated diminished activity in the right superior temporal gyrus at the temporoparietal junction and bilaterally in the inferior frontal gyri during this task (Das et al., 2012). Further, people with schizophrenia have been shown to be less accurate at identifying the interactions and to have increased functional connectivity with the left inferior frontal gyrus and caudate nucleus during the theory of mind and goal directed interactions (Martin et al., 2016).

12.6. Imaging at 7 Tesla

Neuroimaging data are also collected on a Siemens 7 *T* scanner, including minimal structural data, functional MRI, and magnetic resonance spectroscopy. Data acquisition methods for 7 *T* imaging are described in detail in our companion paper (Schallmo et al. (2021) in preparation).

13. Data quality

Multiple, complementary quality assurance procedures were used to ensure that the highest quality imaging data were collected. At acquisition, all imaging data were visually inspected for overall quality. Further, scanner operators provided feedback to participants regarding excessive movement and reacquired data if necessary. For T_1 and T_2 weighted scans,

operators performed a qualitative evaluation of motion artifact and data usability by assessing ghosting level and image sharpness, in particular in the gray/white boundary. This evaluation was performed right after acquisition completion, and reacquisition of the low quality T_1 and /or T_2 scans was typically attempted before proceeding with the scan sequence if the participant was willing and if time allowed, within session *A* (9 participants) and/or within session *B* (12 participants). For diffusion scans, data were evaluated for full brain coverage and slice drop out/dimming during acquisition. A total of 5 participants had one or more replacement diffusion scans acquired during data collection. For functional scans, participant motion and respiration artifacts were closely monitored during acquisition. We also used the freely available FIRMM software to collect and monitor motion-related data quality information of the fMRI during acquisition (Dosenbach et al., 2017). Preliminary results indicate good quality functional data given a FIRMM threshold of 0.3mm, as evidenced by mean percent of volumes meeting the threshold (standard deviation in parentheses): resting fMRI = 80.72 (20.87); MID task = 82.58 (18.95); DPX task = 80.91 (19.32); social cognition task = 81.11 (17.92). However, there was a significant effect of group for resting fMRI ($F(2,123) = 5.62$, $p = .005$) and the DPX task ($F(2,106) = 5.79$, $p = .004$) such that PwP had a lower proportion of retained volumes compared to their biological relatives. There was no significant difference between either group and healthy controls.

After participant imaging data were acquired, a more quantitative process was used to determine which data sets were of sufficient quality for inclusion in our analyses. For structural scans, a rating system was established that closely resembles that of the Connectome Coordination Facility (CCF). Scans were assigned a preliminary data quality score ranging from 1 to 4 (1 = poor, 2 = fair, 3 = good, 4 = excellent). Scan quality was judged based on the presence and severity of banding, ghosting, and poor resolution (as indicated by blurred gray/white matter boundaries). Of the 257 participants who completed MRI scanning, only 6 participants (2.33%) had unusable data due to the presence of pathology or poor quality images and a further 4 participants (1.56%) were excluded based on diagnostic review. The remaining 247 participants with usable structural imaging data are described in this paper. Preliminary examination of T_1 data across these 247 participants revealed adequate signal-to-noise ratio on average (combined sample mean = 18.99, SD = 2.94) as measured in white matter using Freesurfer QA Tools. As of March 2020, there was no significant difference between study groups in signal-to-noise ratio of the T_1 data ($F(2,243) = 1.01$, $p = .365$). For the diffusion data, the FSL tool *eddy* was applied to the data using the slice outlier replacement flag and the default outlier threshold for bad slices of 4 standard deviations. Total number of bad slices per subject and total number of volumes with 5 or more bad slices across subjects was tracked during the study. Based on criteria from the FSL eddy web page no completed diffusion data sets were excluded from analysis based on QA measures. The data quality of all fMRI scans was analyzed using quality assurance metrics generated by AFNI's individual subject processing pipeline design tool *afni_proc.py* (see, e.g., Taylor et al., 2018). Preliminary analysis suggests good quality data overall, with only a small fraction of participants (task: 2.42%; rest: 9.09%) who have more than 20% of volumes exceeding the threshold. For task fMRI, volumes with motion parameters exceeding 0.5mm Euclidean norm (enorm) relative to the previous volume were marked for exclusion from analysis. A significant group difference in task

fMRI data quality ($F(2,204) = 6.04$, $p = .003$) shows that PwP had more motion artifacts that led to more volumes being excluded in comparison to the control ($p = .026$) and biological relative groups ($p = .008$). Further, groups differed such that task fMRI signal-to-noise ratios were lower among PwP ($F(2,198) = 3.25$, $p = .041$) compared to relatives ($p = .049$) but not controls ($p = .203$) For resting fMRI, an enorm threshold of 0.4mm was used. A similar pattern of group differences emerged for resting fMRI such that PwP had more volumes with motion parameters that exceeded the threshold ($F(2,228) = 8.46$, $p < .001$) compared to controls ($p = .005$) and relatives ($p = .002$). However, there were no group differences in resting fMRI signal-to-noise ratios ($F(2,228) = 0.72$, $p = .488$). Finally, incidental findings were logged in the data set should investigators choose to exclude these scans from their analyses. All of the aforementioned data quality indices were used as criteria for: rescan, inclusion in the 7T arm of the study, and inclusion in specific analyses.

14. Data pre-processing

The Connectome Coordination Facility (CCF) performs minimal pre-processing of all imaging data (e.g., discarding the initial 10 data frames or 8 s of fMRI data, converting data files from DICOM to NIFTI format, processing data using the HCP minimal pre-processing pipeline; Glasser et al. 2013). All raw and pre-processed data are made publicly available so that individual investigators may select their own data quality thresholds and perform data processing using tools of their choosing.

15. Data sharing

All data collected as part of the *P*-HCP will be shared with the scientific community. For clinical and behavioral measures, both raw and scaled scores (e.g., estimated IQ; symptom rating measure factors calculated from individual scale items) will be made available upon completion of data collection in late 2021. The NDA release of these data is anticipated for summer 2022. A data dictionary that defines all clinical and behavioral variables will be shared along with the data to aid investigators in selecting their analysis approach. Imaging data are prepared by the Connectome Coordination Facility (CCF; intradb.humanconnectome.org) for consistency with other human connectome projects (e.g., data quality assurance, formatting, pre-processing) prior to being made publicly available in the NIMH Data Archive (NDA; nda.nih.gov) repository. Data release of all 3T imaging data is anticipated by early 2022, assuming adequate harmonization of data.

16. Intended use and limitations

Previous studies are limited by small sample sizes and varying neuroimaging protocols that make generalizing to the population and comparison across studies difficult. Further, much of the psychosis literature is confined to homogenous diagnostic categories with a significant focus on schizophrenia. The P-HCP applied standardized human connectome neuroimaging protocols to a transdiagnostic sample of people with psychotic disorders in order to test hypotheses related to psychotic symptoms that span across a number of clinical diagnoses. The neural functions underlying these psychotic illnesses are investigated using multimodal imaging techniques to measure brain connectivity, function, structure, and their interrelation.

This study is unique in that the sample is large and also includes first-degree biological relatives of people with psychosis, which allows for an examination of the role of genetic liability (e.g., distinguishing predispositioned vulnerabilities from disease biomarkers and sequelae). The goals of the psychosis Human Connectome Project were to investigate neural abnormalities associated with distorted perception in psychotic disorders and biological first-degree relatives and to make the data available to the scientific community.

While the current study has many strengths, certain limitations should be acknowledged. First, even though there is a longitudinal component for a subset of participants who return for follow-up 7 Tesla imaging, the majority of the P-HCP data are cross-sectional in nature. This limits the conclusions that can be made regarding the predictive power of aberrations in neural structure and connectivity. Second, data collection was interrupted by the COVID-19 pandemic, which resulted in a smaller control group as of March 2020. However, the P-HCP was designed to maximize enrollment of people with psychotic psychopathology as well as their biological first-degree relatives to yield an enriched sample. Further, other Human Connectome Projects offer additional control samples that were assessed with similar, if not identical, measures. Third, fMRI data quality may differ across groups as preliminary data show a higher proportion of motion artifacts among PwP, per the fMRI data quality indices described earlier. However, there were no significant group differences in signal-to-noise ratios for resting fMRI, task fMRI (between PwP and controls) or structural scans, as well as no dMRI data quality issues (see details above). Nevertheless, we advise investigators to use the data quality metrics, particularly for fMRI data, that we will make available along with the imaging data and to employ data processing and statistical methods that reduce the impact of motion artifacts in the data.

17. Conclusions

By applying the Human Connectome Project Development and Aging imaging protocol to a thoroughly characterized clinical population, first degree biological relatives and demographically similar healthy controls, and adding a selection of illness-relevant tasks, this project is well poised to inform our understanding of neural mechanisms involved in cognitive and perceptual distortions of psychosis. Advances in delineating the mechanisms involved in perceptual and cognitive disturbances can inform novel treatments for psychotic disorders. The data from this project will be made publicly available so that other researchers can generate and test novel hypotheses regarding neural anomalies in psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The dataset will be made publicly available. Imaging data are prepared by the Connectome Coordination Facility (CCF; intradb.humanconnectome.org) for consistency with other human connectome projects (e.g., data quality assurance, formatting, pre-processing) prior to being made available to the scientific community in the NIMH Data Archive (NDA; nda.nih.gov) repository upon completion of data collection. Thus, all data, including raw and pre-processed neuroimaging data, will be made publicly available so that other researchers can generate and test novel hypotheses regarding neural anomalies in psychosis.

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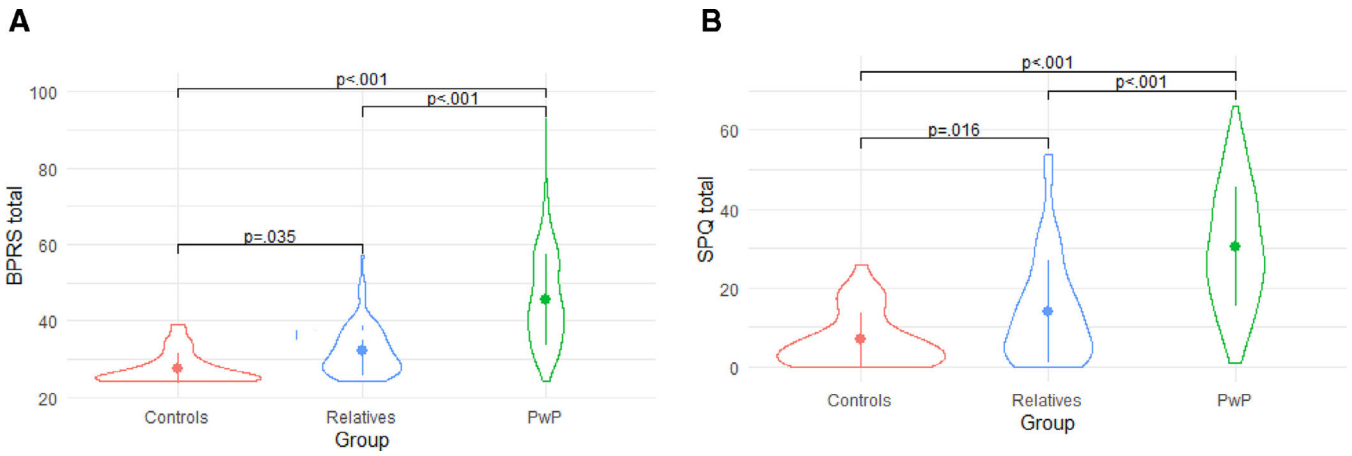

Fig. 1.

(**A**). Mean Brief Psychiatric Rating Scale (BPRS) symptom scores for preliminary sample (*n* = 247; error bars represent standard deviation). (**B**). Mean Schizotypal Personality Questionnaire (SPQ) symptom scores for preliminary sample (*n* = 247; error bars represent standard deviation).

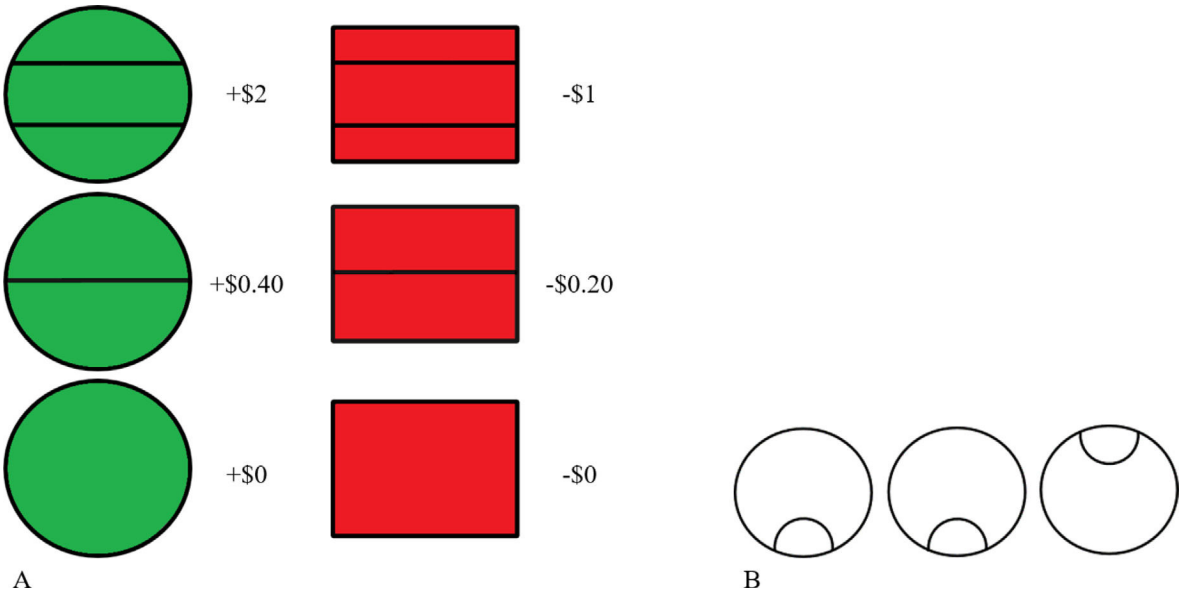

Fig. 2.

The reward cues (A) and the odd-one-out target stimulus (B) used for the cued reinforcement reaction time task (CRRT; adapted from Simon et al. 2015).

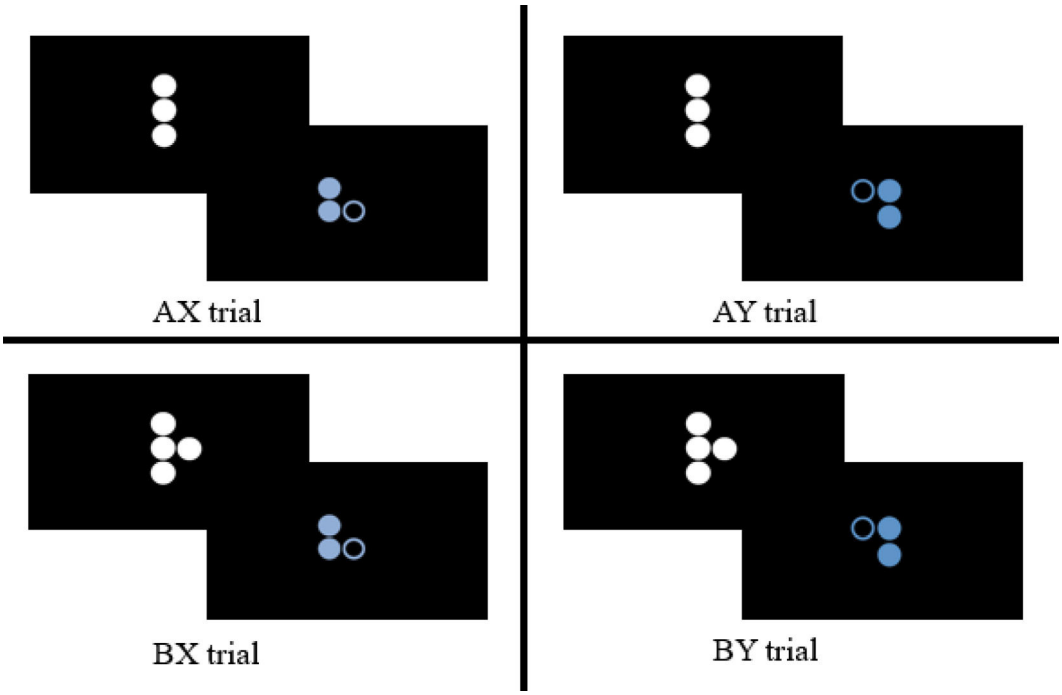

Fig. 3.
Cue-probe pairs of the dot pattern expectancy task.

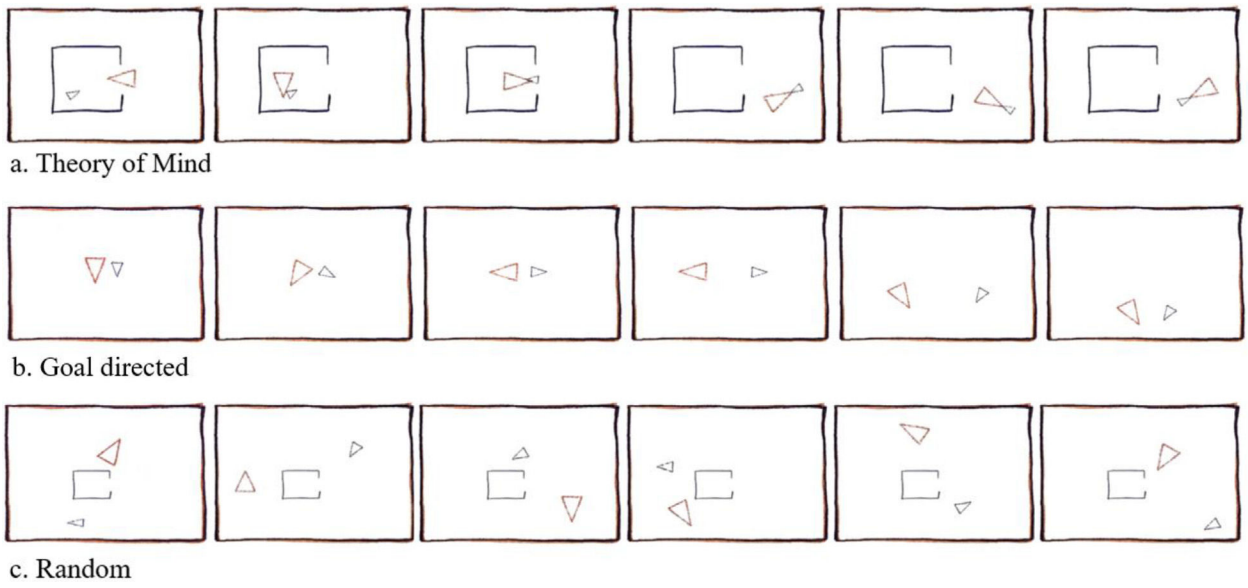

Fig. 4.
Social cognition task conditions.

Table 1

Participant characteristics of the first 247 participants with complete data.

	Healthy Controls (*n* = 42)	Relatives(*n* = 74)	People with Psychosis (*n* = 131)	Statistic	Pairwise comparison
Mean age (SD)	39.19 (13.58)	44.49 (13.98)	38.48 (12.59)	$F(2244) = 5.12$, $p = .007$	PwP < Rel **
Female sex	21 (50.0%)	49 (66.2%)	57 (43.5%)	χ^2 (2247) = 9.80, $p = .007$	PwP < Rel **
Racial identity	-	-	-	χ^2 (10,247) = 15.44, $p = .117$	-
Caucasian, not of Hispanic origin	36 (85.7%)	67 (90.5%)	91 (69.5%)	-	-
African American, not of Hispanic origin	3 (7.1%)	4(5.4%)	24 (18.3%)	-	-
Asian or Pacific Islander	1 (2.4%)	0	5 (3.8%)	-	-
Hispanic	1 (2.4%)	1(1.4%)	4 (3.1%)	-	-
American Indian or Alaska Native	0	0	1 (0.8%)	-	-
Other	1 (2.4%)	2(2.7%)	6 (4.6%)	-	-
Participant years of education	15.88 (2.48)	15.05 (2.33)	14.04 (2.09)	$F(2244) = 12.51$, $p < .001$	PwP < Con *** PwP < Rel **
Parent education	5.43 (1.38)	5.13 (1.15)	5.03 (1.15)	$F(2237) = 1.70$, $p = .185$	-
WAIS IQ estimate	106.36 (11.77)	102.03 (11.01)	97.24 (11.74)	$F(2244) = 11.25$, $p < .001$	PwP < Con *** PwP < Rel *
BPRS total	27.40 (4.05)	32.01 (6.47)	45.63 (11.92)	$F(2244) = 82.13$, $p < .001$	PwP > Con *** PwP > Rel *** Con < Rel *
SANS total (global scores)	-	-	6.81 (3.96)	-	-
SAPS total (global scores)	-	-	5.21 (4.32)	-	-
SPQ total	6.86 (6.94)	14.04 (13.00)	30.27 (15.02)	$F(2244) = 64.91$, $p < .001$	PwP > Con *** PwP > Rel *** Con < Rel *

Note:

* $p < .0$

** $p < .01$

*** $p < .001$

Con = Healthy Controls; Rel = Relatives; PwP = People with Psychosis; Parent education (coded: 1 = 7th grade or less, 2 = 7th –9th grade, 3 = 10th –12th grade, 4 = high school graduate/ GED, 5 = partial college/ vocational/technical school, 6 = 4-year college/ university graduate, 7 = graduate degree, 9 = unknown); WAIS = Wechsler Adult Intelligence Scale; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms (completed by PwP only); SAPS = Scale for the Assessment of Positive Symptoms (completed by PwP only); SPQ = Schizotypal Personality Questionnaire

Table 2

Clinical measures.

Domain	Measure
	Demographics questionnaire Pedigree
Symptoms	Structured Clinical Interview for DSM-IV-TR disorders (SCID) NIMH Diagnostic Interview for Genetic Studies - psychosis section (K-DIGS) Brief Psychiatric Rating Scale - 24 Item Version (BPRS)
	Scale for the Assessment of Negative Symptoms (SANS) & Scale for the Assessment of Positive Symptoms (SAPS)[a]
	Operational Criteria In Psychotic Illness (OPCRIT) [a] Temporal Experience of Pleasure Scale (TEPS)
Functioning	Global Functioning: Social and Role Scales
	Social Functioning Scale [a] (SFS) Social Adjustment Scale - Self Report (SAS-SR Short) Flanagan Quality of Life Scale (QOLS)
Personality	Modified Structured Interview for Schizotypy (SIS) [b] Personality Inventory for DSM-5 (PID-5) Behavioral Approach/Inhibition Scale (BIS/BAS) Schizotypal Personality Questionnaire (SPQ)
Perception	Sensory Gating Inventory (SGI) / Structured Interview for Assessing Perceptual Anomalies (SIAPA)
Physical Health / Functioning	Pittsburgh Sleep Quality Index (PSQI) Medical History Medication List
Substance use	7 Day Alcohol/Smoking questionnaire Drug Abuse Screening Test (DAST-10) Cannabis supplement

Note:

[a]denotes measures that are completed only by/for participants with psychosis

[b]denotes measures that are completed only by relatives and healthy control participants

Table 3

Behavioral measures.

Domain	Measure
Handedness	Edinburgh Handedness Inventory
Cognition	Wide Range Achievement Test (WRAT-4) - word reading
Single word reading ability	
General cognitive ability	Wechsler Adult Intelligence Scale (WAIS-IV):
	Similarities
	Matrix Reasoning
Working Memory	Digit Span (forward and backward)
Sustained attention	Degraded Stimulus-Continuous Performance Task (DS-CPT)
Set shifting	Trails *A* and *B*
Visual processing speed	POSIT visual sweeps
Auditory processing speed	POSIT sound sweeps
	Brief Assessment of Cognition in Schizophrenia (BACS):
Verbal Memory;	Word list;
Working Memory;	Digit Sequencing;
Sensorimotor Processing Speed;	Token Motor Task;
Verbal Fluency;	Semantic Fluency;
Verbal Fluency;	Letter Fluency;
Speed of Processing;	Symbol Coding;
Reasoning/Problem Solving	Tower of London
Emotion	
Emotion Recognition	Penn Emotion Recognition Test (ER-40) POSIT PROID test
Affective state	Positive Affect Negative Affect Scale (PANAS)
Theory of Mind	Social Attribution Task–Multiple Choice (SAT-MC-II)
Vision	PhenX Vision Interview [1]
Vision health	
Visual acuity	Snellen Eye Chart
Contrast acuity	Mars Letter Contrast Sensitivity Test
Color vision	Farnsworth Dichotomous Color Vision Test: Panel D-15

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Domain	Measure
Motor	Abnormal Involuntary Movement Scale (AIMS)
Dyskinesia	
Dexterity	9-Hole Pegboard Dexterity Test
Strength	Grip Strength Test [2]
Endurance	2-Min Walk Endurance Test [2]
Locomotion	4 M Walk Gait Speed Test [2]
Force variability	Force steadiness task
Balance	Postural sway task
Various motor variables	Handwriting task

Note:

[1] denotes measures from the NIH PhenXtoolkit (www.PhenXtoolkit.org)

[2] denotes measures from the NIH toolbox (http://www.nihtoolbox.org/)

Table 4

P-HCP 3 T neuroimaging protocol.

Modality	Matrix	FOV (mm)	Resolu-tion (mm)	Flip Angle	TE (msec)	TR (msec)	Slices/Orient-ation	AF/ MB	Time (min: sec)
Session A									
Localizer	256	300	1.72	15	3	40	1 axl,1 sag,1 cor	-	0:10
Auto Align Head Scout	160	260	1.63	8	1.37	3.15	128 sag	-	0:14
Localizer, aligned	256	300	1.17	15	3	104	1 axl,7 sag,1 cor	-	0:21
Spin echo field maps (AP then PA)	104	208	2	90	66	8000	72 axl	-	0:090:09
Resting state fMRI (AP then PA)	104	208	2	52	37	800	72 axl	-	6:416:41
T_1 w setter	32	256	8	2	4.6	9.9	32 sag	-	0:01
T_1 w MPRAGE, multi-echo	300 × 320	240 × 256	0.8	8	1.81, 3.6, 5.39, 7.18	2500	208 sag	AF = 2	8:22
T_2 w setter	32	256	8	2	6	13	32 sag	-	0:01
T_2 w turbo spin echo SPACE with volumetric navigators	300 × 320	240 × 256	0.8	VAR	564	3200	208 sag	AF = 2	6:35
Spin echo field maps (AP then PA)	104	208	2	90	66	8000	72 axl	-	0:090:09
Task fMRI MID PA (2 runs)	104	208	2	52	37	800	72 axl	MB = 8	13:4713:47
Session B									
Localizer	256	300	1.72	15	3	40	1 axl,1 sag,1 cor	-	0:09
AAHead Scout	160	260	1.63	8	1.37	3.15	128 sag	-	0:14
Localizer, aligned	256	300	1.17	15	3	104	1 axl,7 sag,1 cor	-	0:21
Spin echo field maps (AP then PA)	104	208	2	90	66	8000	72 axl	-	0:090:09
Resting state fMRI (AP then PA)	104	208	2	52	37	800	72 axl	MB = 8	6:416:41
dMRI, dir98 * (AP then PA)	140	210	1.5	78	89.20	3230	92 axl	MB = 4	5:385:38
dMRI, dir99 (AP then PA)	140	210	1.5	78	89.20	3230	92 axl	MB = 4	5:425:42
Spin echo field maps (AP then PA)	104	208	2	90	66	8000	72 axl	-	0:090:09
Task fMRI DPX PA (3 runs)	104	208	2	52	37	800	72 axl	MB = 8	6:116:116:11 “
Task fMRI Social Cognition PA (3 runs)	104	208	2	52	37	800	72 axl	MB = 8	4:074:074:07

Note: FOV = field of view; TE = echo time; TR = repetition time; AF = acceleration factor; MB = multi-band acceleration factor; AP = anterior-to-posterior phase encoding direction; PA = posterior-to-anterior phase encoding direction; axl = axial; sag = sagittal, cor = coronal; VAR = variable flip angle; MID = Monetary Incentive Delay; DPX = Dot Pattern Expectancy

* a subset of the initial participants in the study completed the 98 direction dMRI in session A rather than session B, as described in the dMRI section above