1. Cover Page

Proposal Title: Social and Behavioral Determinants of Health and Associations with Premature Brain Maturation and Psychosis Conversion in Individuals at Clinical-High Risk for Psychosis

Amount of Funding Requested: $10,000

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2. Abstract

Social and behavioral determinants of health (SBDHs), particularly childhood trauma,[1-3] life event stress,[4,5] social isolation,[6,7] and difficult home environment[1], predict psychosis conversion. This has generated enthusiasm for SBDH-focused interventions (e.g., trauma and family-focused therapies[8]) to improve health equity and clinical outcomes.[9] Yet, a crucial piece remains unclear_**how do SBDHs "get under the skin" and influence psychosis.** Converging evidence shows that SBDHs, such as trauma and stress, can trigger biological changes leading to premature maturation, as reflected by early puberty[10-13] and biological aging.[14-18] In turn, this premature maturation is associated with future health problems.[19] Premature brain maturation (or brain aging), a common metric of biological aging, is observed in schizophrenia.[20] Moreover, premature brain maturation predicts psychosis conversion in individuals at clinical high-risk for psychosis (CHR-P).[21] **One hypothesis is that SBDHs directly influence psychosis conversion. Another possibility is that premature brain maturation mediates (at least partially) the process through which SBDHs increases risk for psychosis conversion.** No study has examined how SBDHs are associated with brain maturation in CHR-P individuals. Using an archival dataset from a large multi-site consortium of CHR-P and healthy controls (HC), this proposal aims to: 1) assess prevalence rates of SBDHs and 2) examine brain maturation as a candidate biological intermediary by which SBDHs increase conversion risk. *Findings can inform development of targeted interventions that reduce psychosis conversion risk across the socio-demographically and clinically heterogeneous CHR-P population, who are likely to be exposed to SBDHs. Such targeted interventions, which can slow down premature maturation in children exposed to adversity,[22] have the potential to advance clinical care and public policies aimed at increasing health equity in CHR-P adolescents and young adults.*

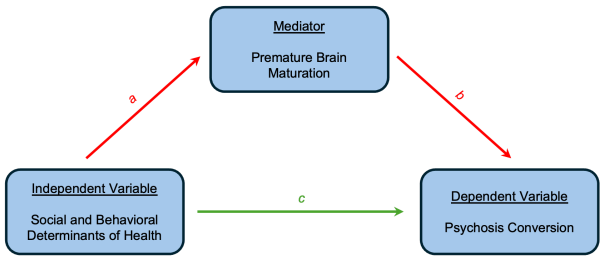
3. Narrative

Background and Aims

Global efforts have focused on prospectively identifying CHR-P individuals and developing treatments to reduce the severity of, or even prevent, emerging psychotic disorders. Meta-analyses indicate that 20-25% of CHR-P progress to full psychosis over 2-3 years,[23] a rate >400 times that of the general population.[24] **Identifying conversion risk factors and elucidating pathways through which they lead to psychosis are critical steps to reducing the incidence and morbidity of psychosis.**

SBDHs are prominent drivers of health inequity in schizophrenia.[6,8] *SBDHs, such as childhood trauma,[1-3] life event stress,[4,5] social isolation,[6] and difficult home environment[1] predict psychosis conversion.* Measures of SBDHs are cost-effective to collect and can serve as modifiable targets for clinical and health equity interventions. And yet, *understanding how SBDHs influence the risk for psychosis conversion in CHR-P individuals remains limited*. **While SBDHs may directly influence risk of psychosis conversion, intermediate processes may also mediate the influence of SBDHs on psychosis risk.** Disentangling the relationship between SBDHs and psychosis conversion risk can provide insights into pathophysiological mechanisms and drive development of novel interventions and health equity policies that allow for precise targeting of risk factors operating during the transition from CHR-P symptoms to full psychosis.

Premature brain maturation may link SBDHs with psychosis conversion. SBDHs, such as trauma and stress, can trigger premature puberty[10-13] and early aging[14-18,25] via biological changes (i.e., cortical reduction/thinning, shortened telomeres, DNA methylation changes). *Converging evidence in chronic schizophrenia[26-28] and other clinical populations[29,30] suggests that these SBDHs also lead to the brain aging faster than normal.* Structural magnetic resonance imaging (MRI) studies[31-41] report accelerated brain aging of 2.5-8 years in schizophrenia[20], resulting from synaptic overpruning[42,43] and excessive cortical reduction/ thinning.[44-47] This premature brain maturation is greatest in the first 5 years post-illness onset,[21] and is evident in CHR-P who convert to psychosis (CHR-C) but not non-converters (CHR-NC).[48,49] In sum, *SBDHs are in some way linked to psychosis conversion, **and** premature brain maturation is linked to psychosis conversion (Fig. 1 arrow 'b'). Thus, the question arises as to whether premature brain maturation mediates the relationship between SBDHs and psychosis conversion (red arrows).* Understanding links between SBDHs and premature brain maturation can set the stage for using brain maturation as a mechanistic measure of target engagement for treatments and health policies aimed at reducing risk of psychosis conversion in CHR-P. *To date, no study has examined whether and how SBDHs are associated with premature brain maturation in CHR-P (arrow 'a') or whether*



brain maturation mediates, at least partially, the relationship between SBDHs and psychosis conversion (red arrows).

A logical next step is to bridge this gap by exploring the pathways through which SBDHs contribute to psychosis conversion. Mediation analyses allow us to examine the relative magnitude of different pathways and the underlying processes by which SBDHs affect psychosis conversion, thus informing how treatments can be developed to address adverse SBDHs and increase positive SBDHs of interest. **This Nancy E. Adler Seed Grant proposal involves analyses of a comprehensive set of SBDHs and MRI brain maturation from a large, multi-site archival study[50,51] (62 HC, 42 CHR-C, 338 CHR-NC) of the CHR-P syndrome.** This study focused on high-quality SBDH metrics with strong validity and possible links to psychosis conversion.

Fig. 1. Theoretical Mediation Model

Aim 1. Characterize SBDHs in CHR-P and HC. *Hypothesis 1a:* SBDHs, particularly trauma, stress, social isolation, and difficult home environment) will be more prevalent in CHR-C vs. CHR-NC and HC.

Aim 2. Examine relationships of SBDHs with brain maturation and psychosis conversion in CHR-P. *Hypothesis 2a:* SBDHs will be directly related to psychosis conversion (Fig. 1 arrow 'c'). *Hypothesis 2b:* SBDHs (chiefly trauma, stress, social isolation, and difficult home environment) will be associated with premature brain maturation (arrow 'a'). *Hypothesis 2c*: Premature brain maturation will mediate, at least partially, the relationship between SBDHs and psychosis conversion (red arrows).

Impact: Findings can help establish the link between SBDHs and premature brain maturation as a psychosis risk biomarker. *Understanding biological intermediaries such as premature brain maturation can improve existing, and inform development of, intervention approaches resulting in more targeted clinical and health equity interventions. Brain maturation could also serve as an intermediate outcome measure in SBDH-focused treatment trials or public health policies that aim to reduce risk of psychosis conversion by normalizing premature brain maturation in CHR-P.*

Significance and Innovation

This proposal is the first in the field to examine the effect of SBDHs on brain maturation and psychosis conversion in CHR-P. As antipsychotic medications are ill-advised for CHR-P individuals due to their adverse side effects, identification of practical treatment targets (SBDHs and brain maturation) early in the disease pathway is critical. *The proposed mechanistic mediation analyses can identify biological pathways linking SBDH exposure to risk of psychosis conversion and inform targeted intervention strategies that 1) reduce SBDHs associated with conversion, 2) increase SBDHs associated with resilience, and 3) normalize brain maturation. These findings can be leveraged to improve health equity by allowing for more precise resource allocation and coordination (i.e., targeted therapy, non-antipsychotic medication, and policy change).* This aligns with recent research showing that targeted therapy can slow down premature maturation in children.[22] Further, this proposal will use archival data from a comprehensive set of SBDH questionnaires with strong validity and links to increased psychosis risk, rather than using data gathered from health records, a method that is more frequently used in this type of research but often lacks reliable data on SBDHs of interest.

Experimental Design and Methods

Population. A large sample of 380 CHR-P and 62 HC (ages 12-35) were recruited for the third wave of the multi-site North American Prodromal Longitudinal Study. Of these, 42 converted to psychosis (CHR-C), and 338 were followed-clinically without converting (CHR-NC).

CHR-P were help-seeking and self- or provider-referred. CHR-P met Criteria of Psychosis-Risk Syndromes based on the Structured Interview for Psychosis-Risk Syndromes.[52,53] Exclusion criteria included history of a psychotic disorder, central nervous system disorder, psychosis-risk symptoms better accounted for by another Axis 1 disorder, or IQ <70. HC could not have a first-degree relative with psychosis or be using psychotropics.

Procedure. Participants completed a structural MRI scan and structured interviews assessing a comprehensive set of SBDHs. Study protocols[50] were approved by Institutional Review Boards at all 9 participating consoritum sites. Participants provided appropriate informed consent or assent.

Social and Behavioral Determinants of Health. Data have been collected and need to be processed. SBDHs of interest are trauma, stress, social isolation, and home environment. As links between SBDHs and psychosis are understudied, exploratory analyses will probe relationships among this broad range of SBDHs.

Trauma. Trauma (bullying; emotional neglect; psychological, physical, and sexual abuse) and its impact at different stages of childhood and adolescence were assessed using the Childhood Trauma Scale.[50]

Life Event Stress. Stress related to life events was assessed using the Peri Life Events Scale.[54]

Social Relationships. Social-sexual aspects of life during childhood, early adolescence, late adolescence and adulthood were assessed with the Cannon-Spoor Premorbid Adjustment of Functioning.[55]

Home Environment. Family income and level of caregiver education were assessed. Factors related to the participant's home environment (residence/neighborhood type; family dynamics and arguments/violence; changes in the household's makeup) were collected with the Peri Life Events Scale.[54]

Education and Role Functioning. Participant education, role functioning (school or work) status, and stress were assessed. School performance and adaptation during childhood, early adolescence, late adolescence and adulthood were assessed with the Cannon-Spoor Premorbid Adjustment of Functioning.[55]

Medical Health. Body mass and occurrence and impact of pre-existing medical conditions were assessed.

Substance Use. Frequency and level of dependence of substance use in the past month was assessed for tobacco, alcohol, cannabis, and other drugs using the Alcohol and Drug Use Scale.[56]

MRI Processing. MRI images have undergone rigorous quality control,[51] and images that passed quality control were processed using the Human Connectome Project's Minimal Preprocessing Pipelines[57] with the open-source Quantitative Neuroimaging Environment & Toolbox (QuNex, qunex.yale.edu). Whole-brain segmentation and surface-based cortical reconstruction was done with FreeSurfer v6.0.

Brain Maturation Computation. Centile BrainAGE algorithm (https://centilebrain.org/#/brainAge2) is a machine learning model for computing brain maturation based on 40,000+ Enhancing Neuro Imaging Genetics by Meta-Analysis (ENIGMA) participants between 3-90 years old. A critical advantage is that this algorithm encompasses our younger sample age (ages 12-35). This model uses non-linear support vector regression[58,59] with radial basis function kernel to calculate predicted brain age using FreeSurfer brain metrics. Predicted biological brain age will be separately calculated by sex using ENIGMA norms. As estimated biological age is overestimated in younger individuals and underestimated in older individuals,[60-62] the Centile algorithm corrects for this bias.[63] Chronological age will then be subtracted from these bias-corrected biological brain age scores.

Data Analysis Plan

Aim 1. Characterize SBDHs in CHR-P and HC. *Hypothesis 1a:* To understand the presence and role of SBDHs, an analysis of variance (ANOVA) will examine group differences in SBDHs among HC, CHR-C, and CHR-NC groups. Post-hoc tests with Tukey correction will be used to parse a significant group difference.

Aim 2. Examine relationships of SBDHs with brain maturation and psychosis conversion. Using path analysis, we will examine direct and indirect pathways in the mediation model (Fig. 1) involving SBDHs (independent variable), brain maturation (mediator), and psychosis conversion (dependent variable). Primary SBDHs of interest are trauma, stress, social isolation, and difficult home environment. *Hypothesis 2a:* Using bootstrapping methods, examine significance of direct pathway (SBDHs→psychosis conversion). *Hypotheses 2b and 2c:* To test mediation, examine significance of indirect pathway (SBDHs→brain maturation→psychosis conversion) and path components (SBDHs→brain maturation; brain maturation→psychosis conversion).

Power analysis. As the sample size of the present study is pre-determined, power analyses identified the minimum detectable effect size at alpha set to $p<.05$ and power set to 80%. For Aim 1, we are powered to detect a medium effect size of at least $f=.15$. For Aim 2, we are powered to detect a small effect size of at least $f=.02$ for direct and indirect pathways.

Transdisciplinary Collaboration Plan

Dr. Daniel Mathalon, UCSF Professor of Psychiatry, will serve as primary mentor. He is a leading expert on characterizing brain morphometry in schizophrenia, with recent published papers on brain maturation. He specializes in CHR-P clinical care and research and is a site-PI of the archival dataset on which this proposal is centered. Dr. Nadra Lisha, UCSF Assistant Professor of Medicine in the Division of Prevention Science, will serve as consultant. She is a biostatistician with structural equation modeling (including path analysis) and prevention research expertise. Through this collaboration, I will gain expertise in incorporating SBDH methodology with neuroimaging analysis of psychosis. This collaboration can lead to future grants integrating SBDHs and mechanisms underlying psychosis, with the aim of refining and developing interventions.

Timetable of Research Activities (November 2024 – February 2026; 15 months)

	Months				
Research Activity	0-3	3-6	6-9	9-12	12-15
Processing / Analysis of Data	✓	✓	✓		

Write Manuscripts		✓	✓	✓	
Present at Conferences				✓	✓
Submit / Revise Manuscripts				✓	✓

Deliverables and Future Directions

- Findings from this pilot proposal will include conference presentations and peer-reviewed publications.
- *Findings can inform an NIH R01 targeting SBDHs associated with brain maturation and psychosis conversion, with interventions aimed at reducing SBDHs associated with increased risk of psychosis conversion, increasing SBDHs associated with resilience, and normalizing brain maturation.*
- Current study data are archival, with plans to collect longitudinal follow-up data. A future NIH R21 can examine associations between SBDHs, brain maturation, and long-term clinical outcomes in CHR-P.
- Although a wide range of SBDHs were collected, future studies could examine how other implicated SBDHs,[8] such as racism/discrimination, affect brain maturation and psychosis conversion.

4. Budget and Budget Justification

Conference Travel ($5,700): As an early career psychologist, conference attendance is critical for building research collaborations within and across different disciplines and gaining exposure to cutting-edge research and methods. The table below details the proposed conference schedule. I will attend the Society of Biological Psychiatry (SOBP; registration fee: $795) annual meeting. The SOBP annual meeting is dedicated to the study and treatment of psychiatric disorders through the elucidation of biological pathways and markers of illness processes. I will also attend the American College of Neuropsychopharmacology Meeting (ACNP; registration fee: $905). The ACNP meeting is dedicated to the study and treatment of the brain, behavior, psychotropic drugs, and their interactions. As a fellow in the Career Development Institute for Psychiatry (2-year mentorship program hosted by Stanford University and the University of Pittsburgh), this is an important conference for me to attend to meet my mentors in this program and to strengthen my existing collaborations with researchers attending this conference. Exact dates and destinations for each conference varies yearly. To cover flight and hotel costs for conferences, additional funds of $2,000 for each conference are requested.

Traveler	Conference	Purpose
Dr. Hua	SOBP	− Disseminate initial study findings − Learn about the latest MRI and SBDHs findings and methods in schizophrenia − Forge new collaborations with clinical researchers − Inspire NIH R01 ideas
Dr. Hua	ACNP	− Disseminate final study findings − Initiate new and strengthen existing collaborations with basic neuroscientists and preclinical researchers. − Inspire NIH R01 ideas

Publication Costs ($4,300): Throughout the award period, we anticipate submitting 2 papers for publication in high-impact scientific journals. Open access processing charges typically range from $1,500–$3,000.

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