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North American Prodrome Longitudinal Study (NAPLS 3): Methods and Baseline Description

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Abstract

The North American Prodrome Longitudinal Study (NAPLS) is a consortium of nine programs focusing on youth at clinical high risk (CHR) for psychosis. Funded by the National Institute of Mental Health (NIMH), the sites are located at Emory University, Harvard University, University of Calgary, University of California at Los Angeles, at San Diego, and at San Francisco, University of North Carolina Chapel Hill, Yale University, and Zucker Hillside Hospital. There

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Contributors

The study was designed by Addington, Cannon, Cornblatt, Cadenhead, Woods, McGlashan, Perkins, Tsuang, Bearden, Walker, Mathalon, & Seidman. Liu undertook data analysis. Addington wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Authors declare they have no conflict of interest with respect to this study.

have been two previous endeavors completed by this consortium, known as NAPLS-1 and NAPLS-2. This paper first offers an overview of the methodology of the third phase of the NAPLS consortium, the second five-year prospective study NAPLS-3, which aims to determine mechanisms of the development of psychosis. In addition, we report on the ascertainment and demographics of the 710 CHR participants in NAPLS-3.

Keywords

psychosis; schizophrenia; clinical high risk; methodology

1. Introduction

The North American Prodrome Longitudinal Study (NAPLS) is a consortium of nine programs focusing on youth at clinical high risk (CHR) of psychosis. Funded by the National Institute of Mental Health (NIMH), the NAPLS sites are located at Emory University, Harvard University, University of Calgary, University of North Carolina Chapel Hill (UNC), Yale University, Zucker Hillside Hospital and the University of California at Los Angeles (UCLA), at San Diego (UCSD), and at San Francisco (UCSF). Although the programs initially developed independently, they previously collaborated to combine their historical datasets and to produce a series of analyses on predictors of psychosis in one of the largest samples of longitudinally followed CHR participants worldwide (Addington et al., 2007). This led to the next phase in the NAPLS consortium, the five-year prospective study “Predictors and Mechanisms of Conversion to Psychosis” (also known as NAPLS-2). Funded by NIMH in 2008, NAPLS-2 consisted of 720 youth at clinical high risk for psychosis (CHR) and 240 healthy comparison participants (Addington et al., 2012). A great many publications have come from this study, however there were two main sets of findings to date, one focused on clinical prediction of risk for psychosis and the other, on brain and blood biomarkers. The first was the development of a calculator designed to determine the risk of developing psychosis for those who already meet criteria for CHR (Cannon et al., 2016). With respect to biomarkers, Cannon et al., (2015) demonstrated that CHR individuals who had made the transition to psychosis, had a steeper rate of gray matter (GM) loss in the right superior frontal, middle frontal and medial orbitofrontal cortical regions, as well as a greater rate of expansion of the third ventricle, compared to those CHR participants who did not develop psychosis, and to healthy control participants (Cannon et al., 2015). Furthermore, the rate of cortical thinning was correlated with levels of proinflammatory cytokines at baseline, which suggested a critical role for migroglial in perturbations of cortical maturation processes associated with the onset of psychosis (Zheutlin et al., 2017).

From these papers and other investigations, there has been substantial progress made in predicting psychosis, yet the mechanisms driving transition to psychosis remain elusive. One reason for the lack of evidence for such mechanisms may be that no studies have examined dynamic changes (e.g. repeated measures) of psychosis prediction characteristics prior to the onset of psychosis.

Our theoretical framework posited that disrupted synaptic function and neuronal connectivity are primary contributors to psychosis onset. As such, magnetic resonance based anatomical and physiologic measures would be expected to change in the period prior to full psychosis. In NAPLS-2, we confirmed an accelerated decline in prefrontal cortex (PFC) GM in CHR participants who made the transition to psychosis based on scans from pre- to post-onset (Cannon et al., In press). This accelerated decline was more pronounced among CHR cases with more recent onset of attenuated psychotic symptoms, was not accounted for by antipsychotics during the follow-up interval, and was predicted by plasma markers of inflammation (Cannon et al., In press), as well as by cortisol and mismatch negativity (MMN) at baseline. However, it is unknown if this decline occurs during the CHR period, reflecting a dynamic process amenable to preventative interventions, or how the sequence and timing of plasticity, inflammation, and hypothalamic-pituitary-adrenal axis (HPA) changes interact prior to onset. We also observed for the first time that disrupted resting-state (rs) thalamo-cortical functional connectivity prior to psychosis predicts transition and is correlated with the rate of decline in GM, but we do not know if rs-dysconnectivity is progressive during the prodrome. Thus, one of our aims in NAPLS-3 is to determine if the pre-onset trajectories of GM decline and rs-connectivity are related pathological features of emerging psychosis.

Furthermore, microglia, resident immune cells in the brain, have recently been shown to regulate synaptic plasticity in health (Schafer et al., 2013; Zhang et al., 2014) and contribute to impaired plasticity in disease (Takano et al., 2014). Dysregulated microglia could potentially represent a common pathway through which multiple contributing factors result in disruptions of brain structure (i.e., decreased synaptic density) and functional connectivity as psychosis develops (Frank et al., 2012; Frick et al., 2013; Hannestad et al., 2012; Schafer et al., 2012a; Schafer et al., 2012b; van Berckel et al., 2008; Zhan et al., 2014). Microglia are activated by peripheral blood cytokines (Perry and Teeling, 2013), and in NAPLS-2, plasma markers of pro-inflammatory cytokines at baseline predicted the rate of GM loss in those CHR who made the transition to psychosis (Cannon et al., In press). These same markers also correlated with rs-dysconnectivity. Similarly, higher levels of cortisol, (a stress hormone that also regulates microglia function (Dey et al., 2014) and lower MMN, a measure of short-term synaptic plasticity (Baldeweg and Hirsch, 2014; Baldeweg et al., 2006; Garrido et al., 2009; Schmidt et al., 2013; Stephan et al., 2006; Stephan et al., 2009; Strelnikov, 2007) predicted psychosis, and the rate of PFC GM decline, and were correlated with each other and with measures of rs-connectivity and cytokines. It is unknown whether inflammation, increased HPA activity, and deficient synaptic plasticity precede or follow the brain changes, whether these factors in fact contribute to psychosis via cascades involving microglial activation and brain dysconnectivity, or whether other factors are at play. Given the multiplicity of biological correlates of psychosis, it is important to determine how different risk-related processes covary over time and whether particular processes represent convergent pathways through which other factors influence risk. Thus, assessments must be timed to have sufficient pre-transition observation points to permit time-lagged analysis for temporal precedence and statistical tests of mediation. Finally, to determine if long term potentiation (LTP)-like synaptic plasticity is disrupted and progressive during the CHR

period, we proposed a novel visual high frequency stimulation (VHFS) event-related potential (ERP) paradigm.

Thus, NAPLS-3 has a goal of recruiting 560 CHR participants and 100 healthy controls to address these objectives. To increase the likelihood of including participants who would subsequently transition to psychosis, CHR participants would have to meet "enhanced criteria" (described in detail below).

Further, to ensure multiple assessments prior to transition, biomarker and clinical assessments would be conducted every two months within the first eight months of participation. This paper offers an overview of the methodology of the NAPLS-3 project and reports on the ascertainment and demographics of the sample.

Aims of the project

The specific aims of the project are 1) to determine the pre-onset trajectories of GM volume decline and disrupted rs functional brain connectivity in CHR individuals who develop psychosis and 2) to identify inflammatory and plasticity mechanisms associated with psychosis transition.

Hypotheses for Aim 1 are

- **a.** Centering on age at the onset of CHR symptoms, more steeply declining growth curve functions in rs thalamo-cortical connectivity and PFC GM will predict transition to psychosis.
- **b.** Modeling will reveal rs-thalamo-cortical connectivity and PFC GM are correlated indicators of latent processes that change dynamically as symptoms progress from CHR state to full psychotic intensity.

Hypothesis for Aim 2 are

- **a.** In CHR participants, abnormalities in biomarkers (peripheral inflammation, neuroinflammation, HPA activation, oxidative stress) and electroencephalography (EEG) based measures of neuroplasticity that will include an auditory roving standard MMN paradigm and a VHFS LTP plasticity paradigm will predict emergence of psychosis.
- **b.** Baseline and/or progressive abnormalities in these biomarkers and plasticity measures will predict faster rates of rs-connectivity disruption and PFC GM loss. In addition to testing direct pathways, mediated pathways will be tested to elucidate how these mechanisms influence each other during the transition to psychosis.

2. Methods

NAPLS 3 is a five-year study with recruitment for three years and follow-up assessments for two years. Clinical and biomarker assessments were conducted every two months for the first 8-months with clinical follow-up assessments occurring at 12, 18 and 24 months. If an individual made the transition to psychosis, they would receive a full clinical and biomarker

assessment at that time. This assessment would then be followed up one year later for a clinical assessment. Measures at each assessment point are presented in detail in section 2.4 below.

2.1 Ascertainment

NAPLS-3 participants are help-seeking. They are referred from health care providers, educators, or social service agencies or are self-referred in response to intensive community education efforts. These initiatives included academic detailing, grand rounds, educational talks, mailings, postings, websites and internet hits, and public service announcements. Each site has developed extensive referral sources in their area, and routinely contacts these sources personally, with mail outs and educational efforts. Potential participants first undergo a telephone screen. Those who screen positive are invited to an in-person eligibility and consent evaluation. The NAPLS-3 sample were recruited between February 2015 until November 2018. Recruitment sources are described in Figure 1 in the supplementary material.

2.2 Sample

The CHR sample all meet the Criteria of Psychosis-Risk Syndromes (COPS) which is based on the Structured Interview for Psychosis- Risk Syndromes (SIPS) (McGlashan et al., 2010). After a comprehensive assessment that included administering the Structure Clinical Interview for DSM-5 (SCID) and the SIPS version 5.6, vignettes were developed for each CHR participant for the purpose of obtaining a consensus diagnosis. The attenuated psychotic symptoms rated on the Scale of Psychosis-Risk Symptoms (SOPS) are described at length and include both recent and longstanding symptoms. The vignette is written so that another rater can review the information under each symptom category and provide a reliable rating. Once approved at the site level, the vignette is presented on a conference call for a consensus decision on the symptom ratings, as well as the diagnosis. The NAPLS-3 consensus calls, chaired by J. Addington, were held once a week and attended by members from each of the nine study sites. Submitted vignettes were individually reviewed and a consensus was reached on each symptom rating, diagnosis and ultimate admission into the study.

Cross-site reliability in the ratings of the SOPS, was conducted on a yearly basis using a new videotape each year. Ratings from all raters at all sites were compared to “gold standard” ratings on the SOPS. Intraclass correlations, over the study years, for the total SOPS scores ranged from 0.83 to 0.91 (mean= 0.88) and for the attenuated psychotic symptom score from the SOPS ranged from 0.83 to 0.94 (mean=0.89). There were minimal differences across the individual sites, and all interclass correlations were in the excellent range.

2.3. Inclusion and exclusion criteria

CHR participants had to be between 12 and 35 years old and meet diagnostic criteria for a psychosis-risk syndrome as per the COPS criteria (McGlashan et al., 2010). Exclusion criteria included (i) meeting criteria for current or lifetime Axis I psychotic disorder, including affective psychoses, (ii) IQ less than 70, (iii) history of a central nervous system disorder, or (iv) diagnostic psychosis-risk symptoms were clearly caused by an Axis 1

disorder. Other non-psychotic DSM-5 disorders were not exclusionary (e.g. substance-related disorders, major depression, anxiety disorders, personality disorders), provided the disorder did not account for the individual's psychosis-risk symptoms. The use of antipsychotics was not an exclusion, provided there was clear evidence that psychosis-risk, but not psychotic symptoms were present when the medication was started. Control participants could not meet criteria for any psychosis-risk syndrome, any current or past psychotic disorder or a Cluster A personality disorder diagnosis, not have a family history (in first degree relatives) of any psychotic disorder or any other disorder involving psychotic symptoms. Controls could not be currently using psychotropic medication.

In addition, to increase the likelihood of predicting transition to psychosis we enriched the sample of CHR participants who met CHR criteria in order to predict a 40% likelihood of transition. This was known as “enhanced criteria” and was based on the Risk Calculator designed from NAPLS 2 (Cannon et al., 2016). Enhanced criteria were that participants had to (i) rate 4 (moderately severe) or higher on either P1-unusual thought content or P2-suspiciousness, or (ii) rate 3 (moderate) on both P1 and P2, or (iii) demonstrate impaired performance on either the Hopkins Verbal Learning Test-Revised (HVLT-R) or the Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding. Impaired performance was a score on the HVLT-R or BACS symbol coding that was at or below the 10^{th} percentile base on norms for youth or for adults.

Since the main aim of this project was to determine mechanisms of transition to psychosis, participants, in addition to meeting study criteria, had to complete the imaging and blood draw components of the assessments.

2.4 Assessments

The selection of measures attempted to reflect both vulnerability-related and progressive neuromaturational processes and was limited to measures which were likely to reflect pathophysiologic changes associated with clinical and/or functional deterioration. The selected measures span multiple critical levels of analysis (e.g. genomic, hormonal, anatomical, physiological and behavioral). Such a multilevel perspective was assumed to be necessary given that the aberrant molecular and cellular processes underlying psychotic disorders were likely to reflect cascading influences across these five critical domains. Assessments were planned at baseline, 2-,4-,6- and 8-months, with additional clinical follow-up assessments at 12-, 18-, and 24-months. The schedule of all measures is presented in Table 1.

Clinical Measures: Baseline-only measures included demographics, the Cannon-Spoor Premorbid Assessment of Functioning (Cannon-Spoor et al., 1982), the Family Interview for Genetic Studies, the Peri Life Events Scale (Dohrenwend et al., 1978), the Childhood Trauma Questionnaire, the Cannabis Scale (Arseneault et al., 2002) and to assess risk of violence in youth, the Structured Assessment of Violence Risk in Youth (SAVRY) (Borum et al., 2002). The Structured Clinical Interview for DSM-5 (SCID-5) was conducted at baseline, and for those who transition to psychosis, at the time of transition and one year after. Clinical measures that are repeated at all assessments include the Structured Interview

for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2010), Scale of Psychosis-Risk Symptoms (SOPS) (McGlashan et al., 2010), the Calgary Depression Scale for Schizophrenia (Addington et al., 1993), the Alcohol and Drug Use Scale (Drake et al., 1996), Daily stress inventory (Brantley et al., 1987) and the Global Functioning social and role scales (Cornblatt et al., 2007). Detailed logs of medications, psychosocial treatments and resource utilization are updated at every assessment.

Biomarker Measures: Assessments of neurocognition, electrophysiology, cortisol, blood draws, and imaging plus an assessment of sleep (the Pittsburgh Sleep Questionnaire) (Buysse et al., 1989) and daily stress occur at baseline, 2,4,6 and 8 months, with additional blood and saliva samples taken at 12 months.

The neurocognitive battery consists of the Wechsler Abbreviated Scale for Intelligence-2 and the Wide Range Achievement Test-Four Reading subtest at baseline only, and at the other timepoints the auditory working memory continuous performance test (CPT), and from the MATRICS battery (Nuechterlein et al., 2008), the BACS symbol coding, the HVLT-R, and the Letter-number-span (LNS). Two other tasks specifically designed for the NAPLS project are included in the neurocognition battery, a map task (McLaughlin et al., 2016) and a social CPT. The social CPT is a newly designed version of the Continuous Performance Test, Identical pairs (CPT-IP) version developed by Cornblatt and colleagues (Cornblatt et al., 1989). This Social CPT-IP is a computerized version of sustained focused attention and involves monitoring a series of multiple digits, shapes, and faces. This task was added with the purpose of validating it in this sample.

The EEG-based paradigms that were collected at baseline and at the follow-up visits are focused on assessing aspects of neuroplasticity. They include a variant of a visual high frequency stimulation (VHFS) paradigm (Cavus et al., 2012; Clapp et al., 2012; Kirk et al., 2010) that induces neuroplastic changes in visual evoked potentials in manner analogous to the synaptic strengthening induced by high frequency electrical stimulation in basic neuroscience studies of long-term potentiation (LTP) (Bliss and Cooke, 2011). The second plasticity-related paradigm is a “roving standard” MMN paradigm that examines short-term plasticity in the service of predictive coding in the auditory system by focusing on the negativity elicited by deviant stimuli, the repetition positivity elicited by standard stimuli as they repeat (reflecting a memory trace effect), and their difference (MMN) (Baldeweg et al., 2006; Haenschel et al., 2005). All NAPLS-3 sites used the same BioSemi Active Two EEG acquisition system (https://www.biosemi.com/) with a 64-channel electrode montage. All EEG data are forwarded to UCSF for centralized data processing and analyses.

To assess cortisol, a minimum of three saliva samples were obtained at each of the five assessments over eight months. In order to maintain uniformity, samples were collected at hourly intervals during the morning of baseline and follow-up assessments. The samples were obtained in specimen tubes prelabeled with an ID, sample numbers, and collection time, and samples are stored at −20°C until assayed. Because diet and activity affect cortisol, participants were given instructions about food, beverage, and substance consumption, and exercise; these data were also recorded for the previous evening and morning. All sites send samples via commercial carrier on dry ice to Emory University where they are inventoried

and stored in freezers upon arrival. For the salivary cortisol assay, the Salimetrics (Salimetrics, LLC, College Park, Pa) High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit was used. This assay captures the full range of salivary cortisol levels (0.003 to 3.0μg/dL) requiring only 25 uL of saliva per test. Samples are assayed in duplicate.

Blood and urine biospecimens are collected and processed at each site according to a detailed protocol with planned analyses with plasma (for immune system biomarkers) and urine (urinary isoprostanes). Biospecimens including plasma, serum, and red blood cells are stored locally at −80°c and shipped in bulk to UNC for long-term storage at −80°c. Blood is processed at each site using Leukolock®, stored at −80°c, and sent in bulk to UCSD for long term storage at −80°c. A blood sample collected in an ACD tube is sent to UNC overnight for leukocyte isolation, with cells stored in liquid nitrogen. Blood collected in PAXgene DNA and RNA tubes is sent to RUCDR for biobanking.

Participants were evaluated with brain imaging at each of the biomarker assessment points. The protocol included high resolution T1-weighted and T2-weighted scans (both at $1mm^3$) to assess brain structure (cortical thickness, regional volumes), a standard single-shell diffusion weighted scan (b-value=1000, $2.5mm^3$, 41 directions) to assess white matter microstructure, and a standard single-band resting state BOLD scan ($3.5mm^3$, 2.5-sec TR) to assess functional connectivity. In addition, for sites operating Siemens Prisma scanners and 32-channel head coils, the protocol included a high-resolution multi-shell diffusion-weighted scan (b-values of 1000 and 2500, $2.0mm^3$, 30 directions per shell) and a high-resolution multiband rs functional scan ($2.0mm^3$, 1-sec TR). A standardized set of scan parameters was implemented across all sites/scanners. Quality assurance methods included the use of a common structural phantom scanned at each site, and a traveling human subjects' sub-study. In the traveling human subjects' sub-study, nine participants were scanned twice at each site, where visual inspection of scans for artifacts, and application of automated processing algorithms for outlier detection, slice drop-out, and other deviances were conducted.

For participants who transition to psychosis, the complete assessment is repeated at the time of transition, in addition to a one-year post-transition assessment to determine the diagnosis.

2.5 Statistical analysis of descriptive data

All analyses in this paper were performed with SPSS version 24 and SAS version 9.4. There are three groups CHR enhanced, CHR non-enhanced (described below) and controls. One-way ANOVAs were used to compare the groups or sites on continuous variables and Post-hoc Tukey tests were used to analyze the group or site pairwise comparisons. Chi-square analyses were used for categorical variables, when the Chi-square test is significant, the group or site comparisons were performed by using the SAS multiple comparison procedure that provided post-hoc Bonferroni corrected pairwise comparisons.

3. Results

3.1 Sample

The sample consists of 560 CHR participants who met enhanced criteria, and 96 healthy controls. We had an additional sample of 150 CHR participants who either did not meet

enhanced clinical criteria or who did meet the enhanced criteria but were unable to complete the imaging component due to braces or who refused the scans and/or blood draws. These participants were included in the overall project as a separate group called “non-enhanced”. They were followed at the regular 6-monthly interviews with clinical but not biomarker assessments.

3.2 Demographics

Demographics are presented in Table 2. The main differences are that both CHR groups were more likely to be living with their family and were not working full-time. The non-enhanced CHR group were significantly younger and had less years of education than both the controls and the enhanced CHR. For the enhanced CHR, across the sites, there were some age differences with participants from Yale having the youngest sample and Emory the oldest. In addition, participants out of Yale had significantly less years of education than UCLA, Emory, Harvard, UNC and UCSD. There were no gender differences. Calgary had significantly more Caucasians than Emory, UCLA and Hillside and UCSF had significantly less than Yale. These details are presented in Supplementary Table 1.

3.3. Clinical presentation

The enhanced CHR participants are a help-seeking sample and as such, present not only with subthreshold psychotic symptoms, but also a wide range of comorbidities. The majority (95%) met criteria for the attenuated positive symptom syndrome with a small proportion meeting other criterion or a combination of criteria. These CHR subtype diagnoses are presented in Table 3. In the smaller sample that we named “non-enhanced” 108 (72%) did meet the clinical enhanced criteria but for a range of reasons were unable or unwilling to complete the brain scans or the blood draws which was a necessary part of eligibility. Of the 42 (28%) non-enhanced that did not meet enhanced criteria 41 met APS criteria and one met GRD criteria.

The CHR sample met a wide range of DSM-5 diagnoses. The most common was depression, with 49% of enhanced and 44% of non-enhanced participants meeting criteria for depression. Many met criteria for different anxiety disorders. These are described in detail in Supplementary Table 3. Although the substance diagnoses for cannabis appear low (8%), these are individuals who meet DSM-5 diagnoses for cannabis misuse/abuse, whereas 23% of the CHR participants rated themselves as current cannabis users.

4 Discussion

NAPLS-3 is one of the largest cohort studies of young people at CHR for psychosis to be followed longitudinally. Not only does it study a wide range of clinical and biological factors prospectively and simultaneously in a large and well-characterized sample, but NAPLS-3 has repeated assessments in the first year following ascertainment. This paper has described the aims and methods of NAPLS-3, in addition to describing recruitment and preliminary descriptive data. Recruitment practices were similar across the sites with very few significant site differences. Yet, one of the advantages of having multiple sites is that they are diverse. Our multi-site approach affords the opportunity to examine regional and

ethnic differences in the ascertainment of CHR individuals, as well as the nature and course of psychosis-risk syndromes. Further, by having multiple sites, we can validate our measures across a range of clinical research facilities, which has important benefits for establishing the generalizability of NAPLS-3 findings.

Future reports will focus on baseline clinical and biological characteristics, longitudinal changes and eventually, predictors of transition to psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of funding source

The NIMH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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Table 1:

Schedule of Events

Assessment	Baseline	2, 4, 6 & 8 Months	12 Months	18 Months	24 Months	Transition	1 Year post transition
Demographics	X						
Family Interview for Genetic Studies	X						
Cannon Spoor Premorbid Assessment of Functioning	X						
Childhood Brain Injury	X						
Structured Assessment of Violence Risk in Youth	X						
Childhood Trauma Questionnaire	X						
SCID-5	X					X	X
Structured Interview for Psychosis-Risk Syndromes	X	X	X	X	X	X	X
Scale of Psychosis Risk Symptoms	X	X	X	X	X	X	X
Calgary Depression Scale for Schizophrenia (CDSS)	X	X	X	X	X	X	
Alcohol/Drug Use Scale (AUS/DUS)	X	X	X	X	X	X	
Global Functioning: Social and Role Scales	X	X	X	X	X	X	
Cannabis Scale	X						
The PERI Life events scale	X						
Structured assessment of violence risk in youth							
Sleep Measure (PSQI-NH)	X	X				X	
Daily Stress Inventory	X	X			X	X	
Neurocognitive Battery	X	X				X	
Blood Draw and Urine Sample	X	X	X			X	
Cortisol/Saliva Sampling	X	X	X		X	X	
Electrophysiology	X	X				X	
MRI	X	X				X	

Table 2.

Demographic Characteristics for Controls, Enhanced CHR, and Non-Enhanced CHR Participants and Controls

	Controls n=96	Enhanced CHR n=560	Non-Enhanced CHR n=150	Test Statistic
Variable		**Mean (SD)**		***F***
Age (years)	18.6(4.22)	18.4 (4.04)	17.3 (3.94)[a]	4.56*
Years of education	12.2(3.38)	11.6 (2.97)	10.8 (3.3 l)[a]	6.05**
	Number (%)			**X^2**
Sex				
Female	48 (50.0)	246 (43.9)	79 (52.7)	4.24
Male	48 (50.0)	314 (56.0)	71 (47.3)	
Race				
Caucasian	52(54.2)	339(60.8)	94(62.7)	2.28
Black	14 (14.6)	67 (12.0)	15 (10.0)	
Other minority	30(31.2)	152 (27.2)	41 (27.3)	
Marital status				
Single, never married	91 (94.8)	540 (96.4)	144 (96.0)	0.61
Other	5 (5.2)	20 (3.6)	6 (4.0)	
Current living arrangement				
Living with family	54 (56.3)	414 (74.1)[a]	113 (75.8)[a]	15.42*
Living with spouse/partner	4 (4.2)	15 (2.7)	6 (4.0)	
Living on own	11(11.5)	36 (6.4)	8 (5.4)	
Living with others[c]	27 (28.1)	94 (16.8)	22 (14.8)	
Current employment				
Working full-time	20 (20.8)	41 (7.4)[a]	11 (7.4)[a]	23.7***
Working part-time	26 (27.1)	135 (24.3)	29 (19.5)	
Worked in past year	18 (18.8)	119 (21.4)	31 (20.8)	
Not worked in past year	32 (33.3)	261 (46.9)	78 (52.3)	

*p<0.05

** p<0.01

*** p<0.001

[a] Significantly differs from controls

[b] Significantly differs from non-enhanced

[c] Includes living with friends (excluding spouse/partners), in a boarding/group home, or academic residence

Table 3.

Prodromal Diagnostic Criteria for Enhanced CHR Participants

Criteria	Enhanced CHR n=560	Percent of total enhanced sample
Attenuated Positive Symptom Syndrome (APSS)	531	94.8
Genetic Risk and Functional Decline Syndrome (GRD)	2	0.36 *
Brief Intermittent Psychosis Syndrome (BIPS)	2	0.36
APSS and GRD	24	4.3
APSS and BIPS	1	0.18

* have high ratings on P1 and P2 but symptoms are longstanding