Cooper Beaman

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www.linkedin.com/in/cooperbeaman

Education

Completed June 2020

University of California, San Diego — La Jolla, CA
Bachelor of Science: Molecular Biology / Cognitive Neuroscience
Major GPA: 3.86/4.00

September 2023 – Expected June 2028

University of California, Los Angeles — Los Angeles, CA
PhD in progress: Neuroscience

Relevant Coursework

- Molecular Biology
- Genetics
- Recombinant DNA Techniques
- Cell Biology
- Systems Neuroscience
- Cellular Neurophysiology
- Linear Algebra
- Calculus I and II
- Probability and Statistics
- Introduction to Python
- Data Science in Practice
- Regulation of Eukaryotic Gene Expression
- Structural and Metabolic Biochemistry
- Neurobiology Laboratory
- The Healthy and Diseased Brain
- Genetic Information for Behavior
- Current Research in Neurobehavioral Genetics
- Current Research in Neuroimaging
- Cell, Developmental, and Molecular Neurobiology

Leadership

January 2019 – January 2020

Bio-Optimization Society at UC San Diego President

- Created and led presentations on various health and bioengineering topics
- Moderated group debates and discussions
- Recruited guest speakers and coordinated presentations

UC San Diego Undergraduate Instructional Assistant

September – December 2018
March – June 2020

Biology Department, *Genetics*
Cognitive Science Department, *Genes, Brains, and Behavior*

Experience

January 2019 – January 2021

UC San Diego Bioengineering Department — La Jolla, CA
rTMS Neuroscience Consultant (P.I. Dr. Milan Makale)

- Presented to UCSD Chair of Psychiatry on rTMS molecular mechanisms and cerebral organoids for biophysical modeling
- Contributed to the development of a portable rTMS device

UC San Diego Health at Moore's Cancer Center — La Jolla, CA **February 2020 – April 2021**
Research Volunteer (P.I. Dr. Shweta Joshi)

- Employed molecular assays, cell culture and genetic mouse models to study the molecular mechanisms regulating myeloid cell recruitment, activation and function in modulating the tumor microenvironment.
- Contributed to the literature review, writing, and figure creation for two academic publications

UC San Francisco Institute for Human Genetics — San Francisco, CA **May 2021 – June 2023**
Junior Specialist (P.I. Dr. Yin Shen)

- Studying the role of cis-regulatory elements in human neurodevelopment and disorder using high-throughput functional CRISPR-Cas9 screening, iPSC models, and genomic tools (ATAC-seq, RNA-seq, HYPR-seq ChIP-seq, Hi-C).
- Led several journal club presentations including an academic writing workshop, presented the results of a genome-scale CRISPR screen to collaborators, and significantly contributed to the drafting of five manuscripts.
- Conducted several functional validation projects, including the investigation of a cancer drug's mechanism with collaborators, the functional characterization of cis-regulatory psychiatric risk loci, and the luciferase reporter validation of 3' UTR variants prioritized by prime editing screen.
- Served as lab manager including ordering items for the lab, onboarding new members, overseeing safety inspections, communicating with manufacturers, troubleshooting broken equipment and resolving other unexpected issues.

Skills

1. DNA/RNA/Protein extraction
2. PCR/RT-PCR/ddPCR
3. Gel electrophoresis
4. Plasmid construction
5. Molecular cloning
6. Viral packaging and transduction
7. Viral and antibiotic titration
8. Academic writing and editing
9. scRNA-seq and bulk gDNA library preparation
10. Mammalian tissue culture (HEK 293T, Cancer, iPSCs, Induced Neurons)
11. High-throughput CRISPRi and PRIME-editing screening
12. Cell village construction and maintenance
13. Computational analysis of CRISPR screens, scRNA-seq data, and imaging genetics datasets (HPC computing, Unix, R, Python)

Publications

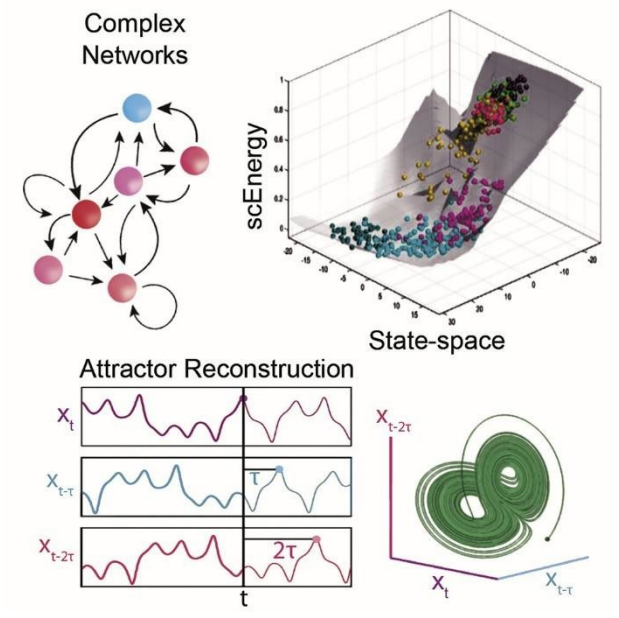
1. Cui, X., Yang, H., Cai, C., **Beaman, C.**, Yang, X., Liu, H., Ren, X., Amador, Z., Jones, I. R., Keough, K. C., Zhang, M., Fair, T., Abnousi, A., Mishra, S., Ye, Z., Hu, M., Pollen, A. A., Pollard, K. S., & Shen, Y. (2025). Comparative characterization of human accelerated regions in neurons. *Nature*. Advance online publication. https://doi.org/10.1038/s41586-025-08622-x
2. Ren, X., Yang, H., Nierenberg, J., Sun, Y., Chen, J., **Beaman, C.**, Pham, T., Nobuhara, M., Takagi, M. A., Narayan, V., Li, Y., Ziv, E., & Shen, Y. (2023). High-throughput PRIME-editing screens identify functional DNA variants in the human genome. *Molecular Cell, 83*(24), 4633–4645.e9. https://doi.org/10.1016/j.molcel.2023.11.021
3. Yang, X., Jones, I. R., Chen, P. B., Yang, H., Ren, X., Zheng, L., Li, B., Li, Y. E., Sun, Q., Wen, J., **Beaman, C.**, Cui, X., Li, Y., Wang, W., Hu, M., Ren, B., & Shen, Y. (2023). Functional characterization of gene regulatory elements and neuropsychiatric disease-associated risk loci in iPSCs and iPSC-derived neurons. *Manuscript submitted for publication to Nature*. (Original preprint: *bioRxiv*. https://doi.org/10.1101/2023.08.30.555359)
4. Rohila, D., Park, I. H., Pham, T. V., Weitz, J., Mendoza, T. H., Madheswaran, S., Ishfaq, M., **Beaman, C.**, Tapia, E., Sun, S., Patel, J., Tamayo, P., Lowy, A. M., & Joshi, S. (2023). Syk inhibition reprograms tumor-associated macrophages and overcomes gemcitabine-induced immunosuppression in pancreatic ductal adenocarcinoma. *Cancer Research, 83*(16), 2675–2689. https://doi.org/10.1158/0008-5472.CAN-22-3645
5. Ishfaq, M., Pham, T., **Beaman, C.**, Tamayo, P., Yu, A. L., & Joshi, S. (2021). BTK inhibition reverses MDSC-mediated immunosuppression and enhances response to anti-PDL1 therapy in neuroblastoma. *Cancers, 13*(4), 817. https://doi.org/10.3390/cancers13040817

Computational Projects

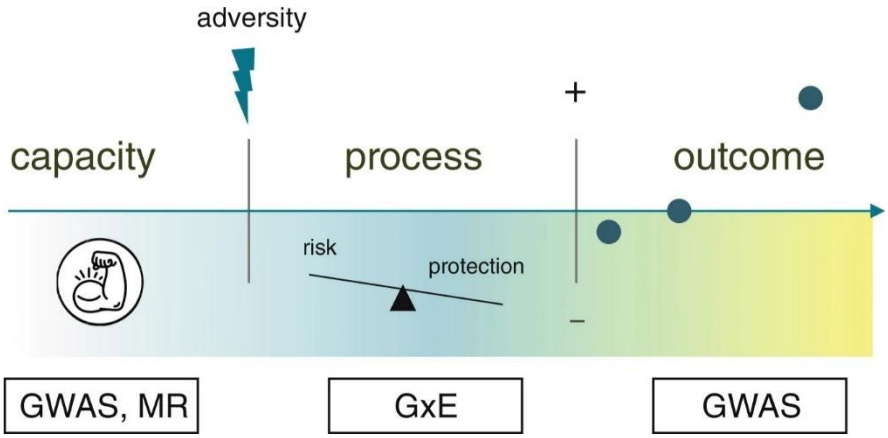
1. **Longitudinal Subcortical Structure GWAS**
   Investigated the genetic determinants of longitudinal neurodevelopmental variation across 17 subcortical structures, biological sex, and three genetic ancestry groups, using structural MRI (sMRI) and genotype data from 2,300 individuals in the Adolescent Brain Cognitive Development (ABCD) study.
   - Responsibilities: Data exploration, characterization, and preparation. GCTA MLMA GWAS analysis and meta-analysis. Post-GWAS visualization, statistical analysis, and bioinformatic exploration.
   - GitHub: https://is.gd/abcd_longitudinal_subcort_gwas
2. **Biological Aging in Bipolar Disorder**
   Analyzed biological aging differences using GrimAge2 in the largest DNA methylation bipolar disorder cohort to date.
   - Responsibilities: Preprocessing DNA methylation data, implementation of epigenetic aging algorithms, visualization and statistical analysis.
   - GitHub: https://is.gd/BP_DNAm
3. **NAPLS Genomic Data Processing Pipeline (ENIGMA-DTI QC)**
   Developed a comprehensive pre-imputation QC pipeline for NAPLS3 genomic data aligned with ENIGMA-DTI specifications, standardizing variant identifiers and ensuring robust data quality to ensure optimal imputation outcomes.
   - Responsibilities: Designed and implemented multi-stage unix shell scripts on the Hoffman2 cluster to generate dbSNP binary files, automate SNP renaming via rsid_tools, conduct duplicate/relatedness checks, and remove ancestry outliers through MDS and analysis; produced detailed QC reports to facilitate downstream analysis.
   - GitHub: https://is.gd/napls_gprep
4. **Disentangling Trauma and Genetic Predisposition in NAPLS**
   Developed an advanced analytical framework to isolate disorder-specific polygenic risk scores by disentangling the shared genetic “p factor” from unique liabilities in individuals exposed to trauma within the NAPLS cohort.
   - Responsibilities: Integrated genomic structural equation modeling (gSEM) and GWAS-by-Subtraction methods to partition shared versus disorder-specific risks for schizophrenia, bipolar disorder, and major depressive disorder; performed rigorous data quality control, statistical analysis, and workflow automation via Unix shell scripting and R.
   - GitHub: https://is.gd/napls_gsem

Research Ideas Topics and Questions Brainstorm

- Most recent version of the DSM was released years ago. Urgently in need of refined nosologies reflecting recent advancements in our understanding of neurodevelopmental psychiatric etiologies and mounting demand/possibility for precision psychiatry and targeted treatments.
    - genetics/epigenetics/relevant neurodevelopmental processes and time points/neural circuits/signaling pathways etc
- cross-disorder/transdiagnostic/pleiotropic, epistatic, convergent, locus heterogeneous, polygenic vs rare and de novo variant differences and commonalities between disorders (subtypes)
    - underlying impacted neurocognitive domains/processes/circuits that everyone including those with no known pathology possess, optimized and pruned over years of evolution and development on a spectrum of aberrant to normal to heightened functioning
- understanding and building a framework of genetic/cellular pathways facilitating the critical human neurodevelopmental processes most vulnerable to genetic, epigenetic and environmental insult to predict isolated and synergistic phenotypic impact of variants including novel de novo mutations
    - complementary genetic mechanisms of psychiatric resilience
- Why do some with high genetic load for psych disorder never go on to exhibit strong or any symptoms of the disorder? Homeostatic regulators, dynamical systems, attractors and compensatory/adaptive resiliency-promoting molecular genetic/epigenetic neurobiological/developmental mechanisms/programs counterbalancing high GxE load toward aberrant neurodevelopment (e.g. factors governing psychosis age of onset).
    - https://doi.org/10.1016/j.patter.2021.100226



    - https://doi.org/10.1038/s41380-019-0457-6



- potential female protective and/or male exacerbating/potentiating mechanisms resulting in resiliency differences, overrepresentation of males with ASD and earlier male SCZ/BP onset

- can we beneficially alter the course of aberrant neurodevelopment. What options remain after neurodevelopment has "completed"?
  - Limits of neuroplastic remodeling in adulthood
- role of neurodiversity, how to maintain while eliminating undesired debilitating symptoms of neurodevelopmental disorders.
- discuss opening of that lit review you did before
- yes different drugs work better for different disorders, but what do they share in common on a cellular and neural circuit level. Understood through cell type specific single cell genomics
- cross-disorder gwas mpra?
- understanding the genetic variation engendering higher order cognitive subprocesses and the circuits/systems (tom, emotional processing, social cognition disrupted by scz/bp, adhd and asd) underlying them on a neurodevelopmental and cellular level through the study of their dysfunction in neurodevelopmental psychiatric disorders
- diagnostic reliability and validity must first be established but can't be with symptomatically-defined diagnostic criteria
- Company measuring many parameters in each cerebral organoids/assembloids (e.g. staining interactions, lengths, quantities, synapses, protein/receptor presence, branching etc) to identify areas of maximum difference between typically-developing-control-derived organoid and crispr-modified or patient-derived organoids
- measuring pleiotropic quantifiable phenotypic effects of psych disorder risk genes as rapid diagnostic biomarkers for psch disorder risk.
- must first understand neurobiological substrate/mechanism/cytoarchitecture/network dynamics/subprocessing of emotional+social+executive functioning to understand how they become disrupted in atypical neurodevelopment [i.e. how these processes work in healthy ppl to understand how they don't in individuals with psych disorders]
  - or alternatively reverse engineering approach studying/comparing dysfunctional/deficit phenotypes to typical function in order to understand/force understanding biological/molecular/neurodevelopmental basis of underlying healthy neurocognitive functioning
  - [a] neurobiological+molecular comparative psychiatry←→[b] understanding of higher order neurocognitive functioning

- is this circular? need a to understand b, but can't understand a without understanding b.
- to do comparative psychiatry, need symptomatically subgrouped individuals to compare against healthy controls and need definitions of disorders/dysfunction.
- collections of symptoms are one way to define health vs disorder
- but not the only way, can also define by biological/genetic differences
- who would you be comparing to who though if you can't use symptoms to define?
- maybe it's ok to use symptoms to group ppl initially as a rough framework and then subgrouping/clustering within by comparing whole genomes to each other and then to general population.
- in doing so, with increasingly defined biological and genetic characterization, would eventually establish symptom-independent taxonomy of each disorder and subgroups
- what's wrong with using symptoms to classify initially?
- i guess if we knew how each neurocognitive domain [complex attention, executive function, learning and memory, language, perceptual–motor function, and social cognition] worked isolated just in typically developing individuals, then we could survey and classify entire population/sample size for variation and extreme deviation in the biomarkers/architecture/etiology of these traits and define disorders this way without ever having to consider symptoms (this would be a theoretically symptom-free taxonomy/diagnostic approach)
- how could you understand basis of neurocognitive domain without the reverse engineering comparative approach using symptoms to define disordered groups to compare with healthy control group?
- could perform normal basic research in typical individuals and then perturb different circuits with optogenetics/genetic lesions until deficits appear. but this approach is way less efficient
- best is comparative/reverse engineering approach still using symptomatic classification of disorder groups, although imperfect because patient group is very heterogeneous especially for asd so effect sizes will be small
- how would you subcluster the patient/disorder group?
    - maybe with wgs or neuroimaging or other quantitative subclustering
    - and then comparing these maximum similarity subgroups with maximum dissimilar and asymptomatic control groups could reveal exactly the highest effect genetic neurodevelopmental differences causing each dysfunction and revealing the critical structures necessary and sufficient for higher-order neurocognitive processes
- what if we could establish necessary and sufficient biomarkers for psychiatric symptoms and then redefine them based on these (and combinations of)/use them to define neurocognitive domains and underlying biology enabling them
- instability of diagnosis too, symptoms aren't consistent and recede/intensify depending on environmental interactions

RESEARCH STATEMENT:

1. Maybe open with an Ethical or other research question regarding psychiatric/behavioral genomics/neuroscience cis-regulatory functional genomics
2. talk about independent projects and how methods were used to answer questions and why questions were asked

3. definitely discuss how independent projects connect to graduate level research (i.e. CRISPR screens, seq techniques, cis-regulatory genomics and fine-mapping because most psychiatric GWAS variants are in regulatory, intergenic or non-protein-coding regions, missing heritability twin studies vs polygenetic risk scores epigenetics gene-environment interactions)
4. organoid and other biological systems, combinatorial prime editing of most common causal cis-regulatory SNPs for neurodev disorders
5. mpra/seq/saturation mutagenesis enhancer function screening methods to study non-coding/cis-regulatory variants?
6. doesn't make sense to use large ASD cohort since so genetically heterogeneous? maybe another way to group cohort based on WGS genetic interpatient similarity and maximum extrapatient dissimilarity to increase statistical power and identify ASD subtypes. GWAS analysis could then be rerun to detect subtype variants and interactions between variants
7. how deterministic are psych/behav gwas variants? penetrance? homeostatic regulation during neurodevelopment and protective antagonistic variants? gene vs environment/epigenetics as regulating liability factors
8. functional genomic pleiotropic convergence at the prefrontal cortex metabotropic glutamatergic synapse (hypofunction) shared across psychiatric disorders and behaviorally in the general population (higher order cognitive processes including social cognition memory executive functioning emotional regulation theory of mind)
9. how do variants interact with each other and the environment at different levels of complexity from gene regulation to gross anatomy and neurophenotypes beyond simple PPI and gene expression correlations (full role of proteins in concert during neurodevelopment)
10. underlying circuit/pathway/neurodevelopmental process multiple genes/disruptions/environments converge on to increase risk for psychiatric disorders
11. intra- and inter- disorder (asd, scz, bp, mdd, add) biological and genetic/epigenetic/cis-regulatory convergence
12. genetic components/molecular mechanisms contributing to spectrum of non-syndromatic human behavioral diversity
13. hiPSC FINE MAPPING and functional characterization of cis regulatory variants associated with neurodevelopmental psychiatric liability
14. assortative mating/modern selective pressure for/against certain behavior/psychiatric phenotypes/traits/dimensions
15. how are enhancers established and linked to specific genes? how did they evolve? why are they in specific locations? what characteristics link specific enhancers to specific promoters? Motifs are important b/c specific to certain TFs but how did those motifs localize/evolve to their current locations relative to their promoters?
16. genetic influence increasing susceptibility/vulnerability to environmental lesions resulting in increased liability for psychiatric disorders
17. relationship between linguistic ability and intelligence/ higher order neurocognitive domains. Language ability limits imagination/creativity in some ways. role of language in the regulation of cognition

BACKUP IF ALL REJECT:
apply for Regal Therapeutics and other gene therapy company's research associate positions

2023_GRAD_APP_BRAINSTORM

NICK BASIC SOP/PERSONAL STATEMENT STRUCTURE:

¶1: TALK ABOUT THE ISSUE IN PSYCH GEN AND CROSS-DISORDER DSM (PSYCH DISORDERS as a lens TO STUDY BEHAV GENETICS IN GENERAL POPULATION) ALSO ETHICS OF INTERVENTION AND VALUE OF NEURODIVERSITY

HiTOP+RDoC etc attempts to establish biologically based underlying abnormality driven nosologies independent of symptoms etiology-first nosology

¶2: THEN TALK ABOUT HISTORY BRIEFLY TALK ABOUT INTERVIEW AT UCSF. LEARNING TO TRUST MYSELF AND MY INSTINCTS. LESSON OF TIME OUTSIDE LAB TO RESEARCH AND THINK DEEPLY TO FIND ANY HOLES IN PLAN BEFORE ACTING

¶3: THEN TALK ABOUT WHY UCSF [OR X PROGRAM] SPECIFIC LABS QUESTIONS PROJECTS ETC AND HOW IT WOULD TIE BACK INTO CONTRIBUTING TO UNDERSTANDING OF ISSUE IN PARAGRAPH 1

Qs:

WHY NEUROSCIENCE INSTEAD OF BMS OR GENETICS?

WHY PhD?

WHAT NEXT/AFTER DEGREE?

JUSTIFY WHY THAT SCHOOL LOCATION INCLUDED (AND WHY NOT ALTERNATIVES)

ADDRESS EACH WEAKNESS ONE BY ONE FROM FIRST TIME IN MIDDLE 1-2 PARAGRAPHS TELLING STORY/HISTORY

NEED TO SELECT A SCHOOL AND NOT ADMIT WANTING TO GO TO INDUSTRY AFTER TO FACULTY IN SOP AND IN PERSON

DEMONSTRATE MATURITY AND DON'T MAKE BEGINNER/FIRST TIME MISTAKES

VERY SPECIFIC ABOUT INTERESTS AND MOTIVATION

TALK ABOUT IMMUNOLOGY ONLY LAB AVAILABLE AT THE TIME, APPLIED TO NEURO LABS BUT IT WAS ONLY ONE THAT WOULD TAKE ME AS VOLUNTEER AS FIRST LAB (WILLING TO TRAIN WITH ZERO EXPERIENCE)

TALK ABOUT HOW YOU OVERCAME CHALLENGES

DEMONSTRATING OWNERSHIP AND UNIQUE THINKING/CREATIVITY YOU BROUGHT TO EACH PROJECT

APPLY NSF FELLOWSHIP BEFORE AND AFTER

Traits:

curiosity, creativity, tenacity/persistence. enjoy ***scientific writing***, reading, communication in lay-mans terms, fastidious and systematic taking an ***engineering approach*** to investigating molecular biology/neuroscience questions. Definitely an empiricist but mindful of the chaos inherent to molecular systems as complex as the human brain

META/STRATEGY:

1. Email labs ahead of time at all schools
2. Apply to higher acceptance rate prograns other than Neuroscience as long as you can work with same faculty (i e. UCSF: [Biochemistry and Molecular Biology (Tetrad), Biomedical Sciences, Cell Biology

(Tetrad), Developmental and Stem Cell Biology, Genetics (Tetrad), Pharmaceutical Sciences and Pharmacogenomics]
3. Apply to other better schools (UCSD Sebat UCLA Geschwind Harvard Smoller MIT?)
4. Apply to other worse schools (UCSC, UCD, UCB)
5. Improve your computational genomics knowledge and experience!
6. need more independent research and experimental design planning experience
7. need more genomic seq experience
8. need to improve efficiency consistency and time management
9. need to study/learn/remember the fundamentals of Shen's lab and specific interests (basic terms and methods papers)
10. need to understand the purpose of each step in protocols and how protocols work together to achieve broad goals and to understand which parameters can be tweaked and how to optimize/achieve specific results
11. need to read more publications and practice writing/speaking/presenting more

STATEMENT of PURPOSE:
1. Growing up and seeing mental health pandemic among the homeless population in San Francisco
2. interest in overlap between disorders rather than differences as well as behavioral genetics and role of genetics in spectrum of human cognitive trait variation
3. link to Lebanese background
4. Talk about transition from Joshi to Shen
5. Story/Journey from undergrad to postgrad to applying to shen to reapplying
6. Talk about how each connects to interests and goals for graduate school
7. can not think of a better university to pursue my PhD at. UCSF Neuroscience is literally perfect for several reasons
8. I THOUGHT i was ready first time I applied but was barely there (i.e. self-roast) (list all reasons you weren't and how you've addressed them in Shen's lab) (e.g. lack if data science/bioinformatics, lack of troubleshooting (multi lib prep 4x for a week until correct just as I would in grad school), lack of independent research experience, lack of genomic/neuroscience experience, now have all levels of lab exp including bioinformatics, genomic bench skills, tissue culture and animal skills)
9. learned independence self sufficiency and self reliance comfort with uncertainty

Research ideas/topics/questions:
- Most recent version of the DSM was released years ago. Urgently in need of refined nosologies reflecting recent advancements in our understanding of neurodevelopmental psychiatric etiologies and mounting demand/possibility for precision psychiatry and targeted treatments.
    - genetics/epigenetics/relevant neurodevelopmental processes and time points/neural circuits/signaling pathways etc
- cross-disorder/transdiagnostic/pleiotropic, epistatic, convergent, locus heterogeneous, polygenic vs rare and de novo variant differences and commonalities between disorders (subtypes)
    - underlying impacted neurocognitive domains/processes/circuits that everyone including those with no known pathology possess, optimized and pruned over years of evolution and development on a spectrum of aberrant to normal to heightened functioning

- understanding and building a framework of genetic/cellular pathways facilitating the critical human neurodevelopmental processes most vulnerable to genetic, epigenetic and environmental insult to predict isolated and synergistic phenotypic impact of variants including novel de novo mutations
    - complementary genetic mechanisms of psychiatric resilience
- Why do some with high genetic load for psych disorder never go on to exhibit strong or any symptoms of the disorder? Homeostatic regulators, dynamical systems, attractors and compensatory/adaptive resiliency-promoting molecular genetic neurobiological/developmental mechanisms/programs counterbalancing high GxE load toward aberrant neurodevelopment (e.g. factors governing psychosis age of onset).
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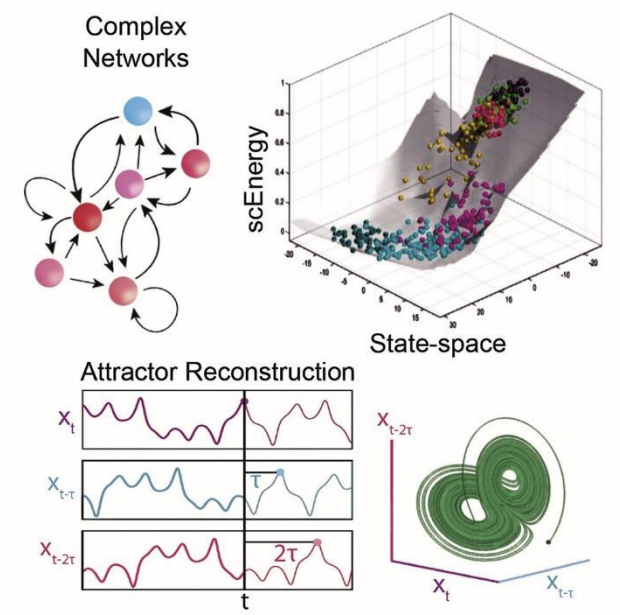

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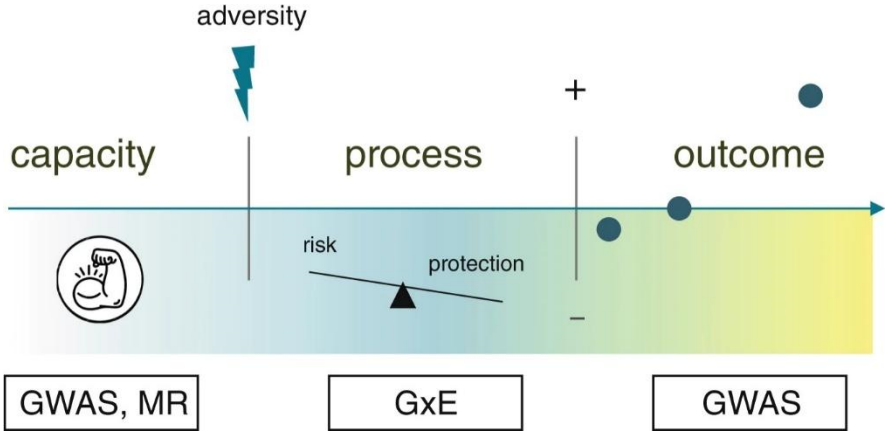

    - potential female protective and/or male exacerbating/potentiating mechanisms resulting in resiliency differences, overrepresentation of males with ASD and earlier male SCZ/BP onset
- can we beneficially alter the course of aberrant neurodevelopment. What options remain after neurodevelopment has “completed”?
    - Limits of neuroplastic remodeling in adulthood

- role of neurodiversity, how to maintain while eliminating undesired debilitating symptoms of neurodevelopmental disorders.
- discuss opening of that lit review you did before
- yes different drugs work better for different disorders, but what do they share in common on a cellular and neural circuit level. Understood through cell type specific single cell genomics
- cross-disorder gwas mpra?
- understanding the genetic variation engendering higher order cognitive subprocesses and the circuits/systems (tom, emotional processing, social cognition disrupted by scz/bp, adhd and asd) underlying them on a neurodevelopmental and cellular level through the study of their dysfunction in neurodevelopmental psychiatric disorders
- diagnostic reliability and validity must first be established but can't be with symptomatically-defined diagnostic criteria
- Company measuring many parameters in each cerebral organoids/assembloids (e.g. staining interactions lengths quantities synapses protein/receptor presencs, branching etc) to identify areas of maximum difference between wt/reference organoid and modified organoids
- MEASURING PLEIOTROPIC QUANTIFIABLE PHENOTYPIC EFFECTS OF PSYCH DISORDER RISK GENES AS RAPID DIAGNOSTIC BIOMARKERS FOR PSCH DISORDER RISK.
- **MUST FIRST UNDERSTAND NEUROBIOLOGICAL SUBSTRATE/MECHANISM/CYTOARCHITECTURE/NETWORK DYNAMICS/SUBRPOCESSING OF EMOTIONAL+SOCIAL+EXECUTIVE FUNCTIONING TO UNDERSTAND HOW THEY GO AWRY IN ATYPICAL NEURODEVELOPMENT [I.E. HOW THESE PROCESSES WORK IN HEALTHY PPL TO UNDERSTAND HOW THEY DON'T IN INDIVIDUALS WITH PSYCH DISORDERS]**
    - **OR ALTERNATIVELY REVERSE ENGINEERING APPROACH STUDYING/COMPARING DYSFUNCTIONAL/DEFICIT PHENOTYPES TO TYPICAL FUNCTION IN ORDER TO UNDERSTAND/FORCE UNDERSTANDING BIOLOGICAL/MOLECULAR/NEURODEVELOPMENTAL BASIS OF UNDERLYING HEALTHY NEUROCOGNITIVE FUNCTIONING**
    - **[A] NEUROBIOLOGICAL+MOLECULAR COMPARATIVE PSYCHIATRY←→[B] UNDERSTANDING OF HIGHER ORDER NEUROCOGNITIVE FUNCTIONING**
    - **IS THIS CIRCULAR? NEED A TO UNDERSTAND B, BUT CAN'T UNDERSTAND A WITHOUT UNDERSTANDING B.**
    - **TO DO COMPARATIVE PSYCHIATRY, NEED SYMPTOMATICALLY SUBGROUPED INDIVIDUALS TO COMPARE AGAINST HEALTHY CONTROLS AND NEED DEFINITIONS OF DISORDERS/DYSFUNCTION.**
    - **COLLECTIONS OF SYMPTOMS ARE ONE WAY TO DEFINE HEALTH VS DISORDER**
    - **BUT NOT THE ONLY WAY, CAN ALSO DEFINE BY BIOLOGICAL/GENETIC DIFFERENCES**
    - **WHO WOULD YOU BE COMPARING TO WHO THOUGH IF YOU CAN'T USE SYMPTOMS TO DEFINE?**
    - **MAYBE IT'S OK TO USE SYMPTOMS TO GROUP PPL INITIALLY AS A ROUGH FRAMEWORK AND THEN SUBGROUPING/CLUSTERING WITHIN BY COMPARING WHOLE GENOMES TO EACH OTHER AND THEN TO GENERAL POPULATION.**
    - **IN DOING SO, WITH INCREASINGLY DEFINED BIOLOGICAL AND GENETIC CHARACTERIZATION, WOULD EVENTUALLY ESTABLISH SYMPTOM-INDEPENDENT TAXONOMY OF EACH DISORDER AND SUBGROUPS**

- **WHAT'S WRONG WITH USING SYMPTOMS TO CLASSIFY INITIALLY?**
- **I GUESS IF WE KNEW HOW EACH NEUROCOGNITIVE DOMAIN [complex attention, executive function, learning and memory, language, perceptual–motor function, and social cognition] WORKED ISOLATED JUST IN TYPICALLY DEVELOPING INDIVIDUALS, THEN WE COULD SURVEY AND CLASSIFY ENTIRE POPULATION/SAMPLE SIZE FOR VARIATION AND EXTREME DEVIATION IN THE BIOMARKERS/ARCHITECTURE/ETIOLOGY OF THESE TRAITS AND DEFINE DISORDERS THIS WAY WITHOUT EVER HAVING TO CONSIDER SYMPTOMS (THIS WOULD BE A THEORETICALLY SYMPTOM-FREE TAXONOMY/DIAGNOSTIC APPROACH)**
- **HOW COULD YOU UNDERSTAND BASIS OF NEUROCOGNITIVE DOMAIN WITHOUT THE REVERSE ENGINEERING COMPARATIVE APPROACH USING SYMPTOMS TO DEFINE DISORDERED GROUPS TO COMPARE WITH HEALTHY CONTROL GROUP?**
- **COULD PERFORM NORMAL BASIC RESEARCH IN TYPICAL INDIVIDUALS AND THEN PERTURB DIFFERENT CIRCUITS WITH OPTOGENETICS/GENETIC LESIONS UNTIL DEFICITS APPEAR. BUT THIS APPROACH IS WAY LESS EFFICIENT**
- **BEST IS COMPARATIVE/REVERSE ENGINEERING APPROACH STILL USING SYMPTOMATIC CLASSIFICATION OF DISORDER GROUPS, ALTHOUGH IMPERFECT BECAUSE PATIENT GROUP IS VERY HETEROGENEOUS ESPECIALLY FOR ASD SO EFFECT SIZES WILL BE SMALL**
- **HOW WOULD YOU SUBCLUSTER THE PATIENT/DISORDER GROUP?**
  - **MAYBE WITH WGS OR NEUROIMAGING OR OTHER QUANTITATIVE SUBCLUSTERING**
  - **AND THEN COMPARING THESE MAXIMUM SIMILARITY SUBGROUPS WITH MAXIMUM DISSIMILAR AND ASYMPTOMATIC CONTROL GROUPS COULD REVEAL EXACTLY THE HIGHEST EFFECT GENETIC NEURODEVELOPMENTAL DIFFERENCES CAUSING EACH DYSFUNCTION AND REVEALING THE CRITICAL STRUCTURES NECESSARY AND SUFFICIENT FOR HIGHER-ORDER NEUROCOGNITIVE PROCESSES**
- **WHAT IF WE COULD ESTABLISH NECESSARY AND SUFFICIENT BIOMARKERS FOR PSYCHIATRIC SYMPTOMS AND THEN REDEFINE THEM BASED ON THESE (AND COMBINATIONS OF)/USE THEM TO DEFINE NEUROCOGNITIVE DOMAINS AND UNDERLYING BIOLOGY ENABLING THEM**
- **INSTABILITY OF DIAGNOSIS TOO, SYMPTOMS AREN'T CONSISTENT AND RECEDE/INTENSIFY DEPENDING ON ENVIRONMENTAL INTERACTIONS**

RESEARCH STATEMENT:

1. Maybe open with an Ethical or other research question regarding psychiatric/behavioral genomics/neuroscience cis-regulatory functional genomics
2. talk about independent projects and how methods were used to answer questions and why questions were asked
3. definitely discuss how independent projects connect to graduate level research (i.e. CRISPR screens, seq techniques, cis-regulatory genomics and fine-mapping because most psychiatric GWAS variants are in regulatory, intergenic or non-protein-coding regions, missing heritability twin studies vs polygenetic risk scores epigenetics gene-environment interactions)
4. organoid and other biological systems, combinatorial prime editing of most common causal cis-regulatory SNPs for neurodev disorders
5. mpra/seq/saturation mutagenesis enhancer function screening methods to study non-coding/cis-regulatory variants?

6. doesn't make sense to use large ASD cohort since so genetically heterogeneous? maybe another way to group cohort based on WGS genetic interpatient similarity and maximum extrapatient dissimilarity to increase statistical power and identify ASD subtypes. GWAS analysis could then be rerun to detect subtype variants and interactions between variants
7. how deterministic are psych/behav gwas variants? penetrance? homeostatic regulation during neurodevelopment and protective antagonistic variants? gene vs environment/epigenetics as regulating liability factors
8. functional genomic pleiotropic convergence at the prefrontal cortex metabotropic glutamatergic synapse (hypofunction) shared across psychiatric disorders and behaviorally in the general population (higher order cognitive processes including social cognition memory executive functioning emotional regulation theory of mind)
9. how do variants interact with each other and the environment at different levels of complexity from gene regulation to gross anatomy and neurophenotypes beyond simple PPI and gene expression correlations (full role of proteins in concert during neurodevelopment)
10. underlying circuit/pathway/neurodevelopmental process multiple genes/disruptions/environments converge on to increase risk for psychiatric disorders
11. intra- and inter- disorder (asd, scz, bp, mdd, add) biological and genetic/epigenetic/cis-regulatory convergence
12. genetic components/molecular mechanisms contributing to spectrum of non-syndromatic human behavioral diversity
13. hiPSC FINE MAPPING and functional characterization of cis regulatory variants associated with neurodevelopmental psychiatric liability
14. assortative mating/modern selective pressure for/against certain behavior/psychiatric phenotypes/traits/dimensions
15. how are enhancers established and linked to specific genes? how did they evolve? why are they in specific locations? what characteristics link specific enhancers to specific promoters? Motifs are important b/c specific to certain TFs but how did those motifs localize/evolve to their current locations relative to their promoters?
16. genetic influence increasing susceptibility/vulnerability to environmental lesions resulting in increased liability for psychiatric disorders
17. relationship between linguistic ability and intelligence/ higher order neurocognitive domains. Language ability limits imagination/creativity in some ways. role of language in the regulation of cognition

BACKUP IF ALL REJECT:
apply for Regal Therapeutics and other gene therapy company's research associate positions

Prompt:

- 1500 words
- The statement of purpose is an integral part of your application for graduate admission and consideration for merit-based financial support. It is used to understand your academic interests, and to evaluate your aptitude and preparation for graduate work, as well as your fit with the proposed program of study. It is also used to assess your ability to write coherent and convincing prose.
- Please respond to the following. You do not need to answer every question; focus on the elements that you feel are most relevant to your candidacy.
    - What is your **purpose in applying for graduate study in your specified degree program? Describe your area(s) of interest, including any subfield(s) or interdisciplinary interests.**
    - **What experiences have prepared you** for advanced study or research in this degree program? What **relevant skills** have you gained from these experiences? Have your experiences led to **specific or tangible outcomes that would support your potential to contribute to this field (examples: performances, publications, presentations**, awards or recognitions)?
    - What additional information about your past experience may aid the selection committee in evaluating your preparation and aptitude for graduate study at UCLA? For example, you may wish to **describe research, employment, teaching**, service, artistic or international experiences through which you have developed skills in leadership, communication, project management, teamwork, or other areas.
    - **Why is the UCLA graduate program to which you are applying is the best place for you to pursue your academic goals?** If you are applying for a research master's or doctoral program, we encourage you to **indicate specific research interests and potential faculty mentors.**
    - What are your **plans for your career after earning this degree**?

How do convergent genes and regulatory programs mediate genetic liability across psychiatric disorders? Which structures, circuits and homeostatic processes are altered during neurodevelopment to disrupt higher order cognition broadly? And where are the boundaries between neurodiversity and disorder? Elucidating these molecular and neurobiological mechanisms will enable the integration of etiology into the existing symptom-based diagnostic framework, toward the development of a more nuanced system, capable of generating precise and personalized treatments, while prioritizing the subjective experiences and autonomy of the people it serves. As a UCLA NSIDP student, I intend to pursue psychiatric genomic research, informing a more personalized approach to psychiatry, and the development of new therapies for individuals experiencing mental disorders. To prepare myself for prospective research characterizing cross-disorder psychiatric risk loci, I have gained a strong background in functional genomics and bioinformatics.

I developed these interests and research goals throughout my personal life and undergraduate studies. Early on, I noticed a pattern in my friend's experiences seeking relief from mental distress. They typically voiced frustrations with the subjective and generic labeling of their symptoms. Many had tried several medications, which often provided inconsistent relief accompanied by undesired side effects. And finally, most had either paused or given up on psychiatric care entirely, sometimes turning to dangerous forms of self-medication instead. My friends' challenges inspired me to delve into the etiology of mental disorders, hoping to personalize psychiatric care, and enable more people to fulfill their potential, unhindered by mental distress. Later, during my freshman year, the true urgency for precision psychiatry hit home when I met my partner's brother. He was diagnosed with autism spectrum disorder (ASD) as a toddler, and continues to experience complications including non-verbal speech apraxia, chronic gastrointestinal issues, and adult epilepsy. As we interacted, his advanced speech comprehension skills and expressive non-verbal communication moved me. I wondered if early interventions or new therapies, informed by the unique genetic etiology of his symptoms, could someday enable the development of speech. Together, these experiences reaffirmed my commitment to study psychiatric genomics to facilitate the development of more precise therapeutics.

As an undergraduate at UCSD, my curiosity about the genetic basis of mental disorders developed further from my molecular biology and neuroscience coursework. Genes, Brains, and Behavior (Dr. Terry Jernigan, spring 2019) and Genetic Information for Behavior (Dr. Ralph Greenspan, winter 2020), demonstrated the interdependence of statistics, computation, and genomics, convincing me to prioritize applied research experience in these areas. These courses also strengthened my belief that genetically-informed interventions will someday encourage more equitable outcomes in education and psychiatry. My professors' compelling argument for the potential and relevance of genetics motivated me to pursue my first research experience. First, I worked with Dr. Milan Makale during my senior year to design a miniaturized rTMS (repetitive transcranial magnetic stimulation) coil with implications for clinical psychiatry. I surveyed the literature on rTMS treatment for mental disorders, and identified stimulation parameters to optimize the device's therapeutic efficacy. After completing this project, I coauthored a manuscript describing our work and its potential applications, currently under review for publication in IEEE Electromagnetics, RF, and Microwaves in Medicine and Biology. Next, after graduating I volunteered with Dr. Shweta Joshi's immuno-oncology lab, where I conducted murine experiments to investigate the immunotherapeutic potentiation of first-line chemotherapies for pancreatic and brain cancers. From this work, I coauthored two manuscripts which we submitted to MDPI Cancers.

After completing my bachelor's degree in 2020, I applied and interviewed for several neuroscience graduate programs. I did not receive an offer of admission. However, I immediately contacted several faculty, current students, and fellow applicants I had met during interviews to reflect and plan my next course of action. Their advice helped me identify three key areas of growth in preparation for graduate school. First, I had to improve my understanding and communication of the literature in my field. Second, I had yet to independently design experiments or analyze genomic data using bioinformatics. And finally, I needed more experience with genomic research methods. To

achieve these goals, I joined Dr. Yin Shen's lab at UCSF in 2021. During my time with the Shen lab, I have led several journal club presentations, presented the results of a genome-scale CRISPR knockout screen to collaborators, and drafted five manuscripts with my team. I also led two functional genomics projects and significantly contributed to several others. These include the investigation of a cancer drug's mechanism, the functional characterization of cis-regulatory psychiatric risk loci, and the luciferase reporter validation of 3' UTR variants prioritized by prime editing screen.

Most significantly, I conducted a Genome-Scale CRISPR Knock-Out screen in fluorescent reporter cells to identify drug effector proteins mediating the antitumor mechanism of bufalin. I subsequently validated the top hits via CRISPR interference. My aim was to discover the molecular mechanism of bufalin-mediated MYCN degradation, thus identifying novel drug targets for the treatment of N-Myc-dependent cancers, without the cardiotoxicity currently hampering bufalin's clinical use. I designed my positive selection screen to enrich for guide RNAs (gRNAs) promoting cell survival in the presence of bufalin, presumably through their knockdown of genes enabling its abrogation of MYCN-AURKA interaction. After extracting and sequencing gDNA from the screen, I used the Model-based Analysis of Genome-wide CRISPR/Cas9 Knockout with Web Visualization pipeline to perform a maximum likelihood estimation of each gene's essentiality, prioritizing the most enriched gRNAs, genes, and pathways likely to mediate bufalin's promotion of MYCN degradation.

To functionally validate the effect of six top ranking genes on bufalin's antitumor mechanism, I cloned CRISPRi plasmids to individually knock down their expression. During the viral packaging phase, I continued to experience low packaging efficiencies despite several months of conventional troubleshooting, significantly delaying the completion of our project. After researching the issue, I learned that plasmid size is inversely proportional to viral packaging efficiency, and developed a novel approach to reduce the size of my plasmids. Instead of attempting to reduce the size of each initial plasmid, which simultaneously delivered the CRISPR editing machinery and gRNAs, I reduced plasmid size by splitting the plasmids into two, sequentially delivering each component to my cells. First, I established a stable dCAS-KRAB-expressing variant of our reporter cells using a vector only containing sequences for virus production, CRISPRi machinery and blasticidin resistance. Then, I constructed plasmids to introduce a gRNA targeting each gene, and a puromycin resistance sequence to these modified cells. Through this approach, I finally repressed the expression of each target gene. Ultimately, following a confirmation experiment by collaborators, my work will prioritize novel protein targets for future drug development or the repurposing of current therapeutics, to achieve bufalin's broad antitumor efficacy without cardiotoxicity.

UCLA's NSIDP is ideal to advance my development as an independent researcher and neuroscience communicator, thoroughly preparing me to continue my lifelong commitment to translational psychiatric genomic research, while educating the next generation of neuroscientists as a tenured professor. I spent five years in San Diego for undergrad and my partner recently completed her master's in urban planning at UCLA, so I am very familiar with the campus and life in southern california. I also have a strong support network of family and friends in southern california to help me persevere throughout my PhD. Finally, I am excited that UCLA's interdisciplinary research environment encourages collaboration not only across fields, but also between researchers, psychiatrists and their patients. This ease of collaboration facilitates data collection from people living with mental disorders and the translation of psychiatric genomic research. Under the supervision of several UCLA PIs, including Professor Geschwind, de la Torre-Ubieta, McCracken, Ophoff or Bhaduri, I see myself pursuing a graduate project addressing an outstanding problem in neurodevelopment or psychiatric genomics. This year, the psychiatric genomics consortium published a study identifying 152 independent loci likely to operate broadly within biobehavioral dimensions, and nine loci acting heterogeneously across disorder subclusters (Grotzinger et al., 2022, Nature Genetics). My research could expand on this work to functionally characterize the neurodevelopmental consequences of the cis-regulatory variants prioritized, identifying areas of

molecular convergence within heterogeneous intradisorder populations, and across disorders with shared symptoms. These projects would employ single-cell CRISPR and regulatory genomic methods, in patient-derived hiPSC, cerebral assembloid, or modular neuronal network models, using electrophysiological, optical, cellular and genetic readouts. Ultimately, such a project would aim to generate discoveries that advance an etiology-informed diagnostic system for neurodevelopmental disorders. It would be a privilege to begin realizing this goal with the UCLA interdepartmental PhD program in neuroscience.

Prompt:

- 500 words
- Please respond to one or more of the following prompts. Your statement can be up to 500 words in length (approximately 1-page, single spaced, using 1-inch margins and 12-point font). To be considered for a Cota-Robles or Graduate Opportunity fellowship, be sure to **describe your contributions to diversity**. The University of California Diversity Statement can be found online
- Are there **educational, personal, cultural, economic, or social experiences, not described in your Statement of Purpose, that have shaped your academic journey? If so, how?** Have any of these experiences provided **unique perspectives that you would contribute to your program, field or profession**?
- Describe **challenge(s) or barriers that you have faced in your pursuit of higher education**. What motivated you to persist, and how did you overcome them? What is the evidence of your persistence, progress or success?
- How have your **life experiences and educational background informed your understanding of the barriers facing groups that are underrepresented in higher education**?
- How do you intend to **engage in scholarly discourse, research, teaching, creative efforts, and/or community engagement during your graduate program that have the potential to advance diversity and equal opportunity in higher education**?
- How do you see yourself contributing to **diversity in your profession after you earn your advanced degree at UCLA**?

Cooper Beaman UCLA Neuroscience Graduate Program Purpose Statement

My best friend's ongoing mental health challenges significantly shaped my desire to research psychiatric genetics, with the goal of informing the personalization of diagnosis and care. In high school, after several misdiagnoses, one suicide attempt, and a slew of psychiatric medications, my friend resorted to drug use and reckless behavior to numb his symptoms. By college, I thought he had stabilized with the support of his family and friends. But one night during my sophomore year, I received several frantic late-night calls from him about a bizarre scheme to quickly secure a large sum of money for his family. He was convinced they were in severe debt, and that he was a failure unless he helped by any means necessary. I did not recognize my intelligent, creative, and principled friend that night. I was so stunned by his surreal plan, that I did not take him seriously. Instead, I calmly tried to reassure him that the situation was not as dire as he felt, and that risky actions would only exacerbate things, irreversibly damaging his future. The next day, I heard about a theft on the news and was immediately overcome with dread. My friend had unfortunately committed this crime, and was so dissociated at the time that he had not concealed his identity. He was quickly recognized from surveillance footage and arrested at his home on the same day. In court, his case was eventually dismissed given his transient psychosis, and since then, he has finally found a more effective treatment plan. But unfortunately, he continues to supplement his care with dangerous self-medication. My friend's difficulties helped me understand the true prevalence of mental distress and the demand for targeted care. Given our similarity, I wondered how many people are one stressful experience away from a mental health diagnosis. Quantifying genetic liability for psychiatric disorders could help prevent their development or progression, and increase the effectiveness of care by tailoring interventions to the distinctive etiology underlying individual symptoms.

More broadly, since returning to the Bay Area after completing my undergraduate neuroscience studies in San Diego, I am starting to view my city through a different lens. I see an overwhelming number of people desperate for relief, many of whom are also experiencing homelessness, and a city in the midst of a mental health emergency. This is an ongoing challenge and was present throughout my childhood, but the magnitude and urgency of this crisis only became apparent to me after college. Now, rather than resigning to compassionate observation, I realize my future research could potentially improve psychiatric diagnosis and care in service of this community. My friend and anyone experiencing mental distress deserve to reach their full potential. I want my research at UCLA to make a meaningful impact toward the advancement of mental health equity.

Prompt:

- ≤10,000 characters (≈1,600 words or ≈3.5 pages single-spaced)
- Include the scientific context of the problem you addressed, method(s) you used and the conclusion(s) you drew from your work.
- Be concise, but do explain fully the extent of your engagement in each research project and emphasize your original contributions (e.g., scientific ideas or questions you came up with, troubleshooting you did or solutions you found when challenges arose, and experiments/analyses performed independently)
- Applicants should emphasize their contributions to and comprehension of their previous research experiences rather than simply listing techniques.
- Evidence of engagement in the research process – from hypothesis generation to troubleshooting to formulation of conclusions – is particularly important to emphasize.
- Use the research statement to describe your prior research experience, whether it was in academic labs, industry, or elsewhere.
    - Some students have worked in multiple labs, whereas others have worked solely in one - there is no single 'best' way to have prior research experience.
- In the research statement, we would like you to explain what questions you attempted to answer (even if you didn't answer them), why they are interesting and important, the goals of your specific project(s), your individual contributions to project(s), information about any publications or future authorship expectations, and anything else you think may be important about your experience.
- Detail your independent contributions to a project, in terms of both experiments and intellectual contributions. Did you present your work at conferences? Did you present in lab meetings? Write a thesis? We want to know as much as possible.

Research Statement:

During my undergrad and postbac research career, I significantly contributed to six projects, spanning transcranial magnetic stimulation, immuno-oncology and cis-regulatory functional genomics.

Seeking research experience with rTMS during my junior year, I worked with Dr. Milan Makale to develop a miniaturized repetitive transcranial magnetic stimulation (rTMS) device for psychiatric applications. Clinical rTMS systems are large and expensive, so miniaturized devices may facilitate treatment access for patients at home. As a member of the bioengineering team, I advised on elements of the device's design relevant to the underlying biology of rTMS. To provide evidence-based recommendations for the design parameters, I reviewed current literature on the molecular mechanisms of rTMS, as well as the optimal stimulation protocols for treating psychiatric disorders. I then established guidelines for the optimal frequency, magnetic field intensity and pulse duration ranges. These guidelines were implemented in the final device. Our in silico simulations and experimental measurements demonstrated the comparable performance of our portable rTMS device relative to larger rTMS coils. Overall, our prototype may inspire the development of more sophisticated portable rTMS systems to treat disorders throughout the day and in remote locations, circumventing the time and size constraints associated with current rTMS units.

Following the rTMS project, I joined Dr. Shweta Joshi's immuno-oncology lab, where I maintained a genetically modified mouse colony, assessed murine tumor growth, and surgically resected organs for two major projects. First, we demonstrated the combined efficacy of Bruton's tyrosine kinase (BTK) inhibition and anti-PD-L1 checkpoint blockade on myeloid-derived suppressor cell (MDSC)-mediated immunosuppression in neuroblastoma. And second, we assessed the combined effects of spleen tyrosine kinase (Syk) inhibition with Gemcitabine in pancreatic ductal adenocarcinoma (PDAC). Project one was inspired by past experiments that reversed MDSC immunosuppression with ibrutinib in murine breast cancer models. Thus, we hypothesized that MDSC depletion would increase immune activation and synergize well with first-line anti-PD-L1 treatment in neuroblastoma. For these experiments, I delivered neuroblastoma cells to mice, administered ibrutinib and other drugs once tumors appeared, and measured tumor growth in each treatment group over time. Overall, we showed that ibrutinib treatment attenuated MDSC immunosuppression in vivo, recapitulating liquid tumor BTK-inhibition in neuroblastoma, and supporting its potential to augment antitumor immune responses in other solid tumors. For project two, we investigated the potentiation of first-line chemotherapeutic gemcitabine by the Syk inhibitor R788 in PDAC. Previous work by our lab demonstrated that Syk inhibition activates immunostimulatory transcriptional programming in tumor-associated macrophages via NF-κB stimulation, and the suppression of tumor growth. Thus, we theorized that concurrent

administration of gemcitabine and R788, would target malignant cells via two independent mechanisms, inducing greater PDAC tumor regression than either drug alone. For this project, I surgically isolated mouse pancreases, seeded tumors, chronically administered gemcitabine and R788, and finally isolated cancerous tissues to quantify tumor weight, volume and metastasis. Through these in vivo experiments, we demonstrated the significant abrogation of macrophage-mediated immunosuppression, and a reduction in PDAC tumor volume, growth and metastasis through the synergistic combination of gemcitabine and R788.

Finally, with the Yin Shen lab at UCSF, I led two functional genomics projects and significantly contributed to a third. For the first project, I conducted a Genome-Scale CRISPR Knock-Out (GeCKO) positive selection screen in fluorescent reporter cells to identify drug effector proteins mediating the antitumor mechanism of a bufadienolide drug, and further validated the top hits via CRISPR interference. I aimed to elucidate the molecular mechanism of bufadienolide-mediated MYCN degradation, to identify novel drug targets for the treatment of N-Myc-dependent cancers, without the cardiotoxicity currently hampering bufadienolides' clinical use. Specifically, the drug bufalin was previously demonstrated to inhibit tumor growth by blocking MYCN-AURKA interaction, destabilizing n-Myc and promoting its degradation. To identify proteins potentially underlying this process, I designed a flow cytometry GeCKO positive selection screen using MYCN-AURKA interaction reporter cells. My screen enriched for sgRNAs promoting cell survival in the presence of bufalin, presumably by knocking out genes encoding the proteins most likely to subserve bufalin's abrogation of MYCN-AURKA interaction. After extracting and sequencing gDNA following the screen, I used the Model-based Analysis of Genome-wide CRISPR/Cas9 Knockout with web visualization (MAGeCK-VISPR) pipeline to perform a maximum likelihood estimation of each gene's essentiality, prioritizing the most enriched sgRNAs, genes and pathways likely to mediate bufalin's promotion of MYCN degradation. Finally, I cloned CRISPRi plasmids to functionally validate the effect of six top ranking genes on the antitumor mechanism of bufalin. During the viral packaging phase, I continued to experience low packaging efficiencies despite several months of conventional troubleshooting, so I developed a novel approach to circumvent the size limitations of my initial plasmids. After researching the issue, I learned that plasmid size is inversely proportional to viral packaging efficiency, so I split the viral packaging phase into two steps to reduce plasmid size. First, I established a stable dCAS-KRAB-expressing variant of our reporter cells using a vector only containing sequences for virus production, editing machinery and blasticidin resistance. Then, I constructed new plasmids to deliver an sgRNA targeting each gene, and a puromycin resistance sequence to the dCAS-KRAB cells. With this approach, I significantly repressed the expression of each target gene. Ultimately, the final validation of these genes by collaborators will prioritize novel protein targets for future drug development or the repurposing of current therapeutics, to achieve bufalin's broad antitumor efficacy without cardiotoxicity.

Next, I led the final validation phase of our group's project for the Encyclopedia of DNA Elements (ENCODE) consortium. The current paucity of cell-type specific, functional cis-regulatory element (CRE) annotation limits the characterization of putative psychiatric and neurodevelopmental regulatory risk variant mechanisms. We previously identified candidate CREs within one million base pairs of genes required for cell proliferation, neuronal differentiation, and fitness via a CRISPRi screen in induced pluripotent stem cells (iPSCs) and excitatory neurons. Many of these regions harbor psychiatric risk variants identified by genome-wide association studies (GWAS), including several fine-mapped schizophrenia (SCZ) single nucleotide polymorphisms (SNPs). These variants colocalize with a CTCF ChIP-seq peak, suggesting their influence on the transcriptional regulation of three nearby fitness genes. To identify regulatory target genes, I cloned and transduced CRISPRi plasmids to selectively decrease chromatin accessibility at each loci in iPSCs and excitatory neurons. Finally, after extracting gDNA from three differentiation time points, I used qPCR to determine which candidate genes were downregulated following CRISPRi of each region, thus outlining the potential consequences of the variants within. These findings will inform further investigation of the genetic etiology of schizophrenia, emphasizing cis-regulatory neurodevelopmental disruptions.

Most recently, I functionally validated CASP8 3'UTR variants identified by our lab's CRISPR prime editing survival screen. Imprecision and variable editing efficiencies across cell types limit the ability of traditional CRISPR screening methods to determine the functional impact of SNPs. Prime editing addresses both limitations and enables the massively parallel functional screening of coding and non-coding variation at base-pair resolution. Our prime editing screen assessed the impact of 1,300 non-coding breast cancer variants, and identified ten within the CASP8 3' UTR that significantly decreased cell survival via CASP8 upregulation. To quantify their impact on CASP8

expression, I designed luciferase reporter plasmids containing each variant. Surprisingly, our first assay demonstrated CASP8 upregulation by only one variant. To verify this finding, I cloned 18 new plasmids, each containing a polyA sequence downstream of the 3' UTR, including three to assess for synergistic effects of multiple variants. The second reporter assay reproduced our initial finding, only demonstrating significant CASP8 upregulation by plasmids containing the significant variant from the first assay. Further clinical research assessing the 3'UTR variant we identified may inspire the development of novel caspase-8-dependent chemotherapies. Overall, our study demonstrates the utility of prime editing screens for characterizing variant impact at nucleotide resolution, potentially transforming the functional analysis of genome function, disease risk prediction, diagnosis and therapeutic target identification.

Each of these projects has progressively developed my scientific reasoning and communication skills, as well as my confidence to independently design, troubleshoot and analyze experiments, ultimately reaffirming my enthusiasm and lifelong commitment to human genomic research. At UCSF, I am eager to begin the next phase of my neuroscience training, culminating in the completion of a novel psychiatric genomics dissertation.

Character Count: 9980/10000

Research Experience & Research Summary:

Name	Institution	Location	Title	Hours per Week	Date
Milan Makale	University of California, San Diego Health at Moores Cancer Center	San Diego, California	Design and Validation of Miniaturized Repetitive Transcranial Magnetic Stimulation (rTMS) Head Coils	5	1/15/2019 - 1/1/2021 (102, 3.2)
Shweta Joshi	University of California, San Diego Health at Moores Cancer Center	San Diego, California	BTK Inhibition Reverses MDSC-Mediated Immunosuppression and Enhances Response to Anti-PDL1 Therapy in Neuroblastoma	20	2/1/2020 - 1/1/2021
Shweta Joshi	University of California, San Diego Health at Moores Cancer Center	San Diego, California	Syk inhibition reprograms tumor-associated macrophages and overcomes Gemcitabine-induced immunosuppression in pancreatic ductal adenocarcinoma	20	11/1/2020 - 4/30/2021 (65, 8)
Yin Shen	University of California, San Francisco Health at Institute for Human Genetics	San Francisco, California	CRISPRi based positive selection FACS screen identifying candidate effector proteins required for bufalin-mediated inhibition of MYCN-AURKA interaction and antitumor activity	40	5/15/2021 - 9/20/2022
Yin Shen	University of California, San Francisco Health at Institute for Human Genetics	San Francisco, California	Functional characterization of gene regulatory elements and neuropsychiatric disease-associated risk loci in iPSCs and iPSC-derived neurons	40	5/15/2022 - 9/15/2022
Yin Shen	University of California, San Francisco Health at Institute for Human Genetics	San Francisco, California	High throughput prime editing screens identify functional DNA variants in the human genome - functional validation of CASP8 3'UTR variants	45	9/15/2022 - 11/15/2022 (137, 18)

Total number of months of prior, full-time research experience (hours per week x number of weeks/160): ~30 months (2.5 years)

Experiences:

Dr. Milan Makale

Portable rTMS bioengineering project

1/1/2019 -

1. Limited involvement in the portable LI-rTMS engineering project
    - ABSTRACT: Repetitive transcranial magnetic stimulation (rTMS) is a rapidly developing therapeutic modality for the safe and effective treatment of neuropsychiatric disorders. However, clinical rTMS systems are large, heavy, and expensive, so miniaturized, affordable rTMS devices may facilitate treatment access for patients at home, in underserved areas, in field and mobile hospitals, on ships, and in space. Condensed rTMS electronics and miniaturized head coils may eventually make possible ambulatory treatment via closed loop integration with scaled down electroencephalogram (EEG) acquisition arrays. Here we pursued a miniaturized rTMS device and compared the resultant B- and E-fields with those generated by a full scale clinical rTMS system. Theoretical considerations and computer simulations defined salient coil parameters, which together with treatment requirements guided the design of the driving circuit. We fabricated a compact system that included a 25 x 22 cm intermediate stage stimulator circuit, capacitor, and rechargeable battery, and several figure-8 coils that weighed only between 8 and 26 gm, and were 50 to 150 mm in length. Induced E- and B-fields were predicted via computer simulations and then validated in bench-top experiments. The maximum E-field value that we measured, 65 V/m at a distance of 1.5cm from the bottom of the coil, is within the E-field intensity range, 60-120 V/m, generally held to be therapeutically relevant. The presented parameters and results delineate coil and circuit parameters for a miniaturized rTMS system able to generate pulsed E-fields of sufficient amplitude for potential clinical use.
    - Take-Home Messages
        - A prototype miniaturized repetitive transcranial magnetic stimulation (rTMS) device capable of generating therapeutically relevant magnetic and electric fields is reported.
        - Magnetic fields of therapeutic intensity (>100mT) are generated using a 76 mm head coil weighing only 12.6 grams, as opposed to the standard 2-4 Kg.

        - Measured electric fields at 1.5 cm from the coil bottom reach >65 V/m, which is in the therapeutic range of 60-120 V/m typically induced by full-scale commercial rTMS systems.
        - rTMS pulses are generated with a prototype electronics board with dimensions 25cm x 22cm which uses a maximum voltage of 300V, and can be battery-powered, which facilitates safe deployment of portable systems.
        - A miniaturized rTMS system holds the promise of advancing treatment beyond the confines of a large medical facility, and may ultimately form the core of a wearable ambulatory device to offer greater dimensionality to the rTMS based management of a range of neuropsychiatric and addictive disorders, including depression, anxiety, obsessive compulsive disorder, substance addictions, brain injuries, and dysregulated sleep cycles.
    - My part of the upcoming presentation/demo
    - Formatting of the manuscript
    - General rTMS neurobiology advice

Dr. Shweta Joshi

Immunotherapies Targeting Macrophages in the Tumor Microenvironment

2/1/2020 -

2. Ibrutinib paper and experiments
    - Mouse treatment with drugs and drug preparation
    - Advanced mouse techniques/surgery, tissue culture, learning assays etc.
    - Summary: Neuroblastoma (NB) is the most common pediatric malignancy, and patients with the high-risk disease show a worse prognosis despite advanced treatments, including immunotherapy. Myeloid-derived suppressor cells (MDSC) frequently accumulate in NB tumors, where they induce immunosuppression and hamper efficient antitumor immune responses. In the current study, we observed that Bruton's tyrosine kinase (BTK) is highly expressed in both monocytic and granulocytic MDSCs isolated from spleens of mice bearing NB tumors and administration of BTK inhibitor ibrutinib reduced MDSC-mediated immunosuppression, tumor growth, and enhanced anti-PDL1 checkpoint inhibitor therapy in mice bearing NB tumors. These studies demonstrated that ibrutinib could serve as a promising therapeutic agent to control MDSC-mediated immune suppression in NB.
    - ABSTRACT: MDSCs are immune cells of myeloid lineage that play a key role in promoting tumor growth. The expansion of MDSCs in tumor-bearing hosts reduces the efficacy of checkpoint inhibitors and CAR-T therapies, and hence strategies that deplete or block the recruitment of MDSCs have shown benefit in improving responses to immunotherapy in various cancers, including NB. Ibrutinib, an irreversible molecular inhibitor of BTK, has been widely studied in B cell malignancies, and recently, this drug is repurposed for the treatment of solid tumors. Herein we report that BTK is highly expressed in both granulocytic and monocytic murine MDSCs isolated from mice bearing NB tumors, and its increased expression correlates with a poor relapse-free survival probability of NB patients. Moreover, in vitro treatment of murine MDSCs with ibrutinib altered NO production, decreased mRNA expression of Ido, Arg, Tgfβ, and displayed defects in T-cell suppression. Consistent with these findings, in vivo inhibition of BTK with ibrutinib resulted in reduced MDSC-mediated immune suppression, increased CD8+ T cell infiltration, decreased tumor growth, and improved response to anti-PDL1 checkpoint inhibitor therapy in a murine model of NB. These results demonstrate that ibrutinib modulates immunosuppressive functions of MDSC and can be used either alone or in combination with immunotherapy for augmenting antitumor immune responses in NB.
    - TROUBLESHOOTING: oral gavage, esophageal damage, mice deaths
3. Syk PDAC work and paper (R788)
    - The aim of this experiment was to follow up on our prior PDAC experiments emphasizing the comparative assessment of Gemcitabine's (masked chain termination) efficacy alone and synergistically in combination with R788/Fostamatinib (SYK inhibition) in the treatment of murine pancreatic cancer. Our outcome measurements for this experiment remain the same as our

prior PDAC experiments [i.e. tumor weight and number of metastatic nodules (in livers, intestines, and spleens)]. This follow-up experiment will include three groups; three vehicle controls, four Gemcitabine + R788 mice and four Gemcitabine only mice.

- ABSTRACT: Pancreatic ductal adenocarcinoma (PDAC) is an insidious disease with a low five-year survival rate. PDAC is characterized by an abundant infiltration of tumor-associated macrophages (TAMs) that promote immune tolerance and immunotherapeutic resistance. Here we report that macrophage spleen tyrosine kinase (Syk) promotes PDAC growth and metastasis. Using orthotopic PDAC mouse models, we showed that genetic deletion of myeloid Syk or pharmacological inhibition of Syk with an FDA-approved inhibitor R788 (fostamatinib) reprogrammed macrophages into immunostimulatory phenotype, increased cytotoxicity of CD8+ T cells, and repressed PDAC growth and metastasis. Furthermore, we found that Gemcitabine (Gem) treatment induces an immunosuppressive microenvironment in PDAC by promoting pro-tumorigenic polarization of macrophages. In contrast, we demonstrated that R788 “reeducates” pro-tumorigenic macrophages towards an immunostimulatory phenotype and boosted CD8+ T cell responses in Gem-treated PDAC, using orthotopic mouse models and an ex vivo human pancreatic slice culture model. These findings illustrate the importance of Syk inhibitor, R788, in enhancing the anti-tumor immune responses in Gem-resistant PDAC and support the clinical evaluation of R788 either alone or together with Gem as a potential treatment strategy for PDAC.

Dr. Yin Shen

Role of cis-regulatory elements in human neurodevelopment and disorder
5/15/2021 - 6/15/2023

1. Bufalin/Cinobufotalin CRISPR KO whole genome Screen GeCKO/FACS validation to identify mechanisms/pathways/novel regulators of MYCN-AURKA interaction
    - Depletion score MAGECK
    - Cloned plasmids, packaged viruses, grew and infected cells
    - TROUBLESHOOTING: Library preparation woes.
        - Multiple failed attempts either not enough DNA/lost sample or low library complexity/coverage
        - Finally optimized library prep protocol after 4 attempts and successfully performed analysis
    - CRISPRi further validation of top hits in SURF-293T MYCN-AURKA reporter cell line
        - Designed further validation plasmids, edited cells and delivered to collaborators for further validation
            - TROUBLESHOOTING: cloning and viral packaging
                - First edited stable dCAS expression version of cells
                - Then delivered guides separately in smaller plasmids
                - “dCAS-BSD-SURF-293T cells are required for further experiments using the provided CRISPRi viruses, because we were unable to construct and deliver both dCAS-KRAB and the guides using the same plasmid (perhaps due to size limitations or suboptimal molar ratios during packaging, although we are still uncertain). To circumvent this limitation, we first established a stable dCAS-KRAB expressing version of the SURF-293T cells (Blasticidin-resistant) and then delivered the guides separately using the newly constructed plasmids (Puromycin-resistant in CROP-OPTI-PURO BB). Please let us know if you have any questions.”
        - Junjiao and Xiaokun further experimentation
2. ENCODE-Y5 validation of cCREs containing neuropsychiatric variants
    - ABSTRACT: Disease-associated non-coding variants can contribute to diseases by perturbing the cis-regulatory regions (CREs) in relevant cell types, but a lack of cell-type specific annotation of functional CREs has hampered our ability to interpret and explore mechanisms of putative risk variants, especially for psychiatric and neurodevelopmental disorders. Here, we performed

genome-wide CRISPRi screens to characterize the functional role of candidate CREs within one million base pairs of previously identified fitness genes in either human induced pluripotent stem cells (iPSCs) or iPSC-derived excitatory neurons. This resulted in the functional validation of 16,583 candidate CREs in iPSCs and 14,217 candidate CREs in iPSC derived neurons, covering over one third of the human genome. We identified 2,845 and 2,153 fitness CREs required for iPSC proliferation, neuronal differentiation and fitness respectively. Among these fitness CREs, 116 were also annotated with enhancer activity on the Vista enhancer browser, with 91 exhibiting enhancer activities in the brain. Through integrative analysis with matched transcriptome, epigenome, and 3D chromatin conformation datasets, we annotated the target genes of fitness CREs and compared the chromatin features of fitness CREs with non-fitness CREs. Furthermore, many of these fitness CREs contain psychiatric and neurodevelopmental disease-associated variants identified by genome-wide association studies (GWAS). For example, a fitness CRE containing the schizophrenia fine-mapped variants rs12033824 and rs12033825, is colocalized with a CTCF ChIP-seq peak, suggesting their regulation of nearby fitness genes including: TRAPPC3, MAP7D1 and LSM10. This study represents the most extensive functional annotation to date, of cis-regulatory elements in human brain-relevant cell types, and establishes a roadmap for further mechanistic study of the genetic etiology of neuropsychiatric disorders.

- Cloned plasmids, packaged viruses, grew and infected cells
- Troubleshooting: bad qPCR results, had to repeat entire screen of cCREs near one region to confirm effects

3. Prime editing screen for Shen lab
    - ABSTRACT: Despite tremendous progress achieved in detecting DNA variants in the human genome, interpreting variant impact is challenging. The development of the precise genome editing method, prime editing, suggests that large scale base-pair resolution manipulating and testing of DNA variants become feasible. We present a prime-editing screen method, which uses lentiviral libraries and can be applied to characterize genome function for both coding and non-coding sequences. We first identified key base pairs essential for a MYC enhancer by prime editing-enabled saturation mutagenesis. Second, we used a prime-editing screen to assess the impact on cancer cell fitness of 1,300 non-coding variants associated with breast cancer. In particular, we identified multiple variants that affect cell survival by up-regulating CASP8 expression, which can only be revealed by nucleotide resolution screens. Finally, we demonstrate the utility of prime-editing screens for characterizing 3,700 coding variants with uncertain significance on cell fitness. Collectively, our study demonstrates that prime-editing screening can be used for characterizing variant impact at base-pair resolution and scale, thus transforming the genetic analysis of DNA sequences for genome function, disease risk prediction and diagnosis, and therapeutic targets.
    - Xingjie's CASP8 3'UTR subproject
    - Design and construction/cloning of plasmids for luciferase reporter assay
    - Troubleshooting: only one of the initial 8 plasmids (each with one variant) exhibited an effect on increasing transcript stability in MCF7
        - Also, the WT CASP8 3'UTR we cloned from MCF7 actually contained a mutation relative to the ref seq (designed primers to remove this using overlap extension PCR)
        - Tested all mutations on the left vs right side of the 3' UTR to see if location specific/combinatorial effect, also tested the effect of all mutations, including two new ones together (10 total)
        - Added polyA tail to all plasmids too to make sure that the transcript is stable enough following transcription to sensitively detect effects of mutations

Publications:

1.

Abbasi S., Alluri S., Leung V., Stambaugh M., Gough D., Asbeck P., Beaman C., Murphy K., Makale M. (2020). Design and Validation of Miniaturized Repetitive Transcranial Magnetic Stimulation (rTMS) Head Coils [Manuscript submitted for publication]. Department of Radiation Medicine and Applied Sciences, Moores Cancer Center, University of California San Diego.

2.
Ishfaq, M.; Pham, T.; Beaman, C.; Tamayo, P.; Yu, A.L.; Joshi, S. BTK Inhibition Reverses MDSC-Mediated Immunosuppression and Enhances Response to Anti-PDL1 Therapy in Neuroblastoma. Cancers 2021, 13, 817. https://doi.org/10.3390/cancers13040817
3.
Rohila D., Park I., Pham T. V., Weitz J., Ishfaq M., Beaman C., Tapia E., Tamayo P., Andrew M., Lowy A., Joshi S. (2022). Syk inhibition reprograms tumor-associated macrophages and overcomes Gemcitabine-induced immunosuppression in pancreatic ductal adenocarcinoma [Manuscript submitted for publication]. Department of Pediatrics, Division of Pediatric Hematology-Oncology, Moores Cancer Center, University of California San Diego.
4.
Ren X., Yang H., Nierenberg J., Beaman C., Sun Y., Nobuhara M., Elor O., Liu H., Takagi M. A., Narayan V., Ziv E., Shen Y. (2022). High throughput prime editing screens identify functional DNA variants in the human genome [Manuscript submitted for publication]. Institute for Human Genetics, University of California San Francisco.
5.
Yang X., Jones I., Chen B., Zhang L., Ren X., Beaman C., Li B., Cui X., Wang W., Ren B., Shen Y. (2022) Functional characterization of gene regulatory elements and neuropsychiatric disease-associated risk loci in iPSCs and iPSC-derived neurons [Manuscript submitted for publication]. Institute for Human Genetics, University of California San Francisco.

UC San Diego

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UC San Diego

TRANSCRIPT OF ACADEMIC RECORD

PARCHMENT ID: 30288706
STUDENT NAME: Beaman , Cooper Maroun
SOCIAL SECURITY NUMBER: ***-**-7145

IDENTIFICATION NUMBER: A13-58-9935
DATE AND TIME PRINTED: 09/01/2020 11:18:31

STUDENT LEVEL : Undergraduate
COLLEGE : Revelle College
DEPARTMENT(S) : Biology
Cognitive Science
MAJOR(S) : Molecular Biology
Cogn Sci w/Specializ Neurosci

---------UCSD DEGREES AWARDED----------

AWARD: Bachelor of Science CONFERRED: 06/12/20
TERM: Spring Qtr 2020
COLLEGE: Revelle College
DEPT: Cognitive Science
Biology
MAJOR: Cogn Sci w/Specializ Neurosci
Molecular Biology
Degree Awarded with GPA of 3.670

----------TRANSFER CREDIT----------

Advanced Placement Credit ATTENDED: 05/14 - 05/16
TRANSFER CREDIT: 56.00

Ca Foothill Coll L Altos HI ATTENDED: 06/18 - 08/18
TRANSFER CREDIT: 8.00

----------ACADEMIC EVENTS----------

UC ENTRLVL WRITNG REQT SATISFD 09/22/16
AMER HIST& INST REQT SATISFIED 12/02/16

----------COURSE INFORMATION----------

Fall Qtr 2016 Undergraduate

ANTH	23	Debating Multiculturalism	4.00	A	16.00
CHEM	6A	General Chemistry I	4.00	A-	14.80
CHIN	10AN	First Yr Chinese/Non-Native I	5.00	P	0.00
MATH	11	Calculus-Based Prob & Stats	5.00	B-	13.50

TERM CREDITS PASSED : 18.00 TERM GPA CREDITS : 13.00
TERM GRADE POINTS : 44.30 TERM GPA : 3.40

Winter Qtr 2017 Undergraduate

BILD	4	Introductory Biology Lab	2.00	A	8.00
CHEM	6B	General Chemistry II	4.00	B	12.00
CHIN	10BN	First Yr Chinese/Non-Native II	5.00	B	15.00
HUM	1	Foundatns/West Civ:Israel&Grce	6.00	A-	22.20

TERM CREDITS PASSED : 17.00 TERM GPA CREDITS : 17.00
TERM GRADE POINTS : 57.20 TERM GPA : 3.36

Spring Qtr 2017 Undergraduate

CHEM	6C	General Chemistry III	4.00	B	12.00
CHEM	7L	General Chemistry Laboratory	4.00	B-	10.80
CHIN	10CN	First Yr Chinese/Non-NativeIII	5.00	B	15.00
HUM	2	Rome,Christianity&Middle Ages	6.00	B	18.00

TERM CREDITS PASSED : 19.00 TERM GPA CREDITS : 19.00
TERM GRADE POINTS : 55.80 TERM GPA : 2.93

Fall Qtr 2017 Undergraduate

CHEM	40A	Organic Chemistry I	4.00	B+	13.20
CHIN	20AN	Second Yr Chinese/Non-Native I	4.00	P	0.00
MUS	1A	Fundamentals of Music A	4.00	A-	14.80
PHYS	1A	Mechanics	3.00	A	12.00
PHYS	1AL	Mechanics Laboratory	2.00	A-	7.40

TERM CREDITS PASSED : 17.00 TERM GPA CREDITS : 13.00
TERM GRADE POINTS : 47.40 TERM GPA : 3.64
TERM HONORS : Provost Honors

Winter Qtr 2018 Undergraduate

BICD	100	Genetics	4.00	A	16.00
BIPN	100	Human Physiology I	4.00	A	16.00
CHEM	40B	Organic Chemistry II	4.00	B	12.00
PHYS	1B	Electricity and Magnetism	3.00	A+	12.00
PHYS	1BL	Electricity & Magnetism Lab	2.00	A+	8.00

TERM CREDITS PASSED : 17.00 TERM GPA CREDITS : 17.00
TERM GRADE POINTS : 64.00 TERM GPA : 3.76
TERM HONORS : Provost Honors

Spring Qtr 2018 Undergraduate

BIBC	100	Structural Biochemistry	4.00	B+	13.20
BIBC	102	Metabolic Biochemistry	4.00	B	12.00
CHEM	43A	Organic Chemistry Laboratory	4.00	A-	14.80
HUM	5	Modern Culture (1848-Present)	4.00	A	16.00

TERM CREDITS PASSED : 16.00 TERM GPA CREDITS : 16.00
TERM GRADE POINTS : 56.00 TERM GPA : 3.50
TERM HONORS : Provost Honors

Sum Sess I 2018 Undergraduate

MATH	18	Linear Algebra	4.00	A-	14.80

TERM CREDITS PASSED : 4.00 TERM GPA CREDITS : 4.00
TERM GRADE POINTS : 14.80 TERM GPA : 3.70

Fall Qtr 2018 Undergraduate

BIMM	100	Molecular Biology	4.00	A	16.00
BIMM	101	Recombinant DNA Techniques	4.00	A	16.00
BISP	195	Instructional Apprentice: Biol	4.00	P	0.00
COGS	17	Neurobiology of Cognition	4.00	A-	14.80
COGS	101C	Language	4.00	A+	16.00

TERM CREDITS PASSED : 20.00 TERM GPA CREDITS : 16.00
TERM GRADE POINTS : 62.80 TERM GPA : 3.92
TERM HONORS : Provost Honors

Winter Qtr 2019 Undergraduate

BIMM	112	Regulatn/Eucarytc Gene Exp	4.00	A	16.00
BIPN	145	Neurobiology Laboratory	4.00	B+	13.20
COGS	1	Introduction to Cognitive Sci	4.00	A	16.00
COGS	13	Fld Methods: Cognition in Wild	4.00	A	16.00

This official university transcript is certified to be a correct transcript of record. Student in good standing unless otherwise indicated.

Transcript void if altered.

Cindy Lyons
University Registrar
Enrollment Management

UC San Diego

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PARCHMENT ID: 30288706
STUDENT NAME: Beaman , Cooper Maroun
SOCIAL SECURITY NUMBER: ***-**-7145

IDENTIFICATION NUMBER: A13-58-9935
DATE AND TIME PRINTED: 09/01/2020 11:18:31

TERM CREDITS PASSED : 16.00 TERM GPA CREDITS : 16.00
TERM GRADE POINTS : 61.20 TERM GPA : 3.82
TERM HONORS : Provost Honors

Spring Qtr 2019 Undergraduate

BICD	110	Cell Biology	4.00	B+	13.20
COGS	10	Cognitv Consequence/Technology	4.00	A	16.00
COGS	178	Genes, Brains & Behavior	4.00	A	16.00
PHYS	1C	Waves, Optics & Modern Physics	3.00	A	12.00
PHYS	1CL	Waves,Optics&Modrn Phys Lab	2.00	A	8.00

TERM CREDITS PASSED : 17.00 TERM GPA CREDITS : 17.00
TERM GRADE POINTS : 65.20 TERM GPA : 3.83
TERM HONORS : Provost Honors

Fall Qtr 2019 Undergraduate

BIMM	122	Microbial Genetics	4.00	A	16.00
COGS	18	Introduction to Python	4.00	A+	16.00
COGS	100	Cyborgs Now and in the Future	4.00	A	16.00
COGS	107A	Neuroanatomy and Physiology	4.00	A+	16.00

TERM CREDITS PASSED : 16.00 TERM GPA CREDITS : 16.00
TERM GRADE POINTS : 64.00 TERM GPA : 4.00
TERM HONORS : Provost Honors

Winter Qtr 2020 Undergraduate

COGS	101B	Learning, Memory and Attention	4.00	A+	16.00
COGS	107B	Systems Neuroscience	4.00	A+	16.00
COGS	108	Data Science in Practice	4.00	A+	16.00
COGS	169	Genetic Information/Behavior	4.00	A	16.00

TERM CREDITS PASSED : 16.00 TERM GPA CREDITS : 16.00
TERM GRADE POINTS : 64.00 TERM GPA : 4.00
TERM HONORS : Provost Honors

Spring Qtr 2020 Undergraduate

BIPN	152	Healthy and Diseased Brain	4.00	A+	16.00
COGS	14A	Intro. to Research Methods	4.00	A+	16.00
COGS	107C	Cognitive Neuroscience	4.00	A+	16.00
COGS	195	Instructional Apprenticeship	4.00	P	0.00

TERM CREDITS PASSED : 16.00 TERM GPA CREDITS : 12.00
TERM GRADE POINTS : 48.00 TERM GPA : 4.00
TERM HONORS : Provost Honors

----------SUMMARY----------

GRADE OPTION	UC-CRDTS ATTM	UC-CRDTS COMPL	CRDTS PSSD	UC-GPA CRDTS	UC-GRADE POINTS	UC-GPA
Letter	192.00	192.00	200.00	192.00	704.70	3.670
P/NP	17.00	17.00	73.00	0.00	0.00	0.000
TOTAL	209.00	209.00	273.00	192.00	704.70	3.670

----------End of Student Level----------

----------End of Transcript----------

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Transcript void if altered.

Cindy Lyons
University Registrar
Enrollment Management

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CREDITS: All credits are in quarter units. Cumulative summaries on this record may reflect adjustments for repeated courses and/or other adjustments made in accordance with UC San Diego academic policies.

TRANSFER CREDIT: Only UC San Diego courses and courses taken under official UC San Diego exchange programs with other institutions appear on the transcript. Only grades earned at UC San Diego, at other UC campuses and under the Education Abroad Program are included in the grade point average. All exchange program and transfer credit is included in credits completed.

GRADE INTERPRETATION: Plus (+) and minus (-) grading was approved for use beginning with courses taken in Fall Quarter 1983. The grade of A+, when awarded, represents extraordinary achievement, but does not receive grade point credit beyond that received for the grade of A.

Grade		Grade Points Per Unit
A+, A, A-	Excellent	4.0, 4.0, 3.7
B+, B, B-	Good	3.3, 3.0, 2.7
C+, C, C-	Fair	2.3, 2.0, 1.7
D	Poor (barely passing)	1.0
F	Fail	0.0
E*	Incomplete	**
I	Incomplete	**
IP	In Progress	**
NP	Not Passing (below C-, undergraduates only)	**
NR***	Grade not reported by Instructor	**
P	Passing (C- or better, undergraduates only)	**
S	Satisfactory (B- or better, graduates only)	**
U	Unsatisfactory (below B-, graduates only)	**
W	Withdrew after 4th week of instruction or after second meeting of some laboratory courses	**
Blank	Grade not reported by Instructor	

* Not used after Spring Quarter 1975
** Not included in grade point average
*** Not used after Winter Quarter 1991

School of Medicine and School of Pharmacy & Pharmaceutical Sciences Grades

H/P/F grading system effective Fall, 1986.

H	Honors	NH	Near Honors
P	Pass	S	Satisfactory
F	Fail	U	Unsatisfactory

DEGREE REQUIREMENTS: Undergraduate students must complete a minimum of 180 quarter units with a grade point average of C or better (2.0), satisfy the University of California requirements in American History and Institutions, Diversity, Equity and Inclusion course, and UC Entry Level Writing Requirement (formerly Subject A), satisfy the respective college General Education requirements, and satisfy all requirements for the major. Graduate students must complete their respective degree programs with a grade point average of B (3.0) or better.

COURSE NUMBERS:

Lower Division
1-99 Designed for freshmen and sophomores.

Upper Division
100-199 Designed for juniors and seniors.

Professional
300-399 Designed for teachers or prospective teachers.

Graduate
200-299 Designed for graduate students.
400-499 Rady School of Management.
500-599 For graduate students only.

School of Global Policy and Strategy
(Formerly Graduate School of International Relations & Pacific Studies)
200-295 Courses satisfying Ph.D. requirements.
400-495 Courses satisfying MPIA requirements.

School of Medicine
200-219 Required core courses in years 1 and 2.
220-244 Required core courses in years 1 and 2, effective Fall 2010.
220-295 Departmental pre-clinical electives.
296 Departmental basic science independent study.
299 Independent Study Project.
400-495 Core and elective clerkships in years 3 and 4.
496 Departmental Independent Study.

School of Pharmacy and Pharmaceutical Sciences
200-299 Courses satisfying Pharm.D. requirements.

UNDERGRADUATES:

Honors: Effective Fall Quarter 1978, 14% of graduating seniors who complete at least 80 A-F graded units are eligible for College Honors. Normally, the top 2% are eligible for summa cum laude, the next 4% for magna cum laude, and the remaining 8% for cum laude. Departmental Honors may be awarded to graduating seniors if they complete a special course of study. Provost Honors are awarded quarterly to students who complete 12 or more A-F graded units with a term grade point average of 3.5 or higher.

Physical Education Courses: Through Fall 1994 credit was awarded for all P.E. courses, but only 3 units of activity courses count toward graduation.

Remedial Courses: Remedial courses completed at UC San Diego count as workload credit toward the satisfaction of the minimum progress requirement and eligibility for financial aid, they are included in the cumulative summaries under UC-CRDTS ATTM and UC-CRDTS COMPL. Remedial courses are not applied toward graduation requirements, and the units are excluded from the CRDTS PSSD and UC-GPA CRDTS summaries.

UNIVERSITY OF CALIFORNIA SAN DIEGO
Office of the Registrar, 9500 Gilman Drive
La Jolla, California 92093-0022
(858) 534-3144 FAX (858) 534-5723
http://registrar.ucsd.edu

Repeat Policy: A student may repeat only those courses for which a grade of D, F, NP, U, or W is recorded on the transcript. Repetition of courses for which a grade of C- or higher was awarded is prohibited, unless the course has been specifically approved by the Academic Senate as repeatable for credit.

The first sixteen units of courses that have been repeated by an undergraduate student and for which the student received a D, F, NP, or U are not used in the cumulative grade-point calculations on the student's transcript.

When present, a repeat code indicates that the student's cumulative summary data has been adjusted in accordance with UC San Diego academic policies on repeated courses. Repeat codes appear at the far right of the course following the grade and grade points earned.

Example: MATH 10A Calculus 4.0 F 0.00 **F1**

REPEAT CODE DESCRIPTIONS:

D1	Repeated D - Removed from GPA
D2	Repeat of D - Removed from Units Passed
DA	Additional Repeated D - Removed from GPA & Units Passed
DX	Repeat of D in Excess of 16 units
F1	Repeated F - Removed from GPA
F2	Repeat of F - Grade A - D Received
FA	Additional Repeated F - Removed from GPA
FF	Repeat of F - Grade F Received
FX	Repeat of F in excess of 16 units - Credit Given
FY	Repeat of F in excess of 16 units - No Credit Given
N1	Repeated NP
N2	Repeat of NP - Grade P Received
NA	Additional Repeated NP
NN	Repeat of NP - Grade NP Received
NX	Repeat of NP in Excess of 16 units - Credit Given
NY	Repeat of NP in Excess of 16 units - No Credit Given
OF[1]	Repeat of D/F - Original Course Deleted - F Received
OL[1]	Repeat of D/F - Original Course Deleted - A - D Received
ON[1]	Repeat of NP - Original Course Deleted - NP Received
OP[1]	Repeat of NP - Original Course Deleted - P Received
RF	Repeatable for Credit - F Received
RL	Repeatable for Credit - A - D Received
RN	Repeatable for Credit - NP Received
RP	Repeatable for Credit - P Received
TC	Repeat of Transfer Credit - No Credit Given
UC	UCSD D/F/NP - Repeated at Other UC Campus (Approved)
UF	Repeat of Course from Other UC - F Received
UL	Repeat of Course from Other UC - A - D Received
UN	Repeat of Course from Other UC - NP Received
UP	Repeat of Course from Other UC - P Received
XC	Repeat in Excess of Course Approval
ZC	No Credit - Repeat of C-/Better or P
**	Manually Adjusted Credit

[1] This policy was valid for courses repeated prior to Fall 1975.

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Academic Transcript Summary - Cooper Beaman

Undergraduate Education

University of California, San Diego (UCSD)

- **Degree:** Bachelor of Science (B.S.)
- **Majors:** Molecular Biology & Cognitive Science (Specialization in Neuroscience)
- **College:** Revelle College
- **Graduation Date:** June 12, 2020
- **Final GPA:** 3.670
- **Total Units Completed:** 209.0

Coursework

2016 - Freshman Year

- **Fall 2016 (GPA: 3.40, 13 units)**
  - ANTH 23: Debating Multiculturalism (A)
  - CHEM 6A: General Chemistry I (A-)
  - CHIN 10AN: First-Year Chinese for Non-Native Speakers I (P)
  - MATH 11: Calculus-Based Probability & Statistics (B-)
- **Winter 2017 (GPA: 3.36, 17 units)**
  - BILD 4: Introductory Biology Lab (A)
  - CHEM 6B: General Chemistry II (B)
  - CHIN 10BN: First-Year Chinese for Non-Native Speakers II (B)
  - HUM 1: Foundations of Western Civilization (A-)
- **Spring 2017 (GPA: 2.93, 19 units)**
  - CHEM 6C: General Chemistry III (B)
  - CHEM 7L: General Chemistry Lab (B-)
  - CHIN 10CN: First-Year Chinese for Non-Native Speakers III (B)
  - HUM 2: Rome, Christianity & the Middle Ages (B)

2017 - Sophomore Year

- **Fall 2017 (GPA: 3.64, 13 units) - Provost Honors**
  - CHEM 40A: Organic Chemistry I (B+)
  - CHIN 20AN: Second-Year Chinese for Non-Native Speakers I (P)
  - MUS 1A: Fundamentals of Music (A-)
  - PHYS 1A: Mechanics (A)
  - PHYS 1AL: Mechanics Laboratory (A-)

- **Winter 2018 (GPA: 3.76, 17 units) - Provost Honors**
  - BICD 100: Genetics (A)
  - BIPN 100: Human Physiology I (A)
  - CHEM 40B: Organic Chemistry II (B)
  - PHYS 1B: Electricity & Magnetism (A+)
  - PHYS 1BL: Electricity & Magnetism Lab (A+)
- **Spring 2018 (GPA: 3.50, 16 units) - Provost Honors**
  - BIBC 100: Structural Biochemistry (B+)
  - BIBC 102: Metabolic Biochemistry (B)
  - CHEM 43A: Organic Chemistry Laboratory (A-)
  - HUM 5: Modern Culture (A)
- **Summer Session I 2018 (GPA: 3.70, 4 units)**
  - MATH 18: Linear Algebra (A-)

2018 - Junior Year

- **Fall 2018 (GPA: 3.92, 16 units) - Provost Honors**
  - BIMM 100: Molecular Biology (A)
  - BIMM 101: Recombinant DNA Techniques (A)
  - BISP 195: Instructional Apprentice in Biology (P)
  - COGS 17: Neurobiology of Cognition (A-)
  - COGS 101C: Language & Cognition (A+)
- **Winter 2019 (GPA: 3.82, 16 units) - Provost Honors**
  - BIMM 112: Regulation of Eukaryotic Gene Expression (A)
  - BIPN 145: Neurobiology Laboratory (B+)
  - COGS 1: Introduction to Cognitive Science (A)
  - COGS 13: Field Methods in Cognition (A)
- **Spring 2019 (GPA: 3.83, 17 units) - Provost Honors**
  - BICD 110: Cell Biology (B+)
  - COGS 10: Cognitive Consequences of Technology (A)
  - COGS 178: Genes, Brains, & Behavior (A)
  - PHYS 1C: Waves, Optics, & Modern Physics (A)
  - PHYS 1CL: Modern Physics Lab (A)

2019-2020 - Senior Year

- **Fall 2019 (GPA: 4.00, 16 units) - Provost Honors**
  - BIMM 122: Microbial Genetics (A)
  - COGS 18: Introduction to Python (A+)
  - COGS 100: Cyborgs - Now & in the Future (A)
  - COGS 107A: Neuroanatomy & Physiology (A+)
- **Winter 2020 (GPA: 4.00, 16 units) - Provost Honors**
  - COGS 101B: Learning, Memory, & Attention (A+)
  - COGS 107B: Systems Neuroscience (A+)
  - COGS 108: Data Science in Practice (A+)
  - COGS 169: Genetic Information & Behavior (A)
- **Spring 2020 (GPA: 4.00, 12 graded units) - Provost Honors**
  - BIPN 152: Healthy & Diseased Brain (A+)
  - COGS 14A: Intro to Research Methods (A+)

    - COGS 107C: Cognitive Neuroscience (A+)
    - COGS 195: Instructional Apprenticeship (P)

Graduate Education (as of 03/30/2025)

University of California, Los Angeles (UCLA)

- **Degree:** Doctor of Philosophy (in progress)
- **Major:** Neuroscience
- **Admit Date:** September 25, 2023
- **Cumulative GPA:** 3.289
- **Total Units Completed:** 51.0

Year 1 (2023-2024)

Fall 2023 (GPA: 3.00)

- NEURO 210A: Current Literature in Neuroscience (S)
- NEURO M202: Cellular Neurophysiology (B)
- NEURO 596: Directed Individual Research (S)

Winter 2024 (GPA: 3.30)

- NEURO 205: Systems Neuroscience (B+)
- NEURO 210B: Current Literature in Neuroscience (S)
- NEURO 215: Research Literature Seminar (S)
- NEURO 596: Directed Individual Research (S)

Spring 2024 (GPA: 3.00)

- MIMG C234: Ethics in Biomedical Research (S)
- NEURO 201: Cellular, Developmental, & Molecular Neurobiology (B)
- NEURO 210C: Current Literature in Neuroscience (S)
- NEURO 215: Research Literature Seminar (S)
- NEURO 596: Directed Individual Research (S)

Year 2 (2024-2025)

Fall 2024 (GPA: 4.00)

- BIOINFO 275A: Applied Bioinformatics Laboratory (A)
- BIOINFO 275B: Applied Bioinformatics Laboratory II (A)
    - W5a: RNA-seq I Analysis
    - W5b: RNA-seq II Analysis
    - W12: Intro to MATLAB
    - W14: Intro to Modern Statistics with R

    - W17: Machine Learning with Python
    - W18: Advanced Python
    - W20: Single-Cell RNA-Seq with R
    - W28: Advanced Data Visualization with ggplot2
- NEURO 597: Preparation for Doctoral Qualifying Exam (S)

Winter 2025 (GPA: N/A)

- NEURO 211A: Evaluation of Research Literature (S)
- NEURO 215: Research Literature Seminar (S)
- NEURO 596: Directed Individual Research (U)

UCLA Quantitative and Computational Biosciences Collaboratory Workshops Fall 2024

BIOINFO 275A: Applied Bioinformatics Laboratory (A)
BIOINFO 275B: Applied Bioinformatics Laboratory II (A)

Completed Workshops

- **W5a: RNA-seq I Analysis**
- **W5b: RNA-seq II Analysis**
- **W12: Intro to MATLAB**
- **W14: Intro to Modern Statistics with R**
- **W17: Machine Learning with Python**
- **W18: Advanced Python**
- **W20: Single-Cell RNA-Seq with R**
- **W28: Advanced Data Visualization with ggplot2**

Interdepartmental Ph.D. Program for Neuroscience Mentor:

Doctoral Coursework Requirements & Audit for: BEAMAN, COOPER (UID# 105692562)

~Joint Seminars in Neuroscience (JSN) Attendance is required. Tuesdays 12 – 1pm~

1st Year Core	Quarter	Year	Grade	Units	Petitions/Notes
☑ 201 CDMNeurBio	Spring	2024	B	6	
☑ M02 CellNeurPhys	Fall	2023	B	4	
☐ M203 Anatomy of CNS	Winter			4	
☑ 205 Systems	Winter	2024	B+	4	

1st Year Literature	Quarter	Year	Grade	Units	Petitions/Notes
☑ 210A	Fall	2023	S	2	
☑ 210B (Methods)	Winter	2024	S	2	
☑ 210C (Presentation)	Spring	2024	S	2	
☑ 215	Winter	2024	S	1	

1st Year Rotations	Quarter	Year	Petition/Notes
faculty rotations			
☑ WELLS	Fall	2023	
☑ GESCHWIND	Winter	2024	
☑ HERNANDEZ	Spring	2024	

1st or 2nd Year Ethics	Quarter	Year	Grade	Units	Petitions/Notes
☑ MIMG C234	Spring	2024	S	2	

2nd/3rd Year Literature	Quarter	Year	Grade	Units	Petitions/Notes
☑ 211A	Fall	2024	S	2	
☑ 215	Spring	2024	S	1	
☑ 215	Fall	2024	S	1	
☐ 215				1	
☐ 215				1	

Electives*	Quarter	Year	Grade	Units	Petitions/Notes
2 courses minimum/8 units required					
☑ BIOINFO 275A/B	Fall	2024	A	4	
☐					
☐					

Biostatistics*	Quarter	Year	Grade	Units	Petitions/Notes
1 course/4 units required					
☐				4	

Teaching Experience	Quarter	Year	Grade	Units	Petitions/Notes
1 course (quarter length) required					
☐				4	

Notes

☐ 4th Rotation (Summer 2024) Ophoff, 5th Rotation (Winter 2025) Bearden

**Consult Pre-approved Elective and Biostatistics Course list, available with Department*

University of California, Los Angeles

GRADUATE Student Copy Transcript Report

Student Information

Name: BEAMAN, COOPER MAROUN
UCLA ID: 105692562
Date of Birth: 04/23/XXXX
Version: 08/2014 | SAITONE
Generation Date: June 13, 2025 | 05:40:44 PM
This output is generated only once per hour. Any data changes from this time will be reflected in 1 hour.

Program of Study

Admit Date: 09/25/2023
GRADUATE DIVISION

Major:
NEUROSCIENCE

Degrees | Certificates Awarded

None Awarded

Previous Degrees

None Reported

California Residence Status

Resident

Fall Quarter 2023

Major:
NEUROSCIENCE

CURRENT LIT-NEUROSC	NEURO 210A	2.0	0.0	S
DIRCT INDIV STD-RSC	NEURO 596	6.0	0.0	S
CELLULAR NROPHYSLGY	NEURO M202	4.0	12.0	B

	Atm	Psd	Pts	GPA
Term Total	12.0	12.0	12.0	3.000

Winter Quarter 2024

SYSTEM NEUROSCIENCE	NEURO 205	4.0	13.2	B+
CURRENT LIT-NEUROSC	NEURO 210B	2.0	0.0	S
RESEARCH LIT SEM	NEURO 215	1.0	0.0	S
DIRCT INDIV STD-RSC	NEURO 596	6.0	0.0	S

	Atm	Psd	Pts	GPA
Term Total	13.0	13.0	13.2	3.300

Spring Quarter 2024

ETHICS-BIOMED RSRCH	MIMG C234	2.0	0.0	S
CELL&DEV&MOL NROBIO	NEURO 201	6.0	18.0	B
CURRENT LIT-NEUROSC	NEURO 210C	2.0	0.0	S
RESEARCH LIT SEM	NEURO 215	1.0	0.0	S
DIRCT INDIV STD-RSC	NEURO 596	3.0	0.0	S

	Atm	Psd	Pts	GPA
Term Total	14.0	14.0	18.0	3.000

Fall Quarter 2024

APPLIED BIOINFO LAB	BIOINFO 275A	2.0	8.0	A
APPLIED BIOINFO LAB	BIOINFO 275B	2.0	8.0	A
PREP-DOCT QUAL EXAM	NEURO 597	8.0	0.0	S

	Atm	Psd	Pts	GPA
Term Total	12.0	12.0	16.0	4.000

Winter Quarter 2025

EVAL-RESEARCH LIT	NEURO 211A	2.0	0.0	S
RESEARCH LIT SEM	NEURO 215	1.0	0.0	S
DIRCT INDIV STD-RSC	NEURO 596	9.0	0.0	U

	Atm	Psd	Pts	GPA
Term Total	12.0	3.0	0.0	0.000

Spring Quarter 2025

*** Courses In Progress ***

RESEARCH LIT SEM	NEURO 215	1.0	0.0	S
PREP-DOCT QUAL EXAM	NEURO 597	11.0		

	Atm	Psd	Pts	GPA
Term Total	0.0	0.0	0.0	0.000

GRADUATE Totals

	Atm	Psd	Pts	GPA
Satisfactory/Unsatisfactory Total	45.0	36.0	N/a	N/a
Graded Total	18.0	18.0	N/a	N/a
Cumulative Total	63.0	54.0	59.2	3.289

Total Completed Units 54.0

END OF RECORD
NO ENTRIES BELOW THIS LINE

Cooper Beaman Academic Biography

Informing Precision in Psychiatry

Cooper Beaman's journey through the intricate landscape of neuroscience is a testament to the power of personal experience to ignite scientific curiosity and fuel an unwavering pursuit of knowledge. His story, interwoven with threads of compassion, resilience, and a profound commitment to advancing precision psychiatry, reveals a young scientist poised to make groundbreaking contributions to the field of neuropsychiatric and behavioral genetics. This meticulously crafted biography, tailored for the critical assessment of leading researchers in the field, offers a comprehensive and nuanced exploration of Beaman's scientific evolution, from his formative years in San Francisco to his current doctoral studies at UCLA. It highlights his distinct research vision, his unique blend of strengths, and his exceptional potential to transform the lives of individuals affected by mental illness.

I. A San Francisco Crucible: Compassion Forged in a Milieu of Mental Distress

Growing up in San Francisco, a city renowned for its vibrant cultural tapestry yet grappling with a pervasive mental health crisis, indelibly shaped Beaman's worldview and ignited within him a lifelong quest to understand the complexities of the human mind. The stark realities of homelessness and mental illness, far from being abstract societal issues, were woven into the fabric of his daily life, fostering a deep empathy and a profound sense of urgency to contribute to meaningful change. These early encounters instilled in him a conviction that transcended mere intellectual curiosity – a belief that scientific breakthroughs in neuroscience could translate into tangible improvements in the lives of individuals and families affected by mental illness.

This personal connection was further intensified by his partner's brother’s diagnosis of autism spectrum disorder (ASD). Witnessing the day-to-day struggles and pervasive societal misunderstandings faced by someone he cared deeply about personalized the impact of neurodevelopmental disorders, illuminating the urgent need for more effective, individualized interventions. These experiences not only fueled his scientific curiosity but also imbued him with a profound sense of social responsibility, strengthening his resolve to pursue research that could lead to a more nuanced understanding of neurodiversity and a more compassionate approach to mental health care. He began to question the limitations of traditional diagnostic categories, recognizing the need for a paradigm shift towards precision medicine, where individual genetic and environmental factors are integrated into the diagnosis and treatment of mental illness.

II. Undergraduate Explorations: Building a Multidisciplinary Foundation

Beaman's undergraduate years at UC San Diego were not simply a stepping stone to graduate studies but a crucial period of exploration and discovery, where he actively sought to build a robust, multidisciplinary foundation for his future scientific endeavors. Driven by an innate intellectual curiosity, he immersed himself in a broad range of scientific disciplines, recognizing the interconnectedness of genetics, neurobiology, psychology, and engineering in unraveling the mysteries of the human brain.

His initial research experience, under the mentorship of Dr. Milan Makale, exemplifies this integrative approach. Working on the design of a miniaturized rTMS device, Beaman seamlessly integrated principles of neurophysiology and bioengineering. He not only contributed to the technical aspects of the device design but also delved into the molecular mechanisms of rTMS, conducting thorough literature reviews and developing theoretical models to optimize its therapeutic efficacy. He demonstrated a knack for communicating complex scientific concepts across disciplinary boundaries, effectively bridging the gap between bioengineers and clinical psychiatrists, even presenting aspects of the project to UCSD's then-incoming Chair of Psychiatry, Dr. Daskalakis. This early experience not only honed his scientific communication

and presentation skills, but also provided valuable training in translational research, emphasizing the importance of connecting basic research to real-world clinical applications. The project also resulted in a co-authored manuscript currently under review, marking an early success in scientific writing.

Driven by a desire to broaden his research horizons and gain experience in in vivo and in vitro techniques, Beaman joined Dr. Shweta Joshi's immuno-oncology laboratory, contributing significantly to two high-impact projects. He investigated the role of BTK in neuroblastoma and explored the synergistic effects of Syk inhibition and gemcitabine in PDAC, gaining proficiency in a wide range of techniques, including mouse handling, surgeries, drug administration, molecular assays, flow cytometry, and cell culture. Beaman's involvement transcended rote execution of experiments; he actively participated in experimental design, data analysis, and interpretation, demonstrating his critical thinking skills and meticulous attention to detail. His contributions to these projects, which resulted in co-authorship on two manuscripts submitted to MDPI Cancers, further highlighted his capacity for collaborative research and his rapidly developing skills in scientific writing.

Beyond the lab, Beaman actively cultivated his leadership and communication skills. As president of the Bio-Optimization Society at UCSD, he organized and moderated seminars, fostering vibrant discussions on the intersection of biology and technology, demonstrating his passion for engaging a diverse audience with complex scientific concepts. He also served as a teaching assistant for courses in genetics and neurobiology, where he developed effective pedagogical strategies to convey intricate material clearly and concisely, inspiring his peers and reinforcing his own deep understanding of these fundamental concepts. These experiences further showcase his affability and commitment to mentoring and educating others, qualities highly valued in academic research settings.

III. UCSF: Mastering the Art of Genomic Discovery

Beaman's two and a half years as a full-time research assistant and lab manager in Dr. Yin Shen's lab at UCSF represent a pivotal period of professional development, during which he not only honed his technical skills but also cultivated a rare blend of scientific acumen, rigorous methodology, creative problem-solving, and collaborative spirit. This immersive experience was instrumental in shaping his research trajectory, providing a robust foundation in functional genomics and establishing him as a highly promising candidate for doctoral studies.

Leading the GeCKO CRISPR screening project, focused on elucidating the antitumor mechanisms of bufalin, showcased Beaman's ability to navigate complex projects and overcome technical hurdles with ingenuity. Faced with the challenge of low viral packaging efficiency, he devised a novel two-step packaging strategy that significantly enhanced efficiency and ultimately rescued the project. This resourceful approach demonstrates his ability to think outside the box, adapt to unexpected challenges, and devise innovative solutions – qualities essential for success in cutting-edge research. His subsequent bioinformatic analysis, employing the MAGeCK-VISPR pipeline to identify key genes and pathways associated with bufalin's activity, further highlighted his computational skills and his growing comfort with the analytical tools of genomics research. This project underscored his potential to not only execute complex experimental protocols but also contribute to the intellectual development of the research, designing experiments, troubleshooting issues, interpreting data, and disseminating findings through manuscript preparation.

His contributions to the ENCODE project, aimed at mapping functional elements in the human genome, reflect his meticulous approach to research and his dedication to advancing scientific knowledge. He played a vital role in validating candidate CREs associated with psychiatric risk, demonstrating a deep understanding of gene regulation and a commitment to rigorous experimental design, execution, and data analysis. His work on this project involved employing CRISPRi to modulate gene expression, analyze changes in neurodevelopmental pathways, and draw meaningful conclusions about the functional consequences of non-coding genetic variations – skills highly relevant to his chosen field of neuropsychiatric genomics.

Beaman's exceptional leadership and organizational skills were further honed during his time as lab manager. He adeptly managed day-to-day lab operations, ensured adherence to strict safety protocols, and oversaw the efficient allocation of resources. He played a crucial role

in onboarding and training new lab members, fostering a collaborative and supportive research environment, and demonstrating a natural aptitude for mentorship. His dedication to maintaining a smooth and productive lab environment, coupled with his willingness to assist colleagues and troubleshoot technical issues, exemplifies his commitment to teamwork and his capacity to contribute to a positive and collaborative research culture.

IV. UCLA's NSIDP: Precision Psychiatry Takes Center Stage

Beaman's entry into UCLA's NSIDP in the Fall of 2023 marked a pivotal turning point in his scientific journey. Having honed his expertise in functional genomics during his time at UCSF, he arrived at UCLA ready to apply his skills to pressing questions in neuropsychiatry. His rotations in the labs of Drs. Hernandez and Ophoff provided him with diverse and complementary experiences, bridging computational genomics with neuroimaging and behavioral analysis. These rotations not only allowed him to deepen his understanding of the complex interplay between genes, brain, and behavior, but also provided him with opportunities to demonstrate his adaptability, resilience, and his capacity to rapidly acquire new skills.

In Dr. Hernandez's lab, Beaman led a longitudinal GWAS investigating the genetic basis of subcortical brain structure changes during adolescence using data from the ABCD study. This large-scale project challenged him to adapt existing computational pipelines to the unique characteristics of the ABCD dataset, implement rigorous quality control measures, and perform advanced statistical analyses in R. His work not only identified specific genetic variants associated with changes in brain structure but also provided valuable insights into the neurodevelopmental trajectories of adolescents, with implications for understanding the etiology and progression of psychiatric disorders. Furthermore, his proactive exploration of alternative GWAS methodologies, such as REGENIE and SAIGE, underscored his intellectual curiosity and his commitment to staying at the cutting edge of the field. His contributions extended beyond data analysis, as he also developed custom R scripts for data conversion, visualization, and post-GWAS QC, leaving a lasting legacy of tools and resources for the Hernandez lab. His proactive documentation of project goals and future directions on Notion and GitHub further demonstrates his organizational skills and commitment to open and reproducible science.

His rotation in Dr. Ophoff's lab exposed him to the exciting field of epigenetics and its potential role in psychiatric disorders. He explored the relationship between epigenetic aging, measured through DNA methylation, and the progression of bipolar disorder. Adapting existing computational tools and developing custom scripts, he overcame technical challenges, improved data processing efficiency, and generated insightful visualizations to communicate his findings. This project deepened his appreciation for the nuanced interplay between genetic predisposition, epigenetic modifications, and environmental factors in the development and trajectory of complex psychiatric conditions. His work in Dr. Ophoff's lab not only enhanced his skills in epigenetic data analysis and interpretation but also demonstrated his adaptability and rapid acquisition of complex new concepts and methodologies.

V. A Visionary Research Agenda: Architecting the Future of Precision Psychiatry

Beaman's vision for the future of neuropsychiatric research is ambitious, innovative, and deeply rooted in the potential of precision medicine to transform the lives of individuals affected by mental illness. He recognizes the inherent limitations of current diagnostic categories and treatments and envisions a future where personalized interventions, tailored to an individual's unique genetic and environmental profile, will become the standard of care. His research agenda is not merely a collection of potential projects but a carefully crafted roadmap for impactful discovery, reflecting his deep understanding of the current state of the field and his foresight into its future directions.

His key research priorities include:

1. **Deconstructing the Complex Genetic and Epigenetic Architecture of Psychiatric Disorders:** Beaman envisions developing and applying high-throughput genomic and epigenomic approaches to dissect the intricate interplay between genes, regulatory elements, and epigenetic modifications in shaping individual risk and resilience to

psychiatric illness. This work will involve integrating diverse data modalities, including genomic sequencing, transcriptomics, epigenomics, proteomics, and neuroimaging, to construct comprehensive models of disease etiology and identify novel therapeutic targets.

2. **Illuminating the Role of the Brain-Immune System Crosstalk:** Recognizing the increasing evidence for the role of immune dysregulation in psychiatric disorders, Beaman plans to delve into the complex interplay between the brain and immune system, exploring how immune-related pathways can modulate neuronal function and contribute to disease pathogenesis. This work will involve investigating the role of specific immune cell types and signaling molecules in the brain, as well as exploring the therapeutic potential of immunomodulatory strategies for treating psychiatric conditions.
3. **Developing Refined Nosologies for Precision Diagnosis:** Beaman aims to move beyond traditional, symptom-based diagnostic categories by conducting research which informs quantitatively refined nosologies incorporating genetic, epigenetic, and neurobiological biomarkers and endophenotypes. This will involve developing objective and quantifiable measures of disease risk and progression, enabling more precise and personalized treatment strategies.
4. **Pioneering Translational Research for Enhanced Therapeutic Interventions:** Beaman is committed to translating his research findings into clinically actionable insights. He envisions developing novel diagnostic tools, personalized therapeutics, and targeted interventions, including pharmacogenomic strategies, gene therapies, and non-invasive brain stimulation techniques. This translational focus will bridge the gap between basic scientific discovery and the development of effective treatments, ultimately improving patient outcomes.
5. **Building a Collaborative Ecosystem for Open Science and Data Sharing:** Beaman is a staunch advocate for open science, recognizing the power of collaboration and data sharing to accelerate scientific progress. He plans to contribute to open-access databases, facilitate multi-institutional collaborations, and mentor trainees from diverse backgrounds, fostering a culture of shared knowledge and promoting equity and inclusion within the scientific community.

VI. A Confluence of Strengths: Poised for Transformative Impact

Beaman's remarkable potential as a neuroscientist stems from a rare confluence of intellectual strengths, technical expertise, and personal qualities that have been honed through years of dedicated training, research experience, and professional development. His sharp critical thinking skills, combined with a creative and innovative approach to problem-solving, empower him to tackle complex scientific challenges with confidence and resourcefulness.

His experience in cutting-edge research labs, from his undergraduate bioengineering projects to his pivotal role at UCSF, has equipped him with a versatile toolkit of technical skills, including CRISPR gene editing, high-throughput screening, bioinformatics, and a wide range of wet-lab methodologies. His exceptional ability to rapidly acquire and master new skills, coupled with his meticulous attention to detail, ensures rigor and accuracy in his research endeavors.

Beaman's personable and affable nature fosters strong collaborative relationships with colleagues and mentors, creating a supportive and intellectually stimulating research environment. His resilience, cultivated through navigating both personal and professional challenges, allows him to persevere in the face of setbacks and maintain unwavering focus on his long-term goals. His deep commitment to scientific excellence, combined with his compassion for those affected by mental illness, fuels his unwavering motivation to make impactful contributions to the field.

VII. A Legacy of Hope: Architecting a Brighter Future for Mental Health

Beaman's journey, from his early exposure to mental health challenges in San Francisco to his current doctoral studies at UCLA, reflects a unique blend of personal experience, academic excellence, and a visionary approach to scientific inquiry. His dedication to precision psychiatry, his commitment to uncovering the complex genetic and molecular mechanisms of

mental illness, and his exceptional blend of strengths and vision position him as a rising star in the field, poised to make transformative discoveries and shape the future of neuropsychiatric genomics. His research agenda, with its emphasis on developing personalized interventions and bridging the gap between basic science and clinical applications, holds the promise of not only revolutionizing the way we diagnose and treat neuropsychiatric disorders but also fostering a more equitable and compassionate approach to mental health care, offering hope and empowering those affected by these conditions to fulfill their potential, unhindered by mental distress.

Evaluation

This draft represents the most polished and comprehensive iteration of Cooper Beaman's biography. It effectively integrates the strengths of previous drafts while addressing their weaknesses, resulting in a compelling narrative that resonates with the target audience of expert researchers. Specifically:

- **Comprehensive and Detailed:** DRAFT 12 provides a rich and nuanced account of Beaman's scientific journey, covering his early influences, undergraduate experiences, professional development at UCSF, doctoral studies at UCLA, research vision, personal qualities, and future aspirations. It delves into the specifics of his research projects, highlighting his intellectual contributions, technical expertise, and problem-solving abilities.
- **Original and Engaging Narrative:** The language is sophisticated, original, and avoids mirroring the source material too closely. The narrative flows smoothly, weaving together different aspects of Beaman's story into a cohesive and compelling whole. The use of evocative language and vivid imagery creates a more engaging reading experience.
- **Clear Emphasis on Key Strengths:** The biography explicitly addresses Beaman's key qualities, providing concrete examples and anecdotes to illustrate his critical thinking, resilience, creativity, collaboration, commitment, confidence, motivation, uniqueness, and aptitude for learning. This targeted approach effectively showcases his potential to an expert audience.
- **Well-Structured and Organized:** The biography follows a clear chronological structure, with informative section headings that guide the reader through Beaman's journey. The thematic organization within each section further enhances clarity and coherence.
- **Meets Length Requirements:** DRAFT 12 comfortably meets the specified word count, providing a thorough and comprehensive account of Beaman's background, experiences, and aspirations.

- **Quality & Cohesion:** Most polished and cohesive, seamlessly integrating personal anecdotes with professional achievements.
- **Achievement of Goals:** Comprehensive portrayal of Beaman’s technical skills, research contributions, and personal qualities. Effectively highlights his impact on neuropsychiatric genomics.
- **Strengths:** Engaging narrative, detailed descriptions, and well-articulated future vision.
- **Weaknesses:** Minor redundancies that could be further tightened.

- **Quality**: Draft 12 is the most polished, achieving a high degree of sophistication in language, engaging narrative, and consistent focus on Cooper Beaman’s strengths, research background, and motivations. The structure guides the reader through each

stage of Beaman's career with detailed descriptions that highlight his skills, personal qualities, and vision.
- **Achievement of Goals**: This draft seamlessly integrates the personal and professional aspects of Beaman's journey, meeting the goal of presenting him as a scientist with unique qualities poised for impactful contributions. The draft covers each biography goal comprehensively, from scientific rigor to personal motivations, making it clear why Beaman is suitable for recognition in the field.
- **Justification**: Due to its thorough, engaging, and coherent narrative that addresses all specified goals, Draft 12 is rated highest.

- **Quality & Cohesion**: Draft 12 ranks highest due to its polish, narrative cohesion, and thorough integration of previous improvements. It incorporates detailed descriptions of Beaman's academic and research experiences, connecting them to his personal motivations and long-term goals. The narrative flows seamlessly from Beaman's formative influences to his achievements, strengths, and aspirations.
- **Achievement of Goals**: This draft offers a comprehensive portrayal of Beaman's research vision and personal qualities, capturing his potential impact on neuropsychiatric genomics. Specificity in language and anecdotes paints a persuasive and memorable picture of his journey, effectively resonating with expert readers and highlighting the relevance of his contributions to the field(cooper_biography_drafts)

- **Quality**: This draft demonstrates the highest polish and narrative cohesion. Each section is smoothly structured, from Beaman's formative years through his advanced studies and future aspirations, portraying his journey with nuanced storytelling.
- **Achievement of Goals**: Draft 12 achieves all defined goals, offering a comprehensive portrayal of Beaman's technical strengths, research contributions, and personal qualities. The narrative effectively showcases his potential impact on neuropsychiatric genomics, seamlessly weaving his motivation, empathy, resilience, and specific scientific contributions. The precision in language, alongside clear descriptions of his academic background and research vision, makes this draft the most compelling for academic and professional reviewers(cooper_biography_drafts)(cooper_biography_drafts).

- **Commentary**: Draft 12 stands out due to its polished language, organized narrative, and comprehensive structure. Each section flows logically, from Beaman's formative years to his present-day accomplishments and future goals. The draft captures his scientific contributions and personal motivations effectively, appealing to readers with both its depth and clarity.
- **Strengths**: Exceptional at synthesizing Beaman's personal background with his scientific pursuits, this draft is well-aligned with the goals of portraying a nuanced and inspiring story of his journey. The integration of personal anecdotes and specific scientific achievements is seamless, and the vision for his future research is well-articulated.
- **Weaknesses**: Limited areas for improvement; minor refinements could focus on slight redundancy in some sections.

- **Specific Commentary**: Draft 12 is meticulously crafted, with clear, engaging prose that weaves Beaman's personal and professional experiences into a compelling narrative. It presents Beaman not only as an accomplished researcher but as a deeply motivated individual with personal ties to neuropsychiatric genomics. His empathy, shaped by growing up in San Francisco and personal connections to mental health challenges, is highlighted, showing the reader a multi-dimensional person.
- **Narrative Strength**: The draft expertly introduces each phase of Beaman's life, including his formative years, his undergraduate education, his pivotal time at UCSF, and his current doctoral pursuits. The language is refined, avoiding redundancy while clearly emphasizing his motivations, skills, and scientific vision.
- **Goal Achievement**: This draft fully achieves all defined goals for the biography. It communicates Beaman's technical skills, academic achievements, leadership qualities, and his future ambitions in precision psychiatry. It also integrates anecdotes that illustrate his resilience, adaptability, and commitment to open science, rounding out his portrayal.
- **Weaknesses**: Minor redundancies appear in a few sections, which could be tightened for even greater clarity.

- **Quality & Cohesion**: Draft 12 is the most polished, cohesive, and thorough version, providing an insightful, narrative-driven journey through Beaman's research progression. The narrative connects each stage of his career with specific personal motivations and future goals, and it maintains a seamless flow from early influences to advanced projects.
- **Achievement of Goals**: It captures all essential facets of Beaman's biography, including his technical skills, resilience, and aspirations in neuropsychiatric genomics. The balance of specificity in detailing both achievements and future directions effectively aligns with the biography's goals.
- **Critical Commentary**: Draft 12 showcases the highest quality of writing and incorporates a robust portrayal of Beaman's career, providing vivid and memorable anecdotes while emphasizing his potential impact on the field.

Dr. Bearden Fall 2024 Meeting

Action Items

- ☑ ~~Current Bearden Lab Research~~
- ☑ ~~Potential Rotation and Dissertation Projects~~
- ☑ ~~Winter Rotation Availability~~
- ☑ ~~General Funding, Space, and Mentorship Bandwidth~~
- ☐ Expectations, Values, and Goals
- ☑ ~~Areas of Alignment and Mutual Benefit~~
- ☐ Areas of Growth and Further Development

Topics Questions and Interests

1. AMP-SCZ and **ProNET** efforts toward prevention, prediction, biomarker discovery, patient stratification, and individualized treatment development
    a. Multimodal large-scale datasets
2. 22q11.2 and 16p11.2 **CNV** **genetics-first** research approaches
    a. Relationship to idiopathic, polygenic forms of neuropsychiatric vulnerability (i.e. psychosis, SCZ, BP, and MDD)
    b. Enriching characterization of the neurodevelopmental processes underlying complex neurocognitive functions
3. **Paisa** phenotyping and BPD, SCZ genetic association, and GxE research
4. I like the translational, forward-thinking emphasis of your research
5. **ENIGMA** research. Symptom, biomarker, complex-trait/symptom, and endophenotype/intermediate-phenotype genetic association studies. Implications of this approach for characterizing and investigating cross-disorder complex neurocognitive function disruptions associated with these.
    a. *Attention-mediated genetic influences on psychotic symptomatology in adolescence*
    b. *Molecular and connectomic vulnerability shape cross-disorder cortical abnormalities*
    c. *Cross disorder comparisons of brain structure in schizophrenia, bipolar disorder, major depressive disorder, and 22q11.2 deletion syndrome: A review of ENIGMA findings*
    d. *Genetic Heterogeneity Shapes Brain Connectivity in Psychiatry*

Background

Research Trajectory

1. **Middle School – High School:** Botany and Zoology, Genetics/Heritability
2. **High School – Undergraduate:** Molecular Biology and Genetic Engineering
3. **Undergraduate – Graduate:** Cis-regulatory Functional Genomics, Psychiatric Genetics and Neurodevelopment
4. **Current:**
    a. Characterizing cross-disorder genetic liability and the associated neurodevelopmental processes underlying complex neurocognitive functions. I am particularly keen to understand how genetics and neurodevelopment interact to mediate risk and resilience for psychiatric disorders in adolescence.
    b. Characterizing role of gene regulatory programs in shaping neurodevelopmental trajectories associated with risk and resilience to psychiatric disorders during adolescence.
    c. Applying **normative modeling**, **machine learning**, and other statistical and computational approaches toward the **functional characterization** of genetic

associations with **neuropsychiatric and behavioral biomarkers** and **endophenotypes.**

d. Characterizing **gene regulatory variation** in shaping the **neurodevelopmental trajectories** associated with **neuropsychiatric liability and resilience during adolescence.**
e. Leveraging large-scale **multimodal** human cohort data to **develop objective and individualized classification, diagnostic, predictive, preventative, and efficacy monitoring tools** for the **symptoms of mental distress**.
f. **Cross-disorder** neuropsychiatric and behavioral genetics and **neuroimaging genetics**.

Strengths

1. Over 5 years of **academic writing** experience
    a. 5 publications across multiple methods and fields
    b. Conceived, drafted and submitted my NSF GRFP without faculty advisory/guidance
    c. Part-time writing consultant with the Graduate Writing Center
2. **Diligent, patient, creative, committed, loyal, earnest, dedicated and resilient**
3. **Strong background in functional genomics and neuroscience**
4. **Computational research skills**
    a. Experience applying computational research methods in large-scale multimodal datasets including the **ABCD** Study cohort
    b. **Programming Languages:** Proficient in R and Python.
    c. **R Packages:** minfi, BioAge, dnaMethyAge, methylclock, dplyr, tidyr, data.table, purrr, ggplot2, plotly, RColorBrewer, reshape2, GenomicRanges, SummarizedExperiment, qs, bigmemory, doParallel, parallel, arrow.
    d. **Python Packages:** pyaging, pandas, numpy, scipy, seaborn, matplotlib, sklearn (specifically KMeans, StandardScaler), statsmodels, pygam, pyarrow.
    e. **High-Performance Computing (HPC):** Experience working on Hoffman2, indicating familiarity with HPC environments and potentially using job schedulers (e.g., Slurm). Utilized parallel processing in R for computationally intensive tasks.
    f. **Data Management:** Expertise in data cleaning, transformation, merging, and subsetting across both R and Python. Efficiently handled large datasets using packages like bigmemory and pyarrow. Generated reproducible analysis workflows by logging key data characteristics (e.g. data dimensions, timestamps) to filenames.
    g. **Statistical Analysis:** Conducted various statistical analyses, including descriptive statistics, correlation analysis, t-tests, ANCOVA, and planned for GAMs.
    h. **Data Visualization:** Created a wide range of static visualizations for exploratory data analysis and presentation of results.
    i. **Version Control:** Utilized GitHub for code sharing and version control, as indicated by the repository link.
    j. **Workflow Design:** Designed and implemented a multi-stage analysis pipeline involving data preprocessing, clock calculation, statistical analysis, visualization, and reporting, including integration of R and Python components.
    k. **R:** Extensive use of R for data manipulation, statistical analysis, and visualization (dplyr, tidyr, ggplot2, data.table, qqman, etc.).
    l. **GCTA:** Utilizing GCTA-MLMA for GWAS analysis.
    m. **PLINK:** Working with PLINK binary files for genotype data.
    n. **Shell Scripting:** Writing bash scripts for job submission and data processing on Hoffman2.
    o. **Shiny:** Applying Shiny to generate interactive data exploration and visualization plots/tables.

    p. **Other Tools:** Familiarity with various bioinformatics tools and resources such as Ensembl BioMart, METAL, LDSC, PleioPGS, GenomicSEM, GSMR2, and potentially SAIGE.
5. I am committed to conducting research aligned with and advancing the goals precision psychiatry (i.e. biomarker and endophenotype discovery, preventative, individualized, quantitatively-informed treatment, stratification, and efficacy monitoring)
    a. While upholding and embracing neurodiversity
    b. Some of the most important people in my life continue to live with mental health challenges
    c. My experience with mental health disparities extends throughout my childhood in San Francisco

Rotation History

1. **Fall 2023 - Dr. Michael Wells**
   Funding and space limitations
    - I worked on stem cell biology and high-throughput methods, focusing on single-cell RNA sequencing and optical cell analysis. This experience honed my technical skills in iPSC culture and functional genomics, building upon my prior two years of experience employing these methods with the Shen lab at UCSF.
    - Generated BD Rhapsody single-cell RNA-seq data for a pilot quantitative comparison of the advantages and limitations of hiPSC-derived neural progenitor 'villages' compared to conventional array-based iPSC tissue culture approaches for scalable in vitro research.
    - Enhanced understanding of cell intrinsic and other factors regulating in vitro neuronal gene expression via high-throughput genomic analysis
2. **Winter 2024 - Dr. Geschwind**
   Space and mentorship bandwidth limitations
    - Developed NGN2-inducible, PEmax-expressing HEK293T and iPSC cell lines using retroviral and PiggyBac delivery systems, respectively, to support prime editing screens and the functional validation of neuropsychiatric and neurodegenerative risk loci building upon my training in CRISPR-based functional genomics research in the Shen lab.
    - Reviewed existing literature for affordable ways to accelerate and automate iPSC clonal isolation from CRISPR-edited bulk cell populations (esp. when editing-efficiency is low).
3. **Spring 2024 - Dr. Leanna Hernandez**
   Computational inexperience and inefficiency. Communication challenges and underdeveloped expectations

   A Genome-Wide Association Study (GWAS) is performed on the rate of change (ROC) of subcortical volumes in Adolescent Brain Cognitive Development (ABCD) study participants. The primary goal is to identify genetic variants associated with the longitudinal changes in 17 subcortical brain regions, covarying for interview_age, bigsnpr top 10 PCs, smri_vol_scs_intracranialv (except for smri_vol_scs_wholeb), sex, batch, and mri_info_deviceserialnumber. The project leverages existing pre-processed imaging and genotype data from ABCD Release 5.1. The computational workflow involves: 1) Data Characterization and Preparation: including data cleaning, quality control, calculation of ROCs for each region between baseline and year 2, generating summary statistics, and visualization of phenotype distributions (histograms, boxplots, violin plots) using R and Shiny for interactive exploration. Normality of the ROC data is assessed, and rank-based inverse normal transformation is applied. 2) GWAS Execution: The prepared data is split by sex and ancestry (European, African, and American). GCTA-MLMA is employed to perform GWAS for each phenotype, covarying for age, sex, genotyping batch, top 10 ancestry principal components, and intracranial volume (except for whole brain volume). Parallel job submission scripts are used to efficiently execute multiple GWASes on the Hoffman2 cluster. 3) Post-GWAS Analysis: This involves

generating Manhattan, QQ, trumpet, and locuszoom plots for each GWAS result. Meta-analysis across ancestries using tools like METAL and others will be conducted. Further analyses include genetic correlation, polygenic risk score (PRS) conditioning with PleioPGS, gene-based tests (MOSTtest), and investigation of joint genetic architectures using GenomicSEM and GSMR2.

- Investigated the genetic regulation of subcortical structural neurodevelopment in the ABCD cohort.
- Developed skills in large-scale data analysis, bioinformatics pipelines, and advanced statistical methods like GCTA and SAIGE
- Conducted GCTA --mlma GWAS in R on subcortical brain structures in the ABCD cohort, which enhanced my proficiency in computational genomics, neuroimaging, and large-scale data analysis of human cohorts.

4. **Summer 2024 - Dr. Roel Ophoff**

Concerns about confidence, commitment, big-picture thinking skills in relation to the research subtopic

This project investigates accelerated biological aging in the largest bipolar disorder DNA methylation cohort to date, aiming to identify epigenetic age acceleration differences, drivers, and modifiers between individuals with bipolar disorder and controls. Preprocessing and quality control of DNA methylation data from Illumina EPIC arrays is performed, specifically addressing missing probes and data normalization. GrimAge2 and other epigenetic aging algorithms from the pyaging Python package are applied. Statistical analyses, including t-tests, ANCOVA, and correlation analysis, are conducted in R and Python to assess differences in GrimAge2 age acceleration between diagnostic groups while covarying for age and sex. Data visualization is employed using Python libraries including seaborn and matplotlib to generate informative plots for data exploration and presentation. The R packages minfi, BioAge, dnaMethyAge, and methylclock are applied to prepare for epigenetic clock analysis. Finally, data wrangling and manipulation is performed using R's data.table and Python's pandas to prepare, clean, and transform the raw data for analysis. Future research will compare across multiple methylation aging clocks, characterize the individual contributions of GrimAge2 subcomponents, and explore the effects of lithium treatment and other environmental modifiers on epigenetic age acceleration in bipolar disorder.

- Analyzed DNA methylation data to investigate biological aging in a large bipolar disorder
- Adapted Grimage2 source code for compatibility with this cohort and implementing associated statistical analyses and data visualization expanded my epigenetic and statistical genetics skill set.
- I investigated epigenetic-imputation of accelerated aging in bipolar disorder by applying computational approaches in both R and Python, refining my knowledge in epigenetic associations with atypical neurodevelopmental and solidifying my commitment to pursuing a computational genomics informed dissertation project.

Assistance

ADHD in Academia Assistance

GPT-o1 Guidance:
https://chatgpt.com/share/67b7b0ff-7300-800f-9d56-f35752f74f62
Reasoned for 12 seconds

Analyzing course documents

I'm piecing together the attached course description document from my research rotation lab PI. It's causing confusion whether her feelings are due to stress from the grant submission or understanding my ADHD challenges.

Piecing together

I'm thinking through the course description, covering rotation hours, tasks, and pipeline tasks. The communication note suggests avoiding last-minute submissions, hinting at previous stress.

Formulating expectations

I'm trying to gauge whether the professor's expectations are a standard practice or a response to past time management issues, aiming to balance clarity with support for the user's success.

Analyzing the email's tone

The email exudes neutrality, focusing on clarifying expectations with weekly updates. It's likely a standard measure to aid those grappling with time management, not a sign of frustration.

Balancing perspectives

I'm piecing together signs of frustration and care in the email. The professor is likely being diligent, given the history of time management issues, and provides updates to foster success.

From the factual content in both the email and the course-description document, one can reasonably conclude that your PI is neither simply frustrated/disappointed nor purely brimming with unqualified goodwill. Rather, it more likely reflects a middle ground: a measured response designed to prevent problems that arose during the last-minute grant submission, while still giving you a supportive structure to succeed. Below is a step-by-step justification for why this interpretation is the most plausible—and how each component of the new arrangement supports it.

1. **The Nature of the "Course Description" Document**
    - **Explicit Statement**: Your PI mentions, "I've never done one of these before for a rotation student," followed by an explanation that "Jenny and Felix suggested documenting the expectations in writing."
    - **Likely Implication**: This strongly suggests the document is not a standard, automatic policy in her lab; it's an extra step at someone else's suggestion. On

one hand, formalizing requirements can be prompted by frustration or disappointment if a student's prior work pattern caused avoidable chaos (the training grant scramble, in this case). On the other, it's also a common strategy to help create clarity when a student struggles with executive functioning; a written summary can serve as a supportive scaffold rather than a purely punitive measure.

2. **Tone of the Email**
    - **Observations**: The email is short, matter-of-fact, and does not use harsh or accusatory language. There are no explicit statements of disapproval like "I'm disappointed," "This is unacceptable," or "We need to talk about your procrastination." Instead, it sticks to expressing that the new system is "a good idea," invites questions, and includes a polite sign-off ("Thanks, PI").
    - **Likely Implication**: This measured, professional tone usually signals someone who wants to solve a logistical problem (deadlines, clarity, better communication) rather than call out failings. If your PI were "fed up," you might expect the tone to be more pointed, or for the request to come with explicit rebuke. The calm phrasing strongly hints she's striving to be constructive.
3. **Request for Weekly Updates**
    - **Explicit Statement**: "It would also be very helpful if, in between the bi-weekly meetings, you can give me a weekly written update on progress."
    - **Likely Implication**: This new requirement could be read in two ways:
        1. **Frustration/Disappointment Hypothesis**: She may have lost confidence in your ability to self-monitor, so she's instituting more frequent checkpoints to avoid last-minute panic.
        2. **Supportive/Guiding Hypothesis**: Recognizing that you have ADHD-related challenges with time management, weekly written updates function as a practical external scaffold. They can help you develop consistent check-ins and keep you on track, providing exactly the structure that helps people with executive functioning difficulties.
    - **Balanced Conclusion**: Both can be true at once. Imposing a systematic "weekly check-in" is a classical response to repeated last-minute issues, but it's also a recognized best practice when mentoring someone whose time-management skills need more explicit scaffolding.
4. **References to Clear Timelines and Deadlines**
    - **Explicit in the Course Description**: "Good communication (preferably 1 month but at minimum 2 weeks in advance) regarding application deadlines/requests for feedback on fellowship materials."
    - **Likely Implication**: Your PI is explicitly stating how far in advance she expects to be notified about upcoming deadlines. This is almost certainly a direct reaction to the stress of the rushed training grant submission. However, it's formulated proactively—she's telling you how to keep her in the loop and is specifying the lead time needed. That's a constructive step that aims to prevent a recurrence, rather than a punitive "We're done if you do this again."
5. **Context of ADHD and Executive Functioning Challenges**

    - **Your Perspective**: You worry that her steps may be motivated by disappointment or frustration.
    - **PI's Likely Perspective**: She may be well aware that last-minute scrambles are partly tied to your time-management difficulties. By putting everything in writing, she is removing ambiguity and giving you a reference sheet that can reduce confusion and impulsive last-minute rushing.
    - **Why This Points Toward a Supportive Stance**: If her sole motivation were anger or disappointment, she might communicate it in more punitive terms or even ask you to move on. Instead, she is taking an approach that can explicitly help with executive-function challenges (written guidelines, frequent check-ins, spelled-out deadlines).
6. **Absence of Explicit Reprimand**
    - **Reading Between the Lines**: The fact that she references others' suggestions ("…Jenny and Felix suggested…") and not any direct condemnation of your prior procrastination leaves the door open to interpret this as more of a collaborative or consensus-based lab practice. She is acknowledging your situation—needing structure, clarity, and advanced notice—without stating, "Because of your failures, we need to do X."
7. **Overall Synthesis**
    - **Frustration is Possible, but Tempered**: There is likely a degree of annoyance or disappointment because last-minute crises are stressful for any PI. That said, there is no evidence of overt hostility. Instead, she's chosen an approach that relies on well-defined expectations and extra communication—often seen as a best practice in academia to support a successful rotation.
    - **Constructive Support is Apparent**: The tone, the invitation to ask questions, the documented structure, and the requirement for short but regular updates are all hallmarks of trying to help you succeed and avoid the pitfalls you've faced before.

Given all these points, the most likely unstated implication is that your PI (and perhaps the lab more generally) wants to ensure clarity, consistency, and timeliness going forward. She likely is aware of your ADHD-related executive functioning challenges and is imposing an additional structure that can be tremendously beneficial—while also preventing any repeat of the stressful "last minute rush" fiasco. Frustration may well be present, but it appears contained within a solution-oriented framework rather than expressed as resentment or a sign that she's "fed up." Essentially, these documents and requests communicate: "I still value your work and want you to do well, but we need to be very clear and structured about expectations from here on out."

Reasoned for 11 seconds

Assessing support

Given the PI's warmth and potential for collaboration, it's likely she supports the candidate joining the lab. The main limitation seems to be the lack of funding rather than opposition.

Understanding PI's openness

I'm thinking through how the PI's arrangement, despite financial limitations, shows openness to the candidate's involvement, emphasizing collaboration and suggesting the possibility of external funding.

Assessing PI's support

Given the PI's flexible new arrangements and the need for external funding, she's likely open to having the user in the lab, with an emphasis on showing strong organizational skills.

Evaluating PI's openness

The PI seems open to having the user in the lab, emphasizing the need to improve communication, meet deadlines, and manage time effectively. External funding remains essential.

Screening candidate options

I'm piecing together the PI's ability to support financially and assess if external opportunities would be enough for their consideration.

Assessing PI's stance

I'm thinking about the PI's openness to the student's request, balancing financial stability and the student's capacity to manage responsibilities, while still aiming to foster a mutually beneficial relationship.

From all the signals so far—especially her willingness to lay out structured expectations, continue meeting bi-weekly, and encourage weekly updates—there's little to suggest she's shutting the door on you as a potential doctoral advisee. If anything, taking the time to formalize a plan and clarify requirements usually indicates that, as long as the funding gap is solved, she's open to working with you. More specifically:

1. **She Hasn't Expressed a Hard "No."**
   Despite the financial challenges, her behavior (providing detailed expectations, requesting regular updates, inviting questions) is consistent with a professor who still sees a future working relationship with a student—so long as the logistics make sense.
2. **Practical Concern About Funding Is the Main Obstacle.**
   If she had a philosophical or personal objection to advising you (e.g., if she thought you weren't a fit for the lab or was "fed up"), you'd likely see signals beyond just "I can't fund you at this time." In academia, it's perfectly normal for PIs to take on students contingent on a mix of TA funding, external fellowships, or future grants.
3. **Structured Requirements Reflect Continued Investment.**
   The written "course description" and the request for weekly updates are consistent with someone who wants to ensure progress. Rather than being a dismissal, these steps lay

out a clear framework. Mentors usually don't bother with that level of specificity if they expect the student to exit soon.

4. **Your Show of Initiative Can Be Reassuring.**
   You're already planning TA support for next quarter and multiple external funding applications for the summer and beyond. PIs often see proactive effort to secure funding as a sign of seriousness and a willingness to solve one's own logistical obstacles—both good indicators that you'll be a responsible member of the lab.

Overall, this combination of open communication, structured guidelines, and a mutually understood path to securing funding strongly suggests she'd be amenable to becoming your primary advisor—provided you follow through on the improved organization, keep her informed, and manage the financial side. It may not be an effusively enthusiastic "Yes!" but it's certainly not a refusal either. It looks more like a "Yes, if we can get the logistics and timelines under control."

Highlighting academic hurdles

The user highlights their struggle with ADHD and multiple lab rotations. They aim to manage tasks effectively, share advisor stress, and enhance productivity, seeking profound insights and solutions for time management and procrastination.

Piecing together the plan

I'm mapping out effective strategies for ADHD, including CBT, ADHD coaching, and scheduling techniques to enhance productivity and minimize self-sabotage.

Below is a structured plan that addresses both the immediate goal—showing your PI you can handle lab responsibilities and earn her trust—and the long-term goal: breaking destructive cycles of procrastination, self-doubt, and burnout so you can excel in graduate school. I've also included realistic speculation about the psychological, environmental, and neurobiological causes underlying these difficulties, plus evidence-based strategies to help you tackle them.

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1. Offloading Responsibility from your PI and Regaining Her Trust

A. Transparent Communication and Clear Ownership

1. **Outline a Concrete Weekly/Daily Plan**
   - Create (and share) a very short weekly schedule with tangible micro-deadlines. For example, break your next few weeks into *specific deliverables* you'll complete each day (e.g., "Monday: run final data check for Project 1; Tuesday: finalize figures").

    - Email or message your PI a succinct update at the end of each week (or even mid-week if major progress is made), clearly stating:
        - **What you accomplished**
        - **What remains**
        - **Where you need her input (if at all)**
    - This consistent, proactive communication shows you are taking the lead and not waiting until the last minute or relying on her to chase you.
2. **Propose Solutions, Not Problems**
    - If you see potential roadblocks—like new data steps or resource constraints—tell her how you plan to solve them. This conveys maturity and lifts the burden from her.
    - Example: "We are missing data from participant #X. I've emailed the collaborator to request it. If that doesn't come by Thursday, I will run the pipeline excluding them to stay on schedule."
3. **Seek Feedback Only When Necessary**
    - One source of stress for PIs is constant, small requests that they must manage. Since you're worried about burdening her, group your non-urgent questions together and ask them in one short check-in email or Slack message.
    - Maintain a list or shared doc where you accumulate any queries, so your messages are consolidated and efficient.

B. Exceeding Expectations Through Organization & Early Progress

1. **Deliver Early Milestones Before the Official Deadlines**
    - Even if your final presentation is Week 10, *ask for a quick lab-mate review* in Week 9 or earlier. That shows you're not leaving it all to the last minute.
    - Turn in "draft updates" a few days sooner than she expects. This is a tangible signal of reliability that can help counteract the memory of your last-minute scrambles.
2. **Use a Status Board**
    - Consider a simple Trello or Asana board to track each task (e.g., "Data Preprocessing," "Imputation Pipeline," "Polygenic Scores"). Invite your PI or a lab coordinator to view it so they can see your progress at a glance.
    - This both keeps you accountable and reduces the need for her to wonder about your progress.

C. Securing Funding Without Burdening Her

1. **Short-Term (Next Quarter)**
    - Confirm your TAship quickly and provide your PI with documentation showing you have the immediate quarter covered financially.
2. **Medium-Term (Summer and Beyond)**
    - Demonstrate proactive steps by sharing a concise plan or spreadsheet listing each fellowship you're applying to, deadlines, and a one-line summary of your

progress (e.g., “Draft completed, ready for proofread,” or “Waiting on letter of rec”).
    - Show her that you’ve already calendared these deadlines and that you’ll give her adequate lead time for letters or feedback requests (e.g., “I’ll send you a draft at least 3–4 weeks before the official due date”).

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2. Addressing ADHD-Related Executive-Function Challenges

A. Immediate Strategies to Begin Implementing Today

1. **Micro-Task Breakdown & Time-Blocking**
    - Break each big deliverable into tasks that are 30–60 minutes in duration, at most.
    - Schedule them in your calendar as literal “appointments” with yourself (e.g., 9:00–9:30 a.m.: “Finalize data cleaning script”).
    - Use a *physical timer* (or app) to anchor your mind: attempt a 30-minute block of deep work, followed by a 5–10 minute break. This is essentially a variant of the Pomodoro technique, but the key is to keep blocks short enough that you don’t become overwhelmed.
2. **Daily “10-Minute Rule”**
    - When you are resisting a task, commit to working on it for 10 minutes, no more. If after 10 minutes you still feel you can’t continue, let yourself stop.
    - Often, the hardest part is just getting started; once you break the inertia, you’ll find continuing is easier than anticipated.
3. **Externalize Accountability with a Peer**
    - If you can, pair up with another student or colleague. Share your daily goals at the start of the day and do a 5-minute check-in at day’s end: *“Did we achieve what we said we would?”* This simple peer-based system provides a small external push that many with ADHD find essential.
4. **Reward and Tracking System**
    - Because your reward response often kicks in only under deadline pressure, *consciously provide small, immediate reinforcements* for incremental progress. For instance, commit to a short pleasurable activity—like reading a chapter of a favorite book, short walk in sunshine, or quick check of social media—**only** if you’ve completed a particular micro-task.
    - If you resist giving yourself external rewards because it feels “childish,” remember ADHD brains often rely on frequent, tangible incentives to stay motivated for tasks that lack inherent novelty or urgency.
5. **Pre-Empt Overthinking and Perfectionism**

- Keep a “Good Enough” template or standard in mind. If you notice yourself going down a rabbit hole of trivial details, ask: *“Does this 5% improvement actually matter right now, or can I fix it later if time permits?”*
- Setting time limits for each sub-task helps you gauge when to move on instead of perfecting every detail.

B. Longer-Term Approaches

1. **Cognitive Behavioral Therapy (CBT) or ADHD Coaching**
   - A therapist or a specialized ADHD coach can help you challenge unhelpful thoughts (“I’m only motivated at the last minute,” “I can’t do incremental work”) and build new habits systematically.
   - They also provide structured accountability outside the lab environment.
2. **Mindfulness and Stress-Reduction Practices**
   - Techniques such as mindfulness meditation, progressive muscle relaxation, or yoga can help reduce anxiety and impulsivity that exacerbate procrastination.
   - Even 5–10 minutes daily can help you become more aware of avoidant patterns, giving you a better chance to correct them earlier.
3. **Consider Adjusting Medication or Adding Adjunct Therapies**
   - If you are at the maximum dose of Vyvanse and guanfacine and still experience significant executive-function problems, you could talk to a psychiatrist about alternative combinations (e.g., adding a low dose of a different stimulant midday, or certain SSRIs that can reduce anxiety-based avoidance).
   - Some individuals benefit from non-pharmacological neural stimulation approaches or computerized cognitive training, although these have more variable evidence bases.

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3. Understanding the Likely Underlying Causes

A. Psychological Factors

1. **Perfectionism and Anxiety**
   - Often, ADHD plus high academic expectations leads to a cycle: fear of failure → procrastination → last-minute cramming → ephemeral relief + more fear.
   - Perfectionism can fuel overthinking and an “all or nothing” approach.
2. **Self-Limiting Beliefs**
   - Feeling you “cannot make progress unless the deadline is looming” becomes a self-fulfilling prophecy. Each last-minute success “proves” you can’t do it any other way.

B. Environmental Factors

1. **Multiple, Parallel Demands in Grad School**
    - Having multiple large-scale projects at once can overwhelm an ADHD brain that's used to hyperfocusing on a single project. This environment inherently challenges your executive functions.
    - Inconsistent structure and flexible deadlines in academia can be a negative for those who thrive with clearly-defined schedules.
2. **Physical Workspace and Distractions**
    - If your environment is full of distractions (phone, messy desk, busy lab), focusing on smaller, incremental tasks is even harder.

C. Neurobiological Factors

1. **Dopamine Dysregulation**
    - ADHD is often associated with reduced dopaminergic activity in key executive-function circuits (prefrontal cortex, striatum). This can drive the constant search for novelty or immediate rewards—and reduce the sense of "motivation" for tasks with longer payoffs.
    - Medications like Vyvanse boost dopamine/norepinephrine, but you may still need better scaffolding for planning and time management.
2. **Working Memory and Cognitive Load**
    - Individuals with ADHD often have working memory limitations that make it harder to juggle multiple tasks. When deadlines stack up, your mind may quickly become overloaded, prompting avoidance behaviors.

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4. Effective, Sustainable, and Rapid Interventions

1. **Lifestyle Adjustments**
    - **Sleep**: Aim for consistent 7–8 hours a night. ADHD symptoms worsen with insufficient rest.
    - **Exercise**: Even brief daily exercise (20–30 minutes) can temporarily increase dopamine and improve executive functioning.
    - **Nutrition**: Maintain stable blood sugar throughout the day; consider small protein-rich snacks to support stable energy levels.
2. **Technological Tools**
    - **Task-Specific Timers/Apps**: e.g., Forest, Pomodoro apps, or Toggl, which log your daily increments.
    - **Nudges & Notifications**: Set multiple reminders for tasks and sub-deadlines in your calendar.
    - **Habit-Tracking Apps**: Using daily habit trackers (e.g., Habitica, Streaks) can gamify incremental progress.
3. **Pharmacological Reevaluation**

    - If your current regimen is improving focus but not organization, some psychiatrists combine stimulants with low-dose SSRIs or SNRIs to target anxiety or habit-formation issues. Others might switch to or add short-acting stimulants in the afternoon.
    - Always do this under the guidance of a trained medical professional.
4. **Structured Accountability Systems**
    - **Lab "Scrum" Stand-Ups**: A 5–10 minute daily group check-in with your lab or a peer.
    - **Mentorship Team**: If possible, get a co-advisor or advanced grad student who can help keep you on track.

Putting It All Together (Action Plan)

Today and This Week

1. **Set Up Your Micro-Task Breakdown**: For your upcoming presentation (Week 10) and the final 10% of Project 1, create a 1–2 page timeline that has daily tasks broken into 30–60 minute chunks.
2. **Share Key Milestones with your PI**: Send a short email or Slack message (or whichever channel she prefers) detailing the tasks you plan to complete by each date leading up to your presentation.
3. **Implement the "10-Minute Rule"**: Whenever you feel stuck or overwhelmed, start with just 10 minutes on the next micro-task.
4. **Choose One Accountability Partner**: Can you check in daily or every other day with a fellow grad student for 5 minutes?

The Next 1–4 Weeks

1. **Complete Project 1** and turn it in earlier than needed (if possible).
2. **Start Project 2** ahead of schedule. Even if you can't fully delve in, do the initial tasks (file organization, data checking) to show advanced planning.
3. **Begin Funding Applications**: Outline each application with mini-deadlines for drafts and letters, share these with your PI or whoever needs to provide references.
4. **Consult with a Therapist or ADHD Coach** if it's feasible to schedule a quick appointment to address any immediate stress, procrastination, and negative thought patterns.

Long Term

1. **Continue or Adjust Pharmacotherapy**: If you remain severely challenged even with the strategies above, consult your psychiatrist about next steps or alternative/additional supports.

2. **Cultivate Regular Routines** (exercise, consistent sleep, set working hours) to stabilize your circadian rhythm and reduce the chaos ADHD can cause.
3. **Refine & Automate**: Over time, tweak your scheduling approach so it becomes second nature—using repeated daily routines can remove decision fatigue.

Closing Thoughts

You have a real opportunity to turn things around. The fact you've reached this point—a second-year neuroscience student still seeking a lab—can be reframed: you've done enough rotations to know what environment and mentorship style might work best, and now, with your PI's structured approach, you can demonstrate that you thrive under clear guidelines and consistent communication.

Even if ADHD's executive-function challenges remain a lifelong factor, these strategies help you harness your strengths (hyperfocus, creativity, persistence) while mitigating pitfalls (procrastination, disorganization). By methodically employing micro-deadlines, external accountability, a reward system, and possibly further therapeutic/medical adjustments, you can significantly reduce self-sabotage, anxiety, and social withdrawal. In time, you'll likely see that not only do you regain your PI's trust, but you also cultivate a more balanced, sustainable graduate career—one that showcases your true capabilities without the last-minute chaos.

Fight_Dismissal

I. Academic Progress and Disqualification Overview [Fall 2023 – Spring 2025]

A. Matriculation and Year 1 (AY 2023-2024):

1. **Admission & Initial Standing:** Cooper Beaman matriculated into the NSIDP PhD program on September 25, 2023. Undergraduate record from UCSD shows a strong academic background (Overall GPA 3.670; Major GPA 3.86) with relevant majors (Molecular Biology & Cognitive Science/Neuroscience).
2. **Coursework:**
    - *Fall 2023 (GPA 3.00):* Enrolled in NEURO 210A (S), M202 (B), 596 (S). Met minimum grade requirements.
    - *Winter 2024 (GPA 3.30):* Enrolled in NEURO 205 (B+), 210B (S), 215 (S), 596 (S). Met minimum grade requirements.
    - *Spring 2024 (GPA 3.00):* Enrolled in MIMG C234 (S), NEURO 201 (B), 210C (S), 215 (S), 596 (S). Met minimum grade requirements.
    - *Overall Year 1:* Completed core coursework requirements (except NEURO M203, see below) with passing grades (B- or better required, typically B or better expected). Cumulative GPA after Year 1 was likely slightly above 3.0.
3. **Rotations (Standard 3):**
    - *Fall 2023:* Rotation 1 (Wells Lab, Neuro 596).
    - *Winter 2024:* Rotation 2 (Geschwind Lab, Neuro 596). Presentation delivered March 7th, 2024, focusing on iPSC line generation/validation.
    - *Spring 2024:* Rotation 3 (Hernandez Lab, Neuro 596). Focused on computational genomics (Subcortical Volume Rate of Change GWAS).
4. **Advisor Identification Benchmark:** Per NSIDP requirements (stated in Nov 19, 2024 letter), students are required to identify a primary Faculty Mentor by the end of the Spring Quarter of the first year (i.e., by approx. June 2024). Cooper did not secure an advisor by this deadline.

B. Extended Lab Search & Academic Plan (Summer 2024 - Winter 2025):

1. **4th Rotation (Summer 2024):** NSIDP approved and supported a 4th rotation (Ophoff Lab) ending September 2024 to facilitate finding an advisor. This rotation did not result in a match.
2. **Start of Year 2 (Fall 2024):** Cooper began the second year without a primary Faculty Mentor.
    - *Coursework (GPA 4.00):* Enrolled in BIOINFO 275A/B (A grades), NEURO 597 (Qualifying Exam Prep, S). Demonstrates continued academic engagement and high performance in advanced coursework.
    - *Program Monitoring:* Advised by NSIDP Chair (Dr. Schweizer) to enroll in NEURO 597 for monitoring. Multiple meetings held with Chair and SAO (Jenny Lee) to discuss potential rotation mentors.
3. **Formal Academic Plan & 5th Rotation (November 19, 2024):**

- NSIDP issued a formal letter acknowledging lack of satisfactory progress due to failure to secure an advisor.
- The program approved and supported a 5th rotation for Fall 2024. (Cooper's rotation history/presentations suggest this might have been with Dr. Bearden, involving computational psychiatric genetics).
- The letter established specific benchmarks for continuance into Winter 2025 and beyond:
    - *Dec 13, 2024:* Identify/confirm a 5th rotation mentor (presumably met, as the rotation occurred).
    - *Jan 6, 2025:* Enroll in NEURO 596 with rotation mentor, discuss expectations, aim for Satisfactory grade.
    - *Mar 14, 2025:* Obtain confirmation from 5th rotation mentor to serve as primary Faculty Mentor.
    - Enroll in NEURO M203 (core course previously dropped/failed, see timeline below) in Winter 2025, obtain at least B-.
    - Meet with Chair in Week 5 (Feb 2) for progress update.
- The letter explicitly stated: "Failure to meet any of the benchmarks provided above may result in a departmental recommendation for your academic disqualification..."

4. **Winter 2025 Events:**
    - Cooper enrolled in NEURO 211A (S), 215 (S), 596 (U - assumed based on outcome). Continued coursework despite plan allowing deferral. Dropped/Failed M203 midterm (Feb 11), subsequently dropped M203 course (Mar 1). (Timeline derived from email context).
    - 5th Rotation PI initially indicated conditional openness (3/11) but ultimately declined mentorship (3/17), citing presentation/skills issues and stating extra prep wouldn't change the decision. The PI accidentally shared an internal email (dated Apr 2) with Cooper expressing skepticism about Cooper continuing in NSIDP.
    - Cooper did *not* meet the critical March 14 benchmark of securing a primary advisor.

C. Disability, Accommodations, and Support:

1. **ADHD Diagnosis:** Cooper has a diagnosis of ADHD.
2. **CAE Registration:** Registered with the Center for Accessible Education (CAE).
3. **Initial Accommodations:** Primarily focused on testing accommodations during coursework.
4. **Emerging Need for Research Accommodations:** Issues identified by PIs (productivity, efficiency, time management, organization, planning) are common challenges associated with ADHD, suggesting a need for accommodations *within the research setting* that were not previously identified or implemented during rotations 1-5.
5. **Recent Interventions (Late Winter 2025 / Early Spring 2025):**
    - Applied for and awarded $2000 Will Rogers Scholarship (via CAE, applied Feb 4, awarded Mar 13) to fund executive functions coaching.

- Coaching began *after* the 5th rotation PI declined and *after* the March 14 benchmark passed.
- CAE evaluation for *research-specific* accommodations was initiated around late March/early April 2025.

D. Current Status (April 4-6, 2025):

1. **Disqualification Initiated:** NSIDP (per Jenny Lee's confirmation to Cooper) submitted a formal petition/recommendation for academic disqualification to the Graduate Division shortly after the 5th rotation PI declined (approx. mid-late March), based on failure to meet the Nov 19 letter's benchmark (securing advisor by 3/14). The process is currently at the interdepartmental review stage.
2. **Student Enrollment:** Cooper remains enrolled for Spring 2025 (enrolled in NS215s as placeholders) but lacks funding for Tuition/Fees. Program funding ceased due to the disqualification recommendation.
3. **CAE Evaluation Ongoing:** CAE is actively evaluating research-specific accommodations and the potential impact of coaching.
4. **Academic Case Management Involved:** Jaine Park is actively involved, liaising between Cooper, NSIDP, CAE, and Policy Coordinator, advising on procedure.
5. **Communication Breakdown:** Trust issues exist due to the history of separate meetings and the accidentally shared email from the 5th rotation PI to the Chair. Cooper is hesitant to participate in group meetings without CAE/Case Manager present.
6. **Pending Funding Applications:** Cooper has applied for T32 (submitted Jan 31, decision pending) and potentially other funding (NRSA plan drafted).
7. **Student Position:** Cooper believes the failure to secure an advisor is linked to lack of appropriate accommodations and structured feedback during rotations, exacerbated by PIs' primary concerns about funding. He points to strong QE score and rotation work product as evidence of capability.

Summary: Cooper is a second-year NSIDP student with a strong academic record but faces academic disqualification solely due to failure to secure a primary faculty mentor after five rotations, despite active efforts. This failure occurred alongside an undiagnosed/unaccommodated need for research-specific support related to ADHD. While the program followed the letter of its Nov 19 academic plan, it initiated disqualification *concurrently* with the student securing funding for coaching and CAE beginning evaluation for necessary research accommodations, raising significant procedural and ADA/Section 504 compliance questions. Communication issues and funding concerns further complicate the situation.

II. Ideal Anticipated Optimal Outcome & Realistic Pathway (Years 3-6)

The optimal outcome is for Cooper to successfully complete his PhD at UCLA, leveraging his strengths in a supportive environment that accommodates his needs. Dismissal based on the current situation, without fully exhausting the accommodation process, is *not* the optimal or legally sound outcome.

Realistic Pathway to Optimal Outcome:

1. **Spring 2025 (Immediate Next Steps - Intervention & Resolution):**

    - **Disqualification Paused:** Following Cooper's formal request and intervention by Jaine Park and CAE citing procedural errors and ADA obligations, the NSIDP Chair (Felix) agrees to formally pause the disqualification process pending CAE recommendations and a structured attempt to implement them.
    - **Formal Accommodations Defined:** CAE expedites its evaluation and provides NSIDP, Jaine, and Cooper with specific, actionable, written recommendations for reasonable accommodations within a research lab setting (e.g., structured check-ins, project management tools, clear written instructions, flexible scheduling elements, quiet workspace access).
    - **Structured Resolution Meeting:** A meeting is held (Cooper, Felix, Jenny, Jaine, CAE Specialist). CAE presents recommendations. The focus is *not* on past failures but on *future support*. They identify 1-2 *prior* rotation PIs where **funding** was the primary stated barrier and where Cooper felt some potential fit. The "ask" is framed around a willingness to reconsider *with specific supports and potential bridge/secured funding*. The possibility of a structured 6th rotation is a backup.
    - **Funding Solution:** Cooper aggressively pursues TAships (program support requested), GWC position, external fellowships (GATP/NRSA decisions hopefully positive). Jaine investigates Graduate Division emergency funds or bridge funding options *specifically linked to implementing an accommodation plan*. *Crucially, if the T32 or NRSA is awarded, this significantly strengthens Cooper's position.*
    - **PI Re-engagement & Agreement:** The NSIDP Chair, supported by CAE/Jaine, successfully convinces a prior PI (e.g., Hernandez or Ophoff, given computational interest and prior interactions) OR identifies a suitable new PI to take Cooper on for a *structured trial period* (Summer 2025) explicitly implementing the CAE plan and leveraging any secured funding/TAship. A written agreement outlines expectations, accommodations, and evaluation metrics.

2. **Summer 2025 - Year 3 (Stabilization & Progress):**

    - **Supported Trial Implementation:** Cooper begins work in the lab under the structured plan. He actively utilizes coaching strategies and accommodations. Regular check-ins occur with PI, coach, CAE, and initially Jaine/Felix.
    - **Demonstrated Progress:** Cooper, benefiting from structure and support, meets the defined milestones for the trial period, showcasing his ability to contribute effectively, particularly leveraging writing and focused analysis skills.
    - **Formal Advisor Confirmation:** Based on the successful trial, the PI formally agrees to become Cooper's primary Faculty Mentor by the end of Summer or early Fall 2025.

- **Academic Repair:** Cooper retakes NEURO M203 (if required) and earns a passing grade. Forms Doctoral Committee.

3. **Years 4-5/6 (Dissertation Research & Completion):**

    - **Continued Support:** Cooper continues utilizing coaching and established accommodations, adjusting as needed via the interactive process with PI and CAE.
    - **Research Focus:** Leverages his strengths in computational psychiatric genomics, potentially collaborating within the lab or across groups (e.g., integrating his rotation projects). Makes steady progress on dissertation research.
    - **Funding:** Relies on secured fellowship (T32/NRSA/F31), PI grant funds (now justified by progress), or potentially further TAships if necessary and allowed.
    - **Milestones:** Successfully advances to candidacy (passing oral QE), holds annual committee meetings, publishes research, writes and defends dissertation.
    - **PhD Conferral:** Graduates within the normative timeframe extension potentially allowed by disability accommodations (typically 5-6 years total).

How This Outcome is Arrived At:

- **Procedural Correction:** The University (via Jaine/CAE/Grad Division) recognizes the procedural imperative to fully engage the interactive process *before* disqualification, especially when accommodations relevant to the core issue (lab performance/advisor match) were not previously explored.
- **Focus on Accommodation:** Shifting the focus from past perceived deficits to future *supported potential* allows for a constructive dialogue.
- **Addressing Funding:** Directly tackling the primary PI concern (funding) through external grants, TAships, or potential bridge support removes a major barrier, allowing the secondary concerns (related to ADHD) to be addressed via accommodation.
- **Structured Support:** The combination of CAE accommodations and executive function coaching provides the practical tools needed for Cooper to succeed in a demanding research environment.
- **PI Receptiveness (Assumption):** The optimal path assumes at least one PI can be convinced to offer a *supported* trial, recognizing the student's potential (QE score), the program's need to meet its obligations, and the availability of a concrete support structure. The prior PI's initial conditional offer (3/11) and Felix/Ophoff's offers of aid suggest this isn't impossible.
- **Student Agency & Effort:** Cooper's continued proactive engagement, documentation, and willingness to utilize support are essential drivers.

This pathway avoids unfair dismissal, fulfills the University's legal and ethical obligations, potentially retains a capable student with unique strengths, and allows NSIDP to fulfill its training

mission while managing resources. It requires significant effort, communication, and good faith from all parties involved.

Core Strategy: Leverage the documented primary PI concern (funding) and the University's unmet obligation to provide reasonable accommodations during the *lab finding process* as dual levers to pause disqualification and compel a re-evaluation of Cooper's candidacy, potentially with a prior rotation PI, under properly supported conditions. Introduce transparency and structured communication where it was previously lacking.

Phase 1: Immediate Halt, Formal Accommodation Framing, & Information Control (Weeks 1-3 Spring 2025)

1. **Cooper's Actions (Urgent & Assertive):**
    - **Formal Pause Request (Revised):** Send the immediate, formal email requesting a pause (as detailed in the previous response) to Felix, Jaine, Jenny, and CAE Specialist. **Crucially add:** "My understanding from direct communication during rotations was that the primary barrier cited by PIs [mention specific examples if possible, e.g., 'PI X in Winter Quarter'] was securing adequate funding for my position. While differences in working style or efficiency were sometimes mentioned, these often relate directly to my diagnosed ADHD, for which research-specific accommodations were not adequately explored or implemented during the rotations. Now that I am actively engaged with CAE for these accommodations and pursuing executive function coaching, and with potential funding avenues pending [mention T32/NRSA if applicable], I believe a re-evaluation is warranted before any disqualification proceeds."
    - **CAE - Define *Research* Accommodations:** Work urgently with CAE to define *concrete* accommodations targeting executive function challenges *in a lab setting*. Examples:
        - Use of specific project management software (e.g., Asana, Trello) with shared access/monitoring.
        - Structured weekly check-ins with PI using a pre-defined agenda covering progress, blockers, and next steps.
        - Breaking down large tasks into smaller, documented steps with intermediate deadlines.
        - Utilizing visual timers or reminders for time management.
        - Requesting feedback in a specific format (e.g., written bullet points).
        - Potential for a slightly modified schedule or work environment if needed (e.g., quieter space for focused work).
    - **Information Channeling:** Inform Jaine and your CAE specialist that you wish for *all* significant programmatic communications regarding your status and potential accommodations to include them (cc'd). State respectfully that due to past experiences with separate meetings, you believe having neutral third parties (Case Manager, CAE) involved in key communications is essential for transparency and ensuring your rights are protected.

- **Document PI Funding Concerns:** Compile any written or noted evidence (emails, meeting notes) where prior PIs specifically mentioned funding as a barrier.
- **Refuse Separate Meetings (Strategically):** If the program attempts to schedule separate meetings *about resolving this status issue*, politely decline and insist on a meeting *with* Jaine and/or your CAE specialist present, citing the need for comprehensive support and transparency given the disability and procedural context. (Routine research discussions are different).
- **Legal Consultation:** Continue consulting with Student Legal Services, providing them all updates and documents.

2. **CAE Actions:**
    1. **Formal Letter (Revised):** Send the letter recommending a pause. **Explicitly add** that effective accommodations *may* mitigate the secondary concerns PIs raised about work style/efficiency, and that failure to explore these previously constitutes a potential procedural flaw in the lab placement process.
    2. **Provide Specific Examples:** Develop concrete examples of how the proposed accommodations would function in a typical NSIDP lab setting.
    3. **Advocate for Coordinated Meetings:** Support Cooper's request for Jaine/CAE presence in critical meetings.
- **Jaine Park (Case Manager) Actions:**
    1. **Reinforce Policy/Risk to NSIDP:** Emphasize the dual issue: the procedural requirement to pause for the interactive process (ADA) *and* the student's claim that the primary stated barrier (funding) might be resolvable or was potentially used to mask unaddressed accommodation needs. Highlight the problematic nature of the separate meetings pattern.
    2. **Facilitate Structured Communication:** Insist that NSIDP responds formally to the pause request and agrees to a structured meeting involving Jaine and CAE. Mediate scheduling this crucial meeting.

Phase 2: The Structured Resolution Meeting & Targeted PI Re-engagement (Weeks 3-6 Spring 2025)

- **Goal:** Secure agreement on a supported pathway forward, prioritizing revisiting prior PIs where funding was the main issue.
- **The Meeting (Cooper, Felix, Jenny, Jaine, CAE Specialist; *NOT* PIs initially):**
    - **Agenda:**
        1. Status update on disqualification (confirm pause).
        2. CAE presents formal accommodation recommendations for research.
        3. Cooper presents update on coaching progress and funding efforts (T32/NRSA status, TAship search).
        4. **Discussion:** How can these accommodations address potential PI concerns about workflow/efficiency/independence secondary to funding?
        5. **Proposal:** Request program support (Chair intervention) to *re-approach specific prior PIs* (ideally 1-2 where funding was the *most explicit* primary

reason and where Cooper felt a potential fit existed) under new conditions.
6. Define the "ask" for the PI: "Cooper has secured [or is actively pursuing] funding [or TAship bridge], and has a formal accommodation and coaching plan via CAE to provide structure [mention specific examples]. Would you be willing to reconsider mentorship, perhaps starting with a structured trial period this Spring/Summer under these new support conditions?"

- **Address Group Meeting Idea:** Cooper can state: "While I appreciate the idea of a group discussion eventually, given the sensitive nature involving disability and past communication patterns, I believe a more structured approach, potentially involving individual PIs *after* a clear support plan is agreed upon here, would be more productive initially."

- **Targeted PI Re-engagement (Led by Felix/Jenny, supported by Jaine/CAE):**
  - If the program agrees to re-approach PIs:
    - The *Chair* (Felix), potentially with Jaine or CAE, contacts the selected prior PI(s).
    - **Framing is Critical:** "We are revisiting Cooper Beaman's situation. Funding availability was previously a major concern. Cooper is now actively pursuing [funding status/TAship] and has engaged CAE to develop specific accommodations and coaching for ADHD to address executive function challenges in the lab [provide brief, non-diagnostic summary of the *support plan*, not the diagnosis itself]. Given these developments and supports, would you be open to discussing a potential structured trial or mentorship?"
    - Highlight Cooper's strengths (QE score, writing skills, specific contributions from rotation).
    - Offer a follow-up meeting *including* Cooper, the PI, CAE specialist, and potentially Jaine/Felix to discuss the specific support plan and expectations.

Phase 3: Implementation of Supported Trial / Contingency (Spring/Summer 2025)

- **If a Prior PI Agrees to a Trial:**
  - Immediately implement the written, accommodated plan developed in Phase 2.
  - Regular check-ins involving all relevant parties are crucial for monitoring and adjustments.
  - Focus on demonstrating capability *with support*.
- **If No Prior PI Agrees (or Trial Fails Despite Accommodation):**
  - **Re-evaluate 6th Rotation:** Is there a PI identified by CAE/Chair as a particularly good fit for implementing the specific accommodations, even if new? This becomes the fallback *research* option.
  - **Formal Appeal:** If disqualification resumes, Cooper and his legal support initiate the formal appeal process focusing heavily on:

        - Failure to provide reasonable accommodations *during the initial 5 rotations and lab search process*, hindering the ability to secure an advisor.
        - Procedural errors in communication (separate meetings, lack of transparency).
        - Evidence that funding, not capability *with accommodation*, was the primary barrier initially cited.
        - Positive academic indicators (QE score).
    - **Negotiate Alternative Exit:** Simultaneously pursue the supported transfer (Masters/MCIP) or voluntary withdrawal *before* a final disqualification decision is rendered by the Dean. Jaine's role in facilitating this discussion with the Graduate Division is key.

Optimal Advice Summary:

- **For Cooper:** Be assertive but professional. Frame everything through the lens of seeking necessary disability accommodations that weren't previously provided. Control the information flow by insisting on CAE/Jaine's presence. Document meticulously. Leverage the "funding first" PI statements. Be prepared with specific accommodation requests for lab work. Consult legal counsel.
- **For CAE:** Be Cooper's strong advocate. Provide specific, research-relevant accommodation recommendations *quickly*. Formally advise the program on ADA obligations and the need to pause. Participate actively in meetings.
- **For Jaine:** Be the procedural watchdog and mediator. Ensure NSIDP follows policy *and* ADA law. Facilitate the crucial structured meetings. Escalate concerns to Graduate Division if NSIDP resists pausing or engaging appropriately with CAE.
- **For Legal/Advocacy:** Advise Cooper on rights, review all documentation and communications, guide the formal pause request, and prepare for potential appeals or negotiations.

This plan directly confronts the program's past communication issues, centers the University's legal obligation to accommodate, strategically leverages the PIs' stated primary concern (funding), and creates the best possible chance to revisit prior opportunities under corrected, supported conditions, thereby avoiding unfair disqualification.

Underlying Principles & Legal Framework:

1. **ADA/Section 504 Compliance is Paramount:** UCLA has a legal obligation to provide reasonable accommodations for documented disabilities and engage in a good-faith interactive process. Failure to do so, especially if it impacts academic evaluation (like rotation performance leading to lack of an advisor), constitutes potential discrimination and procedural error – strong grounds for appeal.
2. **Interactive Process is Ongoing:** The process doesn't end with testing accommodations. It must extend to the research environment and the process of

securing an advisor. The recent engagement with coaching and CAE's current evaluation *necessitates* pausing punitive academic actions.

3. **Timeliness & Mitigation:** The program initiated disqualification *after* the student engaged CAE more deeply and started coaching. The student is actively seeking solutions. Dismissal without allowing these interventions a chance is procedurally flawed.
4. **Documentation is Power:** Every interaction, request, denial, piece of feedback (or lack thereof), and accommodation discussion must be meticulously documented by Cooper and his support team.
5. **Focus on Future Solutions, Leverage Past Failures:** While past rotations are relevant to demonstrate potential procedural failures (lack of accommodation/structured feedback), the focus must be on creating a *supported path forward*.

Optimal Plan - Phased Approach (Effective Immediately, Spring 2025):

Phase 1: Immediate Halt & Formalizing the Process (Weeks 1-3 of Spring Quarter)

- **Cooper's Actions (Urgent):**
    1. **Formal Written Request to Pause:** Draft and send an immediate, formal email to NSIDP Chair (Felix), CC'ing Jaine Park (Case Manager), Jenny Lee (SAO), and Cooper's assigned CAE Specialist.
        - **Subject:** Urgent Request to Pause Academic Disqualification Process - Cooper Beaman (UID: 105692562) - Active CAE Evaluation
        - **Body:**
            - Acknowledge receipt of the Nov 19 plan and the program's concern about not securing an advisor by the 3/14 benchmark.
            - State clearly you are registered with CAE for ADHD and are currently undergoing evaluation for *research-specific* accommodations. Mention you have just begun working with an executive function coach (funded by the Will Rogers Scholarship via CAE) to address specific performance challenges (time management, organization, planning).
            - Respectfully assert that proceeding with disqualification *before* reasonable accommodations are determined, implemented, and given a chance to take effect would violate the University's obligations under ADA/Section 504 and University policy (cite UCLA Standards & Procedures regarding appeals based on procedural error/discrimination).
            - Reference your strong written QE performance as evidence of core capability.
            - Politely note the challenges in previous rotations, including potentially inconsistent feedback structures or expectations that may not have accounted for your disability, hindering your ability to demonstrate full potential or secure an advisor despite good-faith efforts and usable work product.

        - Formally request the disqualification process be *held in abeyance (paused)* pending: a) Completion of CAE's evaluation and formal accommodation recommendations; b) A reasonable period (e.g., through Spring/Summer 2025) to implement and assess the effectiveness of these accommodations and coaching in a research setting.
        - Reiterate your commitment to finding solutions and succeeding in the program. Request a meeting (with CAE/Jaine present) to discuss this pause and next steps.
    2. **Intensify CAE Collaboration:** Meet immediately with your CAE specialist. Provide them *all* documentation (this letter, NSIDP letter, emails, rotation summaries). Discuss specific research tasks (planning experiments, data analysis, time management for lab work, communication with PIs) and brainstorm concrete accommodations (e.g., assistive tech, structured meeting templates, project management support, explicit communication protocols).
    3. **Document Everything:** Save all emails. Take detailed notes after every meeting (date, time, attendees, key points, action items). Keep copies of work produced during rotations.
    4. **Prepare for Group Meeting:** If Felix insists on the group meeting, Cooper should state he will attend *only with* his CAE specialist and/or Jaine present. Prepare an agenda focusing on the need to pause disqualification, implement accommodations, and find a structured path forward. Use the leaked email carefully – perhaps frame it as, "I understand there have been internal discussions about my continuation; I want to ensure all options, including those involving accommodations, are fully explored before any final decisions."
    5. **Consult Student Legal Services:** Immediately schedule a consultation. Provide them all documentation. Get advice on your rights and the University's obligations.
- **CAE Actions (Urgent):**
    1. **Formal Letter to NSIDP/Jaine:** Send a formal letter/email confirming Cooper is registered, undergoing evaluation for research accommodations, and has started coaching. Strongly recommend pausing the disqualification process pending this evaluation and subsequent implementation period, citing ADA/504 interactive process requirements.
    2. **Expedite Evaluation:** Prioritize Cooper's case to provide specific, actionable accommodation recommendations for a *research lab environment* as quickly as possible.
    3. **Attend Meetings:** Assign the specialist to attend the critical interactive process/group meetings with Cooper, NSIDP, and Jaine.
- **Jaine Park (Case Manager) Actions (Urgent):**
    1. **Advise NSIDP on Policy/Risk:** Immediately advise Felix/Jenny that proceeding with disqualification while a CAE evaluation for relevant accommodations is pending is procedurally flawed and carries legal risk. Reference the Standards & Procedures appeal grounds. Strongly recommend a pause.

2. **Escalate if Necessary:** If NSIDP seems intent on proceeding despite CAE involvement, inform the Graduate Division leadership (Associate Dean overseeing NSIDP) of the procedural concerns and potential ADA non-compliance.
3. **Mediate & Document:** Facilitate communication. Ensure NSIDP formally responds to Cooper's pause request. Document the program's response and the ongoing process.

Phase 2: Developing and Implementing a Supported Plan (Weeks 3-10 of Spring Quarter)

- **Goal:** Design a concrete, accommodated plan for Cooper to demonstrate research capability.
- **Formal Interactive Process Meeting:** Once CAE provides initial recommendations, convene the meeting (Cooper, Felix, Jenny, Jaine, CAE Specialist, Coach - if consented).
    - Review CAE recommendations.
    - Discuss how these address past rotation challenges and PI concerns (e.g., if organization was an issue, how will coaching + assistive tech address it?).
    - Brainstorm *specific* ways to implement accommodations in a lab setting.
    - Identify 1-2 potential PIs (perhaps revisit one, or target labs known for structure/mentorship) willing to consider a *structured, accommodated* trial/rotation.
    - Develop a written plan for this trial (e.g., a Spring/Summer rotation or joining a project provisionally).
- **The Plan Document:** Must include:
    - Specific learning objectives and research tasks.
    - Clearly defined accommodations (e.g., weekly check-ins using a specific agenda, use of project management software, explicit written instructions for tasks).
    - Defined roles for coach and CAE support.
    - Measurable metrics for success (realistic, considering accommodations).
    - Regular feedback schedule involving PI, student, and potentially CAE/Chair initially.
    - Clear timeline (e.g., end of Spring or Summer).
- **Addressing PI Concerns (Funding/Productivity):**
    - **Funding:** Cooper continues applying for GATP/NRSA/other funding. The program explores TAships *as bridge support*, acknowledging it doesn't replace research progress but may be a *temporary reasonable accommodation* to allow the supported trial to occur. Can the Will Rogers funds be used flexibly? Can departmental discretionary funds offer short-term support *contingent* on this plan?
    - **Productivity:** Frame the plan around *enabling* productivity *through* structure and accommodation. Success metrics should be adjusted accordingly, focusing on mastery of specific skills and consistent engagement with support structures, not necessarily matching the raw output speed of a neurotypical student *initially*.

Leverage Cooper's writing skills for protocols, figure legends, background sections etc.

Phase 3: Execution and Evaluation (Spring Quarter / Summer 2025)

- **Cooper's Actions:** Fully engage with the supported rotation/trial, coaching, and accommodations. Proactively communicate progress and challenges. Document meeting outcomes.
- **PI Actions (if one agrees):** Implement the agreed-upon accommodations and structured mentorship plan in good faith. Provide regular, specific, documented feedback based on the established plan metrics.
- **NSIDP/CAE/Jaine Actions:** Monitor the plan's implementation via scheduled check-ins. Troubleshoot issues. Document progress and feedback.
- **End-of-Period Evaluation:** Based on the pre-defined plan metrics, assess whether Cooper demonstrated sufficient progress *with accommodations* to warrant securing that PI as a permanent advisor OR to justify seeking another placement with the now-proven support strategies.

Contingency Planning / Addressing Resistance:

- **If NSIDP Refuses to Pause:** Cooper, guided by legal/advocacy, immediately files a formal complaint/grievance with the Graduate Division citing procedural error (failure to pause for interactive process) and potential disability discrimination. Simultaneously explore options like Leave of Absence or transfer.
- **If No PI Agrees to a *Supported* Trial:** This is tougher. Document the outreach and reasons for refusal. If reasons seem pretextual or fail to consider the *proposed accommodations*, this strengthens the procedural error/discrimination claim. At this point, focus shifts heavily to:
    - **Formal Appeal:** If disqualification proceeds, file a formal appeal based on procedural error (failure to provide reasonable accommodation during the *lab finding process*) and potentially discrimination. Use all documentation, QE scores, leaked email, and CAE reports as evidence.
    - **Negotiated Alternative:** Explore a supported transfer to a more suitable program (MCIP, Master's) or a structured voluntary withdrawal, potentially with assistance from the Graduate Division, *before* disqualification becomes official.
- **Funding Gaps:** Relentlessly pursue TAships, GWC roles, need-based aid, and external fellowships. Document these efforts. Lack of funding *alone* is complex; programs are generally expected to support funded students, but PI grant realities are also valid. The key is whether the *search* for funding/placement was hampered by lack of accommodation.

Optimal Outcome: The ideal is for NSIDP to pause disqualification, engage fully with CAE, find a PI willing to implement a structured, accommodated trial, and for Cooper to succeed in that environment, leading to a permanent advisor. This requires flexibility, communication, and a

focus on support over punitive action from the program, coupled with diligent effort and self-advocacy from Cooper and his team. Even if the PhD ultimately proves unviable *after* these steps, a supported transition (Master's, withdrawal) is vastly preferable to a contested disqualification based on potentially flawed procedures.

I. Predicted Likely Scenario (Spring 2025 Quarter - Immediate Aftermath)

1. **Contested Disqualification Process:** NSIDP has initiated the *process* (interdepartmental review) based on failing the benchmark (no advisor by 3/14). However, the Academic Case Manager (Jaine) and Policy Coordinator are now involved and consulting with NSIDP leadership (Felix, Jenny) *before* it likely progresses to the Associate Dean/Graduate Division. This consultation is crucial.
2. **CAE Intervention Becomes Central:** CAE's formal evaluation and recommendations for *research-specific* accommodations (beyond testing) will be completed. Given Cooper's ADHD and executive function coaching, these recommendations will likely focus on structure, planning, communication, and potentially modified expectations during an initial phase. CAE will strongly advocate for these to be implemented *before* a final decision on disqualification is made, framing the past difficulties potentially as a failure of the *system* to provide necessary accommodations during the critical lab-finding phase.
3. **Pressure on NSIDP Leadership:** Felix and Jenny face conflicting pressures: upholding program standards/timelines vs. adhering to ADA/Section 504 requirements for a robust interactive process and reasonable accommodation, now strongly highlighted by CAE and Academic Case Management. The leaked email adds a layer of scrutiny regarding objectivity. Proceeding with disqualification without fully addressing CAE's input is legally and procedurally perilous.
4. **Likely Outcome: Pause & Formal Interactive Process:** The most probable outcome, driven by Academic Case Management/Policy Coordinator advice and CAE's formal intervention, is that **NSIDP will be strongly advised (or required by Graduate Division) to officially pause the disqualification process.** This pause is necessary to:
    - Allow CAE to finalize and formally present accommodation recommendations.
    - Permit the program to engage in a documented *interactive process* with Cooper and CAE to determine how these accommodations can be implemented in finding/succeeding in a lab.
    - Give a *limited, defined timeframe* for the new coaching and potential accommodations to show effect.
5. **Student Status:** Cooper remains enrolled for Spring 2025 but in a precarious position. Securing funding (TAship, GWC, pending fellowships) is critical but may be complicated by the lack of a formal advisor certifying academic progress (a potential workaround might be needed via the Chair or Graduate Advisor temporarily).

II. Optimal Plan to Avoid Dismissal & Achieve Fair Outcome (Detailed Steps for Each Party)

This plan focuses on creating a structured, accommodation-informed opportunity for Cooper to secure an advisor and demonstrate progress, while respecting legitimate constraints.

A. For Cooper Beaman (Student):

1. **Formalize Everything with CAE:**
    - **Action:** Work urgently with your CAE specialist to finalize the list of *specific, reasonable accommodations* needed for success in a *research lab setting*. Examples: structured weekly check-ins with PI using a defined agenda, use of specific project management software, assistance breaking down large tasks, written instructions/expectations, flexibility in work timing (if appropriate), quiet workspace options, clear communication protocols.
    - **Action:** Request CAE formally communicate these approved accommodations to Jaine Park and Felix Schweizer ASAP. Explicitly request these be considered as part of a *revised* academic plan and lab search strategy.
    - **Justification:** Formal CAE documentation is your strongest leverage point under ADA/Section 504. It shifts the focus from past "failures" to future "supported opportunities."
2. **Document Past Barriers:**
    - **Action:** Compile the detailed portfolio of rotation work (as started: `https://is.gd/NSIDP_Rotation_Portfolio`). For each rotation, *briefly and objectively* document: a) specific tasks/projects undertaken, b) deliverables produced (link to data/code/presentations), c) the *specific* feedback received (or lack thereof), d) any *informal* requests for structure/support made, and e) how you believe unaddressed ADHD-related challenges impacted efficiency/productivity *despite your effort*. Share this synthesized summary with CAE and Jaine.
    - **Justification:** Provides concrete evidence of effort, contribution, and the potential impact of unaccommodated disability/mismatched structure. Counters vague claims of insufficient productivity.
3. **Communicate Strategically with NSIDP/Jaine:**
    - **Action:** Formally write to Felix (cc Jaine, Jenny) acknowledging the situation, reiterating your commitment, stating you are working with CAE on *specific research accommodations* and have started coaching, and formally requesting the disqualification process be paused to allow these interventions. Reference your high QE score. Briefly state your concerns about the lack of structured feedback/expectations in prior rotations hindering timely identification of support needs.
    - **Action:** Respond to Jaine about meeting availability. Request your CAE specialist and/or coach be present. Frame the meeting goal as collaborating on a *supported path forward* incorporating CAE recommendations.
    - **Justification:** Formal communication creates a record. Focusing on solutions and accommodations is more productive than dwelling solely on past issues. Involving CAE/Jaine ensures institutional awareness.

4. **Leverage Strengths & Interests:**
    - **Action:** Explicitly highlight your interest and developing skills in *computational psychiatric genetics* (evident from NRSA plan, rotation projects). Frame this as your desired research area.
    - **Justification:** Directs the search towards labs where your hyperfocus and writing skills on computational tasks can be an *asset*, potentially mitigating concerns about wet-lab efficiency if that was a prior issue. Aligns with funding trends (computational/genomic focus).
5. **Consult Student Legal Services:**
    - **Action:** Schedule an immediate consultation. Bring all documentation (Nov 19 letter, emails, rotation summaries, CAE info). Understand your rights regarding disability accommodation in graduate education, procedural fairness, and the appeals process.
    - **Justification:** Ensures you know your rights and options if the program does not follow a fair, accommodation-focused process.

B. For the Center for Accessible Education (CAE):

1. **Expedite & Formalize Recommendations:**
    - **Action:** Swiftly finalize the assessment, focusing on *specific, practical accommodations applicable to a neuroscience research lab environment* (beyond just coursework). Issue a formal Letter of Accommodation (LOA) addendum detailing these research-specific needs.
    - **Justification:** Provides the official basis for the program's obligation to accommodate. Vague recommendations are unhelpful.
2. **Advocate Directly:**
    - **Action:** The assigned CAE specialist should proactively contact Jaine Park and Felix Schweizer to discuss the recommendations, explain the functional limitations of ADHD in a research context, emphasize the potential efficacy of the new coaching, and strongly recommend pausing disqualification to allow implementation.
    - **Justification:** CAE holds expertise and institutional authority on accommodation matters. Direct advocacy is often more effective than relying solely on the student.
3. **Offer PI/Program Training/Consultation:**
    - **Action:** Offer to provide information or a brief consultation to potential PIs or the NSIDP committee on effective strategies for mentoring neurodivergent students, particularly those with ADHD, focusing on structure and clear communication.
    - **Justification:** Proactively addresses PI concerns about mentorship burden by providing solutions and resources.

C. For Academic Case Management (Jaine Park & Policy Coordinator):

1. **Ensure Procedural Hold:**

- **Action:** Strongly advise NSIDP leadership (Felix, Jenny) that proceeding with disqualification while a formal CAE evaluation for research accommodations is pending, and before new interventions (coaching) have been assessed, constitutes a significant procedural flaw and potential ADA violation. Advocate for an official pause.
- **Justification:** Upholds university policy and legal obligations regarding the interactive process. Protects the university from appeals/litigation.

2. **Facilitate the Interactive Process:**
    - **Action:** Convene and mediate the meeting between Cooper, NSIDP leadership, and CAE. Ensure the focus is on understanding the accommodations and developing a *revised, supported academic plan* for securing an advisor.
    - **Justification:** Provides neutral facilitation to de-escalate conflict and focus on required procedures and potential solutions.
3. **Document Official Plan:**
    - **Action:** If a plan for a supported rotation/trial is agreed upon, ensure it is formally documented, including specific accommodations, expectations, timelines, and evaluation metrics, with input from CAE.
    - **Justification:** Creates clarity and accountability for all parties.

D. For UCLA Student Legal Services:

1. **Advise Student:**
    - **Action:** Inform Cooper of his rights under ADA/Section 504, university policies (including appeal procedures outlined in *Standards & Procedures*), and the UAW contract (though less relevant here).
    - **Justification:** Empowers the student with knowledge.
2. **Review Communications:**
    - **Action:** Review the Nov 19 letter, emails (including the leaked one), and any subsequent program communications for procedural compliance and potential evidence of discrimination or lack of good-faith interactive process.
    - **Justification:** Identifies potential grounds for formal appeal if necessary.
3. **Prepare for Appeal (Contingency):**
    - **Action:** If NSIDP proceeds with disqualification despite CAE interventions, assist Cooper in drafting a formal appeal to the Graduate Division based on procedural error (failure to provide reasonable accommodation during the lab search process) and potentially discrimination based on disability.
    - **Justification:** Provides necessary support if the program fails to follow the optimal, compliant path.

E. For NSIDP Chair (Felix Schweizer) & SAO (Jenny Lee):

1. **Immediately Pause Disqualification:**
    - **Action:** Formally notify the interdepartmental committee and Graduate Division that the recommendation process is paused pending completion of CAE

evaluation and implementation of an interactive process regarding research accommodations.
    - **Justification:** Essential first step for compliance and fairness. Allows space for solutions.
2. **Acknowledge & Reset:**
    - **Action:** Communicate directly with Cooper (with Jaine cc'd) acknowledging receipt of his concerns and CAE's involvement, confirming the pause, and committing to a formal interactive process meeting involving CAE to discuss a supported path forward. Address the leaked email directly if possible, perhaps explaining context or reaffirming commitment to a fair process now.
    - **Justification:** Rebuilds a semblance of trust and signals adherence to required procedures.
3. **Actively Seek a *Supported* Placement:**
    - **Action:** Work *with* CAE to identify 1-2 faculty members whose lab structure and mentorship style might be amenable to implementing the recommended accommodations. Approach them not just with the student's record, but with *CAE's proposed support plan*. Explore a *funded* (perhaps using temporary program/bridge funds if T32/PI funds are truly unavailable) trial rotation (e.g., for Spring or Summer) with *explicitly defined accommodations, check-ins, and goals*. Focus on labs aligned with Cooper's computational interests.
    - **Justification:** This is the core "reasonable accommodation" now – providing a *structured opportunity* that didn't exist before. It addresses PI funding/mentorship concerns by involving support structures.
4. **Revise Expectations (Trial Period):**
    - **Action:** For any trial rotation/placement, work with Cooper, the PI, and CAE to set *realistic, written expectations* for the *initial phase*, focusing on specific tasks and skill development relevant to the accommodations and coaching. Productivity expectations should be adjusted initially.
    - **Justification:** Standard rotation expectations may be inappropriate without accommodation. Clear, adjusted goals provide a fair basis for evaluation.
5. **Contingency Planning:**
    - **Action:** If, after a *fully supported and accommodated trial period*, placement is still unsuccessful, *then* discuss alternative pathways (Masters transfer, guided withdrawal) seriously with Cooper, Jaine, and CAE, ensuring all support options were genuinely exhausted. Document this process meticulously.
    - **Justification:** Provides a fair process if the PhD path proves unviable *despite* accommodations, fulfilling obligations before resorting to disqualification.

By following these steps, particularly the immediate pause and the CAE-informed interactive process leading to a *supported* placement attempt, all parties can work towards an outcome that respects Cooper's rights and potential, adheres to legal and university requirements, and addresses the legitimate concerns and constraints of the PIs and the NSIDP program. Dismissal is avoidable if this structured, accommodation-focused approach is implemented in good faith.

I. Predicted Likely Events (Spring 2025 Quarter)

Based on the information provided (NSIDP letter dated Nov 19, 2024, setting benchmarks; immediate initiation of disqualification after 5th rotation failure; the leaked email; ongoing CAE evaluation and new coaching), the immediate next steps are likely to be contested and procedurally complex:

1. **NSIDP Disqualification Process Continues (Initial Phase):**

    - **Likely Action:** The NSIDP Chair (Felix), having already initiated the process based on the unmet benchmark (failure to secure advisor by 3/14), will likely proceed with the interdepartmental vote on the recommendation for disqualification, as indicated by Jenny's communication confirming a formal petition was submitted after the 5th PI declined.
    - **Justification:** Programs often operate based on established written policies and timelines. The Nov 19 letter created a clear (though potentially flawed given the circumstances) basis for initiating this process when the deadline passed without an advisor. The leaked email suggests there might have been internal skepticism about the student's continuation *before* the final deadline, potentially leading to a quicker trigger.
    - **Risk:** Proceeding *without* pausing for CAE's full evaluation and consideration of the new coaching intervention is procedurally risky and potentially non-compliant with ADA/Section 504 interactive process obligations.

2. **CAE Intervention:**

    - **Likely Action:** CAE, now fully engaged, will complete its evaluation focusing on *research-related* accommodations needed due to ADHD (beyond just testing). They will likely identify specific strategies (time management tools, structured communication protocols, project breakdown assistance, environment modifications) and formally communicate these recommendations to the student, NSIDP, and the Graduate Division (via Academic Case Management). The executive function coaching is a key part of this.
    - **Justification:** CAE's mandate is to ensure access and reasonable accommodation. Given the student's documented disability, strong QE performance, and the clear link between executive function challenges (time management, organization) and lab performance/PI concerns, they have a strong basis to recommend specific, previously untried interventions.
    - **Impact:** CAE's formal recommendations carry significant weight. They will likely advocate for the student to be given a chance to succeed *with these accommodations implemented*, potentially recommending a pause in the disqualification process.

3. **Academic Case Management (Jaine Park) & Policy Coordinator Role:**

- **Likely Action:** Jaine will continue to liaise between the student, NSIDP, CAE, and the Graduate Division. She and the Policy Coordinator will consult with NSIDP leadership (Felix, Jenny) regarding the *correct procedure* for disqualification, especially considering the active CAE evaluation and ADA implications. They will review UCLA's *Standards and Procedures for Graduate Study* (especially regarding disqualification appeals, pp. 37-39) and advise NSIDP accordingly.
- **Justification:** Their role is to ensure University policy and procedural fairness are upheld. They recognize the legal sensitivities surrounding disability accommodations.

4. **Student (Cooper Beaman) Actions:**

    - **Likely Action:** Cooper will likely formalize accommodation requests through CAE, continue meeting with the coach, potentially seek legal/advocacy advice (e.g., UCLA Student Legal Services), and attempt to navigate the proposed group meeting while managing the lack of trust created by the leaked email. They will need to decide whether to formally contest the disqualification process immediately based on procedural errors (failure to accommodate) or wait for the formal recommendation and appeal later. Continuing enrollment and seeking TAships/alternative funding remains critical but challenging without an advisor's explicit support for academic progress.
    - **Justification:** These are logical steps to protect their rights, utilize available support, and address the immediate practicalities of enrollment and funding.

5. **Pivotal Point - NSIDP Response to CAE:**

    - **Scenario A (Pause):** Influenced by Jaine/Policy Coordinator's guidance on procedure and CAE's formal recommendations, NSIDP *pauses* the disqualification to allow for a defined period (e.g., Spring quarter) where the student attempts another rotation or trial period *with the newly defined accommodations and coaching support*. This is the procedurally safer and more ethically defensible route.
    - **Scenario B (Proceed):** NSIDP pushes the disqualification vote/recommendation forward, arguing the student already had ample opportunity (5 rotations) and failed to meet the Nov 19 letter's terms, potentially viewing the accommodations issue as separate or too late. This route carries significant risk of a successful appeal by the student based on procedural error (failure to provide reasonable accommodations during the placement process).

Prediction: Given the immediate initiation of disqualification and the leaked email, **Scenario B carries a concerningly high probability unless Jaine/Policy Coordinator and CAE intervene strongly and effectively.** However, the *optimal and most legally sound path* is

Scenario A. The next few weeks, centered around CAE's findings and Jaine's procedural guidance to NSIDP, will be decisive. Dismissal is **not** the only option at this stage if procedures focused on accommodation are correctly followed.

II. Optimal Advice for Achieving the Best Outcome for All

The "optimal outcome" here prioritizes fulfilling the University's educational mission and legal obligations fairly, while acknowledging resource limitations and faculty autonomy. It likely involves giving the student a properly supported chance to succeed, rather than immediate dismissal.

- **For the Student (Cooper Beaman):**
    1. **Document Rigorously:** Compile *all* emails, rotation feedback (or lack thereof), work samples from rotations, QE results, accommodation letters (current and requested), coaching details, funding applications/status, and notes from meetings. Create a timeline (as partially done in the emails).
    2. **Maximize CAE Engagement:** Work intensively with the disability specialist to identify *specific, actionable accommodations* for the lab environment (e.g., weekly structured meetings with PI using a template, project management software, breaking tasks down, preferred communication methods). Request CAE formally communicate these as necessary for equal access to the program. Emphasize that lack of such accommodations during rotations was a barrier.
    3. **Communicate Formally & Assertively (but Professionally):** Write *immediately* to Felix (Chair), cc'ing Jaine (Case Mgr) and Jenny (SAO). State:
        - You are actively engaged with CAE to determine necessary research accommodations for your documented ADHD, which were not fully explored/implemented during prior rotations.
        - You have just begun executive function coaching to address specific challenges.
        - You request the disqualification process be *paused* pending the outcome of the CAE evaluation and a reasonable period to implement/assess new accommodations and coaching strategies.
        - Reference your top QE score and commitment to the program.
        - Politely note the lack of specific, actionable feedback from prior rotations hindered your ability to adjust or seek appropriate support earlier.
    4. **Strategic Group Meeting:** If the meeting proceeds, insist Jaine and/or your CAE specialist attend. Focus the agenda on finding a path forward *with defined supports*. Present CAE's preliminary recommendations. Use it to seek clarity on expectations and realistic options (supported 6th rotation, trial period, transfer support). Avoid getting bogged down in past grievances; focus on solutions *predicated on accommodation*.
    5. **Explore All Options Simultaneously:** Continue seeking external funding. Investigate the Masters/MCIP transfer options Felix mentioned *as a parallel path*,

without prejudice to your right to pursue the PhD with accommodations. Explore TAships/GWC role for funding.

6. **Seek Advocacy:** Consult UCLA Student Legal Services and/or disability rights advocates *immediately*. Understand your rights under ADA/504 and university appeal procedures (outlined in Standards & Procedures, p. 38-39).

- **For the CAE:**
    1. **Prioritize & Expedite:** This case requires urgent attention. Complete the assessment of research-related accommodations swiftly.
    2. **Formal, Strong Recommendations:** Issue clear, specific, written recommendations to NSIDP/Graduate Division. Crucially, *state whether the lack of these accommodations previously constituted a barrier to equal opportunity* in the lab-finding process.
    3. **Advocate for Pause:** Formally recommend NSIDP pause disqualification proceedings to allow for good-faith implementation and evaluation of the recommended accommodations and coaching.
    4. **Offer PI Consultation:** Offer to meet with potential PIs (with student consent) to explain recommended accommodations and support strategies for mentoring students with ADHD. Provide resources.
- **For the NSIDP Chair (Felix Schweizer):**
    1. **IMMEDIATELY PAUSE:** Halt the disqualification process. This is essential for procedural fairness and ADA compliance given the active CAE evaluation, new coaching, and questions about prior accommodation efforts. Inform the committee/Associate Dean the process is paused pending critical disability-related information.
    2. **Acknowledge Procedural Concerns:** Communicate to Cooper and Jaine that the process is paused to allow full consideration of CAE input and coaching. Acknowledge the student's perspective on needing structured support.
    3. **Engage CAE as Primary Partner:** Treat CAE's recommendations as essential guidance. Meet with them and Jaine to understand the necessary accommodations fully.
    4. **Revisit PI Feedback (Critically):** Investigate the lack of clear feedback from PIs 1-4. Address the problematic implications of PI 5's "productivity without mentoring" expectation and the leaked email. This requires candid internal conversations about mentorship standards and potential bias.
    5. **Facilitate a *Supported* Placement Attempt:** Actively seek a faculty member willing to offer a *trial rotation or provisional mentorship* specifically implementing the CAE-recommended accommodations and structured coaching plan. This is the core of the interactive process now. Frame it as a supported trial, not just "another rotation." Consider labs known for structure or strong mentorship.
    6. **Define Success Clearly (with Input):** If a trial placement occurs, work with the student, PI, CAE, and coach to define ***specific, measurable, achievable, relevant, time-bound (SMART)*** goals and evaluation criteria *that account for the accommodations*.

7. **Transparency & Repair:** Address the leaked email's impact. Rebuilding trust requires acknowledging the concern it caused and demonstrating a transparent, supportive path forward. The group meeting, if reframed around implementing CAE recommendations, could help.

- **For the Academic Case Manager (Jaine Park):**
    1. **Ensure Policy Compliance:** Guide NSIDP firmly on adhering to disqualification procedures *and* ADA interactive process requirements. Emphasize the need to pause proceedings pending CAE input, as outlined in UCLA's Standards & Procedures (which allow appeals based on procedural error or discrimination).
    2. **Facilitate Communication:** Serve as the neutral hub ensuring information flows between Cooper, NSIDP, CAE, and Graduate Division leadership. Document key communications and decisions.
    3. **Connect Student to Resources:** Ensure Cooper is aware of all appeal rights, Student Legal Services, Graduate Writing Center, CAPS, and other support structures.
    4. **Monitor Progress:** Keep the Associate Dean informed of the situation, particularly the interplay between academic progress standards and disability accommodation obligations.

Overall Optimal Path: The optimal path involves NSIDP pausing disqualification, fully engaging with CAE's recommendations, and facilitating a final, properly supported attempt for Cooper to secure an advisor *with accommodations and coaching integrated*. This might be a structured 6th rotation or a provisional placement. Success requires clear expectations, defined support, and regular monitoring involving all parties (Student, PI, Chair, CAE, Coach). If this genuinely fails *despite* full accommodation efforts, then options like transferring to a Master's program or voluntary withdrawal become more appropriate considerations than immediate disqualification. Dismissal should only occur after demonstrating that reasonable accommodations could not overcome the barriers to meeting essential PhD program requirements.

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1. Can the Program/Department Still Disqualify the Student?

Yes, theoretically, the program *can* still recommend disqualification, but doing so under these specific circumstances is fraught with legal, ethical, and procedural complexities and requires extreme diligence from the program.

1. **Core Requirement:** Successfully joining a lab and progressing in dissertation research under a faculty advisor is a non-negotiable milestone for a PhD degree. Failure to secure an advisor, regardless of the reason, means the student cannot fulfill degree requirements. This constitutes a failure to make "timely progress toward the degree," which the NSIDP policy explicitly lists as grounds for potential disqualification.
2. **The Crucial Caveats (Why it's not automatic):**
    - **Disability & Accommodations (ADA/Section 504):** The student has a documented disability (ADHD) and is entitled to reasonable accommodations. The University/program has a legal obligation to engage in a good-faith

interactive process to determine and provide effective accommodations. This obligation extends beyond coursework into the research/lab environment, including the process of *finding* a lab.
- **Recent Intervention:** The student has *just* begun working with an executive functions coach. The potential benefits of this intervention may not yet be fully realized or demonstrable. Dismissing the student before this support has a reasonable chance to show effect could be seen as premature.
- **"Good Faith Effort" by Student:** The student has completed multiple rotations, apparently produced usable work (indicating some level of contribution), performed exceptionally well on the written QE, and is actively seeking support (coaching). This demonstrates effort on their part.
- **PI Reasons:** The reasons cited by PIs (funding, space, mentorship capacity) are often legitimate constraints. However, the specific feedback about wanting "higher productivity *without mentoring*" is problematic and potentially indicates unreasonable expectations or a reluctance to engage with the student's needs, potentially including their need for accommodations or structured support. It raises questions about whether the PIs adequately considered accommodations or engaged in the interactive process during the rotations.
- **Pending Funding:** This adds ambiguity. If the student secures substantial external funding (e.g., an F31 fellowship), it could significantly change a PI's willingness/ability to take them on, potentially resolving the issue.

Justification: While the *outcome* (no advisor) might technically trigger disqualification rules, the *process* leading to that outcome is critical. If the program cannot demonstrate that it, and the rotating faculty, rigorously engaged in the interactive process, considered reasonable accommodations *within the lab-finding context*, and exhausted all reasonable avenues to support the student *given their disability*, a disqualification could be successfully challenged legally or internally. The university must ensure its processes didn't inadvertently discriminate based on disability by failing to accommodate the student's needs during the critical lab search phase.

2. Optimal Way Forward for Program Chair and Student

Dismissal should be viewed as an absolute last resort. The optimal path requires immediate, structured, and collaborative intervention, focusing heavily on the disability accommodation aspect:

3. **A. Immediate Action (Program Chair):**
    - **Pause Disqualification:** Put any formal disqualification recommendation on hold.
    - **Information Gathering:** Meticulously document *everything*:
        - Specific, detailed feedback from *all 5* rotation PIs (beyond generic reasons). What *specific* productivity/efficiency/skill issues were observed?

Were these discussed with the student *during* the rotation? Were any accommodations discussed or implemented?
    - Student's perspective on each rotation and the feedback received.
    - Details of the student's current accommodations via the Center for Accessible Education (CAE).
    - Information from the executive function coach (with student's permission) regarding goals, progress, and estimated timelines for improvement.
    - Concrete details about the "pending funding" – type, source, likelihood, timeline.
4. **B. Formal Interactive Process Meeting (Urgent & Mandatory):** This is the cornerstone. The Chair must convene a meeting including:
    - Student
    - Program Chair and/or Graduate Advisor
    - **CAE Disability Specialist** (absolutely critical for guidance on reasonable accommodations in a research setting)
    - Student's Executive Function Coach (if student consents)
    - *Potentially* a faculty member the student trusts or who has disability advocacy experience (as a support person, with student consent).
    - **Goal:** To holistically assess the situation *with the disability as a central factor*.
        - Analyze past rotation challenges: Were expectations clear? Were challenges related to ADHD? Were accommodations appropriate/sufficient/implemented?
        - Assess current support: What strategies is the coach implementing? How can these be applied *specifically* to lab work expectations (e.g., project management tools, communication strategies, structured feedback mechanisms)?
        - Develop a *concrete support plan*: What specific accommodations and support structures (coaching, regular check-ins, modified tasks initially) might enable success in a lab *now*?
        - Clarify funding: What is the realistic impact of the pending funding?
5. **C. Re-Engage Faculty (Strategically & Supported):**
    - The Chair, *potentially accompanied by the CAE specialist*, must approach potential faculty mentors (perhaps revisiting previous ones or identifying new ones known for strong mentorship or structured environments).
    - **Shift the framing:** The conversation is not "Can you take this student who failed 5 rotations?" but "We have a capable student (top QE score) with ADHD who is now receiving targeted executive function coaching and has specific accommodations recommended by CAE. Here is a proposed support plan. Could this student potentially succeed in your lab *with these structures in place*, perhaps on a specific project or with co-mentorship?"
    - Explore Co-Mentorship: Can workload/mentorship/funding be shared?
    - Consider Fit & Structure: Identify labs with more structured project management or mentorship styles. Avoid PIs known to expect high independence with minimal input, especially early on.

6. **D. Define a Clear, Time-Limited Plan:** If a potential path forward is identified (e.g., another rotation with specific supports, a provisional placement contingent on funding):
    - Set clear, realistic, written expectations and milestones *developed in consultation with CAE* and considering the coaching plan.
    - Establish regular check-ins involving the student, PI, Chair, and potentially CAE/coach.
    - Define the timeframe (e.g., one more quarter) and the criteria for evaluating success.
7. **E. Transparency with Student:** Maintain open communication about the steps being taken, the possibilities, the challenges, and the potential outcomes, including the conditions under which disqualification might ultimately be recommended if no viable path materializes *despite these enhanced efforts*.

3. How to Proceed When the Typical Format Hasn't Worked (Avoiding Dismissal)

The typical format (3 rotations -> match) has failed. The process now *must* deviate and explicitly incorporate the disability accommodation framework into the lab placement process:

8. **Leverage CAE:** This office is key. They are experts in reasonable accommodations and can help bridge understanding between the student's needs and faculty expectations/lab realities. Their involvement signals the University is taking its accommodation responsibilities seriously.
9. **Focus on Structure & Support:** The search shifts from finding *any* lab to finding a lab *willing and able* to implement necessary structures, potentially with guidance from CAE and the coach. This might mean a modified rotation goal (e.g., focusing on specific techniques with structured supervision) or a trial period in a lab.
10. **PI Education/Consultation:** The Chair may need to (sensitively) consult with potential PIs about best practices for mentoring students with ADHD, leveraging resources from CAE or faculty development programs.
11. **Explore All Programmatic Options:** Are there teaching opportunities, curriculum development roles, or other program-related activities the student could engage in *temporarily* (e.g., for one quarter) to remain enrolled while coaching progresses and the funding situation clarifies, allowing more time for a lab match? This is unconventional but might be a *reasonable accommodation* if it keeps the student progressing academically while addressing the immediate barrier.
12. **Document Everything:** Every attempt to place the student, every accommodation discussed/offered/implemented, every PI interaction, and every meeting outcome needs meticulous documentation to show the program exhausted all reasonable options.

Is Dismissal the Only Option?

No, not yet, and perhaps not at all. Dismissal should only become the *final* option if:

1. The **rigorous interactive process**, explicitly involving CAE and considering the new coaching support, fails to identify *any* reasonable accommodation or placement strategy that allows the student to secure an advisor.
2. Despite structured support and accommodations, and sufficient time for coaching to take effect, the student is demonstrably unable to meet the *essential, non-discriminatory* requirements for PhD-level research progress in *any* suitable lab environment within the program.
3. No faculty member is willing to serve as advisor, even with proposed supports and accommodations, due to *legitimate, documented, non-discriminatory* reasons (e.g., complete lack of funding across all potential labs, genuine lack of scientific fit with *all* available PIs after thorough exploration).

Before reaching that point, the program must demonstrate it has gone above and beyond the "typical format" by actively implementing and exploring disability-related supports within the advisor-finding process itself. Failure to do so opens the door to legitimate grievances or legal challenges based on disability discrimination. Exploring alternative endpoints like a Master's degree should also be part of the conversation if the PhD path proves untenable *after* all accommodation efforts are exhausted.

Part 1: Mandates for Faculty to Hire Graduate Students

1. **Explicit Mandate Tied to Employment?**

    - **Validation:** Based on standard University of California academic personnel policies and typical graduate program operations, there is **no validated evidence of a formal, system-wide, or typical departmental/program mandate stating that tenured or associate professors *must* take a graduate student every X number of years simply to remain employed or retain tenure.**
    - **Justification:** Faculty hiring decisions for their own research labs are traditionally considered part of their academic freedom and purview, particularly when the position is funded by their own research grants (as is common for many GSRs and Postdocs in GPBio). Tenure and employment security are governed by separate Academic Senate reviews focusing on research, teaching, and service contributions over a career, not usually by a quota for specific trainee types within a short timeframe. Forcing a PI to hire a specific type of personnel for *their own grant-funded lab* would be highly unusual and likely infringe on their autonomy to direct their research and manage their funds.

2. **Indirect Pressures and Expectations (Significant):**

    - **Programmatic Need & Mission:** Graduate programs like NSIDP/GPBio *exist* to train PhD students. Their success, reputation, and often their funding (especially via training grants) depend on faculty participation in mentorship. There is a

strong *cultural and professional expectation* that faculty engaged with the program will train students.

- **Training Grant (T32) Participation:** NSIDP relies heavily on NIH T32 training grants. Faculty listed as trainers on these grants have a *strong obligation* to mentor students, including those funded by the T32 slots. Consistent refusal to mentor T32-eligible students could jeopardize a PI's continued participation as a trainer on the grant, which can impact their lab funding and standing within the program.
- **Departmental/Program "Citizenship":** Faculty contributions to graduate training (mentoring, teaching graduate courses, serving on committees) are significant components of their regular academic reviews for merit increases and promotions. Consistently refusing to train graduate students, while perhaps not grounds for dismissal, could negatively impact these reviews and the PI's standing within their department and program.
- **Resource Allocation:** Access to program resources, eligibility for certain internal funding or awards, or desirable committee/teaching assignments might implicitly favor faculty who actively contribute to the core training mission, including taking students.
- **PI Funding Reality:** As established, GSRs, *even when the PI pays all costs*, often represent a lower *total dollar outlay per year* compared to a Postdoc (especially an experienced one). For PIs with limited funding, a GSR might be the *only* affordable option to bring in new personnel, creating a practical pressure.

3. **Decision Factors for PIs (Hiring GSR vs. Postdoc vs. None):**

    - **Funding:** Can they *afford* the ~$60k+ for a GSR or ~$75k+ for a Postdoc? Do they have T32 slots available (shifting cost burden)? Does the potential hire have their own fellowship?
    - **Research Needs:** Does the project require independent work and advanced skills *now* (favors Postdoc) or can it accommodate a trainee's development (suitable for GSR)?
    - **Time Investment:** Does the PI have the significant time required for intensive GSR mentorship vs. the generally less (though still substantial) time for Postdoc supervision?
    - **Availability:** Are there suitable Postdoc candidates? Are there promising rotation students?
    - **Lab Balance/Training Philosophy:** What is the PI's desired mix of trainees? What is their commitment to the graduate training mission?

Conclusion for Part 1: While there isn't a formal mandate tying employment/tenure directly to hiring a GSR every X years, significant indirect pressures (programmatic, funding-related, T32 obligations, review criteria) strongly encourage active faculty participation in graduate training within NSIDP/GPBio. PIs *can* choose to hire only Postdocs or no one, but doing so consistently,

especially while remaining listed as program faculty or T32 trainers, would likely have negative professional repercussions and may be practically difficult due to funding constraints.

Part 2: Scenario - Student Completes Rotations, No Lab Match

This is a challenging situation. Let's rigorously analyze the likely actions of the NSIDP/GPBio leadership based on the provided program document and standard academic practices:

1. **Allowing Additional Rotations:**

    - **Policy/Practice:** The NSIDP document outlines 3 required rotations. While not explicitly stated in the provided text, it is *common practice* in many UC graduate programs to allow a student facing difficulty finding a lab *one*, perhaps even *two*, additional rotations or an extended period (e.g., through the summer or into the next fall) to secure a mentor, provided the student is otherwise in good academic standing (coursework, GPA).
    - **Justification:** The goal is generally to help the student succeed if possible. An extra rotation provides another chance for a match. It acknowledges that finding the right fit is complex and sometimes takes more time. The program has invested in the student's first year.

2. **Addressing "Arbitrary" PI Decisions:**

    - **PI Autonomy:** PIs retain significant autonomy in selecting members for their lab, based on their assessment of scientific fit, productivity potential, interpersonal dynamics, project direction, and funding availability.
    - **Program Role:** The advising chair/committee (as described in the NSIDP doc) monitors progress and counsels students. If a student reports difficulty finding a lab despite good-faith efforts, the chair/committee *would likely intervene* by:
        - Discussing the situation with the student to understand the feedback they received.
        - Potentially speaking (informally or formally) with PIs the student rotated with or is interested in, to understand their perspectives and encourage consideration.
        - Facilitating introductions or suggesting alternative faculty who might be a better fit or have funding.
    - **Challenging a PI:** Directly challenging a PI's assessment of a student's "productivity" during a short rotation is difficult unless there's clear evidence of bias or unprofessional conduct (which would trigger different university policies). Programs usually respect the PI's judgment about their own lab needs, even if they encourage giving students a fair chance.

3. **Mandating a Professor Take the Student:**

- **Feasibility:** This is **highly unrealistic and extremely unlikely** in the standard UC system.
- **Justification:**
    - **Undermines Mentorship:** Forcing a mentorship relationship where the PI is unwilling is detrimental to the student's training and experience. It creates a poor foundation for the multi-year commitment required for a PhD.
    - **PI Autonomy/Funding:** PIs are responsible for the scientific direction and funding of their labs. Mandating they accept a specific student infringes on this autonomy and responsibility. Who pays if the PI doesn't have grant funds budgeted for that student?
    - **Lack of Mechanism:** There is typically no formal policy or procedural mechanism allowing a program chair to *force* a tenured/independent faculty member to accept a specific graduate student into their research group against their will.
    - **Mutual Agreement:** The NSIDP document mentions a "Faculty Mentor Approval Form (co-signed by the mentor)," implying a necessary mutual agreement, not a mandate.

4. **Academic Disqualification:**

    - **Policy:** The NSIDP document explicitly states that failure to make "timely progress toward the degree" is grounds for recommending academic disqualification. Securing a research advisor and lab is a fundamental requirement for progressing towards a PhD dissertation.
    - **Process:** If, after reasonable extensions (e.g., an extra rotation or search period) and facilitation efforts by the program leadership, the student *still* cannot find a faculty member willing to serve as their primary advisor, the program would **realistically have to conclude** that the student cannot meet the requirements for continuing in the PhD program.
    - **Outcome:** The program chair/committee would then likely recommend academic disqualification to the Graduate Division, following the established University Policy and Academic Senate regulations outlined in the NSIDP document. This is considered a last resort after other avenues have been exhausted.

Conclusion for Part 2: The most realistic and justifiable course of action for NSIDP/GPBio leadership, as of today, when a student fails to find a lab placement after the standard rotations despite good-faith effort, is **Option A (modified):**

1. **Facilitate:** The program leadership (advising chair/committee) actively intervenes to counsel the student and communicate with potential PIs.
2. **Extend:** Grant a limited extension, likely allowing at least one additional rotation or a defined period to secure a lab.

3. **Last Resort - Disqualify:** If, after these good-faith efforts by *both* the student and the program over a reasonable extended timeframe, no faculty mentor agrees to take the student, the program will recommend academic disqualification based on failure to make timely progress. They would **not** typically attempt to *mandate* a faculty member accept the student.

This approach balances the program's commitment to student success with the realities of faculty autonomy, funding, the importance of a functional mentor-mentee relationship, and the ultimate degree requirement of completing dissertation research under faculty guidance.

Here's a thinking process to arrive at the revised answer:

1. **Identify the Core Correction:** The user explicitly states a critical factual correction: *In UCLA GPBio/NSIDP, PIs typically cover tuition, fees, and health insurance for their GSRs directly from their grants*, contradicting the initial assumption of central University funding for these items. The user also raises valid points about GSR vs. Postdoc work hours, skill level, independence, and the PI's time investment, questioning the value proposition if GSRs are *more* expensive for the PI.

2. **Acknowledge and Internalize the Correction:** This is the most crucial step. The previous analysis hinged on the assumption of University subsidies. This assumption is now invalid for this specific context (UCLA GPBio/NSIDP). The entire cost structure for GSRs from the PI's perspective needs recalculation.

3. **Re-evaluate Cost Components for GSRs (PI Perspective - UCLA GPBio):**

    - **Salary:** Remains the same calculation based on 50% FTE appointment (BR Art 32). Using Oct 1, 2024 scale: ~$34,565 (Point 1), ~$37,244 (Point 2), ~$40,130 (Point 3). *This is a direct PI cost.*
    - **Tuition & Fees:** *Crucial Change:* The University remission (BR Art 10) doesn't apply *to the PI's grant burden* in this specific scenario. The PI must cover these costs.
        - Need current UCLA tuition/fee figures. Search for "UCLA graduate tuition and fees 2024-2025" or use institutional knowledge if available. Let's estimate this conservatively at ~$18,000-$20,000 per year (combining tuition, student services fee, campus fees, potentially NRST initially). *This is now a direct PI cost.*
    - **Health Insurance (GSHIP):** *Crucial Change:* The 100% premium remission (BR Art 13) doesn't apply *to the PI's grant burden* here. The PI must cover the full GSHIP premium.
        - Need current UCLA GSHIP premium figures. Search for "UCLA GSHIP rates 2024-2025". Estimate this at ~$7,000 per year. *This is now a direct PI cost.*
    - **Childcare:** Remains $0 direct PI cost (University fund, BR Art 4).

- **Retirement:** Remains negligible direct PI cost (part of overhead).

4. **Re-evaluate Cost Components for Postdocs (PI Perspective):**

    - **Salary:** Remains the same calculation (PX Art 4). Using Oct 1, 2024 projected rates: ~$66,737 (Level 0), ~$69,208 (Level 1), ~$71,769 (Level 2). *Direct PI cost.*
    - **Tuition & Fees:** Remains $0 (N/A).
    - **Health Insurance (PSBP):** Remains the same calculation – PI pays employer share (PX Art 3, Appx A). Using 2024 projected employer share: ~$7,800 - $8,200+. *Direct PI cost.*
    - **Childcare:** Remains $0 direct PI cost (University fund, PX Art 37).
    - **Retirement:** Remains negligible direct PI cost (part of overhead).

5. **Recalculate and Compare Total PI Costs (UCLA GPBio context):**

    - **Starting GSR (50% FTE, PI Pays All):**
        - Salary: ~$34,565
        - Tuition/Fees: ~$18,000 - $20,000+
        - GSHIP Premium: ~$7,000
        - **Total Direct PI Grant Cost: ~$59,565 - $61,565+**
    - **Starting Postdoc (100% FTE, Level 0):**
        - Salary: ~$66,737
        - Tuition/Fees: $0
        - PSBP Premium (Employer Share): ~$7,800 - $8,200+
        - **Total Direct PI Grant Cost: ~$74,500 - $75,000+**

6. **Refine the Financial Comparison Conclusion:**

    - *Initial Finding (Incorrect):* Postdoc much more expensive for PI.
    - *Revised Finding (Corrected for UCLA GPBio):* Postdoc is *still* more expensive than a starting GSR for the PI, *but the gap is significantly smaller* than initially calculated. The difference is now roughly **$13,000 - $15,000+** per year, not $40,000+.
    - *Crucial Nuance:* This difference narrows or even reverses as the GSR gains experience (moves up salary points) while the Postdoc might still be at Level 0 or 1. A Point 3 GSR (~$40,130 salary + ~$20k fees/tuition + ~$7k GSHIP = ~~$67,130+) is much closer in total cost to a starting Postdoc~~ ($75k).

7. **Address the User's "Why Hire GSR?" Question:** Now that the cost difference is smaller (or potentially reverses with experienced GSRs), the qualitative factors become much more important in the PI's decision:

    - **Cost:** Postdocs *start* more expensive, but the gap narrows. Experienced GSRs can approach or exceed starting Postdoc costs for the PI.

- **FTE/Work Hours:** Postdoc = 100% FTE (nominally 40+ hrs/wk). GSR = 50% FTE appointment (nominally 20 hrs/wk *paid* research effort, plus their own academic/coursework time). PIs get significantly more dedicated research hours per week from a Postdoc.
- **Skills/Independence:** Postdocs generally have completed their PhD, possess advanced skills, require less direct supervision, can mentor others, and contribute more independently to research design, execution, and grant writing. GSRs are trainees, developing these skills, requiring significant PI time investment for mentorship and training.
- **Project Needs:** Does the project require advanced, specialized skills immediately (favors Postdoc)? Or is it suitable for a trainee who can learn and grow into the role (favors GSR)?
- **Mentorship Goals/Lab Culture:** PIs have a responsibility/desire to train the next generation (favors GSR). A balance of trainees and more senior researchers is often desired.
- **Funding Mechanisms:** Some grants are specifically for Postdoc or predoc training (e.g., F31/F32, T32 slots). PI R01s offer more flexibility.
- **Availability:** Finding qualified Postdocs can be challenging. There might be a strong pool of interested rotation students who become GSRs.

8. **Re-evaluate Predicted Impacts (incorporating corrected costs and qualitative factors):**

    - **Impacts on Students:**
        - Financial stability remains positive *relative to pre-contract*.
        - Recruitment remains positive *relative to pre-contract*.
        - *New:* Potential shift in *PI preference*? If experienced GSRs become more expensive than starting Postdocs *for the PI*, PIs *might* slightly favor hiring postdocs *if funding allows and project needs dictate*, especially given the higher FTE and independence. This could subtly increase competition for PI-funded GSR slots *beyond* University budget constraints.
        - Value perception/Safety net points remain.
    - **Impacts on PIs:**
        - Grant budget pressure remains high for *both* roles.
        - *Revised Hiring Preference:* The strong incentive towards GSRs is *weakened*. The decision becomes a more complex calculation of cost vs. experience, FTE, independence, and project needs. A PI might hire a Postdoc even if slightly more expensive if they need 100% FTE and advanced skills *now*. Conversely, they might still choose a GSR for training goals or if a suitable Postdoc isn't available, even if the cost gap narrows. The PI must weigh the *total cost* against the *expected research output and required mentorship time*.

        - Difficulty funding Postdocs remains, perhaps slightly eased if experienced GSR costs approach Postdoc levels, making the Postdoc value proposition stronger *relative* to an experienced GSR.
        - Administrative load remains.
    - **Impacts on NSIDP:**
        - Budgetary strain shifts focus – less about central remission costs (as PI pays) and more about ensuring PIs *can* secure sufficient grant funding to cover these high personnel costs for *both* roles.
        - Training environment points remain, but potential for PIs needing to make harder choices based on grant funds.
        - Lab composition shift is less predictable – might see PIs opting for Postdocs more often *if they can afford it*, or struggling to afford *either*, leading to smaller labs or reliance on fellowship-funded trainees.
        - Need for support shifts - perhaps less about central funding *pools* and more about grant writing support, bridge funding, and potentially managing PI expectations vs. trainee costs.
        - Contract renegotiation planning remains crucial.

9. **Structure and Refine the Answer:**

    - Start by explicitly acknowledging the user's correction and thanking them. State the revised understanding of the UCLA GPBio funding model.
    - Present the recalculated PI cost breakdown for GSR vs. Postdoc, highlighting the *direct PI costs* for salary, tuition/fees (GSR), and health insurance (GSR GSHIP full premium, Postdoc PSBP employer share).
    - State the revised conclusion on financial investment – Postdocs still generally start more expensive for the PI, but the gap is much smaller, and experienced GSRs can approach/exceed starting Postdoc costs *for the PI*.
    - Directly address the "Why hire a GSR?" question by elaborating on the multi-faceted decision-making process PIs undertake (cost, FTE, skills, independence, mentorship, funding, availability).
    - Provide the revised predictions for impacts on students, PIs, and the program, ensuring the logic flows from the corrected cost analysis and the qualitative factors. Emphasize the increased complexity of the hiring decision for PIs.
    - Maintain a quantitative and detailed approach where possible (using estimated costs), but acknowledge the qualitative aspects are now more critical given the smaller cost differential.
    - Add a concluding sentence summarizing the key takeaway: the decision is now a complex balancing act for PIs in this specific funding context.

You are absolutely right to push back and clarify the specific funding context for UCLA Graduate Programs in Biosciences (GPBio), including the Neuroscience IDP (NSIDP). My apologies – the initial analysis relied on the *general* UC model where central funds cover GSR tuition/fees/GSHIP, which is **not** the typical practice in many grant-funded Life

Science/Bioscience programs at UCLA, where PIs are indeed often responsible for covering these costs directly from their research grants.

Thank you for that crucial correction. Let's re-evaluate rigorously with the understanding that **UCLA GPBio/NSIDP PIs typically bear the full cost (salary, tuition, fees, GSHIP) for their GSRs.** We also need to factor in the points you raised about FTE, skills, and independence.

Revised I. PI Financial Investment Comparison (as of April 6, 2025 - PI Pays All GSR Costs)

10. **Salary/Stipend:**

    - **GSR (50% FTE):** Using the Oct 1, 2024 scale (BR Art 32.C):
        - Point 1 (< 2 sem/3 qtr): **~$34,565**
        - Point 3 (> 4 sem/6 qtr): **~$40,130**
        - *Direct PI Cost*
    - **Postdoc (100% FTE):** Using Oct 1, 2024 projected rates (PX Art 4):
        - Level 0 (0-11 mos): **~$66,737**
        - Level 2 (24-35 mos): **~$71,769**
        - *Direct PI Cost*

11. **Tuition & Fees (GSR Only):**

    - **Crucial Change:** The PI's grant must cover this. UCLA Graduate Tuition & Fees vary slightly year to year but are substantial. For 2024-2025, let's estimate the typical *in-state* costs (Tuition, Student Services Fee, Campus Fees) at approximately **~$19,000 - $20,000 per year.** (Note: NRST would add significantly more, ~$15,100, but many PhD students establish residency after the first year, or NRST might be covered by central program funds in some cases, though we are assuming PI covers core costs here).
    - **PI Cost (GSR): ~$19,000 - $20,000+**
    - **PI Cost (Postdoc): $0** (N/A)

12. **Health Insurance:**

    - **GSR (UC SHIP): Crucial Change:** PI's grant must cover the full premium. The 2024-2025 GSHIP premium is roughly **~$7,000 per year.**
    - **PI Cost (GSR): ~$7,000**
    - **Postdoc (PSBP):** PI's grant covers the employer share. Based on 2024 rates (PX Appx A), this is plan-dependent:
        - PPO (Employer Share): ~~$681/mo = **~~$8,172 / year**
        - HMO (Employer Share): ~~$652/mo = **~~$7,824 / year**
    - **PI Cost (Postdoc): ~$7,800 - $8,200+**

13. **Other Costs (Childcare, Retirement):** These remain largely unchanged ($0 direct PI cost for childcare subsidies; retirement handled via benefits overhead).

Revised Summary of Approximate Yearly *Direct PI Grant* Investment (April 2025):

- **Starting GSR (50% FTE, Point 1, PI Pays All):**
    - Salary: ~$34,565
    - Tuition/Fees: ~$19,500 (using midpoint estimate)
    - GSHIP Premium: ~$7,000
    - **Total Direct PI Grant Cost: ~$61,065**
- **Experienced GSR (50% FTE, Point 3, PI Pays All):**
    - Salary: ~$40,130
    - Tuition/Fees: ~$19,500
    - GSHIP Premium: ~$7,000
    - **Total Direct PI Grant Cost: ~$66,630**
- **Starting Postdoc (100% FTE, Level 0):**
    - Salary: ~$66,737
    - PSBP Premium (Employer Share): ~$8,000 (using midpoint estimate)
    - **Total Direct PI Grant Cost: ~$74,737**
- **Experienced Postdoc (100% FTE, Level 2):**
    - Salary: ~$71,769
    - PSBP Premium (Employer Share): ~$8,000
    - **Total Direct PI Grant Cost: ~$79,769**

Revised Conclusion on PI Investment:

Under the specific UCLA GPBio/NSIDP funding model where PIs cover all GSR costs:

1. A **starting Postdoc (~$74.7k)** is still **more expensive** than a **starting GSR (~$61k)** for the PI by approximately **$13,000 - $14,000** per year.
2. However, an **experienced GSR (~$66.6k)** becomes **significantly less expensive** than a **starting Postdoc (~$74.7k)** by about **$8,000** per year, and *much* less expensive than an experienced Postdoc (~$80k).
3. The cost gap has narrowed considerably compared to the scenario where the University covers GSR tuition/fees/GSHIP.

Justification & Addressing "Why Hire a GSR?":

You raise the absolutely critical point: if an experienced GSR costs nearly as much as (or potentially more than, if including NRST) a starting Postdoc *to the PI*, while offering only 20 hrs/wk of paid research effort and requiring more mentorship, why hire one?

The decision is now a complex equation balancing *multiple* factors beyond just the direct cost:

1. **Cost vs. Experience Level:** While a *starting* GSR is cheaper, an *experienced* GSR (after 2+ years) approaches the cost of a *starting* Postdoc. The PI must weigh if the skills gained by the experienced GSR justify that cost relative to bringing in a new, potentially more skilled Postdoc for a similar or slightly higher price.
2. **Research Hours (FTE): This is a major factor.** A Postdoc provides 100% research effort (40+ hrs/wk). A GSR provides 50% paid research effort (20 hrs/wk), with the rest of their time dedicated to coursework, rotations (early years), qualifying exams, and dissertation writing. **Per dollar invested by the PI, a Postdoc delivers significantly more direct research hours.**
3. **Skills & Independence:** Postdocs arrive with completed PhD training, advanced technical skills, greater project management capability, and the ability to work more independently, potentially mentor junior lab members, and contribute significantly to grant writing. GSRs are trainees *acquiring* these skills, requiring substantial PI time for training, supervision, and mentorship.
4. **PI Time Investment:** Training a GSR requires a much larger investment of the PI's personal time and effort compared to onboarding and supervising a Postdoc. This "cost" in PI time is significant.
5. **Nature of the Project:** Projects requiring immediate application of highly specialized techniques or independent leadership may necessitate a Postdoc. Projects that can accommodate a learning curve and benefit from long-term development are suitable for GSRs.
6. **Lab Ecosystem & Training Mission:** Most academic labs aim for a mix of personnel. PIs have a fundamental role in training the next generation of scientists (GSRs). Relying solely on Postdocs would neglect this core academic mission. GPBio/NSIDP exists *to train* graduate students.
7. **Funding Source Restrictions:** Some funding mechanisms (e.g., T32 training grants) are specifically designated for predoctoral students (GSRs) or postdoctoral fellows. PI R01s offer more flexibility but budgets are tight.
8. **Availability & Recruitment:** Recruiting high-quality Postdocs can be very challenging. There is often a strong internal pipeline of rotation students who are eager, known to the PI, and committed to joining the lab as GSRs.
9. **Continuity:** A GSR typically stays for 4-6 years, potentially offering longer project continuity than a Postdoc who might stay for 2-4 years.

Therefore, a UCLA GPBio PI might still hire a GSR despite the high PI-borne costs because:

- **Training Mission:** It's fundamental to the program and the PI's role.
- **Availability:** Good rotation students are often readily available and enthusiastic.
- **Long-term Potential:** Investing in a student for 5+ years can yield significant results by the later stages.
- **Funding Restrictions:** Specific funds (like T32 slots) may mandate hiring students.
- **Lab Culture:** A desire for a mixed lab environment including trainees.
- **Lower Starting Cost:** Even with PI paying all, a *starting* GSR is still cheaper than a *starting* Postdoc, allowing PIs with tighter budgets to bring someone in.

However, the **value proposition** is indeed much tighter now. The increased costs make the Postdoc's higher FTE and independence look relatively more attractive *per dollar spent by the PI*, especially when compared to an experienced GSR.

Revised II. Predicted Impacts (2025 - Contract Expirations - UCLA GPBio PI Pays All Context)

1. **Impacts on Graduate Students:**

    - Financial stability/Recruitment points remain positive *relative to pre-contract status*.
    - **Increased Selectivity/Competition for PI-Funded Slots (Negative):** With PIs bearing the full, high cost, they will be extremely selective. Fewer PIs may be able to afford to take on *new* GSRs solely funded by their R01s/equivalent grants, increasing reliance on training grants (T32s) or fellowships (F31s) secured by the student. Competition for funded lab slots will likely intensify.
    - **Pressure to Secure External Funding (Negative):** Students may face greater pressure to secure their own fellowships (F31, foundation grants) to offset the PI's cost burden.
    - Safety net/Value perception points remain.

2. **Impacts on PIs:**

    - **Severe Grant Budget Pressure (Negative):** The need to cover salary + full tuition/fees + GSHIP for GSRs, *plus* the high cost of Postdocs, puts immense strain on research grants. PIs will need larger grants or support fewer personnel.
    - **Difficult Hiring Decisions (Challenge):** The choice between an experienced GSR and a starting Postdoc becomes extremely difficult, balancing slightly lower cost (GSR) vs. higher FTE and independence (Postdoc). PIs may delay hiring, seek fellowship-funded trainees, or opt for Postdocs if project needs demand immediate high-level skills and full-time effort *and the budget allows*. The decision is highly constrained by available funds.
    - **Reduced Lab Size/Shift in Composition (Likely):** Many PIs may simply be unable to afford the same number of personnel as previously. Labs might shrink, or the ratio might shift slightly towards Postdocs *if* external Postdoc fellowships

are secured or grant funding is unusually robust. More likely is a general reduction or stagnation in hiring.
- **Increased Importance of T32s/Fellowships (Strategic Shift):** PIs will more heavily rely on institutional training grants (like the NSIDP T32) and encourage/require students/postdocs to apply for individual fellowships to alleviate direct grant costs.

3. **Impacts on UCLA's NSIDP:**

- **Challenge for PI Recruitment/Retention (Negative):** The high cost of supporting trainees makes UCLA potentially less attractive for new faculty recruitment or could challenge existing PIs compared to institutions where trainee costs are more centrally subsidized.
- **Increased Reliance on Training Grants (Strategic Shift):** The health and funding level of the NSIDP T32 and similar mechanisms become even more critical for maintaining student cohort size and supporting PIs.
- **Potential Impact on Cohort Size (Risk):** If PIs struggle to secure sufficient grant funding to cover the full cost of GSRs, and central program funds/T32 slots cannot expand sufficiently, the overall number of funded positions available to incoming students could decrease over time.
- **Focus on Grant Competitiveness:** Increased emphasis on training students and PIs in securing external grant funding (Fs, Ks, R-series) will be necessary.
- **Strain on Bridge Funding/Internal Support:** Programs may face more requests for internal or bridge funding from PIs struggling to cover the high personnel costs between grant cycles.

In conclusion, understanding that UCLA GPBio PIs bear the full cost significantly changes the calculation. While Postdocs still generally start with a higher total cost to the PI than starting GSRs, the gap narrows considerably, especially compared to experienced GSRs. The decision to hire involves a much more intense weighing of cost against research hours, required independence/skills, PI time investment, and the fundamental training mission, all under severe budgetary pressure. This will likely lead to increased competition for funded slots, greater reliance on external fellowships and training grants, and potentially impact overall lab size and composition within the NSIDP.

Here's a breakdown of the thinking process to answer the user's request comparing the financial investment for GSRs vs. Postdocs at UCLA for a PI in the Graduate Programs in Biosciences (GPBio):

1. **Deconstruct the Request:**

- **Core Task:** Compare the *PI's* financial investment for a Graduate Student Researcher (GSR - BR contract) vs. a Postdoctoral Scholar (PX contract) at UCLA.
- **Target Audience:** UCLA GPBio PI.
- **Specific Focus:** *Yearly* financial investment *specifically by the PI*. Identify costs shiftable to the university (especially for NSIDP students). Quantify the difference ("approximately how much"). Justify the reasons.
- **Timeframe:** Current situation (based on contracts, effective dates, and today's date - April 6, 2025).
- **Future Prediction:** Predict the *specific impacts* of these contracts on graduate neuroscience students, PIs, and UCLA's NSIDP from ratification through expiration (Sept 30, 2027 for PX, May 31, 2025 for BR - *Correction needed here, the Side Letter extends BR/BX to Jan 1, 2026*). Justify the predictions.
- **Required Tone/Methodology:** Rigorous, systematic, methodical, quantitative, meticulous, comprehensive, intuitive, practical, detailed, accurate.
- **Source Material:** The provided OCR'd UAW contracts (BR and PX).

2. **Initial Information Gathering & Keyword Extraction (Mental Scan/Skim):**

    - **Identify Key Articles:** Scan the Tables of Contents for both contracts. Look for articles related to:
        - Compensation/Wages/Salary (BR Art 32, PX Art 4)
        - Benefits (PX Art 3, BR doesn't have a dedicated article but mentions eligibility)
        - Fee Remission (BR Art 10)
        - Childcare (BR Art 4, PX Art 37)
        - Appointments/Duration (BR Art 2, PX Art 2, 41)
        - Leaves (BR Art 17, PX Art 12)
        - Training (BR Art 25, PX Art 27)
        - Travel (BR Art 29, PX Art 28)
        - Immigration (BR Art 15, PX Art 38)
        - Workspace/Materials (BR Art 35, PX Art 35)
        - Recognition/Titles (BR Art 1, PX Art 1, 26)
    - **Extract Specific Costs/Rates (Detailed Reading):** Go to the identified articles and pull out concrete numbers and policies affecting PI costs.

3. **Comparative Analysis - PI Financial Investment (Today - April 6, 2025):**

    - **Salary/Stipend:**

        - **GSR (BR Contract):** Find the current salary scale (Table 22, effective Oct 1, 2024). Note the different points based on experience (Art 32.B.3.b). A new GSR (0-1 semesters/0-2 quarters) would likely start at Point 1

($69,129 annual / $34,564.50 for 50% FTE). *Crucially, the PI usually funds this.*

- **Postdoc (PX Contract):** Find the current salary scale (Table 23, effective Oct 1, 2024). Note the experience levels (Art 4.B). A new Postdoc (Level 0) would be at $64,480 *base* (as of Oct 1, 2023 scale), *but* also gets experience increases (Art 4.C). The Oct 1, 2024 scale increase is 3.5% (Art 4.B.3). Apply this: $64,480 * 1.035 = $66,736.80. A Level 1 postdoc (12-23 months) would be $66,868 * 1.035 = $69,208.38. *Crucially, the PI usually funds this.*
- **Initial Comparison:** Postdoc minimums are generally higher than a *starting* GSR 50% FTE rate, but the *full* GSR rate is higher than the *starting* postdoc rate. The PI typically covers the salary/stipend for both *directly from grants*.

- **Tuition & Fees:**

  - **GSR:** Article 10 mandates 100% remission of Tuition, Student Services Fee, and Campus Fees (from AY 2023-24). NRST is also covered for eligible students (advancement to candidacy reduces it). *This is a HUGE cost that is NOT borne by the PI's grant but by the University/Campus/Program.* This is a major cost-saving aspect for the PI when hiring a GSR.
  - **Postdoc:** Not students, so no tuition/fees. This cost category doesn't exist.

- **Health Insurance (GSHIP/PSBP):**

  - **GSR:** Eligible for UC SHIP. Article 13 states the plan terms are not employment conditions. Premium remission is covered (Art 10.A.1 refers to fee remission program covering tuition *and fees*, implicitly including GSHIP). Crucially, *the University covers 100% of the premium.* Child dependents also get 100% remission if income limits are met (Art 13.D). *This cost is NOT borne by the PI's grant.*
  - **Postdoc:** Eligible for PSBP (Postdoctoral Scholar Benefits Plan) (PX Art 3.A.1). PIs must ensure funding is available. *Crucially, the PI's funding source typically covers the bulk of the premium.* Postdocs contribute a percentage (2% HMO, 4% PPO as of Jan 2024 - see PX Appx B and Art 3.B.4). The *employer portion* comes from the PI's grant funds. Look up the *current* PSBP rates (Appendix A in PX contract is for 2023 & 2024). Find the *total* premium (UC + Postdoc Share) for 2024 (e.g., Single HMO: $651.57 + $13.30 = $664.87/month; Single PPO: $681.06 + $28.38 = $709.44/month). *This IS a significant PI cost.*

- **Childcare Reimbursement:**

- **GSR (BR Art 4):** Up to $1375 *per fiscal quarter* ($5500/year) effective Oct 1, 2023. *This is funded by the University, NOT the PI.*
- **Postdoc (PX Art 37):** Up to $2600 *per calendar year* effective Oct 1, 2024 (increasing annually). *This is funded by the University, NOT the PI.* Note the Professional Travel Childcare Expense program also draws from this fund.
- **Comparison:** Both get University-funded support, Postdocs get less annually but GSRs get it quarterly. *No direct PI cost.*

- **Retirement:**

  - **GSR (BR Art 5):** May be required to contribute to DC Plan (Safe Harbor). Not eligible for UCRP unless prior service. *Costs are employee contributions or standard University costs, not typically direct PI grant costs.*
  - **Postdoc (PX Art 3.C):** Employees (Title 3252) contribute 7.5% to DC Plan (Safe Harbor). Not eligible for UCRP unless prior service. Fellows/Paid Directs (3253/3254) generally don't participate via UC. *Costs are employee contributions or standard University costs, not typically direct PI grant costs.*

- **Other Potential Costs (Less Frequent/Direct for PI):**

  - Travel Reimbursement (BR Art 29, PX Art 28): Usually comes from grant funds if required for research. Discretionary travel may or may not be reimbursed.
  - Workspace/Materials (BR Art 35, PX Art 35): PI provides required items, standard lab operating costs from grants.
  - Training (BR Art 25, PX Art 27): University required training is paid time. Costs for internal training usually covered by UC; external might come from grants/fellowships.
  - Immigration Fees (BR Art 15, PX Art 33/38): Campus recharge fees paid by Dept/Program/Unit, not passed to the scholar (PX Art 33.C). Implicitly not a direct PI grant cost unless the unit *is* the PI's grant. Visa costs themselves are complex and often fall to the scholar or specific programs, but PI grants might sometimes cover them depending on sponsor rules. This is a grey area but less direct than salary/benefits.

- **Synthesize the PI Cost Comparison (2025):**

  - **GSR:** PI pays 50% FTE Salary (e.g., ~~$34,564 starting).~~ ~~*University/Program covers* Tuition/Fees~~ ($15k+ GSHIP), GSHIP premium (~$5k+), Childcare ($5.5k max).

- **Postdoc:** PI pays 100% Salary (e.g., ~~$66,737 starting). PI pays *Employer portion* of PSBP premium (~~$7.5k-$8k+). University covers Childcare ($2.6k max).
- **Quantify:** Postdoc Salary ($67k) + Postdoc Benefit Premium ($8k) = ~~$75k. GSR Salary ($35k). The direct cost *to the PI's grant* is significantly higher for a Postdoc (~~$40k more per year than a starting GSR).
- **Justification:** The primary difference is the University subsidy for GSR Tuition/Fees and Health Insurance (GSHIP). Postdoc salaries are also higher, and their benefits are directly charged to the PI's funding source.

4. **Predicting Impacts (Ratification to Expiration):**

    - **Identify Contract Expiration Dates:** PX: Sept 30, 2027. BR: May 31, 2025 (*but Side Letter extends to Jan 1, 2026*). *Use the correct BR date.*

    - **Consider Key Contractual Changes & Timelines:**

        - **Salary Increases:** Both contracts have scheduled annual increases (BR: Oct 1, 2023 & Oct 1, 2024 defined; PX: Oct 1, 2023, 2024, 2025, 2026 defined). These directly increase PI costs.
        - **Benefit Costs:** PSBP premiums for Postdocs likely increase annually. GSHIP premiums for GSRs also increase, but are covered by UC. This widens the PI cost gap.
        - **Childcare:** Modest annual increases ($100/yr) for Postdocs. GSR amount increases Oct 2023, Oct 2024. Still University funded.
        - **Transitional Pilot Program (BR/BX Side Letter):** Implemented within 90 days of ratification (ratification was Dec 2022, so this should be active). Provides short-term funding for GSRs/ASEs needing to switch labs due to conflict/PI departure. *Impact:* Potential temporary cost *relief* for a PI taking on a transitional student, but primarily a *University* cost/program. Provides a safety net for students.
        - **Experience Steps:** Both GSRs and Postdocs move up salary scales with experience, increasing PI costs over time.
        - **Contract Expiration/Renegotiation:** BR contract expires Jan 1, 2026. PX expires Sep 30, 2027. Future contracts are uncertain but likely trends (higher salaries, maintaining benefits) will continue.

    - **Brainstorm Impacts on Stakeholders:**

        - **Graduate Students (NSIDP):**
            - *Positive:* Increased salaries, guaranteed fee/GSHIP remission (huge financial relief), childcare support, defined leave policies, stronger protections (non-discrimination, respectful workplace,

grievance procedures). Transitional Pilot Program offers a safety net. Better financial stability might attract more/better students.
        - *Potential Negative:* PIs facing higher costs *might* hire fewer GSRs, potentially reducing research opportunities or increasing workload expectations for existing GSRs. Competition for fully funded slots could increase. *However*, the large university subsidy for GSRs makes them *still* much cheaper for the PI than Postdocs.
    - **PIs (UCLA GPBio):**
        - *Negative:* Significantly increased direct costs, especially for Postdocs (salary + benefits). Increased GSR salaries. Budgetary pressure on grants. May need to write grants for higher amounts. Potential reduction in lab size or shift in hiring preference towards GSRs over Postdocs due to the cost differential, *if* grant funding is the main constraint. Administrative overhead of tracking experience steps.
        - *Positive:* Clearer contract terms might reduce ambiguity. Happier/more secure trainees might be more productive. Potential for attracting strong students due to better compensation/benefits.
    - **UCLA NSIDP (Neuroscience Interdepartmental Program):**
        - *Positive:* Increased attractiveness of the program due to guaranteed funding/benefits for GSRs. Clearer employment framework.
        - *Negative:* Increased *University* costs for fee/GSHIP remission and childcare support. Potential pressure from PIs regarding funding limitations impacting training capacity. Need to ensure central resources (like Transitional Pilot funding) are adequate. Potential strain on departmental/programmatic funds used to supplement PI grants or cover central costs. May need enhanced fundraising or internal budget reallocation.

- **Structure the Prediction:** Organize by stakeholder group (Students, PIs, Program). Within each, list specific, justified impacts, considering both positive and negative aspects and the timeline (immediate post-ratification vs. subsequent years). Emphasize the *most likely* scenarios based on the quantitative cost difference. The PI cost difference *strongly* favors hiring GSRs if grant funds are the primary limiter.

5. **Refine and Format:**

- **Review against Prompt:** Ensure all parts of the request are addressed (comparison, justification, quantification, prediction, justification, detail, accuracy, audience focus).
- **Clarity and Tone:** Write clearly for a PI. Use headings and bullet points. Define acronyms (GSR, PX, PI, FTE, GSHIP, PSBP, NRST, FTE, NSIDP, GPBio, etc.).

- **Quantitative Detail:** Include specific salary figures, benefit cost estimates, and the calculated PI cost difference. Clearly state assumptions (e.g., starting salary points, 50% FTE for GSR).
- **Accuracy Check:** Double-check contract articles, dates, and figures. Ensure the distinction between PI costs and University costs is consistently maintained. *Self-correction: Corrected the BR contract expiration date based on the Side Letter.* Add a disclaimer about benefit rates changing annually.
- **Practicality:** Frame the advice and predictions in practical terms relevant to a PI making hiring decisions and managing a lab budget. Acknowledge that factors beyond cost (experience level needed, project scope) also influence hiring.

Okay, let's break down the financial implications and potential impacts of hiring a Graduate Student Researcher (GSR) versus a Postdoctoral Scholar (PX) at UCLA under the current UAW contracts, specifically for a PI in the Graduate Programs in Biosciences (GPBio), considering today's date, April 6, 2025.

Disclaimer: This analysis is based on the provided contract documents (UAW BR Agreement ending Jan 1, 2026 per Side Letter; UAW PX Agreement ending Sept 30, 2027) and publicly available information. Health benefit costs and specific campus fees change annually; the figures used are based on the latest available information within the contracts or recent patterns but should be verified with current campus resources for precise budgeting.

I. PI Financial Investment Comparison (as of April 6, 2025)

The core difference lies in *who pays for what*. GSRs, as students, benefit from significant University subsidies for tuition, fees, and health insurance, which are *not* typically charged directly to a PI's grant. Postdocs are employees whose salary and benefits costs are *primarily* borne by the PI's funding source (e.g., grants).

Let's break down the major cost categories *from the PI's perspective*:

6. **Salary/Stipend:**

    - **GSR (BR Contract):** GSRs are typically appointed at 50% FTE during the academic year. The salary scale was significantly updated post-ratification. Using the scale effective **October 1, 2024** (BR Art 32.C):
        - A *starting* GSR (Point 1, < 2 semesters/3 quarters experience) earns $69,129 annually full-time.
        - **PI Cost (50% FTE): $34,564.50**
        - A GSR with 2 semesters/3 quarters experience (Point 2) would be at $74,487 annually. PI Cost (50% FTE): $37,243.50.
        - A GSR with 4 semesters/6 quarters experience (Point 3) would be at $80,260 annually. PI Cost (50% FTE): $40,130.00.
        - *Note:* PI grants typically cover this salary cost directly.

- **Postdoc (PX Contract):** Postdocs are full-time (100%) employees. The salary scale is experience-based (PX Art 4.B). Using the scale effective **October 1, 2023** ($64,480 base) plus the **3.5% general range adjustment for October 1, 2024** (PX Art 4.B.3):
    - Level 0 (0-11 months experience): $64,480 * 1.035 = **$66,736.80**
    - Level 1 (12-23 months experience): $66,868 * 1.035 = **$69,208.38**
    - Level 2 (24-35 months experience): $69,342 * 1.035 = **$71,769.00**
    - *Note:* Postdocs also receive annual experience-based increases on Oct 1 or Apr 1 (PX Art 4.C), moving them to the next step minimum or receiving >=3% increase, whichever is greater. The PI's grant covers this salary directly.

7. **Tuition & Fees:**

- **GSR:** For GSRs with qualifying appointments (>=25% FTE), the University provides **100% remission** for Tuition, Student Services Fees, and Campus Fees (BR Art 10.B). Non-Resident Supplemental Tuition (NRST) is also typically covered or waived/reduced after advancement to candidacy (BR Art 10.D).
    - **PI Cost: $0** (This is a massive cost, ~$15,000-$20,000+ per year depending on residency and specific campus fees, fully subsidized by the University/Campus/Program).
    - *NSIDP Specific:* As part of the Graduate Programs in Biosciences, NSIDP students typically have central program support covering these costs, reinforcing that this is not a direct PI grant expense.
- **Postdoc:** Not applicable. Postdocs are not students and do not pay tuition or student fees.
    - **PI Cost: $0**

8. **Health Insurance:**

- **GSR (UC SHIP):** Eligible GSRs receive 100% premium remission for the UC Student Health Insurance Plan (UC SHIP) (BR Art 10.A refers implicitly via fee remission program; Art 13.B confirms). Eligible child dependents also receive 100% premium remission if GSR income exceeds Medi-Cal thresholds but the family does not (BR Art 13.D).
    - **PI Cost: $0** (Another significant University subsidy, GSHIP premiums are ~$5,000-$7,000+ per year).
- **Postdoc (PSBP):** Postdocs participate in the Postdoctoral Scholar Benefits Plan (PSBP) (PX Art 3). They pay a small portion of the premium (4% for PPO, 2% for HMO as of 2024, PX Art 3.B.4 & Appx B). The *bulk* of the premium (the employer share) is paid from the PI's funding source.
    - **PI Cost (Estimate based on 2024 rates, PX Appx A):**
        - Single PPO: ~~$681/month = **~~$8,172 / year**
        - Single HMO: ~~$652/month = **~~$7,824 / year**

        - Costs are higher for +Partner, +Child(ren), +Family coverage.
    - *Note:* These rates increase annually. This represents a substantial direct cost to the PI's grant.

9. **Childcare Support:**

    - **GSR (BR Art 4):** Eligible for up to $1375 *per fiscal quarter* ($5,500/year) from the University system-wide fund.
        - **PI Cost: $0**
    - **Postdoc (PX Art 37):** Eligible for up to $2600 *per calendar year* effective Oct 1, 2024 (increasing to $2700 Oct 1, 2025; $2800 Oct 1, 2026) from the University fund. Includes Professional Travel Childcare expenses.
        - **PI Cost: $0**

10. **Retirement:**

    - **GSR (BR Art 5):** May be required to contribute 7.5% to DC Plan Safe Harbor. No direct PI cost beyond standard institutional overhead recovery on salaries.
    - **Postdoc (PX Art 3.C):** Employee Postdocs (3252) contribute 7.5% to DC Plan Safe Harbor. No direct PI cost beyond standard institutional overhead recovery on salaries. Fellows/Paid Directs usually ineligible via UC.

Summary of Approximate Yearly PI Financial Investment (April 2025):

- **Starting GSR (50% FTE):**

    - Salary: ~$34,565
    - Tuition/Fees: $0 (UC Pays)
    - Health Insurance (GSHIP): $0 (UC Pays)
    - **Total Direct PI Grant Cost: ~$34,565**

- **Starting Postdoc (100% FTE, Level 0):**

    - Salary: ~$66,737
    - Tuition/Fees: $0 (N/A)
    - Health Insurance (PSBP Employer Share): ~$7,800 - $8,200+ (depending on plan choice)
    - **Total Direct PI Grant Cost: ~$74,500 - $75,000+**

Conclusion on PI Investment:

Hiring a **Postdoctoral Scholar requires a significantly greater direct yearly financial investment from the PI's grant funds** compared to hiring a GSR. In 2025, the difference is approximately **$40,000 per year** for starting-level individuals.

Justification: This large difference is almost entirely due to the University covering the substantial costs of tuition, fees, and health insurance (GSHIP) for eligible GSRs, treating these as part of the student support package. For Postdocs, the PI's grant must cover both the higher full-time salary and the employer portion of the more expensive PSBP health insurance premiums.

II. Predicted Impacts (2025 - Contract Expirations)

Based on the contracts and the financial realities described above:

Impacts on Graduate Students (UCLA NSIDP):

1. **Improved Financial Stability (Positive):** The guaranteed salary increases, full fee/GSHIP remission, and childcare support provide unprecedented financial security compared to pre-contract times. This makes pursuing a PhD less financially burdensome.
2. **Enhanced Recruitment (Positive):** UCLA/NSIDP becomes more attractive to prospective students due to the strong, contractually guaranteed support package.
3. **Potential Reduction in Available Positions (Negative/Risk):** While GSRs are cheaper *for the PI* than postdocs, the overall cost *to the University* for GSR support (tuition/fees/GSHIP remission) has increased. If University/Program budgets become strained, there *could* be pressure to limit the *total number* of funded GSR slots available across departments/programs, potentially increasing competition. However, the PI cost incentive still strongly favors GSRs over Postdocs if a PI *can* get a GSR slot funded centrally.
4. **Increased Value Perception (Positive):** Being part of a union with a strong contract elevates the professional standing and recognition of GSR labor.
5. **Safety Net (Positive):** The Transitional Position Pilot Program (active since ~March 2023) offers crucial support for students facing irreparable conflict or PI departure, reducing precarity (BR/BX Side Letter, Nov 2024).

Impacts on PIs (UCLA GPBio):

1. **Increased Grant Budget Pressure (Negative):** PIs must budget for significantly higher Postdoc costs (salary + benefits) and increased GSR salaries due to annual raises. Grant applications will need to reflect these higher personnel costs. Securing funding may become more challenging or require seeking larger grants.
2. **Shift in Hiring Preference Towards GSRs (Likely):** Given the ~$40k+ yearly difference in direct grant costs, PIs facing funding constraints are strongly incentivized to hire GSRs over Postdocs whenever the required tasks and experience level permit. This trend will likely intensify as costs diverge further each year.
3. **Potential Difficulty Funding Postdocs (Negative):** It may become harder to support Postdocs, especially multiple Postdocs, potentially impacting the lab's ability to tackle

projects requiring more experienced researchers or limiting the training of future independent scientists. PIs might rely more heavily on Postdocs who bring their own fellowship funding.
4. **Increased Administrative Load (Minor Negative):** Managing different salary scales, experience steps, and contract compliance adds a layer of administrative work.
5. **More Stable Workforce? (Potential Positive):** Better compensated and supported trainees might lead to higher morale and potentially lower turnover, although the temporary nature of both roles remains.

Impacts on UCLA's NSIDP:

1. **Budgetary Strain (Negative):** The University/Campus/Program bears the significant cost of GSR tuition/fee/GSHIP remissions. While predictable under the contract, the overall expense is substantial and requires robust central funding mechanisms (e.g., return-to-aid from overhead, programmatic training grants like T32s, departmental funds). Strain on these resources could impact other programmatic activities or support structures if not adequately budgeted for.
2. **Strengthened Training Environment (Positive):** Enhanced financial security and benefits make NSIDP a more attractive and equitable training program, potentially improving the quality and diversity of the student body.
3. **Potential Shift in Lab Composition (Neutral/Observation):** A potential PI-driven shift towards hiring more GSRs and fewer grant-funded Postdocs could alter the overall composition of research labs within the program. This might affect the types of research undertaken or the training dynamics within labs.
4. **Need for Robust Central Support (Challenge):** Ensuring adequate funding for the Transitional Pilot Program and managing the increased central costs of GSR support requires ongoing institutional commitment and resource allocation.
5. **Planning for Contract Renegotiations (Ongoing):** The program and university administration must anticipate future cost increases and complexities arising from the next rounds of bargaining (BR contract expires Jan 1, 2026; PX expires Sept 30, 2027).

In summary, while both contracts significantly increase costs compared to historical levels, the University's subsidization of GSR tuition/fees/GSHIP creates a stark difference in the direct financial burden placed on a PI's grant. This financial reality strongly incentivizes PIs to hire GSRs over Postdocs when possible, a trend likely to shape lab compositions and potentially increase competition for centrally funded GSR positions within programs like NSIDP through the current contract durations.

Research Ideas Questions

1. How well do multimodal longitudinal normative modeling ai-guided endophenotype/biomarker clusters/biotypes recapitulate symptom-based DSM-5-TR diagnostic categories?
2. **Longitudinal Normative modeling**/**Normative Trajectory Modeling** ABCD, NAPLS, Pronet, 22q comparison (recapitulation) etc.?
    a. Related ideas from Rune [ABCD and NAPLS]
        i. Compare/benchmark existing cross-sectional normative modeling approaches.
        ii. Develop/train true *longitudinal* normative modeling approaches and compare to existing cross-sectional methods.
3. Characterizing environmental and genetic determinants of biological, developmental and functional variation in complex neurocognitive functions, the development and variation of reward processing, executive function, social and emotional processing, and other dimensional subfactors of psychopathology.
4.
5. Investigating neurodevelopmental divergence, shared biomarkers/endophenotypes across psychopathology, and the variable expression of genetic liability to psychotic spectrum disorders in adolescence.
6. Design research questions, rigorously and optimally extracting maximum novel information from the target data sets (ABCD/NAPLS) maximally addressing/informing their specific missions and goals using methods of interest like longitudinal normative modeling, Deep learning AI (GAN etc) and any other recent and robust multimodal statistical methods/approaches.
7. Quantitatively modeling to describe neurobiological correlates of transient biotyping of symptomatic improvement. Relevance for quantitative efficacy tracking tracking, augmentation of therapeutic interventions and stratification/characterization of risk.
8. Investigate the pleiotropic and convergent genetic liability, molecular and cellular pathways impinging on downstream higher order neurocognitive functions and neural substrates associated with the general psychopathology factor, aberrant neurodevelopment, and neuropsychiatric disorder broadly.
   - *"Psychiatric disorders constitute a diverse set of conditions, variously impinging on all domains of mental function and affecting the most fundamental human attributes: language, thought, perception, mood and sense of self."*
   Following the genes: a framework for animal modeling of psychiatric disorders [11 November 2011]

Topics

Partitioned Polygenic Scores and Normative Brain Trajectories for Early Psychosis Risk and Resilience in Adolescence

Deep-Learning–Derived Brain States & Gene Expression

Concept: Use dynamic fMRI states from NAPLS, cluster them via deep learning (e.g., variational autoencoders), then correlate each state's "deviation pattern" with Allen Brain Atlas transcriptomic profiles to see which gene expression sets parallel these abnormal states.
Novelty: Bridges *time-varying connectivity* with *postmortem expression data*, identifying specific gene sets linked to dynamic dysconnectivity.

Relevance: Pinpoints excitatory/inhibitory or synaptic genes behind transient psychosis-related states.

Concept & Rationale

Despite robust evidence that **time-varying functional connectivity** (dynamic FC) signals abnormal network states in psychosis-risk youth, the mechanistic underpinnings remain unclear. By combining **deep learning–based clustering** of dynamic FC with **postmortem gene-expression data** (Allen Human Brain Atlas, AHBA), we can pinpoint which neurobiological pathways (e.g., synaptic or excitatory-inhibitory genes) drive the **transient brain state alterations** observed in clinical high-risk (CHR) adolescents (e.g., from the NAPLS dataset).

Specific Aims

1. **Extract and Cluster Dynamic Brain States via Deep Learning**
    - **Method**:
        - Preprocess NAPLS **resting-state fMRI** time series.
        - Apply a **variational autoencoder (VAE)** to learn low-dimensional representations of each time point's connectivity profile (sliding window or time-based embeddings).
        - **Cluster** these latent representations into recurring "brain states."
    - **Innovation**:
        - VAE-based embedding can capture nonlinearities and higher-order interactions in FC data, outperforming traditional k-means or GMM clustering in identifying subtle state transitions.
2. **Identify "Deviation Patterns" and Overlap with Transcriptomic Data**
    - **Method**:
        - For each identified state, quantify "abnormality" by comparing CHR fMRI patterns to a normative reference (e.g., ABCD or healthy controls from public datasets).
        - Map these abnormal connectivity patterns to **spatial maps** (i.e., which cortical/subcortical regions deviate).
        - **Correlate** these spatial maps with region-wise gene-expression data from AHBA to pinpoint genes (or gene sets) whose expression tracks with these state-specific disruptions.
    - **Innovation**:
        - Directly links **time-varying connectivity states** to known gene-expression gradients, bridging dynamic neurophysiology and molecular architecture.
3. **Functional Annotation and Validation**
    - **Method**:
        - Perform **gene set enrichment analysis** (e.g., using WebGestalt, GSEA) on significantly correlated genes.
        - Focus on excitatory/inhibitory or synaptic plasticity sets to see if dynamic connectivity "hotspots" align with specific molecular pathways.
        - Cross-validate with additional transcriptomic resources (e.g., PsychENCODE) to confirm relevant gene networks.
    - **Innovation**:
        - Identifies **specific synaptic, E/I, or neuroinflammatory pathways** that might underlie dynamic "dysconnectivity states" in CHR.

Expected Impact

- **Mechanistic Insight**: Shows how ephemeral brain states reflect underlying molecular processes.

- **Targeted Interventions**: If states correlate with genes regulating E/I balance or synapse formation, new biomarker-driven interventions (e.g., modulating excitatory tone) can be explored.
- **Temporal Relevance**: Sheds light on which dynamic connectivity states are clinically most predictive of symptom escalation.

22q11.2 “Protective” Rare Variants & Normative Modeling

Concept: Some 22q adolescents never develop psychosis. Hypothesis: They carry protective rare variants or other polygenic backgrounds. Use existing 22q datasets and normative referencing from ABCD, to identify brain “super-normal” patterns correlated with protective variant sets within a 22q11.2 genetic background.
Novelty: 22q is well studied for *risk*, but focusing on “protection” (both variant-level and brain-level) is fresh and clinically transformative.

Concept & Rationale

While 22q11.2 Deletion Syndrome is a strong genetic risk factor for psychosis, **not all** deletion carriers develop illness. We hypothesize that certain **protective rare variants** or beneficial polygenic profiles offset this risk, manifesting as near-normal (or “super-normal”) brain trajectories. By integrating **normative modeling** of structural/functional brain data (using ABCD as a reference) with **rare-variant genomic analyses** in 22q, we can uncover the genetic architecture of resilience in this high-risk population.

Specific Aims

1. **Identify 22q Adolescents Exhibiting “Super-Normal” Brain Profiles**
    - **Method**:
        - Apply **normative modeling** (e.g., Gaussian Process Regression) to an ABCD-based reference to derive each 22q participant’s brain “z-deviation.”
        - Focus on those scoring within normal or above-normal ranges across cortical thickness, subcortical volumes, or key functional connectivity metrics despite known 22q risk.
    - **Innovation**:
        - Shifts the lens from “who’s at risk” to “who’s defying risk,” highlighting a protective phenotype.
2. **Rare Variant & Polygenic Profiling**
    - **Method**:
        - Perform **rare-variant calling** (e.g., using GATK or REGENIE for burden tests) in 22q carriers.
        - Construct polygenic resilience scores (using schizophrenia and typical development GWAS data).
        - Compare the genetic architectures of “super-normal” vs. “high-deviation” subgroups.
    - **Innovation**:
        - Moves beyond the standard 22q deletion alone, searching for **additional** rarities (e.g., partial duplication in complementary pathways) or protective polygenic backgrounds.
3. **Link Protective Genetic Features to Neurological Resilience**
    - **Method**:
        - Correlate identified protective alleles with more normative (or even “above-average”) cognitive/clinical outcomes.
        - Conduct **pathway analyses** for these protective variants (e.g., identify enrichment in synaptic maintenance or neural plasticity).
    - **Innovation**:

        - Potentially uncovers **molecular routes** for novel interventions that bolster resilience in 22q or other neurodevelopmental syndromes.

Expected Impact

- **Clinical Translatability**: Potential to identify biomarkers or genetic "modifiers" that could predict *which* 22q youth might fare well, guiding personalized monitoring.
- **Conceptual Advance**: Contrasts the usual "risk" vantage in 22q by systematically searching for protective genotype-phenotype couplings.
- **Broader Relevance**: Methods generalizable to other CNV populations (e.g., 16p11.2) to find protective mechanisms.

Gene-by-Environment Interactions for Trauma & Brain Trajectories

Concept: Investigate how trauma exposure interacts with partitioned PRS to accelerate or buffer normative brain trajectories in CHR youth. Focus on fronto-limbic networks.
Novelty: Goes beyond main effects of PRS by testing synergy with adversity, identifying subgroups "most sensitive" vs "unexpectedly resilient."
Relevance: GxE for deepening personalized interventions (stress reduction, family therapy).

Concept & Rationale

In CHR youth, **early trauma** or adversity can exacerbate genetic predispositions to psychosis. We hypothesize that certain **partitioned PRS** (targeting stress-response, immune, or excitatory/inhibitory networks) may interact with trauma to produce accelerated or derailed brain trajectories (especially in fronto-limbic regions). Uncovering these **GxE** effects is crucial for personalized interventions focusing on stress reduction or therapy for the most "gene-activated" subgroups.

Specific Aims

1. **Quantify Trauma and Partitioned Genetic Risk**
    - **Method**:
        - From NAPLS, compile **trauma exposure** metrics (e.g., CTQ, timeline interviews).
        - Construct **partitioned PRS** for psychosis-related gene sets (e.g., doping the sets with stress-response, inflammatory pathways).
    - **Innovation**:
        - Focus on gene sets specifically relevant to neurobiological stress reactivity (HPA axis, immune-related).
2. **Normative Modeling of Fronto-Limbic Networks**
    - **Method**:
        - Use **longitudinal sMRI/fMRI** data in CHR youth, referencing ABCD for typical development.
        - Calculate each individual's "deviation score" in amygdala-prefrontal connectivity or structural measures.
        - Identify if (Trauma * pPRS) synergy predicts deviant or accelerating fronto-limbic alterations.
    - **Innovation**:
        - Tracks how GxE synergy shapes real-time brain changes, not just cross-sectional snapshots.
3. **Identify "Sensitive" vs. "Unexpectedly Resilient" Subgroups**

    - **Method**:
        - Segment CHR youth into (High pPRS + High Trauma) vs. (High pPRS + Low Trauma) vs. other combos.
        - Evaluate deviant vs. near-normative fronto-limbic slopes over time.
        - Test for **protective** psychosocial factors (e.g., supportive environment) that mitigate the GxE effect.
    - **Innovation**:
        - Pinpoints subgroups who are genetically at-risk but remain stable if they avoid or mitigate severe trauma, guiding targeted family therapies.

Expected Impact

- **Clinical Utility**: More fine-grained risk stratification combining genotype + trauma metrics.
- **Preventive Interventions**: If specific subgroups are "most sensitive," specialized CBT-stress management or family therapy could preempt the pathological trajectory.
- **Novel Mechanistic Insights**: Clarifies how environment "activates" certain gene sets, culminating in abnormal fronto-limbic development.

Longitudinal Normative "Tipping Points" in CHR

Concept: Model each youth's deviance slope over time—do small increments in pPGS or environment push them across a "threshold" in normative z-scores that precipitates symptom onset?
Novelty: Finescale approach to identifying dynamic tipping points for clinical stage transitions.
Relevance: Could yield a time-sensitive biomarker to flag imminent decompensation.

Concept & Rationale

Psychosis might occur when **small, incremental changes** in genetic liability or environmental stress cross a "tipping point" in brain development. By measuring each adolescent's **normative deviation slope** over repeated imaging sessions and linking these slopes with incremental shifts in partitioned PRS or environment, we can discover the exact thresholds that predict conversion or acute symptom exacerbations.

Specific Aims

1. **Model Deviance Slopes & Potential Tipping Points**
    - **Method**:
        - Fit **longitudinal normative models** (e.g., hierarchical Bayesian or Gaussian processes) to measure how each CHR youth's brain structure/function deviates over time.
        - Use advanced dynamic modeling or **change-point detection** (e.g., hidden Markov approaches) to see if abrupt transitions coincide with symptom surges.
    - **Innovation**:
        - Goes beyond linear slopes to detect non-linear "inflection points," capturing early signs of imminent decompensation.
          Decompensation: the failure to generate effective psychological coping mechanisms in response to stress, resulting in personality disturbance or disintegration, especially that which causes relapse in schizophrenia.
2. **Link Tipping Points to Genetic & Environmental Changes**
    - **Method**:

        - Track monthly or quarterly updates to stress levels, medication, or new psychosocial adversity.
        - Incorporate **partitioned PRS** as a stable background risk, but evaluate emergent epigenetic or environment changes as triggers.
    - **Innovation**:
        - Integrates dynamic environment measures with a pre-existing genetic backdrop to see *what exactly pushes* the neural trajectory over the threshold.
3. **Test Predictive Value of Tipping Points**
    - **Method**:
        - Evaluate if detection of an "approaching threshold" in normative z-scores can forecast (within 3–6 months) a major clinical event (e.g., psychosis onset, hospitalization).
        - Potentially develop an **alert system** (risk-of-tipping) for CHR clinics.
    - **Innovation**:
        - A **time-sensitive biomarker** approach that is more acute than broad risk calculators, thus more actionable.

Expected Impact

- **Clinical Translation**: Real-time monitoring of deviance slope to alert clinicians of a "critical shift."
- **Preventive Care**: Identifying adolescents approaching a "psychosis threshold" allows targeted intensification of therapy or medication.
- **Theoretical Advancement**: Provides a dynamic systems perspective on psychosis, validating the concept of "phase transitions" in mental health.

Relevant Literature

Method

1. Using normative models pre-trained on cross-sectional data to evaluate intra-individual longitudinal changes in neuroimaging data [v3] [January 06 2025]
2. Connecting genomic results for psychiatric disorders to human brain cell types and regions reveals convergence with functional connectivity [January 04 2025]
3. A Multimodal Foundation Model for Discovering Genetic Associations with Brain Imaging Phenotypes [November 04 2024]
4. Isolating transdiagnostic effects reveals specific genetic profiles in psychiatric disorders [April 11 2024]
5. Gene-SGAN: discovering disease subtypes with imaging and genetic signatures via multi-view weakly-supervised deep clustering [January 08 2024]
6. PRSet: Pathway-based polygenic risk score analyses and software [February 07 2023]

Applied and Review

1. The Landscape of Shared and Divergent Genetic Influences across 14 Psychiatric Disorders [January 15 2025]
2. Embracing variability in the search for biological mechanisms of psychiatric illness [November 06 2024]
3. Unraveling the link between CNVs, cognition and individual neuroimaging deviation scores from a population-based reference cohort [November 01 2024]
4. Genomic analysis of intracranial and subcortical brain volumes yields polygenic scores accounting for variation across ancestries [October 21 2024]

Broad Goals

Title 1: Toward a Quantitative Taxonomy of Neurodivergence and Psychopathology

Title 2: Longitudinal Normative Modeling of Neurodivergence and Psychopathology

Abstract:
This project aims to harmonize[1] large-scale imaging genetics datasets (e.g., ProNET, Paisa, ENIGMA, NAPLS, ABCD, UKB, IMAGEN, CHIMGEN, ADNI, cVEDA, PNC, HCP, PING) to characterize transdiagnostic dimensions of neurodivergence and psychopathology. First, structural and functional MRI data will be mapped onto population-based reference curves via normative modeling approaches, to establish individualized profiles of neurocognitive deviation. Next, common-variant genomic data—including analyses via Genomic Structural Equation Modeling (Genomic-SEM)[3] and GWAS-by-Subtraction[4]—will be leveraged to link these brain signatures with psychosis risk, mood instability, and other clinically relevant dimensions. Finally, deep learning pipelines (e.g., Gene-SGAN[5], COMICAL[6], or other multimodal architectures) will integrate imaging, genomic, and other features to cluster participants into meaningful subgroups, with cross-validation to establish reproducibility across diverse populations and rare variant. By generating data-driven endophenotypes that transcend conventional diagnostic boundaries, this research will facilitate early identification of high-risk adolescents and inform more precise interventions in youth mental health.

Techniques:
Neuroimaging (structural and functional MRI), Normative modeling (population-based deviation mapping), Common-variant genomic analyses (Genomic-SEM, GWAS-by-Subtraction), Deep learning and contrastive AI architectures (Gene-SGAN, COMICAL), Multimodal clustering and validation (cross-cohort replication)

Title 3: Multimodal Taxonomy of Neurodivergence: Integrating Imaging Genetics for Precision Mental Health

Abstract:

This project aims to establish a quantitative and multimodal taxonomy of neurodivergence and psychopathology through the harmonization of large-scale imaging genetics datasets, including ABCD, UK Biobank, ENIGMA, and NAPLS 3. Central to this effort is understanding the divergent pathways of psychopathology in chronically high-risk youth, particularly those with exposure to trauma or adversity. Leveraging longitudinal normative modeling, structural and functional MRI data will be analyzed to derive individualized neurocognitive profiles mapped onto population-based reference curves. These profiles will be integrated with genomic data using Genomic Structural Equation Modeling (Genomic-SEM) and GWAS-by-Subtraction, isolating disorder-specific genetic risks from transdiagnostic genetic factors such as the p factor. Rare variant contributions will be explored through specialized pipelines, enhancing the understanding of the interplay between trauma and genetic propensity toward specific disorders like schizophrenia or bipolar disorder.

Deep learning approaches will unify these multimodal datasets, employing scalable frameworks for clustering participants into reproducible subgroups validated across cohorts. By identifying data-driven neurogenetic endophenotypes and investigating why individuals with similar trauma histories diverge into distinct psychopathological trajectories, this research seeks to advance early detection of high-risk adolescents and enable targeted, precision interventions in youth mental health.

Techniques:

Neuroimaging Analysis: Application of advanced pipelines for structural and functional MRI processing. Normative modeling to quantify deviations from typical neurocognitive trajectories in youth with varying levels of trauma exposure.
Genomic Integration: Genomic-SEM and GWAS-by-Subtraction to disentangle shared and unique genetic risk factors across disorders. Rare-variant analysis to complement common-variant findings, offering a more comprehensive view of genetic contributions.
Multimodal Deep Learning: Scalable frameworks that integrate imaging, genomic, and clinical data. Use of generative and contrastive architectures to identify reproducible subgroups stratified by trauma exposure and genetic risk.
Data Harmonization: Robust preprocessing and quality control methodologies for seamless integration of datasets from ABCD, UK Biobank, ENIGMA, and NAPLS 3. Cross-cohort harmonization techniques to ensure reproducibility and comparability of findings.
Validation: Cross-cohort replication studies to test the generalizability of identified neurogenetic subgroups. Specific focus on cohorts with high trauma exposure to validate disorder-specific genetic and neurocognitive risk profiles.

Course Requirements

The course requirements listed below are designed to provide a solid, common foundation that is useful in all areas of genomic analysis. These course requirements have been kept to a minimum since all trainees will also have substantial course requirements from their major departments. However, approximately one course per quarter, taken for a grade, from the requirements listed below will be expected from the trainees until the course requirements are satisfied. In addition, the required ethics course ***must*** be taken by the end of the first year as a trainee.
For any course listed below trainees may petition to substitute an equivalent or more advanced course, that they have already taken or plan to take, from UCLA or other institutions, by showing substantial overlap in the covered material and approval by the GATP steering committee.
Search the UCLA Schedule of Classes

1. Molecular Biology Fundamentals

Trainees are required to take ***one*** of the following courses.

- **Chemistry and Biochemistry**
  - 153A. Biochemistry: Introduction to Structure, Enzymes, and Metabolism. Units: 4. Lecture, four hours; discussion, one hour. Structure of proteins, carbohydrates, and lipids; enzyme catalysis and principles of metabolism, including glycolysis, citric acid cycle, and oxidative phosphorylation.
  - 153B. Biochemistry: DNA, RNA, and Protein Synthesis. Units: 4. Lecture, three hours; discussion, one hour; tutorial, one hour. Nucleotide metabolism; DNA replication; DNA repair; transcription machinery; regulation of transcription; RNA structure and processing; protein synthesis and processing.
- **Ecology and Evolutionary Biology**
  - 121. Molecular Evolution. Units: 4. Lecture, three hours; discussion, one hour. Molecular biology, with emphasis on evolutionary aspects. DNA replication, RNA transcription, protein synthesis, gene expression, and molecular evolution.
- **Microbiology, Immunology, and Molecular Genetics**
  - 101. Introductory Microbiology. Units: 4. Lecture, three hours; discussion, one hour. Historical foundations of microbiology; introduction to bacterial structure, physiology, biochemistry, genetics, and ecology.
  - 102. Introductory Virology. Units: 4. Lecture, three hours; discussion, one hour. Requisites: Life Sciences 3, or 7A, 7B, and 23L with grades of C- or better. Biological properties of bacterial and animal viruses, replication, methods of detection, interactions with host cells and multicellular hosts.
- **Molecular, Cell, and Developmental Biology**
  - 144. Molecular Biology. Units: 5. Lecture, three hours; discussion, one hour. Development of sophisticated understanding of DNA, RNA, and protein as well

as capability of designing experiments to address fundamental questions in biology and interpreting experimental data.

2. Probability and Statistics Fundamentals

Trainees are required to take ***one*** of the following ***two-quarter sequences***.

- **Statistics**
  - 100A. Introduction to Probability Theory. Units: 4. Lecture, three hours; discussion, one hour. Probability distributions, random variables, vectors, and expectation.
  - 100B. Introduction to Mathematical Statistics. Units: 4. Lecture, three hours; discussion, one hour. Survey sampling, estimation, testing, data summary, one- and two-sample problems.

The above "B" quarter can be substituted with:

- 236. Introduction to Bayesian Statistics. Units: 4. Lecture, three hours; discussion, one hour. Introduction to statistical inference based on use of Bayes theorem, covering foundational aspects, current applications, and computational issues. Topics include Stein paradox, nonparametric Bayes, and statistical learning.
- **Biostatistics**
  - 100A. Introduction to Biostatistics. Units: 4. Lecture, three hours; discussion, one hour; laboratory, one hour. Introduction to methods and concepts of statistical analysis. Sampling situations, with special attention to those occurring in biological sciences. Topics include distributions, tests of hypotheses, estimation, types of error, significance and confidence levels, sample size.
  - 100B. Introduction to Biostatistics. Units: 4. Lecture, three hours; discussion, one hour; laboratory, one hour. Introduction to analysis of variance, linear regression, and correlation analysis.
  - 216. Mathematical Methods for Biostatistics. Units: 2. Lecture, two hours. Requisites: Mathematics 31A, 31B, 33A. Designed for incoming first-year MS and PhD students. Review, and in some cases introduction, of specialized topics in linear algebra, multivariable calculus, and scientific computing. Interplay between mathematical methods and scientific computing within R statistical computing environment. Detailed training on numerical algorithms used in linear algebra and probabilistic simulations commonly used by statisticians.
  - 203B. Introduction to Data Science. Units: 4. Lecture, three hours; laboratory, two hours. Requisite: course 203A. Principles of data science. Topics include Health Insurance Portability and Accountability Act (HIPAA) and data ethics, databases and data retrieval, data merging and cleaning, data visualization and web presentation, reproducible research, collaborative research, cluster computing, and cloud computing.
  - 257. Computational Methods for Biostatistical Research. Units: 4. Lecture, three hours; discussion, one hour. Requisites: course 250A or Statistics 100C, Mathematics 115A. Preparation for quantitative research in statistics and data sciences. Numerical analysis and hands-on computing techniques for handling big data. Numerical analysis topics include computer arithmetic, solving linear equations, Cholesky factorization, QR factorization, regression computations, eigenvalue problems, iterative solvers, numerical optimization, and design and analysis of statistical simulation experiments. Computing techniques include basics of R programming, reproducible research using R and RStudio, collaborative research, parallel computing, and cloud computing. No prior knowledge of R assumed.

3. Quantitative Genomics Courses

The following course is ***required***.

- **Human Genetics**
  - 236A. Advanced Human Genetics A: Molecular Aspects. Units: 4. Lecture, three hours. Advanced topics in human genetics related to molecular genetics and relevant technologies. Topics include genomic technologies, human genome,

mapping and identification of disease-causing mutations, transcriptomics, proteomics, functional genomics, epigenetics, and stem cells.

Trainees are required to take ***two*** of the following courses.

- **Human Genetics**
  - 224. Computational Genetics. Units: 4. Lecture, four hours; discussion, two hours; outside study, six hours. Introduction to computational analysis of genetic variation and computational interdisciplinary research in genetics.
  - 244. Genomic Technology. Units: 4. Lecture, three hours; discussion, one hour. Survey of key technologies that have led to successful application of genomics to biology, with focus on theory behind specific genome-wide technologies and their current applications.
  - 265. Computational Methods in Genomics. Units: 4. Lecture, two and one half hours; discussion, two and one half hours; outside study, seven hours. Introduction to computational approaches in bioinformatics, genomics, and computational genetics and preparation for computational interdisciplinary research in genetics and genomics. Computational techniques and methods include those from statistics and computer science.
- **Bioinformatics**
  - 260A. Introduction to Bioinformatics. Units: 4. Lecture, four hours; discussion, two hours. Introduction to bioinformatics and methodologies, with emphasis on concepts and inventing new computational and statistical techniques to analyze biological data. Focus on sequence analysis and alignment algorithms.
- **Biomathematics**
  - 207A. Theoretical Genetic Modeling. Units: 4. Lecture, three hours; discussion, one hour. Mathematical models in statistical genetics. Topics include population genetics, genetic epidemiology, gene mapping, design of genetics experiments, DNA sequence analysis, and molecular phylogeny.
  - 207B. Applied Genetic Modeling. Units: 4. Lecture, three hours; laboratory, one hour. Covers basic genetic concepts. Topics include statistical methodology underlying genetic analysis of both quantitative and qualitative complex traits. Laboratory for hands-on computer analysis of genetic data; laboratory reports required.
  - 211. Mathematical and Statistical Phylogenetics. Units: 4. Lecture, three hours; laboratory, one hour. Theoretical models in molecular evolution, with focus on phylogenetic techniques. Topics include evolutionary tree reconstruction methods, studies of viral evolution, phylogeography, and coalescent approaches. Examples from evolutionary biology and medicine. Laboratory for hands-on computer analysis of sequence data.
- **Ecology and Evolutionary Biology**
  - 200A. Units: 4. Lecture, two hours; discussion, two hours. Current concepts and topics in evolutionary biology, including microevolution, speciation and species concepts, analytical biogeography, adaptive radiation, mass extinction, community evolution, molecular evolution, and development of evolutionary thought.
  - 235. Population Genetics. Units: 4. Lecture, three hours; discussion, one hour. Basic principles of genetics of population, dealing with genetic structure of natural populations and mechanisms of evolution. Equilibrium conditions and forces altering gene frequencies, polygenic inheritance, molecular evolution, and methods of quantitative genetics.
- **Microbiology, Immunology, and Molecular Genetics**
  - 256. Human Genetics and Genomics. Units: 5. (Same as Molecular, Cell, and Developmental Biology CM256.) Lecture, three hours; discussion, one hour. Requisites: Life Sciences 3, 4, and 23L, or 7A, 7B, and 7C. Application of genetic principles in human populations, with emphasis on genomics, family studies, positional cloning, Mendelian and common diseases, cancer genetics, animal models, cytogenetics, pharmacogenetics, population genetics, and genetic

counseling. Lectures and readings in literature, with focus on current questions in fields of medical and human genetics and methodologies appropriate to answer such questions. Concurrently scheduled with course CM156. Independent research project required of graduate students.

- **Statistics**
  - 254. Statistical Methods in Computational Biology. Units: 4. Lecture, three hours; discussion, one hour. Introduction to statistical methods developed and widely applied in several branches of computational biology, such as gene expression, sequence alignment, motif discovery, comparative genomics, and biological networks, with emphasis on understanding of basic statistical concepts and use of statistical inference to solve biological problems.

4. Career Development Course

Trainees are required to the following course is required to be taken each year they are on the grant.

- **Human Genetics**
  - Human Genetics 282. Topics on Scientific Careers. Units: 2. Lecture, two hours. Covers topics related to scientific careers such as scientific writing and presentation (including to non-scientific audiences), grant writing and reviewing, curricula vitae, hiring process, social media usage, developing short- and long-term goals, balancing career and non-work life, and social and ethical issues in biomedical research. Exploration of differences between industry, government, teaching-college, and research-college careers. S/U grading.

5. Ethics Course

Trainees are required to take Microbiology, Immunology, and Molecular Genetics 234 or Biomathematics M261 by the end of their first year as a trainee.

- **Microbiology, Immunology, and Molecular Genetics**
  - 234. Ethics and Accountability in Biomedical Research. Units: 2. Seminar, two hours. Responsibilities and ethical conduct of investigators in research, data management, mentorship, grant applications, and publications. Responsibilities to peers, sponsoring institutions, and society. Conflicts of interest, disclosure, animal subject welfare, human subject protection, and areas in which investigational goals and certain societal values may conflict. S/U grading.
- **Biomathematics**
  - M261. Responsible Conduct of Research Involving Humans. Units: 2. Lecture, two hours; discussion, two hours. Discussion of current issues in responsible conduct of clinical research, including reporting of research, basis for authorship, issues in genetic research, principles and practice of research on humans, conflicts of interest, Institutional Review Board (IRB), and related topics. S/U or letter grading

STATEMENT OF RESEARCH INTEREST

Cooper Beaman Second-Year PhD Student, Neuroscience Interdepartmental Program

"While we mapped the genes for schizophrenia, people with this disease were still dying 20 years early." —Thomas Insel

This sobering reminder of the translational gap in psychiatric and behavioral genetics research motivates my commitment to computational psychiatric genomics. Witnessing the impact of acute stressors in precipitating psychotic or affective episodes in those seemingly at risk in my community, I became determined to investigate the molecular and neurobiological mechanisms that underlie individual differences in risk and resilience. My long-term objective is to develop computational methods for dissecting cross-disorder genetic liability, clarifying why certain individuals exhibit resilience to severe mental illnesses despite high genetic risk. I aim to characterize shared genetic liability to psychopathology and the associated neurodevelopmental processes underlying complex neurocognitive functions. I am particularly keen to investigate how genetic and neurodevelopmental variation intersect to mediate risk and resilience for psychiatric disorders in adolescence. Through the Genomic Analysis Training Program (GATP), I hope to deepen my skills in large-scale computational genomics—particularly advanced statistical modeling, data integration, and machine-learning approaches—and enhance the rigor of my multivariate analysis of environmental, quantitative trait, and multi-omic interaction across spectrums of normative and divergent neurodevelopment in adolescence.

Research Focus and Aims

My dissertation research will leverage longitudinal neuroimaging, advanced genomic methods, and computational modeling to disentangle shared from specific genetic liabilities for psychiatric disorders. Using large-scale datasets, including the Adolescent Brain Cognitive Development (ABCD) study and the North American Prodrome Longitudinal Study (NAPLS), I will address three core aims:

Aim 1: Partitioning Shared and Disorder-Specific Genetic Risk.

I will extend Genomic Structural Equation Modeling (gSEM) and GWAS-by-Subtraction to isolate unique genetic risk loci for specific clinical trajectories, independent of shared genetic factors (e.g., the “p factor”). This involves adapting existing pipelines to incorporate longitudinal data from ABCD and NAPLS, which tracks clinical high-risk (CHR) youth. By identifying genetic variants specifically associated with psychotic, affective, or other symptom dimensions, I aim to move beyond the broad “p factor” to uncover more targeted biological mechanisms. I will test whether certain “purified” polygenic risk scores (PRS) selectively predict divergent outcomes in adolescents with comparable transdiagnostic genetic loading.

Aim 2: Characterizing Individual Brain Trajectories via Longitudinal Normative Modeling.

I will apply and refine normative modeling techniques to quantify individual deviations from typical brain trajectories in CHR youth. This involves generating individualized “z-deviation” maps based on longitudinal sMRI and fMRI data from NAPLS, using ABCD as a normative reference. I will correlate these brain deviation profiles with partitioned genetic risk scores (Aim 1) to identify pathway-specific associations (e.g., synaptic pPGS to fronto-temporal thickness deficits). Furthermore, I will adapt existing normative modeling approaches to incorporate longitudinal data, allowing for the detection of non-linear “inflection points” in brain trajectories that may signal imminent decompensation. I will also explore the use of advanced dynamic modeling techniques, such as hierarchical Bayesian or Gaussian processes, and change-point detection methods (e.g., hidden Markov approaches) to identify these critical shifts.

Aim 3: Elucidating Gene-by-Environment (GxE) Interactions.

I will integrate trauma exposure metrics from NAPLS and ProNET with partitioned PRS to examine how gene-environment synergy impacts brain development. This involves compiling trauma exposure metrics (e.g., Childhood Trauma Questionnaire (CTQ), timeline interviews) and constructing partitioned polygenic risk scores (pPRS) for psychosis-related gene sets. By segmenting CHR youth into subgroups based on their genetic risk and trauma exposure (e.g., High pPRS + High Trauma vs. High pPRS + Low Trauma), I aim to identify subgroups that are genetically at risk but remain resilient due to protective environmental factors. I will also investigate how trauma and genetic liability interact to influence normative “tipping points” in structural or functional brain development, identifying subgroups most likely to benefit from preemptive interventions.

Prior Preparation and Relevant Experience

My background in computational genomics, neuroimaging genetics, and high-performance computing (HPC) provides a strong foundation for this research.

Computational Genomics Rotations:

In the Hernandez lab, I led a longitudinal GWAS of subcortical volume changes in the ABCD Study using GCTA and PLINK, adapting existing pipelines and implementing rigorous quality control measures. This project enhanced my proficiency in large-scale data analysis and advanced statistical methods. In the Ophoff lab, I investigated epigenetic aging in bipolar disorder using DNA methylation clocks, developing custom scripts and generating insightful visualizations. In the Wells lab, I gained experience applying computational methods to high-throughput data, implementing Cellpose3 segmentation and tracking algorithms for analyzing images of iPSC-derived neuronal cultures.

UCSF Research (Pre-PhD):

Under Dr. Yin Shen's mentorship, I led a genome-scale CRISPR knockout screen to elucidate the anti-tumor mechanism of bufalin. This involved designing CRISPR libraries, troubleshooting technical challenges, and using bioinformatic pipelines like MAGeCK-VISPR for data analysis. I also contributed to the ENCODE project, employing CRISPRi technology to validate candidate cis-regulatory elements associated with psychiatric risk. This work provided critical training in functional genomics, high-throughput screening, and CRISPR-based methods.

Programming & HPC:

I am proficient in R (e.g., tidyverse, GenomicSEM, data.table) and Python (e.g., pandas, NumPy, SciPy, Scikit-learn), and I have extensive experience using the Hoffman2 cluster for parallel computing. My programming skills are complemented by a strong foundation in biostatistics and advanced statistical modeling.

Alignment with GATP and NHGRI Priorities

The GATP's interdisciplinary training aligns perfectly with my research goals. The required coursework in Probability and Statistics (Statistics 100B) and Advanced Human Genetics (Human Genetics 236A) will deepen my expertise in Bayesian statistics and genomic mapping, respectively. Elective courses such as Computational Genetics (Human Genetics 224) and Computational Methods in Genomics (Human Genetics 265) will further refine my skills in large-scale genomic data analysis and integration.

The GATP's emphasis on collaboration will provide access to faculty expertise across multiple disciplines, including biostatistics, human genetics, and computational biology. This collaborative environment will be invaluable as I work to integrate multi-ancestry genomic modeling, refine cross-disorder factor modeling, and develop reproducible HPC pipelines. Additionally, the career development course (Human Genetics 282) will enhance my scientific writing, grant-proposal, and presentation skills, which are essential for leading collaborative research in computational psychiatry.

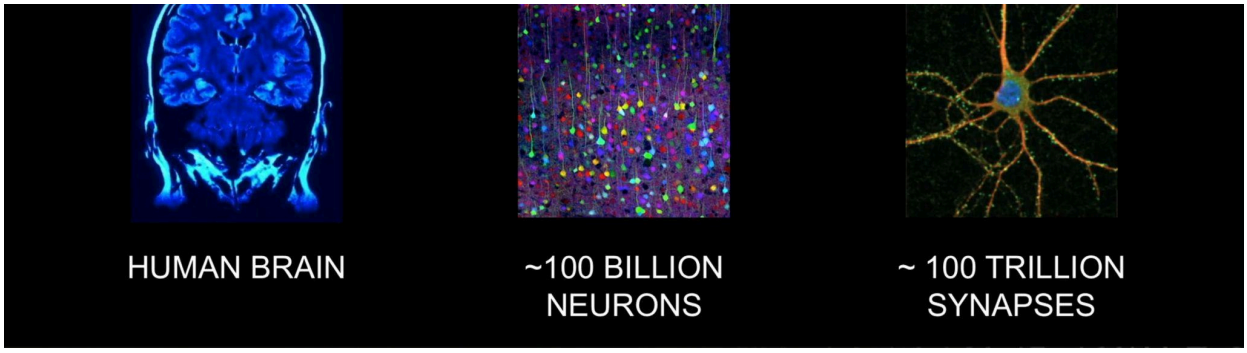
My research directly supports NHGRI's mission to interpret and functionally characterize genetic variation. By focusing on early identification of high-risk youth and understanding the interplay between genetic and environmental factors, my work bridges the gap between large-scale psychiatric GWAS and clinically actionable insights in adolescence.

Long-Term Vision

My long-term goal is to lead an academic lab focused on computational psychiatric genomics, integrating partitioned genetic liabilities, normative brain modeling, and robust HPC-driven pipelines to develop more precise, biologically grounded treatments. The GATP's emphasis on rigorous, reproducible genomic science and extensive quantitative training will anchor my trajectory toward independent research and mentorship in this rapidly evolving field.

Conclusion

Through the GATP, I aim to refine my skills in advanced statistical modeling, data integration, and machine-learning approaches, enhancing the rigor of my multivariate analysis of environmental, quantitative trait, and multi-omic interaction across spectrums of normative and divergent neurodevelopment in adolescence. By combining partitioned polygenic risk analysis with adolescent neuroimaging cohorts, I hope to differentiate transdiagnostic from disorder-specific genetic influences, clarify how adversity modulates neurodevelopmental trajectories, and identify clinically actionable early biomarkers. The Genomic Analysis Training Program's rigorous coursework, interdisciplinary collaboration, and strong quantitative mentorship will be integral to achieving these goals. I am excited to devote my computational skillset and research passion to help realize a more precise, proactive future for youth mental health and contribute to the GATP community.



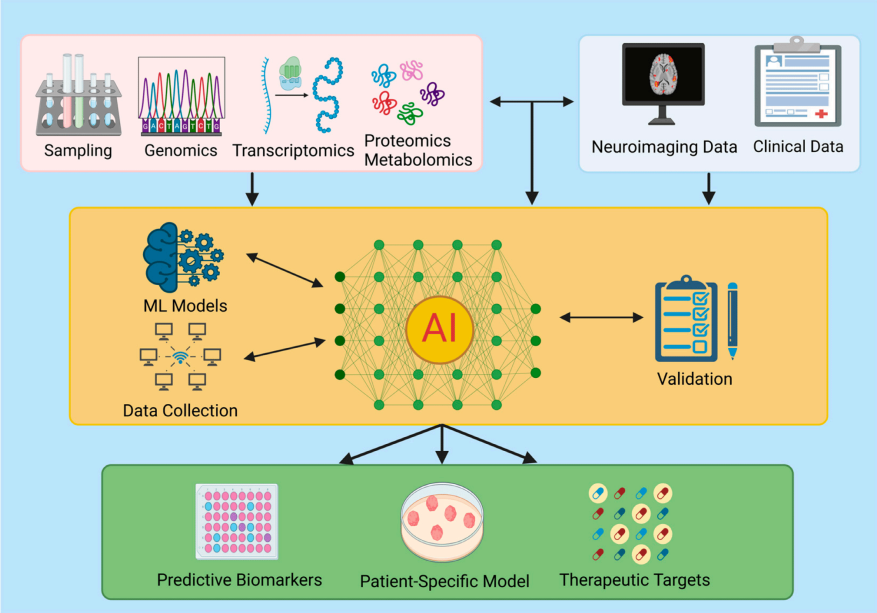
NRSA F31 Research Training Project Planning

Research Gaps [2020–2025]

Mental health disorders arise from complex interactions among genetic, molecular, neural, and environmental factors. Traditional single-modality or diagnosis-centric studies often fail to capture this complexity, yielding biomarkers that are inconsistent and largely correlational (Restoring the missing person to personalized medicine and precision psychiatry - PMC). In response, a **precision psychiatry** paradigm has emerged, emphasizing integrative, data-driven approaches that transcend categorical diagnoses (Restoring the missing person to personalized medicine and precision psychiatry - PMC). Cutting-edge methods from computational neuroscience and AI are converging to unravel the molecular and neurobiological etiology of mental distress and neurodivergence in a *disorder-agnostic* manner. Below, we review novel, high-impact methodologies – many not yet widely applied – and highlight how they synergistically advance our understanding of psychopathology. We then identify **3–4 critical research gaps** poised for a PhD dissertation, each with a feasible research question targeting translational, mechanistic insight.

Frontier Methods in Computational Psychiatry and Multimodal Integration

Modern precision psychiatry integrates multi-omics (genomics, transcriptomics, proteomics, metabolomics), neuroimaging, and clinical data via AI/ML models. This holistic pipeline enables identification of predictive biomarkers, patient-specific models, and novel therapeutic targets. Such frameworks move beyond single-variable analyses toward a system-level understanding of mental disorders.



From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC (Figure - PMC)

- **Multi-omics Data Integration with AI:** One cutting-edge approach is the fusion of genomic, transcriptomic, epigenomic, and other "omics" data using machine learning to pinpoint molecular drivers of psychiatric phenotypes (Pharmaco-Multiomics: A New Frontier in Precision Psychiatry) (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC). For example, advanced **pharmaco-multiomics** pipelines integrate DNA variants, gene expression, proteomics, and metabolomics to predict medication response in psychiatry (Pharmaco-Multiomics: A New Frontier in Precision Psychiatry). Deep learning models can absorb these high-dimensional datasets to discover polygenic risk markers and gene networks underlying symptoms. Such integration is still nascent in psychiatry due to data and methodological challenges, but it promises patient-specific insights (e.g. identifying a *molecular subtype* of anhedonia). Importantly, AI can handle nonlinear relationships at scale, uncovering hidden multi-omic patterns that classical statistics might miss (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC). This is directly aligned with precision medicine goals – recent reviews highlight that combining AI with multi-omics yields far richer predictive power and biomarker discovery than single-modality analyses (Pharmaco-Multiomics: A New Frontier in Precision Psychiatry) (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC).

- **Graph Neural Networks and Network Science:** In computational neuroscience, **graph neural networks (GNNs)** have emerged as powerful tools to model brain connectivity and multimodal neural data (Graph Neural Networks in Brain Connectivity Studies: Methods, Challenges, and Future Directions - PMC). Traditional graph-theory analyses of brain networks (connectomes) are limited in capturing nonlinear, high-dimensional interactions (Graph Neural Networks in Brain Connectivity Studies: Methods, Challenges, and Future Directions - PMC). GNNs can learn complex connection patterns across brain regions, enabling disease classification, outcome prediction, and even

patient stratification based on whole-brain network topology. Recent studies show that GNNs can integrate multiple imaging modalities (fMRI, DTI, EEG) within a unified graph model, yielding more holistic brain network biomarkers (Graph Neural Networks in Brain Connectivity Studies: Methods, Challenges, and Future Directions - PMC). For instance, a GNN-based model can simultaneously ingest functional connectivity and structural connectivity to predict symptom severity, outperforming separate models. GNNs thus address the *"dynamic connectivity"* problem by capturing time-varying and multi-scale networks in psychiatric conditions (Graph Neural Networks in Brain Connectivity Studies: Methods, Challenges, and Future Directions - PMC) (Graph Neural Networks in Brain Connectivity Studies: Methods, Challenges, and Future Directions - PMC). Notably, GNNs also offer a path toward **interpretability** by analyzing which subnetworks or nodes most influence predictions (Graph Neural Networks in Brain Connectivity Studies: Methods, Challenges, and Future Directions - PMC). Although GNN applications in psychiatry are still preliminary, they represent a novel method to link circuit-level dysconnectivity with clinical phenomena (e.g. identifying a dysregulated fronto-limbic subnetwork associated with mood dysregulation). Early evidence suggests GNNs can improve diagnostic accuracy and personalization in mental health, but further work on explainability and training data size is needed (Graph Neural Networks in Brain Connectivity Studies: Methods, Challenges, and Future Directions - PMC).

- **Transformers and Deep Learning for Multimodal Fusion:** Transformers – the deep learning architecture revolutionizing NLP – are now being applied to neuroimaging and multimodal data fusion. **Vision transformers** with cross-attention can learn joint representations of brain scans, genomics, and clinical data in an interpretable way. For example, a 2024 study introduced *MultiViT*, a multimodal vision transformer that fuses 3D MRI brain maps with fMRI connectivity matrices via cross-attention, achieving superior accuracy in schizophrenia diagnosis (A multimodal vision transformer for interpretable fusion of functional and structural neuroimaging data - PubMed) (A multimodal vision transformer for interpretable fusion of functional and structural neuroimaging data - PubMed). MultiViT not only improved classification (AUC 0.83 vs lower baselines) but also produced attention maps highlighting which brain regions and networks were salient for schizophrenia (A multimodal vision transformer for interpretable fusion of functional and structural neuroimaging data - PubMed) (A multimodal vision transformer for interpretable fusion of functional and structural neuroimaging data - PubMed). This exemplifies **interpretable deep learning**, where the model itself suggests candidate biomarkers (e.g. specific gray matter regions contributing to illness). Beyond imaging, transformer models can handle *multisequence data*: e.g. treating a patient's genomic variant profile, brain signals, and life history as "tokens" in a unified sequence for integrative analysis. Similarly, **dynamic graph transformers** have been proposed to capture evolving brain network states, showing promise in identifying transient connectivity abnormalities in disorders (Dynamic Graph Transformer for Brain Disorder Diagnosis - medRxiv). These advanced architectures remain cutting-edge – they are not yet common in psychiatric research – but they hold high impact potential. They bring improvements in *feature learning from raw data*, the ability to leverage unstructured data (like imaging pixels or EEG time-series) directly, and scalability to big datasets. Over the next few years, we expect to see transformers enabling richer multimodal models (genome × connectome × environment) with built-in interpretability, directly addressing the heterogeneity of mental illness.

- **Computational Behavioral Modeling (Computational Psychiatry):** Beyond pattern recognition, *computational psychiatry* uses generative models and simulations to link biology with behavior. Innovative work is translating cognitive neuroscience theories (e.g. reinforcement learning, Bayesian inference, network control theory) into quantitative markers of mental dysfunction (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC) (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). For example, **reinforcement learning (RL) models** of decision-making have been used to quantify anhedonia and apathy by measuring how patients update expectations of reward (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). These model parameters (learning rates, reward sensitivity) can serve as *computational endophenotypes* that are heritable and map to neural circuitry. One recent study modeled schizophrenia's "jumping to conclusions" reasoning bias with Bayesian belief updating, tying it to dopaminergic midbrain dysfunction (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). Another line of work applies **predictive coding models** in autism to explain sensory overload and social difficulties as aberrant precision weighting of predictions (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). These mechanistic models are cutting-edge because they move us toward *causal* understanding: e.g. linking a gene variant to a neurotransmitter perturbation to an RL parameter to a clinical symptom. While computational modeling has been discussed for years, it's now bolstered by larger datasets and better algorithms to fit models to individual subjects. Over the next 3–4 years, we anticipate wider use of *hybrid approaches* that combine data-driven ML with computational models (for instance, using neural network function approximators to fit reinforcement learning models at scale). Such approaches remain outside mainstream clinical research, but they align perfectly with a translational PhD: they are disorder-agnostic, focus on specific deficits (cognitive flexibility, threat learning, etc.), and can incorporate multimodal data (e.g. use fMRI to inform a model's neural priors). Ultimately, these methods yield **quantitative biomarkers** – like an abnormal decision-making parameter – that can be linked back to circuit dynamics and genetics, offering a new angle on precision psychiatry.

- **Digital Phenotyping and Environmental Data Integration:** A particularly novel frontier is the integration of *real-world behavioral and environmental data* (often via smartphones or wearables) with biological data. **Digital phenotyping** refers to collecting high-frequency data on an individual's activities, physiology, and context (e.g. smartphone GPS, accelerometer for movement, social media or speech patterns) to infer mental states (Modern views of machine learning for precision psychiatry - PMC). These data capture environmental risk factors and symptom fluctuations in vivo, complementing static genomics or infrequent brain scans. AI models can mine digital phenotypes for patterns predictive of relapse or distress – for example, changes in speech tone and reduced mobility might flag a depressive episode onset (Modern views of machine learning for precision psychiatry - PMC). Integrating this with, say, a person's polygenic risk score or imaging markers could greatly enhance predictive power for outcomes like suicide risk (Modern views of machine learning for precision psychiatry - PMC). Cutting-edge projects are exploring **multimodal wearables+genetics** platforms: imagine an app that continuously monitors sleep, heart rate, and social interaction, and an ML model that combines those features with the user's genomic and neuroimaging profile to generate a personalized mental health forecast. Early attempts at such integration are underway (e.g. combining mobile sensor data with EEG for relapse prediction), but accuracy and validation remain challenges (Modern views of machine

learning for precision psychiatry - PMC). This approach is very much *translational*: it seeks to bring computational insights into everyday clinical monitoring (e.g. an alert when a patient's behavioral data deviates significantly, given their risk profile). Over the next few years, we foresee small-scale trials of **closed-loop systems** – for instance, detecting heightened suicide risk from digital data and automatically adjusting an intervention (a prompt to seek support or a change in therapy plan) in real time. Methodologically, this calls for **time-series ML, anomaly detection, and federated learning** (to handle privacy of personal data). It's a creative, interdisciplinary area combining environmental psychiatry and AI, and it squarely targets the *high-impact goal of early intervention*.

- **Explainable and Causal AI Approaches:** As powerful AI models enter psychiatry, a crucial emphasis is on *interpretability* and *causal inference*. New methods are being developed to ensure that complex models can be understood and trusted by clinicians and neuroscientists. For example, **explainable AI (XAI)** techniques like attention maps, feature attribution, and concept extraction are being applied to neural networks in mental health (Modern views of machine learning for precision psychiatry - PMC) (Modern views of machine learning for precision psychiatry - PMC). An interpretable model might highlight that "reduced connectivity in fronto-striatal circuit" plus "high polygenic load in synaptic genes" drove its prediction of non-response to treatment – information far more actionable than a black-box prediction. Likewise, there is growing interest in **causal modeling** (e.g. causal Bayesian networks, *Granger causality*-inspired neural nets) to move beyond association to understanding *mechanisms*. One novel approach proposed a *causality-inspired GNN* to identify which brain sub-network influences others the most, effectively mapping directed interactions in brain graphs (CI-GNN: A Granger Causality-Inspired Graph Neural Network ... - arXiv). Another emerging idea is using **Mendelian randomization integrated with machine learning** to test causal links: for instance, using genetic variants as instrumental variables to infer if a brain imaging trait *causes* a symptom or is merely correlated. These approaches remain cutting-edge and are not yet common in psychiatric research. However, they are **high-impact** because they address two major needs: (1) making AI findings biologically and clinically interpretable (to bridge the "black box" gap), and (2) identifying targets that are likely causal and thus promising for intervention. Notably, recent reviews stress that emphasizing model transparency and biological plausibility will be key for the field's acceptance (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC) (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). For a PhD researcher, developing or applying an XAI method in a multimodal model (for example, to explain how multi-omics features drive a brain network abnormality linked to psychosis) would be both novel and valuable. Ultimately, explainable and causal AI will maximize translational relevance – ensuring that computational findings actually inform new therapies or precision diagnostics, rather than remaining inscrutable statistical artifacts.

Toward Disorder-Agnostic, Translational Frameworks

A consistent theme across these methods is their **transdiagnostic** focus. Instead of siloing research by DSM diagnosis, cutting-edge approaches target core dimensions of dysfunction and *endophenotypes* (measurable intermediate traits) that cut across disorders. This aligns with the NIMH's Research Domain Criteria (RDoC) framework, which promotes studying fundamental processes (cognition, reward processing, emotion regulation, etc.) across

traditional categories (Restoring the missing person to personalized medicine and precision psychiatry - PMC). Empirically, genomic studies have shown that psychiatric disorders share large portions of genetic risk and likely lie on continua rather than being discrete entities (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC) (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC). For example, schizophrenia and bipolar disorder have overlapping polygenic architectures, and many mental illnesses show common brain network disruptions (e.g. default-mode network hyperconnectivity in depression, PTSD, and anxiety). These findings "provide further support to the notion that current psychiatric diagnoses do not represent distinct pathogenic entities" (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC). In parallel, clinical research observes that symptoms like anhedonia, impulsivity, or cognitive impairment manifest in multiple disorders. Together, these insights motivate *disorder-agnostic frameworks*: rather than asking "what causes **disorder X**," researchers ask "what biological perturbations cause **symptom Y** (which may appear in X, Y, Z diagnoses)?" and "how can we subgroup patients by biology instead of label?"

The novel methods above are especially suited to this paradigm. For instance, computational modeling can isolate specific cognitive deficits (e.g. reward learning deficits found in both depression and schizophrenia) and relate them to circuit dysfunction (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC) (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). Multimodal ML can cluster patients by brain-behavior phenotypes, sometimes revealing subtypes that don't align with DSM labels. A recent unsupervised learning study on mood and trauma disorders identified two biotypes via EEG connectivity that cut across PTSD and major depression – these subtypes differed in treatment response, illustrating the power of a transdiagnostic approach (Modern views of machine learning for precision psychiatry - PMC) (Modern views of machine learning for precision psychiatry - PMC). Similarly, network analysis of psychopathology treats symptoms as nodes in a graph, identifying communities of co-occurring symptoms that might share neural substrates (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). The ability of AI to integrate diverse data (neuroimaging, genetics, life stress, cognitive tests, etc.) is crucial for characterizing such *endophenotypes* and biomarkers that are not tied to one diagnosis. This is also inherently translational: focusing on a debilitating symptom (say, social withdrawal) and its biomarker can directly inform treatment (regardless of whether it's in autism, schizophrenia, or depression). In sum, the field is moving toward **precision psychiatry** that is *person-centered and phenotype-based* (Restoring the missing person to personalized medicine and precision psychiatry - PMC). High-impact research now aims to map multi-level data to clinically relevant, specific outcomes (like treatment non-response, suicide attempt, cognitive decline), rather than broad diagnoses. This shift addresses the heterogeneity within diagnoses – by homing in on more narrowly defined phenotypes, we increase the chance of finding strong, reproducible brain and molecular correlates (Brain Imaging and Cognitive Deficits in Psychiatric Disorders) (Brain Imaging and Cognitive Deficits in Psychiatric Disorders). For a PhD candidate, adopting a transdiagnostic framework (for example, studying "neurocognitive impairment in serious mental illness" as a whole, using integrative methods) not only aligns with funding priorities (e.g. NIMH's emphasis on biotypes and RDoC), but also maximizes clinical impact. The goal is to yield knowledge that can generalize across disorders and inform personalized interventions based on an individual's unique biomarker profile rather than their diagnostic label.

Priority Research Gaps and Proposed Directions

Despite recent advances, several critical gaps remain unaddressed as of 2025. We identify **four high-priority gaps** that a 3–4 year PhD project could feasibly tackle using novel integrative approaches. Each gap is formulated with a clear research question, designed to advance the field by resolving an unmet need. These questions emphasize *translational potential* (e.g. informing interventions or diagnostics) and are scoped to be achievable within a doctoral timeframe, leveraging available data and cutting-edge methods.

Gap 1: Integrating Multi-Scale Data to Uncover Mechanistic Pathways

The gap: We still lack a deep mechanistic understanding of *how* genetic risk factors, brain circuit abnormalities, and environmental influences interplay to produce mental distress. Most studies to date examine one level at a time (genome *or* brain *or* environment), leaving a siloed view. This is a major barrier – the "complex interplay" of genetic, molecular, and environmental factors in psychiatry remains *poorly understood* (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC). For example, genome-wide analyses identify risk loci, and neuroimaging finds brain differences in patients, but we rarely know how a given risk gene leads to the observed brain network change that leads to a symptom. There is a clear **need for multimodal integration**: as one review put it, we must *"go beyond unidimensional case–control studies"* and adopt frameworks that jointly consider clinical, genetic, blood biomarkers, neuroimaging, **and environmental factors** (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC). This integration is challenging, requiring interdisciplinary expertise and robust data infrastructure (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC), which is exactly why it remains a gap.

Why it matters: Bridging this gap would mean moving from correlational findings to *causal, multi-level models* of mental illness. If we can integrate multi-omic data with brain imaging and environmental exposure data, we can start identifying the **biological pathways** from molecule to mind – for instance, discovering that a set of inflammation-related genes (perhaps activated by early-life stress) alter connectivity in mood-regulating circuits, resulting in depression symptoms. Such insights are high-impact: they could reveal novel treatment targets (e.g. intervening on that inflammation pathway or circuit) and biomarkers that are far more specific. Importantly, an integrative approach can handle heterogeneity: two patients with the same symptom might arrive there via different pathways (genetic vs. environmental), which we can only discern by analyzing all modalities together. This gap is highlighted in the literature as a major obstacle to precision psychiatry (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC) (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC). Addressing it aligns with NIH priorities to map the **"gene-brain-behavior"** axis for mental illnesses.

Proposed research question: *How can we integrate genomics, neuroimaging, and environmental exposure data to identify convergent pathways that lead to specific psychiatric symptomatology?* For example: "Can a combined analysis of whole-genome sequences, brain connectivity MRI, and childhood trauma metrics reveal mechanistic links between early stress and the emergence of paranoid thinking?"

Approach: This project would apply a **multimodal machine learning** framework to a large dataset that has all three data types (potential sources: UK Biobank for genetics+imaging+environment surveys, or a psychiatric cohort with those measures). Novel data-fusion techniques – such as multi-kernel learning or deep autoencoders that learn a joint latent space – would be used to find patterns spanning modalities. For interpretability, **network analysis** could be incorporated: e.g. building an integrative network where genes connect to brain features via known gene expression in brain regions, and environment connects via stress hormone pathways. This would allow identification of "hub" factors (say, a particular gene network and a hippocampal volume reduction jointly linked to trauma exposure) as candidate pathways (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC). By focusing on a *symptom* or endophenotype (paranoid ideation in the example question) rather than a broad diagnosis, the analysis remains disorder-agnostic and mechanistic. Feasibility is high given existing datasets and computational tools; the novelty lies in truly combining them. Over 3–4 years, a PhD student could process the data, develop the fusion model, and validate one or two emerging pathways experimentally (for instance, checking in a separate sample or using Mendelian randomization to test causality).

Expected impact: Filling this gap would provide a template for understanding multifactorial causation in psychiatry. The project could, for the first time, demonstrate how a certain **genetic profile interacts with environmental stress to produce brain circuit dysfunction**, explaining a psychiatric phenotype. This integrative methodology could be generalized to other symptoms, accelerating discovery of robust biomarkers that incorporate genetic and environmental context (key for *precision* risk assessment). Moreover, identifying convergent biological pathways enables translational research – e.g. if an inflammation-to-circuit pathway is implicated, one could trial an anti-inflammatory adjunct treatment in those patients. In summary, this research tackles the core complexity of mental illness head-on and would significantly advance the field toward *mechanism-based classification and intervention*. It addresses the oft-cited "knowledge gap" that has impeded the development of truly effective, personalized psychiatric treatments (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC) (From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care - PMC).

Gap 2: Characterizing Heterogeneity and Discovering Transdiagnostic Subtypes

The gap: Mental health disorders are incredibly heterogeneous – patients with the same diagnosis can have different symptoms, different biology, and vary in treatment response. Current diagnostic categories lump together diverse individuals, which dilutes signals in research. A fundamental challenge is thus to parse this heterogeneity and identify **meaningful subgroups or dimensions** that better reflect underlying neurobiology (Brain Imaging and Cognitive Deficits in Psychiatric Disorders). Despite calls for transdiagnostic and data-driven subgrouping, most studies still use case–control designs comparing one disorder to healthy controls (Brain Imaging and Cognitive Deficits in Psychiatric Disorders). As noted in a recent editorial, relying on broad diagnostic groups is *"less effective in developing clinically applicable biomarkers"* (Brain Imaging and Cognitive Deficits in Psychiatric Disorders). We lack widely accepted biomarker-defined subtypes (or biotypes) in psychiatry, unlike in oncology where subtyping is routine. In sum, there's a gap in methods and consensus on how to stratify patients in a disorder-agnostic way. The heterogeneity problem also means we haven't fully exploited the potential of **endophenotypes** – intermediate traits (like working memory deficits or amygdala hyper-reactivity) that might cluster patients across diagnoses.

Why it matters: Unraveling heterogeneity is crucial for precision medicine. If we continue treating all "depression" or "schizophrenia" as single entities, we risk missing therapeutic targets that only pertain to a subset. Addressing this gap will directly improve clinical outcomes: for example, if we identify a subtype of depression characterized by high inflammation and anhedonia, we could target treatments (like anti-inflammatories or dopaminergic agents) to that subtype, whereas another subtype might benefit from a different approach. Scientifically, defining transdiagnostic subtypes could reconcile inconsistent findings – it might explain why one study finds a brain change in disorder X and another doesn't, if those studies had different mixes of subtypes. The literature emphasizes that overlapping symptoms and shared biology across disorders call for such re-stratification (Brain Imaging and Cognitive Deficits in Psychiatric Disorders) (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC). From a public health perspective, moving toward *biologically informed diagnoses* (or at least supplements to diagnoses) would mark a paradigm shift, much like how cancer care was revolutionized by subtyping tumors with molecular markers. This gap is also timely: large datasets (e.g. dimensional studies like the ABCD project, or international consortia) now make it feasible to search for data-driven subgroups with adequate power.

Proposed research question: *Can we identify and validate transdiagnostic patient subtypes or symptom biotypes using multimodal data, and do these subtypes predict clinical outcomes better than conventional diagnoses?* For example: "Using brain connectivity patterns, cognitive testing, and polygenic risk scores, can we uncover distinct biotypes that span schizophrenia, bipolar, and autism – such as a 'neurodevelopmental cognitive impairment' subtype – and demonstrate their relevance for functional impairment and treatment response?"

Approach: This project would leverage **unsupervised and semi-supervised learning** on a large psychiatric cohort that includes multiple diagnoses and rich phenotyping. Methods like clustering (e.g. Gaussian mixture models, **sparse K-means on EEG connectivity** as done in prior work (Modern views of machine learning for precision psychiatry - PMC)) or dimensionality reduction (e.g. factor analysis, variational autoencoders) can be used to group individuals based on biological signatures and symptoms rather than labels. A key novelty is to incorporate **multimodal features**: rather than clustering on symptoms alone or imaging alone, combine them. For instance, create a feature set that includes functional network connectivity metrics, cognitive task performance, and genomic risk scores for each individual. The algorithm might reveal, say, one cluster with high default-mode connectivity and rumination across diagnoses, and another with fronto-striatal dysfunction and impulsivity. Once identified, these subgroups would be validated: do they replicate in an independent sample? Do they differ on external outcomes (e.g. does subgroup A have worse social functioning or distinct treatment response compared to subgroup B)? The project could also employ **graph-based clustering** where each patient is a node connected to others by similarity, finding communities in that graph (graph clustering can capture non-linear similarities). Another modern approach is **normative modeling** – defining a norm of brain structure vs. age and seeing how individuals deviate – to identify outliers that cluster into subtypes of abnormality. All these techniques are feasible within a PhD, especially using open datasets (like the Healthy Brain Network or BSNIP for psychosis spectrum).

Expected impact: Successfully delineating transdiagnostic subtypes would be a breakthrough for precision psychiatry. It directly addresses the critique that current diagnoses "do not represent distinct pathogenic entities" (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC). The immediate

impact would be a better explanation of variance in clinical outcomes – for instance, one could show that these subtypes have markedly different 1-year hospitalization rates or respond differently to a medication, whereas the DSM diagnosis alone did not predict those. In the long term, it would guide research and treatment: clinical trials could start selecting patients by biomarker subtype, potentially yielding clearer results. It also furthers the move toward **disorder-agnostic, mechanism-based classification**: the subtypes might be named by their dominant characteristic (e.g. "hypoconnectivity cognitive-affective subtype") rather than a diagnostic label. This gap is critical to close because, without resolving heterogeneity, any quest for "the" biomarker for depression or schizophrenia will remain elusive. By tackling heterogeneity with new integrative methods, the PhD work would provide a model for how to redefine psychiatric phenotypes in a way that is reproducible and clinically useful – a high priority for the field (Brain Imaging and Cognitive Deficits in Psychiatric Disorders) (Brain Imaging and Cognitive Deficits in Psychiatric Disorders). The approach embodies translation: each subtype can be studied for tailored intervention, moving us closer to *personalized care*.

Gap 3: Enhancing Interpretability and Causal Insight in AI Models

The gap: As machine learning and AI models grow more complex in psychiatry, a significant gap lies in making these models *explainable, transparent, and causally informative*. Currently, many ML studies end with "black-box" predictors – e.g. a deep neural network that can predict diagnosis or outcome, but offers little insight into *why* or *how* it made its decision. This opaqueness is problematic for several reasons: clinicians are less likely to trust or adopt tools they don't understand, and black-box models do not necessarily advance scientific understanding (they might even latch onto spurious dataset-specific correlations). Moreover, most ML findings in mental health remain correlational. There's an **interpretability gap** and a **causality gap**. We rarely derive clear mechanistic knowledge from these models (e.g. which gene→brain→symptom pathway is actually driving the result). In fact, recent critiques note that discovered biomarkers often remain at a correlational level and don't reveal modifiable causal pathways (Restoring the missing person to personalized medicine and precision psychiatry - PMC). Additionally, biases in data (such as demographic biases) can make models misleading if not interpreted correctly (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC) (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). While fields like computer vision have made strides in XAI (e.g. heatmaps on images), psychiatry lags in systematically deploying interpretability techniques or causal modeling strategies. This gap is essentially the distance between **prediction and explanation**.

Why it matters: Bridging this gap is critical for **translational relevance**. If we can explain model decisions, we can extract human-readable biomarkers or rules that clinicians can use. For example, an explainable model might tell us that a certain combination of features (high amygdala reactivity + specific gene variant + severe childhood trauma) yields high risk for PTSD – this could inform both risk screening and a mechanistic hypothesis to test (maybe that gene moderates stress hormone response). Without interpretability, we risk ML becoming a tech demo with minimal real-world impact. Causal insight is equally important: mental health interventions require knowing *leverage points* in the system (you want to target a causal factor, not just an associated marker). If an AI finds a pattern, we need to discern if it's likely causal or just a proxy (for instance, is reduced hippocampal volume causing memory symptoms, or is it a downstream epiphenomenon of something else?). Methods that incorporate causal reasoning (like leveraging random genetic variants or longitudinal designs) can elevate findings from association to inference. Ultimately, enhancing interpretability and causality will improve **generalizability** and **ethical use** of AI. It addresses concerns that current models may not translate to new populations or could even perpetuate stigma if misinterpreted (Current status,

challenges and future prospects in computational psychiatry: a narrative review - PMC) (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). Funders and regulatory bodies (like the FDA, in the case of clinical decision support tools) are increasingly demanding evidence of how an algorithm works, not just its accuracy. Therefore, this gap is not just academic – it stands between us and deployable precision psychiatry tools.

Proposed research question: *Can we develop and apply explainable AI techniques to multimodal psychiatric prediction models to reveal actionable biological insights, and can we integrate causal inference methods to distinguish true disease mechanisms from spurious correlations?* For example: "Using an explainable graph neural network that predicts relapse in schizophrenia from brain connectivity and polygenic risk, what key brain subnetworks and gene sets drive the prediction, and do these factors causally influence relapse as validated by longitudinal data or genetic instruments?"

Approach: The research would proceed in two thrusts. First, implement state-of-the-art **XAI methods** on a relevant AI model. Suppose we have a model that predicts a clinical outcome (relapse, treatment response, symptom severity) from multimodal data. We would apply techniques like **SHAP (Shapley Additive Explanations)** values to identify which features (or combinations) contribute most to each prediction. We might also use **attention mechanisms** in neural networks to focus on interpretable elements – e.g. an attention-based fusion model could tell us which modality or which brain region-timepoint pairing was most influential (A multimodal vision transformer for interpretable fusion of functional and structural neuroimaging data - PubMed) (A multimodal vision transformer for interpretable fusion of functional and structural neuroimaging data - PubMed). For imaging data, visualization of salient regions (via Grad-CAM or similar) could highlight neuroanatomical biomarkers. For genomic features, one could incorporate pathway analyses on the features the model deems important (are those genes clustering in synaptic pathways or immune pathways?). The second thrust is introducing **causal analysis**. One approach: use **Mendelian Randomization (MR)** on genetic/imaging data to test if the features identified by the model have causal effects. For instance, if the model says "hippocampal atrophy and BDNF gene score are important for outcome X," one can test with MR if genetically predicted hippocampal volume is linked to outcome X, strengthening a causal claim. Another approach is **longitudinal cross-lagged modeling** or **Granger causality** analysis on time-series (if available) to see if changes in one domain precede changes in another. The PhD student could also develop a novel hybrid: e.g. a **"causal graph neural network"** that enforces (or searches for) directed connections consistent with known biology, thereby producing an inherently interpretable structure (some initial work exists in this direction (CI-GNN: A Granger Causality-Inspired Graph Neural Network ... - arXiv)). The feasibility is reasonable: XAI toolkits are readily available, and genetic instruments for many brain and behavior traits have been published, enabling MR. Designing a bespoke interpretable model might require more work, but within 3–4 years, a prototype focusing on a specific problem (e.g. interpretable polygenic risk × fMRI model for anxiety) is doable.

Expected impact: By answering the question, we would demonstrate a **proof-of-concept for interpretable precision psychiatry models**. Concretely, the outcome might be a set of clear findings like "patients who relapsed had model profiles characterized by X and Y; these were the top contributors in the model and evidence suggests X and Y are upstream causal factors." That is actionable: X and Y could be targeted for monitoring or intervention. The impact on the field is to provide a roadmap for **responsible AI deployment** – showing that we can open the black box and extract meaningful science. This research would also produce **open-source tools or frameworks** for other researchers (for example, a pipeline to apply SHAP to multimodal clinical

data, or a validated list of causal biomarkers for an outcome). By prioritizing interpretability, the work addresses the call for transparency: *"Emphasizing model transparency and biological plausibility can facilitate more widespread acceptance and use"* of computational approaches in psychiatry (Current status, challenges and future prospects in computational psychiatry: a narrative review - PMC). Another important impact is improved **generalizability**: models that are interpretable can be stress-tested (if the model relies on a certain brain feature, we can check that feature's distribution in new cohorts to predict model performance), thereby avoiding hidden biases. In terms of clinical translation, an interpretable model could be more easily converted into an actionable test – for instance, a doctor could be provided with a report that a patient's "brain-network dysconnectivity score" is high and gene X risk is high, implying a specific risk level, which is far more informative than a generic risk percentage. Overall, this research gap must be closed to ensure that the amazing patterns AI finds actually contribute to *knowledge* and *care*, not just journal accuracy metrics. The PhD project addressing this would significantly push the field toward that goal by illustrating how to integrate explainability and causality into the fabric of computational psychiatry.

Gap 4: Dynamic Modeling of Trajectories and Gene–Environment Interactions

The gap: Most psychiatric research and predictive models are static – they take a snapshot of data and associate it with outcomes. However, mental health is highly dynamic: symptoms wax and wane, and risk factors accumulate or change over time. A major gap exists in our ability to model **trajectories** of mental illness and to incorporate time-varying environmental factors alongside biological predispositions. In practice, this means we're not great at predicting *when* a person will deteriorate or improve, or understanding the temporal sequence of risk exposures leading to illness onset. Additionally, while gene–environment (G×E) interactions are known to be important (e.g. how stress triggers illness in a genetically susceptible person), our statistical models for G×E are often simplistic (linear interactions) and do not capture the complexity or *timing* of exposures. We lack integrative longitudinal approaches that can, for example, use streams of **real-time data** (like wearable metrics or frequent surveys) in conjunction with genomics to forecast mental health outcomes. Early efforts like digital mood tracking show promise, but their integration with deep biological data is minimal so far (Modern views of machine learning for precision psychiatry - PMC). The result is a gap in **preventative precision psychiatry**: we often detect issues after they fully manifest rather than anticipating them. In summary, current methods underutilize temporal information and environmental context – a critical gap given that mental distress often emerges from a *chain of events* interacting with one's baseline vulnerability.

Why it matters: Addressing this gap could transform mental healthcare from a reactive to a proactive discipline. If we can accurately model trajectories, we might predict a psychotic break months in advance or catch when a remitted patient is on track to relapse, allowing preemptive intervention. Incorporating G×E in a nuanced way is central to **personalized prevention** – two individuals with the same genetic risk might need very different monitoring or early interventions depending on their life stress, sleep patterns, or substance use over time. Scientifically, dynamic models also shed light on *disease mechanisms*: for instance, identifying that increased stress hormone levels precede depressive episodes in high-risk genotypes would clarify the causal role of stress reactivity. The importance of time is well recognized (e.g. "staging" models of psychosis, or that childhood and adolescence are critical periods), but methods to analyze longitudinal, multi-source data are still emerging. With the rise of smartphones and wearables, we now have the *means* to collect dense temporal data on environmental exposure and behavior – the challenge is integrating that with genetics/neuroscience. This gap is critical because many debilitating events (suicide attempts, manic episodes, etc.) might be preventable

if we had timely warnings. Also, capturing dynamics is essential for understanding **treatment response trajectories** (who will improve quickly vs slowly vs not at all). In short, without dynamic, multimodal models, precision psychiatry remains incomplete.

Proposed research question: *How can we develop a dynamic, multimodal predictive model that combines genetic risk, neurobiological markers, and real-time environmental data to forecast individual mental health trajectories or acute episodes?* For example: "Can we predict impending mood episodes in bipolar disorder by using a machine learning model that continuously updates with patients' polygenic risk scores, monthly inflammation biomarker levels, and daily smartphone sensor data (sleep and activity), and what does this reveal about the interaction of chronic genetic risk and short-term triggers?"

Approach: This project would break new ground in **longitudinal multimodal modeling**. One approach is to use **time-series models** (like Long Short-Term Memory networks or Temporal Gaussian Processes) that take sequences of input data over time and output a risk prediction for the next time interval. The input sequences could include dynamic environmental measures (daily stress level self-reports, activity from accelerometers, social media linguistic tone) and occasionally updated biological measures (e.g. quarterly blood biomarker readings, annual MRI scans – treated as time points in the sequence). Genetic data, which is static, would act as a *modifier* in the model (for instance, polygenic risk could be an input that modulates how strongly certain environmental features are weighted). A concrete design: a **multimodal LSTM** that has one stream processing daily digital phenotyping features and another stream with slower-changing clinical/biological features, merging them to predict something like "probability of significant symptom worsening next week." Another complementary method is **network dynamic modeling**: constructing person-specific networks where nodes could be different symptom ratings and sensor metrics, then using network analysis or dynamical systems theory to find when the system approaches a tipping point (some have done this with early warning signals in mood disorders). Additionally, incorporating G×E could be done by **interaction-aware algorithms** – for example, a model that learns that certain features only matter given a genetic context (there are ML methods that can automatically learn interactions). One could employ **reinforcement learning** framing as well: treat the environment changes as inputs and symptom states as outputs in a state-space model, and learn the state transitions. Crucially, this project might require collecting an intensive dataset (unless one exists – e.g. the NIMH-funded **BD²** project on bipolar has elements of this, or some digital phenotyping studies that also collected genetics). A PhD could realistically carry out a smaller-scale version: enroll, say, 50 individuals with high risk (e.g. offspring of patients), track them for a year with a phone app and a couple of lab visits for biomarkers, and analyze that. Or the student could partner with an ongoing study to obtain data. The computational aspect (developing the model and validating its predictive accuracy) is very feasible within a few years, given modern libraries and computing power.

Expected impact: If successful, this research would provide one of the first **blueprints for dynamic precision psychiatry**. It would demonstrate that by continuously integrating data, we can achieve predictions that static models can't – for instance, identifying that *"in a person with high polygenic risk, three nights of poor sleep and elevated heart rate variability predict a 80% chance of a panic attack the next day."* That level of prediction could enable **just-in-time interventions** (apps prompting use of coping skills or clinicians reaching out proactively). The work would also likely highlight which environmental factors are most impactful for which genetic profiles, informing public health strategies (e.g. individuals with certain risk genotypes might be counseled to be extra cautious about maintaining sleep hygiene during stress). Moreover, methodologically, it would introduce to the field a new class of analytical tools – bridging **digital**

psychiatry and biological psychiatry. The importance of gene–environment interplay would be underlined with empirical results, moving beyond the abstract notion that both matter to a concrete understanding of how they dance together over time (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC) (New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications - PMC). Additionally, by focusing on *trajectories*, we may discover early biomarkers of conversion to illness (e.g. subtle changes in activity patterns that precede a first psychotic episode in youth at risk). This gap, once addressed, pushes psychiatry towards a future of continuous, personalized care rather than episodic snapshots. It leverages the full richness of data now accessible (thanks to wearables and big data) for predictive modeling. For the field, it means a shift toward **preventive psychiatry** – analogous to how cardiology uses cholesterol and blood pressure trends to prevent heart attacks, we would use mood, sleep, and perhaps EEG trends to prevent psychiatric crises. In sum, closing this gap would significantly reduce the burden of mental illness through earlier intervention and would deepen our understanding of how risk unfolds into illness in real-world conditions, fulfilling a key translational promise of precision medicine.

Conclusion: The above research gaps – multimodal mechanism mapping, heterogeneity deconvolution, interpretability measures, and modeling dynamics – represent the frontier of computational psychiatry and precision neuroscience. Tackling these challenges with novel AI and integrative methods will not only yield high-impact publications , but also generate tools and knowledge with genuine clinical and translational relevance. By focusing on disorder-agnostic frameworks and specific dysfunctional processes, this research agenda moves the field toward a future where **mental health care is data-driven, individualized, and proactive**. Each proposed direction is ambitious yet feasible, and together they address the critical needs that, if met, could revolutionize our etiological understanding and treatment of mental distress and neurodivergence in the coming years.

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Psychiatric Genomics, Neuroimaging, and Computational Medicine Overview [2019–2024]

Recent years have witnessed rapid methodological and computational innovations that are transforming psychiatric genomics, neuroimaging, and computational modeling. Leveraging large-scale datasets – including the Adolescent Brain Cognitive Development (ABCD) study, the North American Prodrome Longitudinal Study (NAPLS), and the Psychosis Risk Outcomes Network (ProNET) – researchers are integrating multi-modal data to unravel the molecular and neurobiological mechanisms underlying mental disorders. Below, we review key advances from the past four years, highlighting novel methodologies such as genomic structural equation modeling (gSEM), **GWAS-by-Subtraction**, longitudinal **normative modeling**, and deep learning approaches. We then identify three critical research gaps and propose high-impact research questions (aligned with NRSA criteria of significance, innovation, and feasibility) to address these gaps and advance our understanding of the etiology of mental illness.

Innovations in Psychiatric Genomics and Molecular Mechanisms

Genomic Structural Equation Modeling (gSEM): Genome-wide association studies (GWAS) have yielded hundreds of risk loci for psychiatric disorders, but interpreting the shared and distinct genetic architecture across disorders required new multivariate tools. **Genomic SEM (gSEM)** has emerged as a powerful approach to model the genetic covariance between traits using GWAS summary statistics (Genetic architecture of 11 major psychiatric disorders at

biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC) (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC). For example, a 2022 study applied gSEM to GWAS data on 11 major psychiatric disorders (average N≈157k each) and identified **four latent genetic factors** – Neurodevelopmental, Compulsive, Psychotic, and Internalizing – underlying their genetic correlations (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC) (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC). Notably, the **Psychotic** factor (capturing schizophrenia, bipolar with psychosis, etc.) was enriched for **protein-truncating-variant–intolerant genes expressed in excitatory and GABAergic neurons**, highlighting specific molecular pathways (glutamatergic and GABAergic dysfunction) that broadly contribute to psychotic disorders (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC). This stratified gSEM approach also pinpointed gene sets disproportionately contributing to shared risk versus disorder-specific risk, offering a refined view of how **pleiotropic genes** influence multiple disorders versus unique illness phenotypes (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC) (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC). Such findings exemplify how multivariate genomics can elucidate etiological mechanisms: rather than a single "p-factor" of psychopathology, genetic risk aggregates into intermediate dimensions with distinct biological signatures (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC) (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC).

GWAS-by-Subtraction: A recent innovation for dissecting genetic overlap is **GWAS-by-Subtraction**, which isolates genetic effects unique to one phenotype by conditioning out shared influences of a related phenotype. In essence, GWAS-by-Subtraction performs a genome-wide analysis on *Trait B* after "subtracting" genetic effects of *Trait A*, thereby identifying variants specifically associated with *Trait B independent of A* (GWAS-by-subtraction reveals an IOP-independent component of primary open angle glaucoma - PMC). This approach has been used to distinguish overlapping psychiatric or behavioral traits. For example, a study in 2023 parsed the genetics of well-being vs. depression by subtracting out depression-related effects from a well-being phenotype, thereby uncovering genetic variants linked to positive affect that are not simply the inverse of depression (Distinguishing happiness and meaning in life from depressive ...). Similarly, in a medical context, GWAS-by-Subtraction helped identify an intraocular-pressure–independent genetic component of glaucoma (GWAS-by-subtraction reveals an IOP-independent component of primary open angle glaucoma - PMC). By applying genomic SEM, researchers could model SNP effects on a target trait (e.g. glaucoma) via two latent variables – one shared with the covarying trait (IOP) and one unique (GWAS-by-subtraction reveals an IOP-independent component of primary open angle glaucoma - PMC). This yielded novel loci for the unique component that standard GWAS would miss (GWAS-by-subtraction reveals an IOP-independent component of primary open angle glaucoma - PMC). In psychiatry, GWAS-by-Subtraction holds promise for dissecting highly comorbid conditions. For instance, one could differentiate genetic factors driving **schizophrenia vs. bipolar disorder**, or **anxiety vs. depression**, by subtracting the shared risk and finding variants tied to each disorder's distinct features. Early applications demonstrate that **GWAS-by-Subtraction can reveal trait-specific genetic architecture** even when phenotypes are strongly correlated (GWAS-by-subtraction reveals an IOP-independent component of

primary open angle glaucoma - PMC) (GWAS-by-subtraction reveals an IOP-independent component of primary open angle glaucoma - PMC). This methodological advance improves our ability to map genetic influences to particular symptom domains or subtypes, thus sharpening the search for molecular mechanisms unique to each disorder.

From Genes to Biology – Functional Genomics and gSEM: Another crucial development is integrating genomic findings with functional genomic data to identify molecular mechanisms. Deep learning models have begun to bridge this gap by predicting biological effects of psychiatric risk variants. For example, **INTERACT**, a transformer-based deep learning model, was recently developed to predict cell type–specific DNA methylation patterns in human brain tissue (Deep learning predicts DNA methylation regulatory variants in specific brain cell types and enhances fine mapping for brain disorders - PMC). INTERACT can identify noncoding genetic variants that alter gene regulation in specific brain cell types (neurons or glia), achieving extremely high predictive accuracy (AUC ~0.99) for methylation profiles (Deep learning predicts DNA methylation regulatory variants in specific brain cell types and enhances fine mapping for brain disorders - PMC). Importantly, variants predicted by this model to affect methylation in neural cells were found to be enriched for heritability of psychiatric disorders, linking genetic risk to epigenetic regulation in relevant cell populations (Deep learning predicts DNA methylation regulatory variants in specific brain cell types and enhances fine mapping for brain disorders - PMC). Incorporating such predictions significantly **improved fine-mapping of causal variants** for schizophrenia and depression (Deep learning predicts DNA methylation regulatory variants in specific brain cell types and enhances fine mapping for brain disorders - PMC), pointing to specific DNA changes and target genes that mediate disorder risk. In parallel, genomic SEM has been extended to bridge genes and brain phenotypes: a 2023 study applied gSEM to identify **"Genetically Informed Brain Networks"** – latent dimensions of cortical structure genomics – and found these genetic brain factors had distinct correlations with psychiatric disorders (e.g. a network of larger cortical surface area had positive genetic correlation with bipolar disorder but negative with ADHD) (Genomic Structural Equation Modeling Reveals Latent Phenotypes in the Human Cortex with Distinct Genetic Architecture - PMC) (Genomic Structural Equation Modeling Reveals Latent Phenotypes in the Human Cortex with Distinct Genetic Architecture - PMC). Together, these advances illustrate how *molecular genomics and statistical genetics are converging*: by leveraging big data and new algorithms, researchers are moving from lists of GWAS loci to biologically interpretable pathways (e.g. cell-type specific regulatory mechanisms, synaptic signaling genes) that contribute to mental illness. The ability to *statistically link genetic risk factors to brain changes and functional outcomes* is a major step toward understanding the molecular etiology of psychiatric conditions.

Advances in Neuroimaging and Longitudinal Normative Modeling

With the advent of large neuroimaging cohorts and sophisticated models, our understanding of brain development and alteration in mental illness has deepened. **Normative modeling** has emerged as a key framework in computational psychiatry to characterize how individual brains deviate from a healthy trajectory. In contrast to traditional case–control comparisons, normative modeling maps population-level trajectories (e.g. how brain structure changes with age in typically developing individuals) and then situates each individual relative to that *normative range* (Evidence for embracing normative modeling - PMC) (The Normative Modeling Framework for Computational Psychiatry - PMC). By charting the centiles of variation in brain measures across age, sex, and other covariates, this approach can detect whether a given patient shows **statistically extreme deviations** in brain metrics, which may serve as

personalized biomarkers (The Normative Modeling Framework for Computational Psychiatry - PMC) (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC). For example, the recent *Brain Charting* project aggregated MRI data across **≈100,000 individuals** to create lifespan normative growth charts for brain structure (Evidence for embracing normative modeling - PMC). Using these charts, researchers demonstrated that normative-feature deviations improved detection of group differences: in one benchmark, using deviation scores (how far an individual's brain measure lies from age-normative expectation) significantly enhanced classification of schizophrenia vs. control, compared to using raw MRI measures (Evidence for embracing normative modeling - PMC). Thus, normative models increase sensitivity to subtle brain abnormalities by leveraging large reference distributions.

Crucially, normative modeling has now been applied to high-risk populations. A 2024 ENIGMA consortium study examined **clinical high-risk for psychosis (CHR)** individuals (N≈1,340) with structural MRI, asking whether they exhibit deviations outside the normal range of brain morphometry and whether those deviations predict outcomes (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC) (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC). Each CHR individual's cortical thickness, surface area, and volume were converted to a **z-score relative to a healthy reference** (age- and site-matched), quantifying how "infra-normal" (below 2nd percentile) or "supra-normal" (above 98th percentile) their brain measures were (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC). This allowed investigators to move beyond average group differences and instead assess what proportion of CHR youth have extreme neuroanatomical alterations. The study found that only a small subset of CHR individuals showed marked deviations in regional brain measures (e.g. 3–5% had abnormally low cortical thickness in certain areas, similar to the proportion in healthy controls for many regions) (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC) (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC). Global measures (like total brain volume) showed slight shifts – CHR converters tended to have smaller volumes on average – but large heterogeneity remains. Interestingly, *greater variability* in brain deviation patterns was noted in those CHR who later developed psychosis, suggesting that idiosyncratic brain anomalies might signal higher risk (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC) (Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis - PMC). Normative modeling in CHR is still evolving, but it provides a nuanced view: rather than all at-risk youth having "smaller hippocampi" or other uniform deficits, it appears that **only specific individuals have extreme neural deviations**, which may help pinpoint those in need of early intervention. This individualized approach aligns with precision psychiatry goals.

Longitudinal normative modeling is an emerging extension of this work. While most current models are cross-sectional (baseline deviations), new methods aim to chart **normative developmental trajectories** and detect when an individual's *change over time* is abnormal. For instance, researchers have proposed using pre-trained cross-sectional normative models as baselines to evaluate follow-up scans, thereby measuring if a person's brain maturation (e.g. cortical thinning per year) falls outside the expected range (Using normative models pre-trained on cross-sectional data to evaluate longitudinal changes in neuroimaging data) (Using normative models pre-trained on cross-sectional data to evaluate longitudinal changes in neuroimaging data). Early studies in adolescents show promise: applying normative models in a longitudinal ABCD sub-sample illustrated how deviations can wax or wane with development (Human Brain Mapping | Neuroimaging Journal - Wiley Online Library). Moreover, a 10-year follow-up of first-episode psychosis patients found progressive cortical thinning in some

individuals; normative trajectory modeling helped determine which patients' cortical loss exceeded typical age-related changes (10-Year Longitudinal Study of Brain Cortical Thickness in People ...). Such approaches are still being refined (e.g. ensuring the models accurately capture intra-individual change (Using normative models pre-trained on cross-sectional data to evaluate longitudinal changes in neuroimaging data)), but they highlight a key advance – moving beyond static snapshots to dynamic, person-specific growth charts of the brain. This is particularly relevant for illnesses like schizophrenia that evolve over adolescence and early adulthood.

Deep learning in neuroimaging: In parallel, deep learning methods have been leveraged to detect complex brain patterns associated with psychiatric disorders. High-dimensional neuroimaging data (MRI, fMRI, diffusion scans) are well-suited to convolutional neural networks (CNNs) and other deep architectures that can learn subtle spatial features. For example, Menon et al. (2021) developed a multimodal 3D CNN that ingested structural MRI, diffusion MRI, and resting-state fMRI from the ABCD study to classify children with disruptive behavior disorders (DBDs) vs. typically developing children (Frontiers | Multimodal Ensemble Deep Learning to Predict Disruptive Behavior Disorders in Children). By integrating three MRI modalities, the model achieved ~72% accuracy (70% sensitivity, 72% specificity) in distinguishing children with conduct or oppositional defiant disorders (Frontiers | Multimodal Ensemble Deep Learning to Predict Disruptive Behavior Disorders in Children). Notably, this **ensemble CNN outperformed models using any single imaging modality**, underscoring the value of multimodal integration (Frontiers | Multimodal Ensemble Deep Learning to Predict Disruptive Behavior Disorders in Children). The study also used **Grad-CAM (gradient-weighted class activation mapping)** to interpret the network's predictions, revealing that the classifier focused on specific cortical and subcortical regions (e.g. portions of the prefrontal cortex and amygdala) that contributed most to differentiating DBDs (Frontiers | Multimodal Ensemble Deep Learning to Predict Disruptive Behavior Disorders in Children). This exemplifies how deep learning not only boosts predictive power but can generate neuroscientifically meaningful maps of disorder-related brain features.

Beyond classification, deep learning models are being applied for dimensional and generative analyses. Autoencoders and graph neural networks have been used to learn low-dimensional representations of functional connectivity, identifying latent "brain network phenotypes" related to symptoms. For instance, a graph CNN applied to ABCD connectome data uncovered network patterns linked to externalizing behaviors (Frontiers | Multimodal Ensemble Deep Learning to Predict Disruptive Behavior Disorders in Children). Similarly, **brain age prediction** via deep neural networks (predicting an individual's age from MRI) has become a popular technique; the difference between predicted age and true age (the "brain age gap") is essentially a deviation score that has been associated with psychiatric conditions and cognitive impairment. These deep models, when trained on tens of thousands of neuroimages, capture subtle distributed changes (e.g. diffuse cortical thinning pattern) that simpler models miss. The ability of deep learning to handle **multimodal, longitudinal data** is also driving new insights. For example, recurrent neural network models have been tested to incorporate time-series imaging data and predict future clinical outcomes in high-risk youth, offering a data-driven way to forecast who might benefit from preventive treatment.

Deep Learning and Multimodal Integration in Psychiatry

A unifying theme across genomics and neuroimaging advances is the push toward **integrative modeling** – combining data across levels (genetic, neural, cognitive, clinical) to build a more complete picture of psychiatric illness. Large consortia like NAPLS and ProNET are explicitly

multimodal: they collect genomic DNA, MRI scans, EEG, cognitive tests, and clinical assessments in individuals at risk for psychosis (Psychosis Risk Outcomes Network (ProNET) | Path Program) (Psychosis Risk Outcomes Network (ProNET) | Path Program). This has enabled the development of **multimodal predictive models**. For instance, in NAPLS-2, incorporating polygenic risk scores (PRS) for schizophrenia alongside neurocognitive and clinical features improved the prediction of which CHR individuals would convert to psychosis (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC) (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC). Perkins et al. (2020) showed that a PRS could modestly stratify risk in CHR youth (those who converted had higher genetic risk load on average) (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC). Building on this, recent efforts (e.g. Davenport et al., 2021) have combined **structural MRI measures plus PRS** in risk calculators. In one study, a model integrating MRI-based brain features and a psychosis PRS (along with cognition and symptoms) achieved high sensitivity in identifying CHR individuals who would develop psychosis, outperforming individual predictors (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC). Interestingly, this data-driven model was very sensitive (catching most true converters) whereas clinician assessments were more specific but missed some cases (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC). Such findings suggest that **algorithmic tools can complement clinical judgment**, flagging subtle risk indicators (e.g. slight thinning in cortical regions together with high polygenic load) that a clinician might overlook. The **significance** is clear: by integrating multimodal data, we move closer to early detection of illness and personalized intervention.

Methodologically, new computational techniques facilitate this integration. **Joint factor analysis** and multimodal autoencoders can fuse genetic and imaging data to discover linked patterns. For example, one can perform a genomic SEM linking psychiatric disorder GWAS with neuroimaging GWAS (from ENIGMA or ABCD) to identify shared genetic factors that influence both brain phenotypes and clinical diagnoses (Genomic Structural Equation Modeling Reveals Latent Phenotypes in the Human Cortex with Distinct Genetic Architecture - PMC) (Genomic Structural Equation Modeling Reveals Latent Phenotypes in the Human Cortex with Distinct Genetic Architecture - PMC). The “Genetically Informed Brain Networks” study cited earlier did exactly this: it found latent genetic factors that simultaneously explained covariance among cortical surface areas and had meaningful genetic correlations with disorders (e.g. a factor reflecting high surface area in frontoparietal regions had genetic overlap with bipolar disorder) (Genomic Structural Equation Modeling Reveals Latent Phenotypes in the Human Cortex with Distinct Genetic Architecture - PMC) (Genomic Structural Equation Modeling Reveals Latent Phenotypes in the Human Cortex with Distinct Genetic Architecture - PMC). This kind of analysis directly connects **neuroimaging endophenotypes** with psychiatric genetics, offering hypotheses about how certain brain circuit differences (possibly those influenced by specific gene sets) confer risk for illness. Likewise, **mediation models** in ABCD have tested whether brain measures lie on the pathway between genes and behavior. Karcher et al. (2022) found that polygenic risk scores for schizophrenia and cross-disorder traits were associated with smaller brain volumes in children, and that lower brain volume partly mediated the link between genetic risk and psychotic-like experiences in youth (Psychotic-like experiences and polygenic liability in the ABCD Study® - PMC). In other words, children with high polygenic load had slightly reduced total cortical volume, which in turn was related to reporting more psychotic-like symptoms, hinting that **genetic risk may manifest as early neurodevelopmental changes** (Psychotic-like experiences and polygenic liability in the ABCD Study® - PMC). These multimodal analyses are strengthening the bridge from molecules to mind: for example, if a particular gene network leads to aberrant synaptic pruning (molecular mechanism) causing

subtle cortical thinning (neuroimaging finding) that produces cognitive or perceptual abnormalities (clinical symptom), integrative modeling is how we detect and confirm such pathways.

Deep learning for multimodal data is especially promising. Researchers have started training neural networks that take genetic data (e.g. polygenic scores or even raw SNP sets) *and* imaging data as joint inputs to predict psychiatric outcomes. Although in its infancy, this approach could learn complex nonlinear interactions (e.g. a specific genetic profile might only lead to illness if a certain brain connectivity pattern is also present). One example combined SNP data and fMRI connectivity to classify autism spectrum disorder, using a hybrid model of CNNs for imaging and multilayer perceptrons for genetic features, achieving improved accuracy over single-modality models (2019, ini et al.). In another vein, graph neural networks have been used to represent individuals as nodes in a population graph with edges encoding similarity in genetic profile and brain features – the GNN then predicts symptom severity by leveraging population structure (intuitively, grouping subjects with similar gene–brain profiles). These cutting-edge techniques remain experimental, but they illustrate the trend towards **holistic modeling**: rather than treating "genetics vs. environment" or "brain vs. behavior" as separable, modern computational psychiatry tries to model them together. As data from ABCD, ENIGMA, and AMP-SCZ (which encompasses ProNET and related studies) accumulate, the field is poised to apply these tools at unprecedented scale. The ultimate goal is a unified model that can explain how genetic liability, brain maturation, and environmental factors dynamically interact to produce mental distress – a far cry from the siloed studies of the past.

Unaddressed Research Gaps and Proposed High-Impact Questions

Despite remarkable progress, several critical gaps remain unfilled. We highlight **three priority gaps** and propose an innovative dissertation research question for each. Each question is crafted to be **significant** (addressing an important unmet need with clear impact on understanding etiology), **innovative** (employing novel integrative methods), and **feasible** for a predoctoral NRSA project (leveraging available data and tools in a tractable study design). By targeting these gaps, the proposed research will advance knowledge of the molecular and neurobiological mechanisms of mental illness.

Gap 1: Integrating Genomic and Neurodevelopmental Data to Trace Etiological Pathways

Gap Description: We lack a clear understanding of *how genetic risk translates into abnormal brain development* in youth vulnerable to psychiatric disorders. Genomic studies identify risk variants and imaging studies find brain differences, but these remain largely separate literatures. **No study to date has fully integrated polygenic risk measures with longitudinal brain trajectories** to pinpoint when and how genetic risks manifest in the brain. For example, schizophrenia polygenic risk scores are associated with slightly smaller brain volumes in childhood (Psychotic-like experiences and polygenic liability in the ABCD Study® - PMC), but it is unknown whether high-risk youth show *accelerated divergence* from normative brain development as they age. Most existing models are either purely genetic or purely neuroimaging-based; an integrative, longitudinal approach is needed. This gap is crucial because filling it would elucidate the developmental neurobiology of genetic risk – a key to early intervention. By understanding which brain changes mediate genetic vulnerability (and *when* they occur), we can target those mechanisms preventatively.

Proposed Research Question: *How do polygenic risk factors for serious mental illness influence adolescent brain developmental trajectories, and can integrative genomic-neuroimaging modeling identify early-deviating neural patterns that predict the emergence of psychotic or mood disorders?*

- **Significance:** This question tackles the fundamental problem of linking genes to brain to psychopathology. It will determine whether youth with high polygenic risk (for schizophrenia, bipolar, etc.) show measurable deviations in brain growth (e.g. cortical thinning, network connectivity) during adolescence, which could serve as biomarkers before clinical symptoms fully emerge. Aligning with NIMH's emphasis on developmental origins of mental illness, this research could reveal *when* and *how* genetic liability exerts its effects, informing early detection and mechanistic intervention strategies (high clinical and theoretical significance).
- **Innovation:** The project will use a novel **integrative model combining genomic SEM and longitudinal normative modeling**. For example, it might apply genomic SEM to derive a latent "polygenic risk factor" from GWAS of multiple disorders, then use longitudinal normative modeling on ABCD and/or ProNET MRI data to see how this genetic factor relates to individual-specific brain trajectories (an approach not previously done). The use of **GWAS-by-Subtraction** could further isolate genetic influences on brain change that are specific to, say, psychosis risk vs. general developmental variation. This creative fusion of methods (genomic SEM + normative growth modeling + possibly deep learning for trajectory prediction) is highly innovative and can uncover gene–brain relationships that a single-method study would miss.
- **Feasibility:** ABCD provides ~12,000 youths with genetic data and longitudinal imaging (multiple timepoints), and ProNET/AMP-SCZ is collecting multimodal data in high-risk adolescents. These existing datasets ensure the project has sufficient sample size and available measures to succeed, without needing new data collection. The applicant can utilize established pipelines for computing PRS, normative modeling (e.g. using the PCNToolkit (The Normative Modeling Framework for Computational Psychiatry - PMC)), and statistical mediation/SEM. The scope – analyzing already-collected data with advanced analytics – is realistic for a PhD timeline. Furthermore, preliminary evidence of gene–brain links in ABCD (Psychotic-like experiences and polygenic liability in the ABCD Study® - PMC) underscores feasibility: there are detectable signals to build on. The project is aligned with NRSA training goals, providing interdisciplinary training in genomics, neuroimaging, and computational modeling.

Gap 2: Dissecting Shared vs. Disorder-Specific Mechanisms in Psychopathology

Gap Description: Psychiatric disorders have overlapping genetic and neural signatures, yet it remains unclear what biological factors are **unique to particular disorders or symptom dimensions**. Most current analyses emphasize shared risk (e.g. the transdiagnostic p-factor) (Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic, and molecular genetic levels of analysis - PMC), but this can obscure critical differences – for instance, why does one person develop bipolar disorder vs. schizophrenia even if they share many risk genes? We currently lack methods to explicitly parse **disorder-specific molecular and neurobiological pathways**. This gap is evident in clinical high-risk cohorts: many risk factors (cognitive deficits, polygenic load, brain abnormalities) predict a general increase in illness risk (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC) (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC), but we don't know which factors tip a trajectory toward one outcome vs. another. Addressing this gap is essential for refining diagnoses and developing targeted

treatments. If we can identify unique genetic or neural features of, say, schizophrenia, we can pursue those as specific therapeutic targets, rather than treating all serious mental illness as one entity.

Proposed Research Question: *What genetic and neuroimaging signatures distinguish closely related psychiatric outcomes – for example, differentiating youth who develop schizophrenia-spectrum psychosis vs. those who develop mood disorders – and what do these disorder-specific biomarkers reveal about divergent biological pathways in mental illness?*

- **Significance:** This question directly addresses the heterogeneity problem in psychiatry. By focusing on *differences* rather than just commonalities, it aims to uncover biomarkers that are uniquely associated with specific diagnostic trajectories (e.g. psychotic disorder vs. affective disorder) among high-risk individuals. This has high significance for precision medicine: if we find, for instance, that unique neural circuitry disruptions or distinct sets of genes (perhaps related to glutamate vs. calcium signaling) distinguish schizophrenia from bipolar disorder, it could lead to diagnostic assays or tailored interventions for each condition. It also enriches etiological understanding by showing how distinct illnesses *diverge* at the biology level despite overlapping risk factors. This fills an acknowledged gap in NIMH's strategic objectives to identify biomarkers that clarify disease boundaries.
- **Innovation:** The project will apply the cutting-edge **GWAS-by-Subtraction** method in combination with multimodal data analysis. For example, it could subtract the genetic effects of bipolar disorder from schizophrenia (using existing GWAS) to find SNPs that specifically increase schizophrenia risk but **not** bipolar risk (GWAS-by-subtraction reveals an IOP-independent component of primary open angle glaucoma - PMC). Similarly, it can use **subtraction on imaging features**: leveraging normative models, one could subtract the "shared" brain deviation pattern in all converters from the pattern in those who specifically develop schizophrenia. The study might also utilize **multivariate classification (e.g. deep learning)** on combined imaging + genetic features to classify outcome diagnoses in CHR youth, and then interpret the model to see which features drive class discrimination. No published study has yet applied GWAS-by-Subtraction to psychiatric phenotypes in this way, nor integrated it with neuroimaging data – this is a novel conceptual approach to disentangle etiology. It is a creative synthesis of methodologies (genetic subtraction, normative brain mapping, deep classifiers), thus highly innovative.
- **Feasibility:** There are ample data to support this research. The NAPLS and ProNET consortia collectively have thousands of CHR participants, of whom a subset developed schizophrenia-spectrum psychosis and others developed depression or bipolar outcomes (Psychosis Risk Outcomes Network (ProNET) | Path Program) (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC). GWAS summary statistics for major disorders are publicly available (PGC datasets), enabling the genomic subtraction analyses. Computationally, genomic SEM software can perform GWAS-by-Subtraction, and tools like *XGBoost* or neural networks can handle multimodal classification. Feasibility is strengthened by the relatively balanced numbers of different outcomes in CHR samples (ensuring statistical power to compare them) and by existing preliminary findings (e.g. evidence that certain cognitive profiles distinguish those who convert to psychosis vs. those who don't (Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis - PMC)). The project's design (secondary analysis of large open datasets) is low-cost and time-efficient, fitting well within a predoctoral timeline. By leveraging the sponsor team's expertise in both

genetics and neuroimaging, the applicant can realistically execute this high-risk/high-reward project with NRSA support.

Gap 3: Interpretable Deep Learning for Mechanistic Insights in Psychiatric Neuroscience

Gap Description: While deep learning models have shown promise in predicting mental health outcomes from brain scans or genes, **interpretability and mechanistic insight remain limited**. Black-box models can identify patterns correlating with disease (e.g. a CNN can detect a "fingerprint" of ADHD in fMRI data), but we often cannot extract biological meaning – i.e., *why* the pattern is predictive. This gap means we risk having powerful models that improve diagnosis but do not advance understanding of disease mechanisms. Additionally, current deep learning efforts rarely integrate multi-scale data in an interpretable way. We lack approaches that use deep learning not just for prediction, but to *generate hypotheses* about molecular and neurobiological processes (for example, identifying which brain networks and gene expression changes underlie a model's decision). Addressing this gap is vital to ensure that computational advances translate to knowledge advances. An interpretable, biologically grounded AI model could reveal novel targets (say, a particular circuit or cell type) that drive a network's classification of patients vs. controls, thereby pointing scientists to investigate that target's role in pathophysiology.

Proposed Research Question: *Can we develop a deep learning framework that combines genomic and neuroimaging data to predict mental health outcomes **and** provides interpretable feedback mapping the molecular and neural features most critical to those predictions – thereby shedding light on specific gene-brain mechanisms of mental illness?*

- **Significance:** This question addresses the need for *explainable AI* in psychiatric research. Its significance lies in pushing beyond prediction to explanation: a model that not only tells us who is at risk, but also highlights which genes or brain regions are implicated in that risk, would be immensely valuable. This aligns with NRSA's training emphasis on projects that contribute new knowledge – here, the knowledge gain is mechanistic understanding distilled from a complex model. If successful, this project could produce a tool that, for example, identifies a combination of a particular polygenic signature and hyperconnectivity of the amygdala as the key driver of an adolescent's anxiety disorder prediction. Such insight would direct molecular biologists and neuroscientists to probe the amygdala-related genes or pathways flagged by the model. The public health impact is also notable: interpretable models engender clinician trust and could be used in practice to both predict outcomes and guide personalized treatment (e.g. suggesting which biological domain to target).
- **Innovation:** The project is highly innovative in both approach and expected outcome. It proposes to design an **integrative deep learning model (e.g. a hybrid network)** that ingests multimodal inputs – possibly high-dimensional polygenic scores, brain connectivity matrices, and clinical variables – and yields individualized risk predictions. The novelty comes from coupling this with state-of-the-art interpretability techniques. For instance, the student might adapt **Layer-wise Relevance Propagation or attention mechanisms** within the network to quantify the contribution of each input feature (or feature type) to the prediction. Another creative aspect is linking the model's internal representations to biology: e.g., enforcing a layer in the network that corresponds to biological groupings (like sets of SNPs mapped to gene pathways, or brain regions grouped by networks) to make the latent factors more interpretable. This **"biologically-informed deep learning"** is cutting-edge and relatively unexplored. By the end, the model might output not just a risk score but an explanatory map:

highlighting a subset of genome variants (perhaps in stress-hormone genes) and specific brain anomalies (perhaps hyperactive hippocampus) that together drove the decision for a given patient. This level of interpretability and data fusion has not been achieved before in our field, marking the project as innovative.

- **Feasibility:** Feasibility is supported by the convergence of available resources and techniques. Large labeled datasets (like ABCD, with thousands of participants having genotype, MRI, and behavioral data) are ideal for training deep models. Compute infrastructure for deep learning is widely accessible (GPUs, cloud computing via NRSA funds). Moreover, the project can start with existing architectures (e.g. multi-input CNNs, graph neural networks) and focus on adding interpretability modules – a tractable engineering task given modern frameworks (TensorFlow/PyTorch have packages for neural attention, etc.). Importantly, preliminary work (like the 2021 study using Grad-CAM on a CNN for DBDs (Frontiers | Multimodal Ensemble Deep Learning to Predict Disruptive Behavior Disorders in Children)) shows that interpreting neuroimaging DL models is possible; this project would extend that idea to multi-modal inputs and more granular interpretation (e.g. gene-level). The scope (developing and testing a model) is doable within 3–4 years, especially with transfer learning strategies (pre-training on one dataset, fine-tuning on another). The mentorship team likely includes computational neuroscientists and data scientists to guide the model development, ensuring the student can overcome technical hurdles. In sum, the project is feasible and aligns perfectly with NRSA's dual aim of **research training** (the fellow would gain skills in AI, neuroscience, and genomics) and **science advancement** (creating an interpretable multi-modal AI tool for psychiatry).

Research Ideas and Questions

1. How well do multimodal longitudinal normative modeling ai-guided biotypes recapitulate symptom-based DSM-5-TR diagnostic categories?
2. Near/Sub-significance threshold genetic variant/quantitative biomarker functional characterization/validation
3. **Longitudinal Normative modeling/Normative Trajectory Modeling** ABCD, NAPLS, Pronet, 22q comparison (recapitulation) etc.?
    a. Related ideas from Rune [ABCD and NAPLS]
        i. Compare/benchmark existing cross-sectional normative modeling approaches.
        ii. Develop/train true *longitudinal* normative modeling approaches and compare to existing cross-sectional methods.
4. Investigation of discordant subset brain deviation vs predicted genetic liability across disorders (resilience/protective factors)
5. Genetic determinants of proresilient variation in reward sensitivity/processing, motivation, working memory, and social cognitive neurobiological correlates in Clinical High Risk Youth.
6. Characterizing environmental and genetic determinants of biological, developmental and functional variation in complex neurocognitive functions, the development and variation of reward processing, executive function, social and emotional processing, and other dimensional subfactors of psychopathology.
7. Modeling genetic vs environmental protective/resilience conferring factors to genetic liability for neurodevelopmental disorders.
8. Comparative biotyping of the subthreshold symptomatic space in undiagnosed individuals, a network analytic normative modeling approach.

9. Investigating neurodevelopmental divergence, shared biomarkers/endophenotypes across psychopathology, and the variable expression of genetic liability to psychotic spectrum disorders in adolescence.
10. Design research questions, rigorously and optimally extracting maximum novel information from the target data sets (ABCD/NAPLS) maximally addressing/informing their specific missions and goals using methods of interest like longitudinal normative modeling, Deep learning AI (GAN etc) and any other recent and robust multimodal statistical methods/approaches.
11. Quantitatively modeling to describe neurobiological correlates and the transient biotypes characterizing symptomatic improvement in a clinical context of mental distress. Relevance for quantitative efficacy tracking tracking, augmentation of therapeutic interventions and stratification/characterization of risk.
12. Investigate the pleiotropic and convergent genetic liability, molecular and cellular pathways impinging on downstream higher order neurocognitive functions and neural substrates associated with the general psychopathology factor, aberrant neurodevelopment, and neuropsychiatric disorder broadly.

Literature

Method

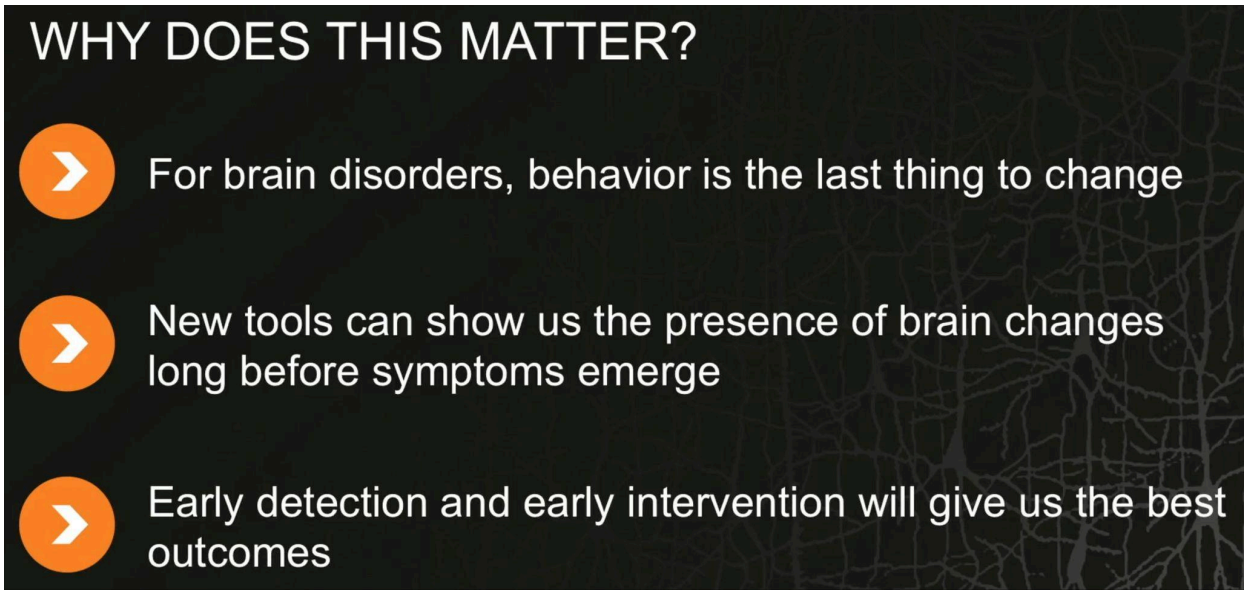
1. Using normative models pre-trained on cross-sectional data to evaluate intra-individual longitudinal changes in neuroimaging data [v3] [January 06 2025]
2. Connecting genomic results for psychiatric disorders to human brain cell types and regions reveals convergence with functional connectivity [January 04 2025]
3. A Multimodal Foundation Model for Discovering Genetic Associations with Brain Imaging Phenotypes [November 04 2024]
4. Isolating transdiagnostic effects reveals specific genetic profiles in psychiatric disorders [April 11 2024]
5. Gene-SGAN: discovering disease subtypes with imaging and genetic signatures via multi-view weakly-supervised deep clustering [January 08 2024]
6. PRSet: Pathway-based polygenic risk score analyses and software [February 07 2023]

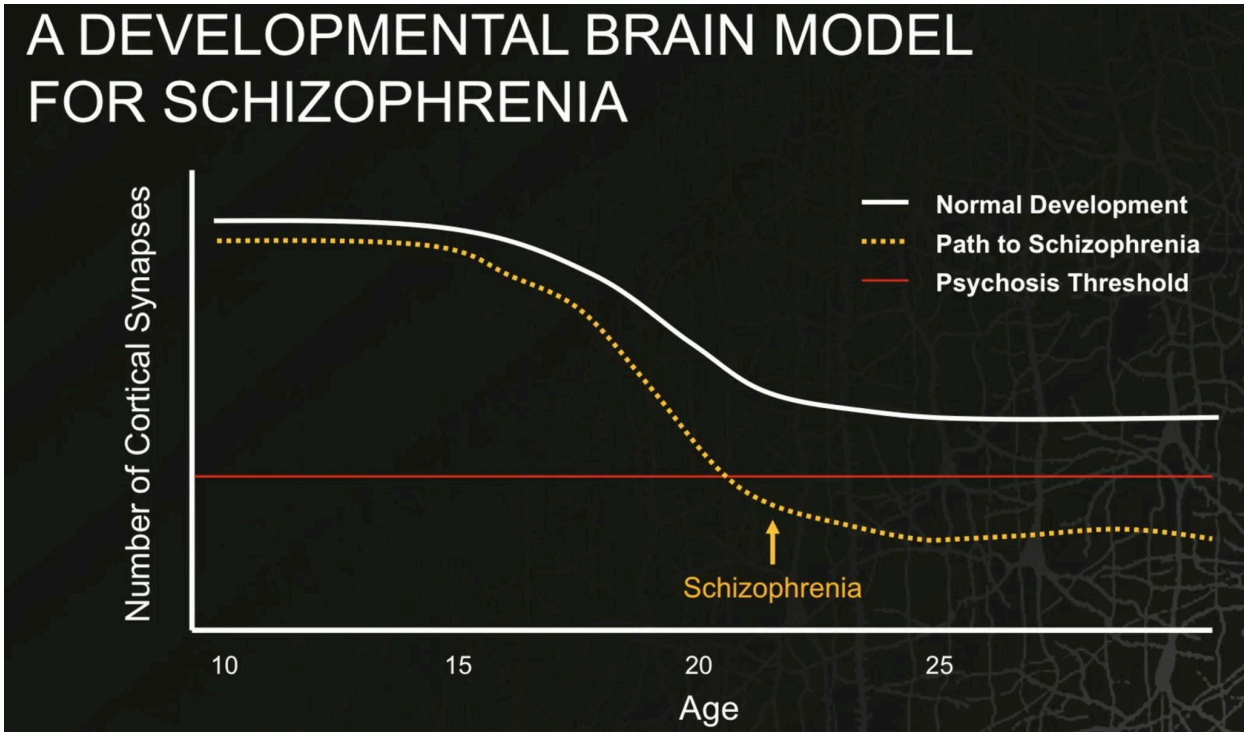
Applied

1. The Landscape of Shared and Divergent Genetic Influences across 14 Psychiatric Disorders [January 15 2025]
2. Embracing variability in the search for biological mechanisms of psychiatric illness [November 06 2024]
3. Unraveling the link between CNVs, cognition and individual neuroimaging deviation scores from a population-based reference cohort [November 01 2024]
4. Genomic analysis of intracranial and subcortical brain volumes yields polygenic scores accounting for variation across ancestries [October 21 2024]
5. Bridging the scales: leveraging personalized disease models and deep phenotyping to dissect cognitive impairment in schizophrenia [February 27, 2025]
6. Genetic, transcriptomic, metabolic, and neuropsychiatric underpinnings of cortical functional gradients [March 05, 2025]

Images

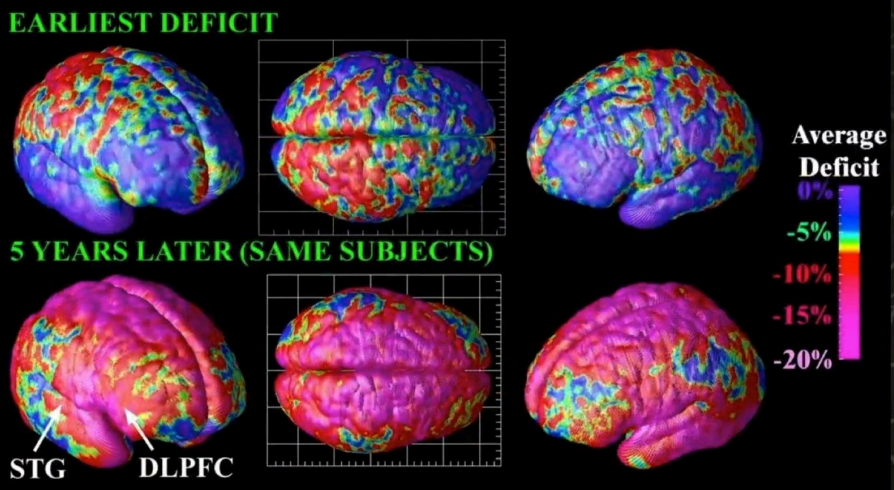
[Toward a new understanding of mental illness [Thomas Insel | TEDxCaltech • Jan 2013]]





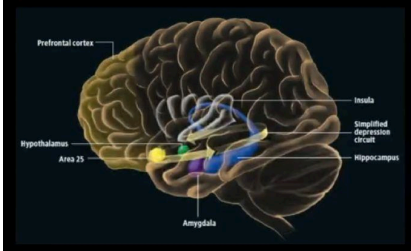
SCHIZOPHRENIA AS A BRAIN DISEASE

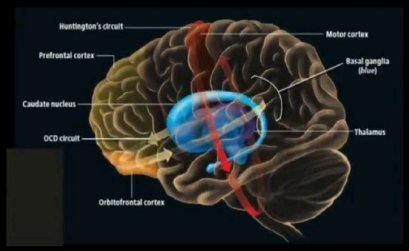
Early and Late Gray Matter Deficits in Schizophrenia

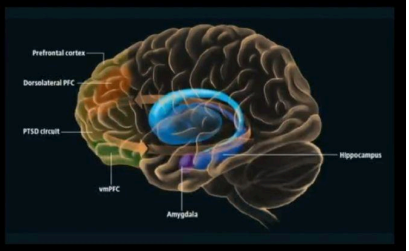


SOURCE: THOMPSON ET AL, 2001

DISORDERS OF THE HUMAN CONNECTOME







DEPRESSION OCD PTSD

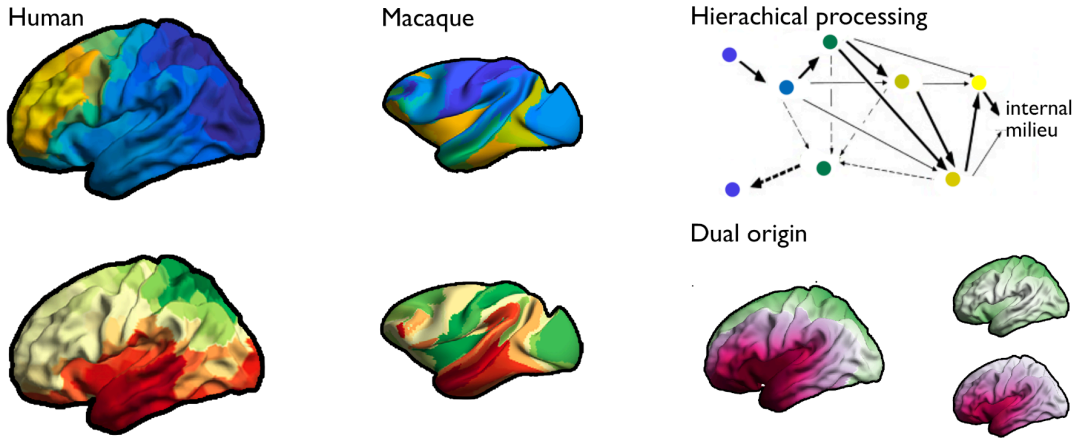
~~Mental Disorders~~

~~Behavioral Disorders~~

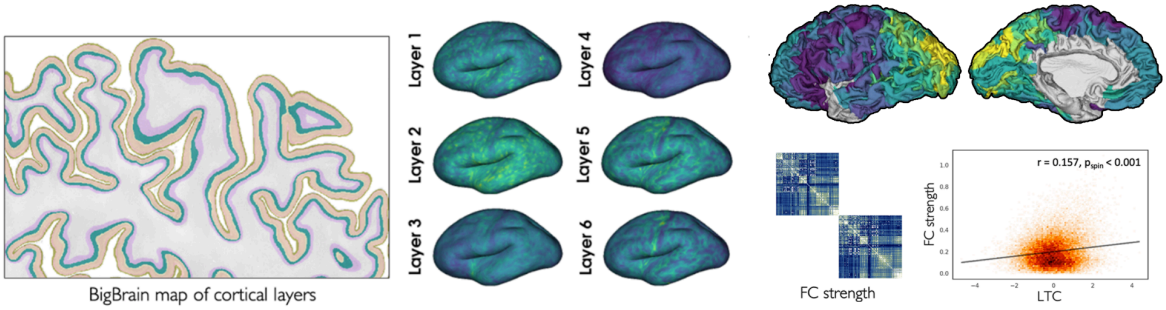
Brain Disorders

Cognitive Neurogenetics Lab Research Areas and Goals

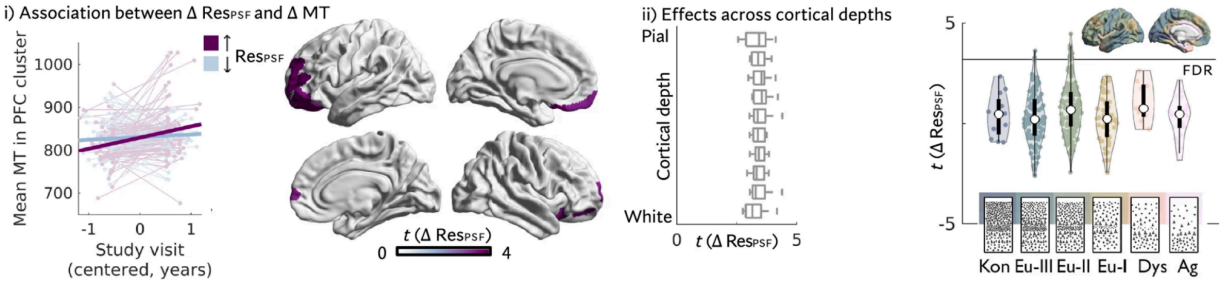
A. Genetic correlation of brain structure



B. Covariance of layer thickness and link to functional connectivity

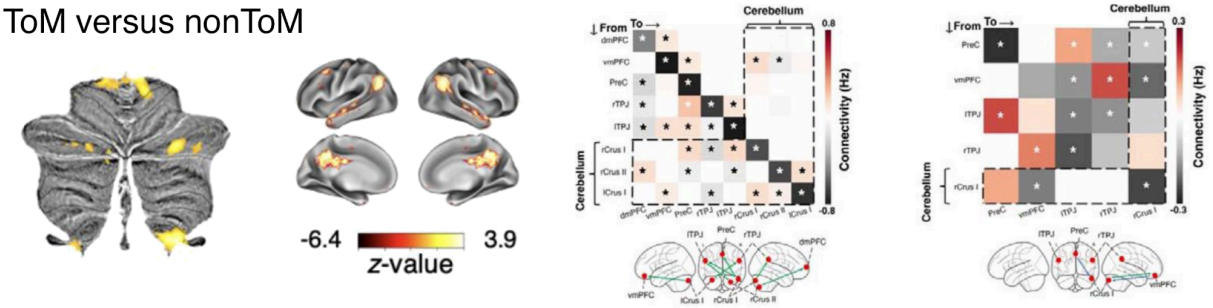


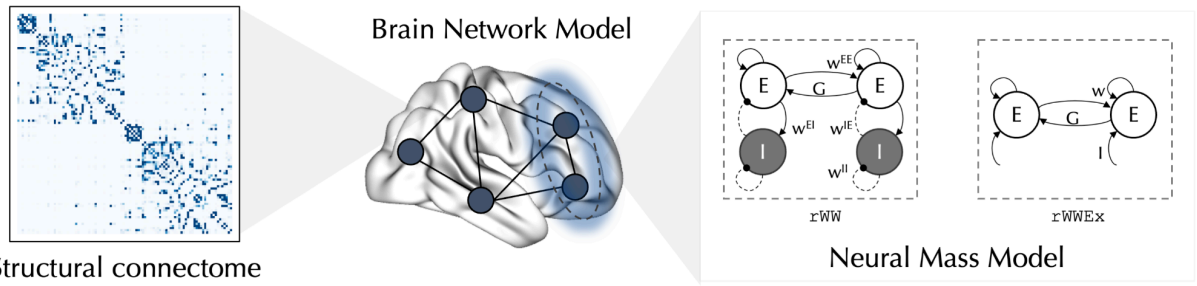
A. Longitudinal variation in resilient psychosocial functioning is associated with ongoing cortical myelination



B. The cerebellum supports the emergence of Theory of Mind

ToM versus nonToM





Quotes

[Toward a new understanding of mental illness [Thomas Insel | TEDxCaltech • Jan 2013]]

In approximate descending order by timeliness, impact, and salience

1. “What I've been talking to you about so far is mental disorders, diseases of the mind… They are disorders of behavior, and they are disorders of the mind. But what I want to suggest to you is that both of those terms, which have been in play for a century or more, are actually now impediments to progress, that what we need conceptually to make progress here is to rethink these disorders as brain disorders.”
Justification: This perspective has gained significant traction over the past decade. The shift from viewing mental illnesses purely as behavioral or mind disorders to recognizing them as brain disorders has led to more targeted research and treatment strategies.

Initiatives like the Research Domain Criteria (RDoC) by the National Institute of Mental Health emphasize a biologically-based framework for understanding mental disorders, moving beyond traditional symptom-based classifications.

2. "That is precisely what we do today when we decide that everybody with one of these brain disorders, brain circuit disorders, has a behavioral disorder. We wait until the behavior becomes manifest. That's not early detection. That's not early intervention."
   Justification: The emphasis on early detection and intervention has become a cornerstone in mental health care. Programs like Coordinated Specialty Care (CSC) have been developed to provide early and comprehensive treatment for individuals experiencing first-episode psychosis, aiming to improve long-term outcomes by addressing symptoms promptly.

3. "Why does this matter? Well first because, for brain disorders, behavior is the last thing to change."
   Justification: Understanding that behavioral symptoms often emerge after significant brain changes has underscored the importance of identifying neurological markers for early diagnosis. Advances in neuroimaging and genetic research have facilitated the detection of these markers before behavioral manifestations, allowing for proactive interventions.

4. "Look at this closely and you can see that actually they've crossed a different threshold. They've crossed a brain threshold much earlier, that perhaps not at age 22 or 20, but even by age 15 or 16 you can begin to see the trajectory for development is quite different at the level of the brain, not at the level of behavior."
   Justification: This observation aligns with current research emphasizing the importance of adolescence in the development of mental disorders. Early identification of atypical brain development trajectories has become crucial in preventive psychiatry, leading to interventions during critical developmental periods.

5. "Here we're talking about traffic jams, or sometimes detours, or sometimes problems with just the way that things are connected and the way that the brain functions."
   Justification: This analogy reflects our evolving understanding of mental disorders as disruptions in neural connectivity and circuitry. Research in neurogenomics and connectomics has provided insights into how these "traffic jams" contribute to various psychiatric conditions, influencing new therapeutic approaches.

6. "Now, already in the case of the brain disorders that I've been talking to you about—depression, obsessive compulsive disorder, post-traumatic stress disorder—while we don't have an in-depth understanding of how they are abnormally processed or what the brain is doing in these illnesses, we have been able to already identify some of the connectional differences, or some of the ways in which the circuitry is different for people who have these disorders."
   Justification: Since 2013, research has further elucidated the neural circuitry involved in various mental disorders, leading to more precise interventions. However, the complexity of these conditions means that our understanding, while improved, remains incomplete.

7. "You could, if you want, compare this to, on the one hand, a myocardial infarction, a heart attack, where you have dead tissue in the heart, versus an arrhythmia, where the organ simply isn't functioning because of the communication problems within it."
   Justification: This comparison has helped in conceptualizing mental disorders as

functional disruptions rather than structural damages, influencing both public perception and treatment modalities.

8. "As we think about this, probably it's better to actually go a little deeper into one particular disorder, and that would be schizophrenia, because I think that's a good case for helping to understand why thinking of this as a brain disorder matters."
   Justification: Focusing on schizophrenia as a brain disorder has led to advancements in early intervention strategies and a better understanding of its neurobiological underpinnings, although challenges in treatment efficacy persist.

9. "The important piece here is that as you begin to look at people who have these disorders, the one in five of us who struggle in some way, you find that there's a lot of variation in the way that the brain is wired, but there are some predictable patterns, and those patterns are risk factors for developing one of these disorders."
   Justification: Recognizing both the variability and predictability in brain wiring has been fundamental in identifying individuals at risk for mental disorders, leading to personalized prevention strategies.

10. "When we talk about the brain, it is anything but unidimensional or simplistic or reductionistic. It depends, of course, on what scale or what scope you want to think about, but this is an organ of surreal complexity, and we are just beginning to understand how to even study it."
    Justification: While the brain's complexity remains a significant challenge, advancements in neuroscience have provided deeper insights into its functioning, making this statement less impactful today.

Healing - Our Path from Mental Illness to Mental Health [Thomas Insel | Feb 2022]

1. On Diagnostic Labels as Barriers

"In mental health, the development of treatments, both medical and psychological, remains handicapped by outdated, imprecise diagnostic labels. We're stuck where the rest of medicine was in 1990, prior to the use of genomics for diagnosis."
Justification: Highlights the current gap and urgent need to transition towards precision medicine, aligning mental health with advances seen in other medical fields.

2. Brain Disorders as Connectional Problems

"The idea of mental illness as a 'chemical imbalance' has now given way to mental illnesses as 'connectional' or brain circuit disorders."
Justification: Reflects a crucial shift in understanding mental illnesses as problems of neural connectivity, pivotal for contemporary neuroscience.

3. DSM's Clinical Limitations

"Clinical trials of new treatments in people with biologically different disorders give modest or negative results... we have seen little progress beyond medications discovered by serendipity and psychological treatments created decades ago."
Justification: Critically assesses the limitations of symptom-based diagnosis (DSM approach) for effectively guiding treatment development.

4. Neurological vs. Mental Disorders

"Certainly for the brain disorders classified as neurological, location counts... Mental disorders do not have an observable brain lesion... Mental disorders are the arrhythmias, not the infarctions."
Justification: Offers a sharp analogy distinguishing observable structural lesions (neurological disorders) from functional disruptions (mental disorders).

5. DSM's Structural Problem
"DSM labels could simply be creating disorders where none exist... Emerging data from genetics and neuroimaging revealed little biological basis for the categories."
Justification: Directly confronts the DSM's problem of fabricating artificial diagnostic categories divorced from underlying biology.

6. Precision Medicine for Mental Health
"Precision medicine recognizes that one road to better outcomes runs through better diagnosis... For mental illness, we have never found such a lesion... scientists have been rightly reluctant to conduct brain biopsies without knowing where to look."
Justification: Captures the unique challenges in mental health diagnostics and highlights precision medicine as a necessary but currently unrealized goal.

7. Heterogeneity in Mental Illness
"There is little question that many of the categories are heterogeneous, even at the level of symptoms... there are 227 combinations of symptoms that can lead to the same label."
Justification: Emphasizes the extensive heterogeneity within current diagnostic labels, underscoring their inherent imprecision.

8. Diagnostic Labels and Treatment Mismatch
"If our approaches to heart disease were to diagnose 'chest pain,' our treatment plan might end with analgesics. Our medications for anxiety, depression, and psychosis might be like analgesics for chest pain: helpful in the short term but not addressing the core problem."
Justification: Provides a powerful metaphor exposing the superficiality of current symptom-based treatment paradigms.

9. Mental Illness as Developmental Brain Disorders
"The most important insight... is not the discovery of a mutation, but a new view of mental illness: these disorders increasingly look like developmental brain disorders."
Justification: Introduces a critical conceptual framework reframing mental illness as developmental in nature, integrating genetic and environmental contexts.

10. Limitations of Genomic Findings in Psychiatry
"The genomics of mental disorders turned out to be much more complicated... we found so many [genomic variations]. For schizophrenia, more than two hundred variations in DNA have been identified... none can be considered causal."
Justification: Highlights current genomic challenges, setting realistic expectations for the utility of genetic discoveries in clinical psychiatry.

Uncategorized

1. *"Psychiatric disorders constitute a diverse set of conditions, variously impinging on all domains of mental function and affecting the most fundamental human attributes: language, thought, perception, mood and sense of self."*

Following the genes: a framework for animal modeling of psychiatric disorders [11 November 2011]

UCLA NSIDP Rotation Background

Rotation History

0. May 2021 – June 2023 - Dr. Yin Shen [Ph.D., UCLA Department of Human Genetics, 2008; Professor, UCSF Department of Neurology, Faculty since 2015]

Full Time Research Associate/Junior Specialist and Lab Manager
In the Shen lab, I led two functional genomics projects and substantially contributed to a third, employing advanced CRISPR-based screening methodologies (GeCKO, CRISPRi, Prime Editing) within human iPSC and differentiated neuron systems. My responsibilities encompassed the design and execution of genome-scale screens, including systematic troubleshooting and optimization of low-efficiency viral packaging for a GeCKO screen. I performed downstream computational analysis using established pipelines such as MAGeCK-VISPR for drug target prioritization. Key contributions include the functional characterization of candidate cis-regulatory elements linked to neurodevelopment (ENCODE project validation via qPCR) and non-coding variants associated with breast cancer (CASP8 3'UTR variants via luciferase assays following Prime Editing screens), substantially developing my expertise in CRISPR editing, iPSC differentiation, and diverse genomic data analysis techniques.

a. Led a genome-scale GeCKO positive selection CRISPR screen and the subsequent CRISPRi validation of prioritized variants to identify protein mediators of bufalin-induced MYCN degradation, independently developing a novel viral packaging strategy to overcome plasmid size limitations and analyzing results with the MAGeCK-VISPR pipeline.
b. Functionally validated cis-regulatory elements prioritized by an ENCODE CRISPRi screen using targeted CRISPR perturbations in iPSCs/neurons and qPCR, and characterized CASP8 3'UTR variants identified via Prime Editing screens through multi-stage luciferase reporter assays.
c. Significantly contributed to the drafting of five manuscripts, led a writing workshop encouraging the development of scientific writing skills for lab members with limited english writing experience, delivered multiple internal and external research presentations (journal clubs, collaborator meetings), and served as lab manager, handling operational responsibilities including ordering, safety, and onboarding.

1. Fall 2023 - Dr. Michael Wells

Funding and space limitations

a. I employed stem cell biology and high-throughput methods, focusing on single-cell RNA sequencing and optical cell analysis. This experience honed my technical skills in iPSC culture and functional genomics, building upon my prior two years of experience employing these methods with the Shen lab at UCSF.
b. Generated BD Rhapsody single-cell RNA-seq data for a pilot quantitative comparison of the advantages and limitations of hiPSC-derived neural progenitor 'villages' compared to conventional array-based iPSC tissue culture approaches for scalable in vitro research.
c. Enhanced understanding of cell intrinsic and other factors regulating in vitro neuronal gene expression via high-throughput genomic analysis.

2. Winter 2024 - Dr. Daniel Geschwind

Space and mentorship bandwidth limitations

a. I developed NGN2-inducible, PEmax-expressing HEK293T and iPSC cell lines using retroviral and PiggyBac delivery systems, respectively, to support prime editing screens and the functional validation of neuropsychiatric and neurodegenerative risk loci building upon my training in CRISPR-based functional genomics research in the Shen lab.
b. Reviewed existing literature for affordable ways to accelerate and automate iPSC clonal isolation from CRISPR-edited bulk cell populations (esp. when editing-efficiency is low).

3. Spring 2024 - Dr. Leanna Hernandez

Computational inexperience and inefficiency. Communication challenges and underdeveloped expectations

A Genome-Wide Association Study (GWAS) is performed on the rate of change (ROC) of subcortical volumes in Adolescent Brain Cognitive Development (ABCD) study participants. The primary goal is to identify genetic variants associated with the longitudinal changes in 17 subcortical brain regions, covarying for interview_age, bigsnpr top 10 PCs, smri_vol_scs_intracranialv (except for smri_vol_scs_wholeb), sex, batch, and mri_info_deviceserialnumber. The project leverages existing pre-processed imaging and genotype data from ABCD Release 5.1. The computational workflow involves: 1) Data Characterization and Preparation: including data cleaning, quality control, calculation of ROCs for each region between baseline and year 2, generating summary statistics, and visualization of phenotype distributions (histograms, boxplots, violin plots) using R and Shiny for interactive exploration. Normality of the ROC data is assessed, and rank-based inverse normal transformation is applied. 2) GWAS Execution: The prepared data is split by sex and ancestry (European, African, and American). GCTA-MLMA is employed to perform GWAS for each phenotype, covarying for age, sex, genotyping batch, top 10 ancestry principal components, and intracranial volume (except for whole brain volume). Parallel job submission scripts are used to efficiently execute multiple GWASes on the Hoffman2 cluster. 3) Post-GWAS Analysis: This involves generating Manhattan, QQ, trumpet, and locuszoom plots for each GWAS result. Meta-analysis across ancestries using tools like METAL and others will be conducted. Further analyses include genetic correlation, polygenic risk score (PRS) conditioning with PleioPGS, gene-based tests (MOSTtest), and investigation of joint genetic architectures using GenomicSEM and GSMR2.

a. Investigated the genetic regulation of subcortical structural neurodevelopment in the ABCD cohort.
b. Developed skills in large-scale data analysis, bioinformatics pipelines, and advanced statistical methods like GCTA and SAIGE
c. Conducted GCTA --mlma GWAS in R on subcortical brain structures in the ABCD cohort, which enhanced my proficiency in computational genomics, neuroimaging, and large-scale data analysis of human cohorts.

4. Summer 2024 - Dr. Roel Ophoff

Concerns about confidence, commitment, higher level thinking skills in relation to the research subtopic

This project investigates accelerated biological aging in the largest bipolar disorder DNA methylation cohort to date, aiming to identify epigenetic age acceleration differences, drivers, and modifiers between individuals with bipolar disorder and controls. Preprocessing and quality control of DNA methylation data from Illumina EPIC arrays is performed, specifically addressing missing probes and data normalization. GrimAge2 and other epigenetic aging algorithms from the pyaging Python package are applied. Statistical analyses, including t-tests, ANCOVA, and correlation analysis, are conducted in R and Python to assess differences in GrimAge2 age acceleration between diagnostic groups while covarying for age and sex. Data visualization is employed using Python libraries including seaborn and matplotlib to generate informative plots for data

exploration and presentation. The R packages minfi, BioAge, dnaMethyAge, and methylclock are applied to prepare for epigenetic clock analysis. Finally, data wrangling and manipulation is performed using R's data.table and Python's pandas to prepare, clean, and transform the raw data for analysis. Future research will compare across multiple methylation aging clocks, characterize the individual contributions of GrimAge2 subcomponents, and explore the effects of lithium treatment and other environmental modifiers on epigenetic age acceleration in bipolar disorder.

a. Analyzed DNA methylation data to investigate biological aging in a large bipolar disorder
b. Adapted Grimage2 source code for compatibility with this cohort and implementing associated statistical analyses and data visualization expanded my epigenetic and statistical genetics skill set.

5. Winter 2025 - Dr. Carrie Bearden

Funding scarcity primarily, compounded by time-management, communication and productivity concerns.

During this rotation, I developed and implemented a comprehensive pre-imputation QC pipeline for NAPLS3 raw genomic data in accordance with ENIGMA-DTI specifications, creating multi-stage Unix shell scripts on Hoffman2 to generate dbSNP binaries, standardize variant identifiers, perform duplicate/relatedness checks, remove ancestry outliers via MDS, and produce detailed QC reports. Concurrently, I drafted an analytical framework to disentangle shared genetic liability (“p factor”) from disorder-specific risks via genomic SEM and GWAS-by-Subtraction. I outlined the partitioning of polygenic risk scores for schizophrenia, bipolar disorder, and major depression, and prepared rigorous QC and statistical analysis pipelines in R and shell scripts. These planned workflows will establish standardized data foundations and novel polygenic partitioning tools to advance precision psychiatric genetics in clinical high-risk cohorts.

a. Designed and implemented multi-stage unix shell scripts on the Hoffman2 cluster to generate dbSNP binary files, automate SNP renaming via rsid_tools, conduct duplicate/relatedness checks, and remove ancestry outliers through MDS and analysis
    i. Produced detailed QC reports to facilitate downstream analysis.
b. Integrated genomic structural equation modeling (gSEM) and GWAS-by-Subtraction methods to partition shared versus disorder-specific risks for schizophrenia, bipolar disorder, and major depressive disorder
    i. Performed rigorous data quality control, statistical analysis, and workflow automation via Unix shell scripting and R.

Research Trajectory

1. Middle School – High School:

a. Botany and Zoology
b. Genetics/Heritability

2. High School – Undergraduate:

a. Molecular Biology
b. Genetic Engineering

3. Undergraduate – Graduate:

a. Cis-regulatory Functional Genomics
b. Psychiatric Genetics
c. Neurodevelopment

4. Current:

a. Characterizing cross-disorder genetic liability and the associated neurodevelopmental processes underlying complex neurocognitive functions. I am particularly keen to understand how genetics and neurodevelopment interact to mediate risk and resilience for psychiatric disorders in adolescence.
b. Characterizing role of gene regulatory programs in shaping neurodevelopmental trajectories associated with risk and resilience to psychiatric disorders during adolescence.
c. Applying **normative modeling**, **machine learning**, and other statistical and computational approaches toward the **functional characterization** of genetic associations with **neuropsychiatric and behavioral biomarkers** and **endophenotypes**.
d. Characterizing **gene regulatory variation** in shaping the **neurodevelopmental trajectories** associated with **neuropsychiatric liability** **and** **resilience** **during** **adolescence.**
e. Leveraging large-scale **multimodal** human cohort data to **develop** **objective** **and** **individualized** **classification**, **diagnostic**, **predictive**, **preventative**, **and** **efficacy** **monitoring** **tools** for the **symptoms of mental distress**.
f. **Cross-disorder** neuropsychiatric and behavioral genetics and **neuroimaging** **genetics**.

Strengths

1. Over 5 years of **academic writing** experience
    a. 5 publications across multiple methods and fields
    b. Conceived, drafted and submitted my NSF GRFP without faculty advisory/guidance
    c. Part-time writing consultant with the Graduate Writing Center
2. **Diligent, patient, creative, committed, loyal, earnest, dedicated and resilient**
3. **Strong background in functional genomics and neuroscience**
4. **Computational research skills**
    a. Experience applying computational research methods in large-scale multimodal datasets including the **ABCD** Study cohort
    b. **Programming Languages:** Proficient in R and Python.
    c. **R Packages:** minfi, BioAge, dnaMethyAge, methylclock, dplyr, tidyr, data.table, purrr, ggplot2, plotly, RColorBrewer, reshape2, GenomicRanges, SummarizedExperiment, qs, bigmemory, doParallel, parallel, arrow.
    d. **Python Packages:** pyaging, pandas, numpy, scipy, seaborn, matplotlib, sklearn (specifically KMeans, StandardScaler), statsmodels, pygam, pyarrow.
    e. **High-Performance Computing (HPC):** Experience working on Hoffman2, indicating familiarity with HPC environments and potentially using job schedulers (e.g., Slurm). Utilized parallel processing in R for computationally intensive tasks.
    f. **Data Management:** Expertise in data cleaning, transformation, merging, and subsetting across both R and Python. Efficiently handled large datasets using packages like bigmemory and pyarrow. Generated reproducible analysis workflows by logging key data characteristics (e.g. data dimensions, timestamps) to filenames.
    g. **Statistical Analysis:** Conducted various statistical analyses, including descriptive statistics, correlation analysis, t-tests, ANCOVA, and planned for GAMs.
    h. **Data Visualization:** Created a wide range of static visualizations for exploratory data analysis and presentation of results.
    i. **Version Control:** Utilized GitHub for code sharing and version control.

    j. **Workflow Design:** Designed and implemented a multi-stage analysis pipeline involving data preprocessing, clock calculation, statistical analysis, visualization, and reporting, including integration of R and Python components.
    k. **R:** Extensive use of R for data manipulation, statistical analysis, and visualization (dplyr, tidyr, ggplot2, data.table, qqman, etc.).
    l. **GCTA:** Utilizing GCTA-MLMA for GWAS analysis.
    m. **PLINK:** Working with PLINK binary files for genotype data.
    n. **Shell Scripting:** Writing bash scripts for job submission and data processing on Hoffman2.
    o. **Shiny:** Applying Shiny to generate interactive data exploration and visualization plots/tables.
    p. **Other Tools:** Familiarity with various bioinformatics tools and resources such as Ensembl BioMart, METAL, LDSC, PleioPGS, GenomicSEM, GSMR2, and potentially SAIGE.
5. I am committed to conducting research aligned with and **advancing the goals precision psychiatry** (i.e. biomarker and endophenotype discovery, preventative, individualized, quantitatively-informed treatment, stratification, and efficacy monitoring)
    a. While upholding and embracing neurodiversity
    b. Some of the most important people in my life continue to live with mental health challenges
    c. My experience with mental health disparities extends throughout my childhood in San Francisco

Cooper’s Rotation Status Update

December 14th 2023

Agenda

1. Village vs. Array 2.0 (VxA 2)
    A. Background
    B. Results
        i. Optical proliferation analysis (Cellpose)
        ii. BD Rhapsody Modifications and QC
        iii. Preliminary Dropulation Results
2. SnAP induction for Ana's project
3. Future Directions
    A. Other project ideas
4. Conclusions

VxA 2 - Motivation

Advantages of Villages vs Arrays

1. Time and Money Saved
2. Potential reduction of well-specific effects (i.e. middle vs corner)
3. Potential reduction of transcriptomic and proliferative variation generally

Unknowns/Concerns:

1. Does the village format alter growth rates between village replicates vs between array replicates? If so, by how much?
2. Does the village format alter growth rates generally vs array format?
3. Does the village format alter gene expression vs array format?

VxA 2 - Goals

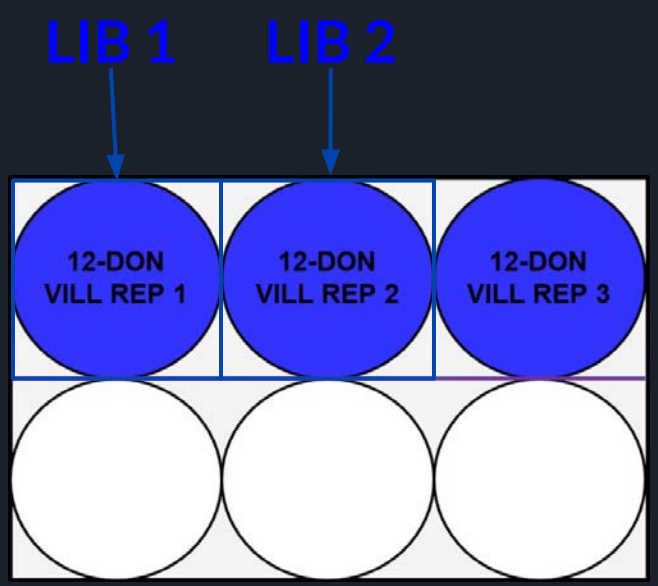
1) Compare INTRA-donor variation (between replicates of same format) in village vs. array

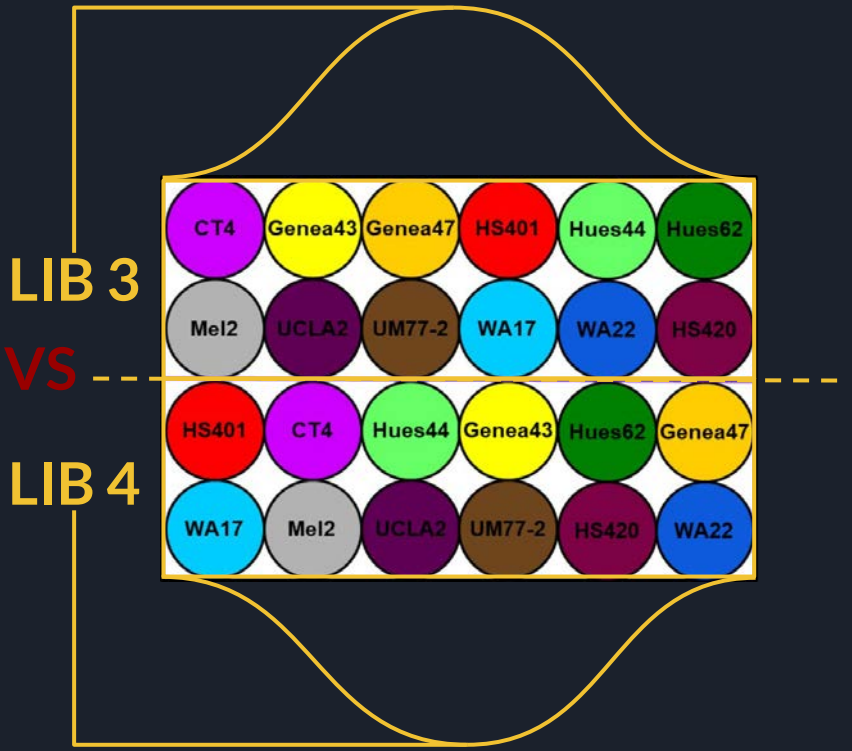
2) Compare INTER-donor variation (between different formats) in V vs. A

3) Evaluate differences in cell intrinsic factors V vs. A

4) Assess well-specific affects corner vs. center on cells from the same donor

VxA 2 - Design


LIB 1
LIB 2
12-DON VILL REP 1
12-DON VILL REP 2
12-DON VILL REP 3


LIB 3
VS
LIB 4
CT4
Genea43
Genea47
HS401
Hues44
Hues62
Mel2
UCLA2
UM77-2
WA17
WA22
HS420
HS401
CT4
Hues44
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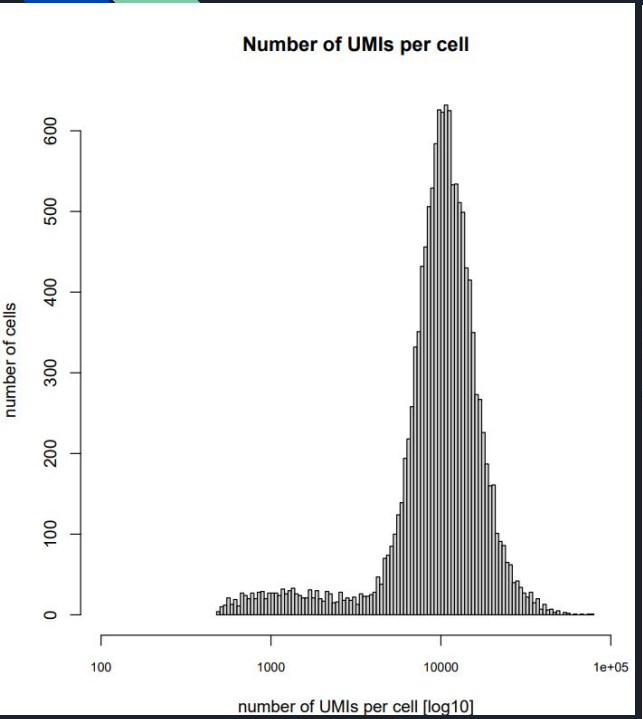
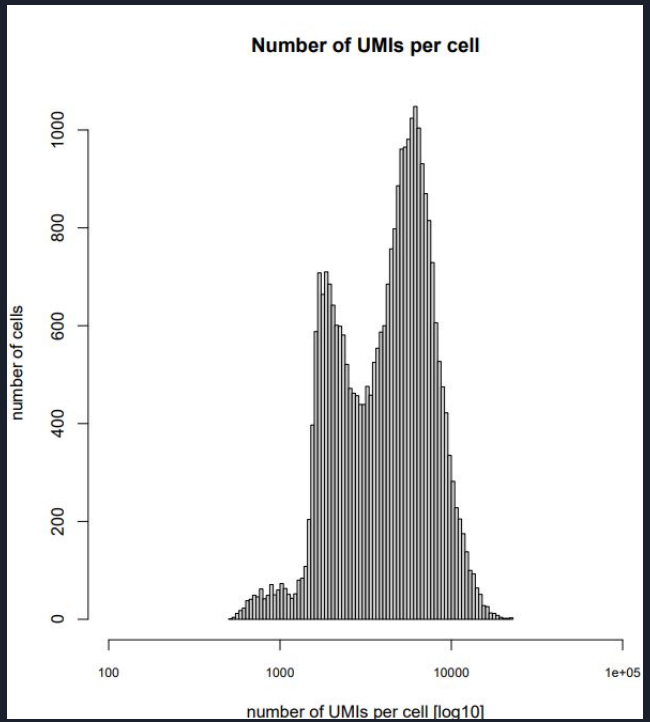
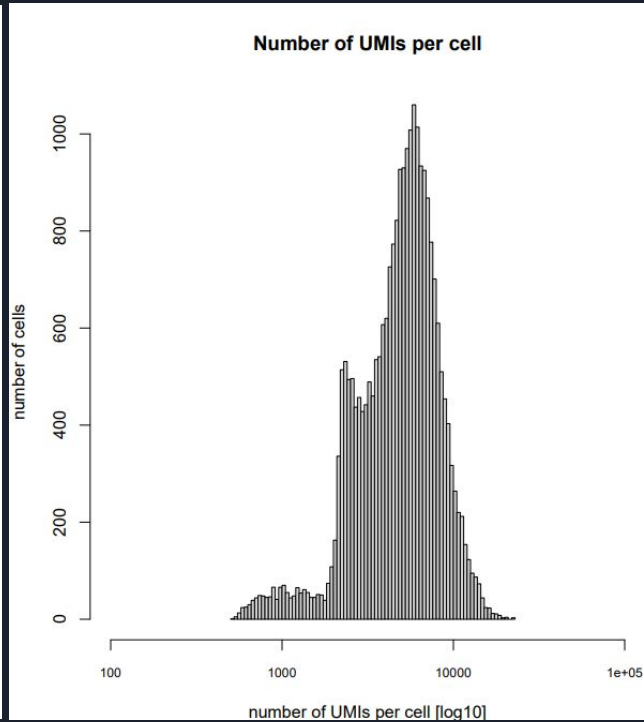
WA17
Mel2
UCLA2
UM77-2
HS420
WA22

Bimodal UMI Concerns







10x
[jan2023 12-donor village]

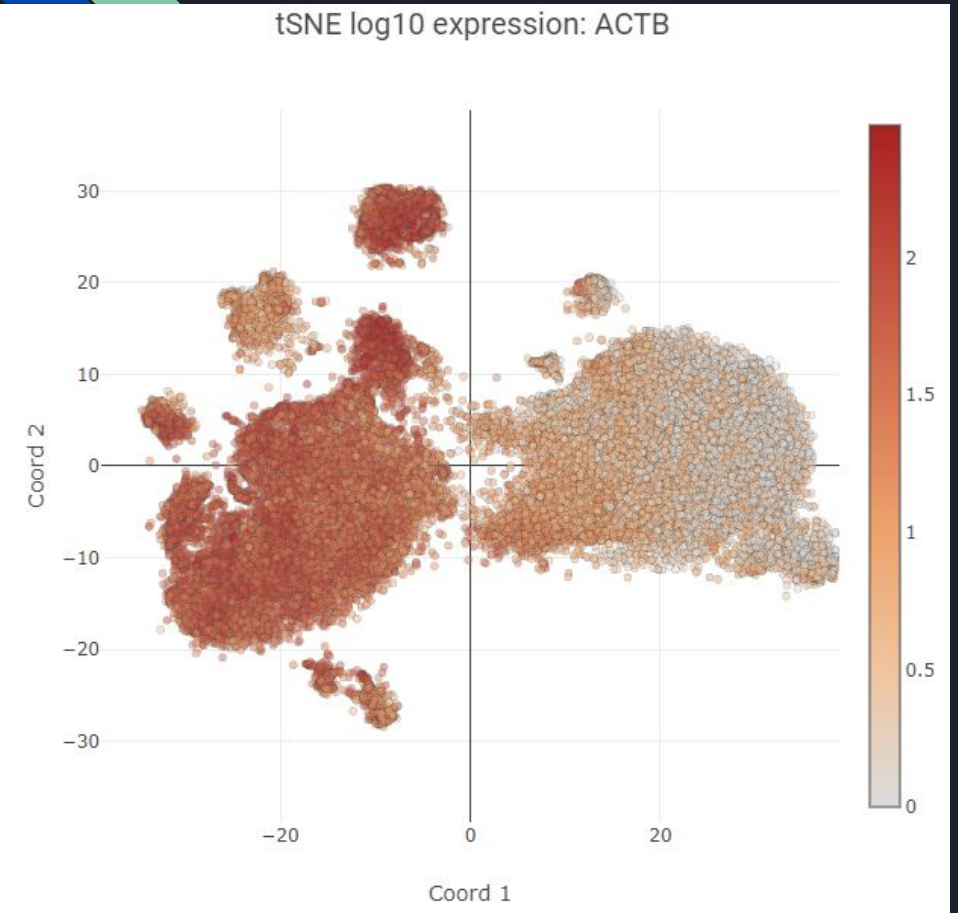
BD Rhapsody
[VxA 12-donor village]

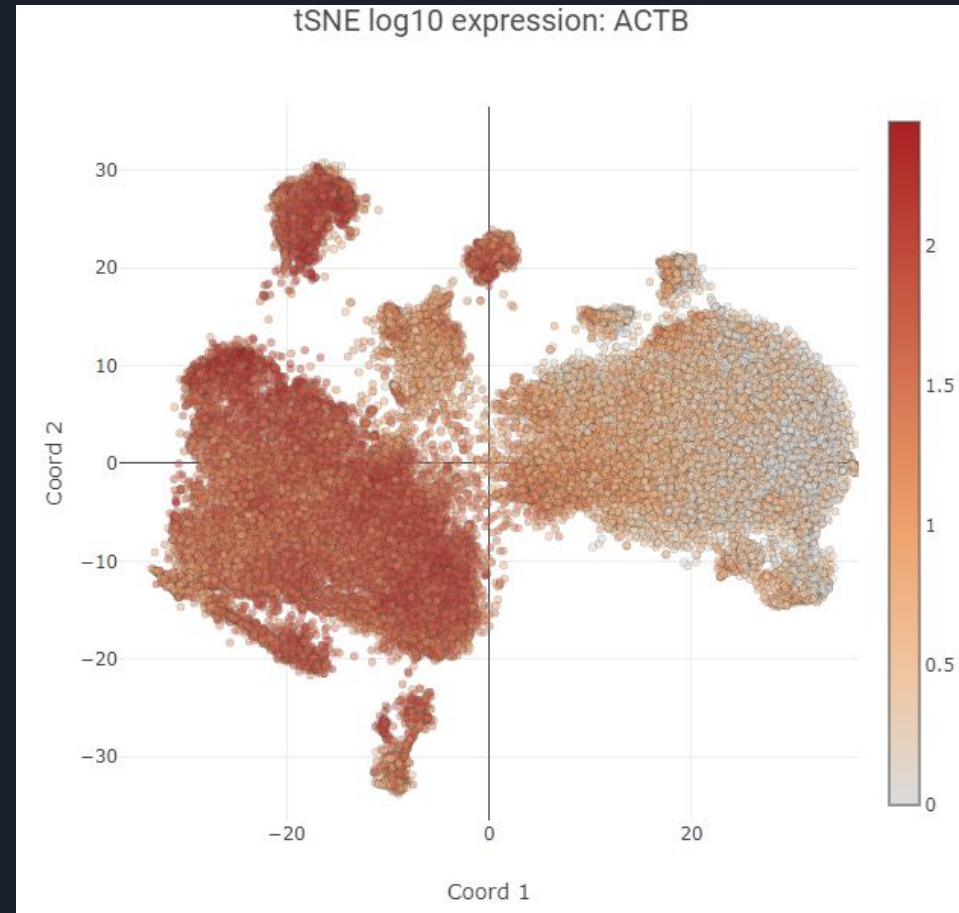
BD Rhapsody (more stringent)
[VxA 12-donor village]

Village 1

Housekeeping (Beta-actin)

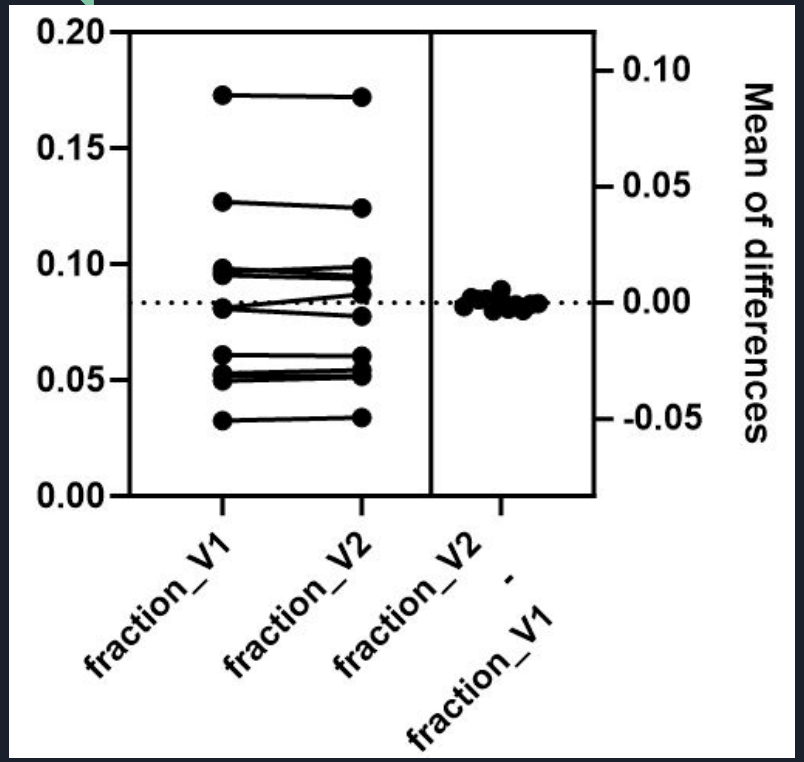
Array 1



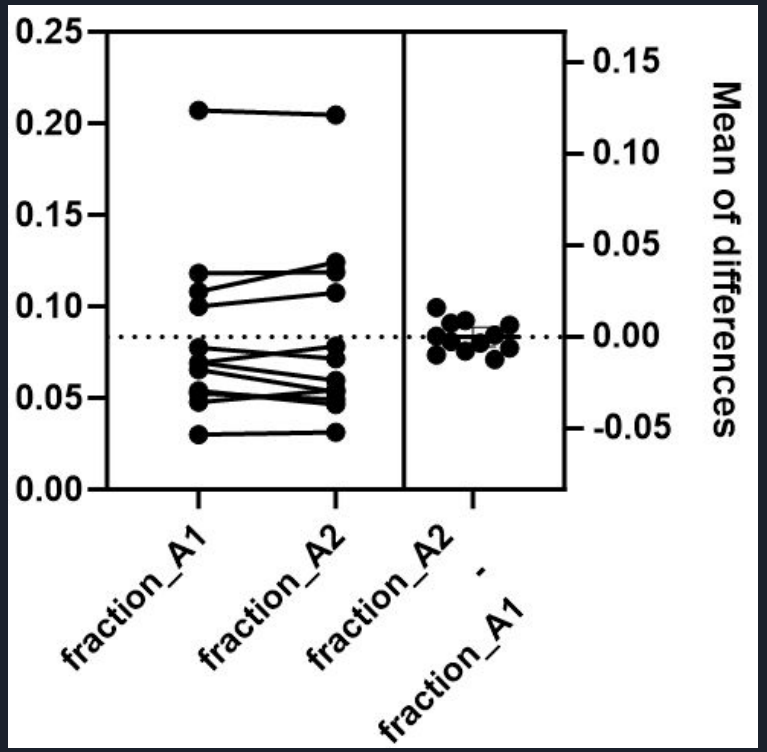


Dropulation Donor Fraction Differences

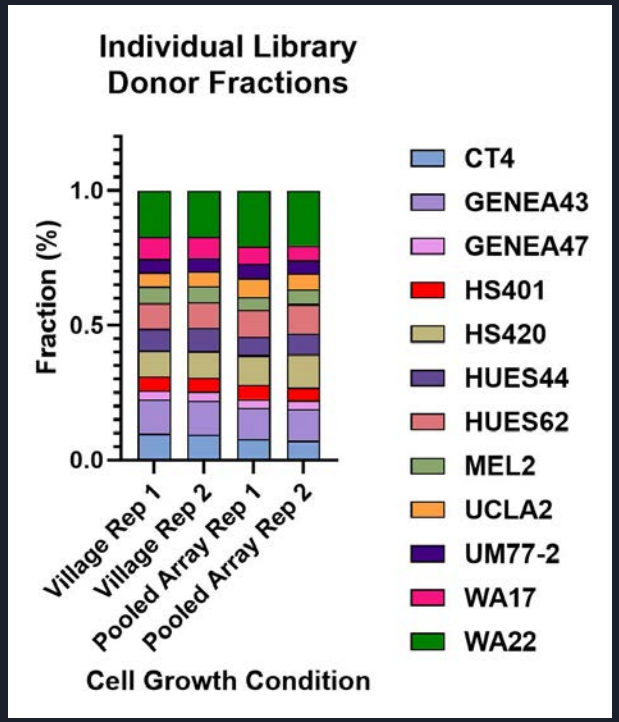
Village 1 vs 2 differences in donor proportions

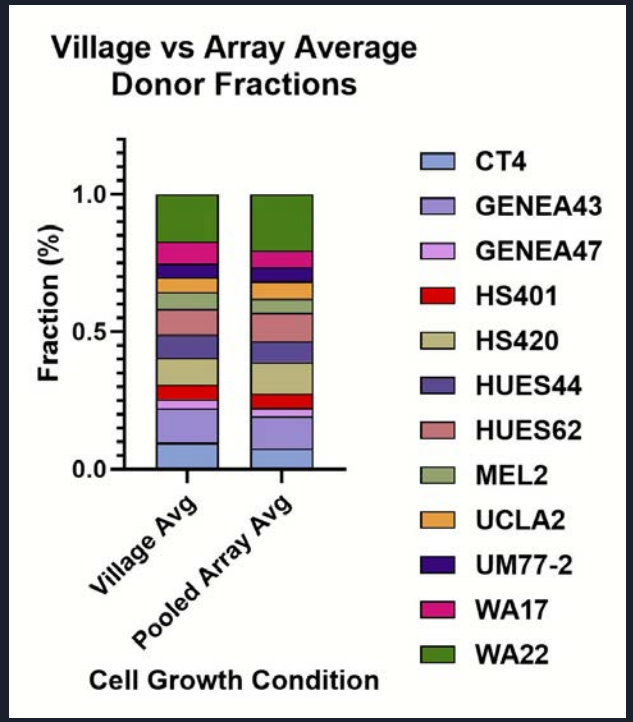


Array 1 vs 2 differences in donor proportions



Dropulation Called Donor Fractions

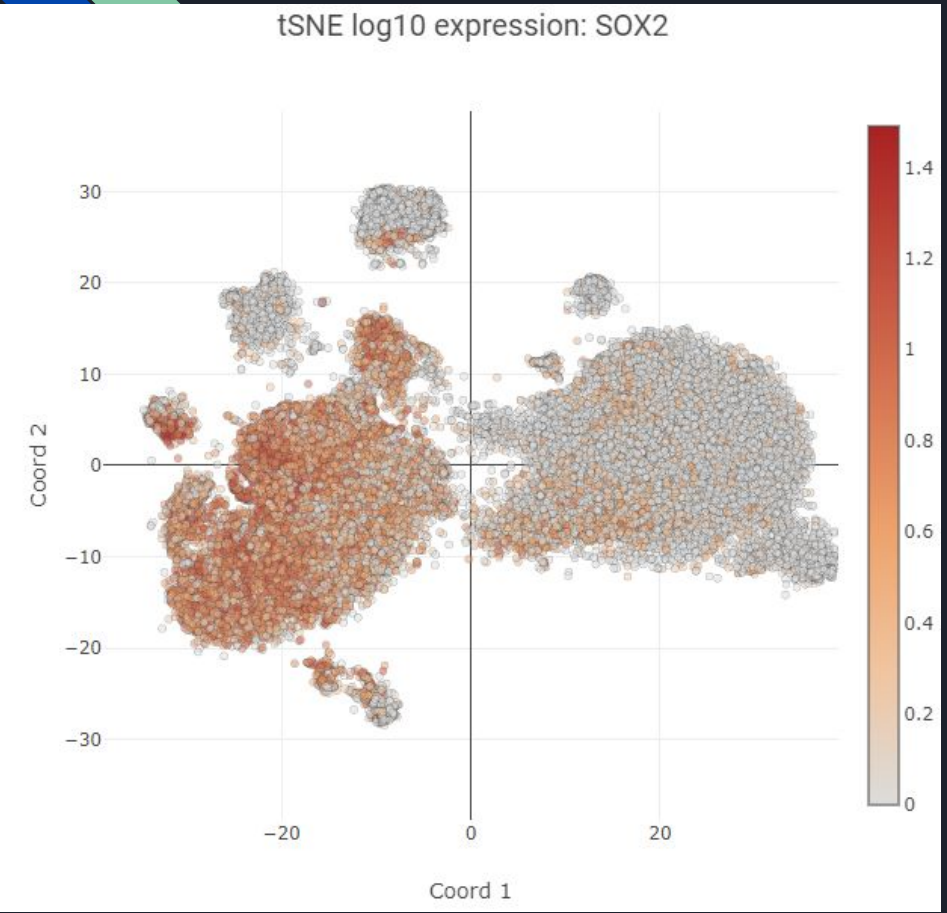


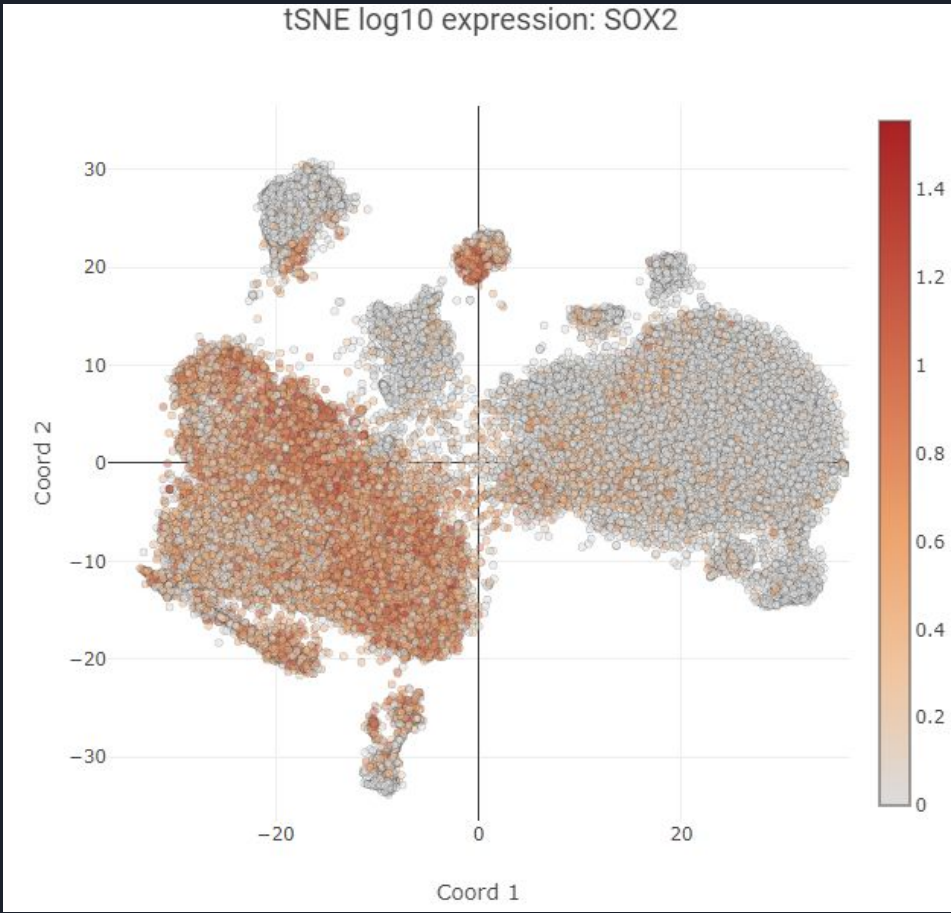


Village 1

NPC Marker (SOX2)

Array 1

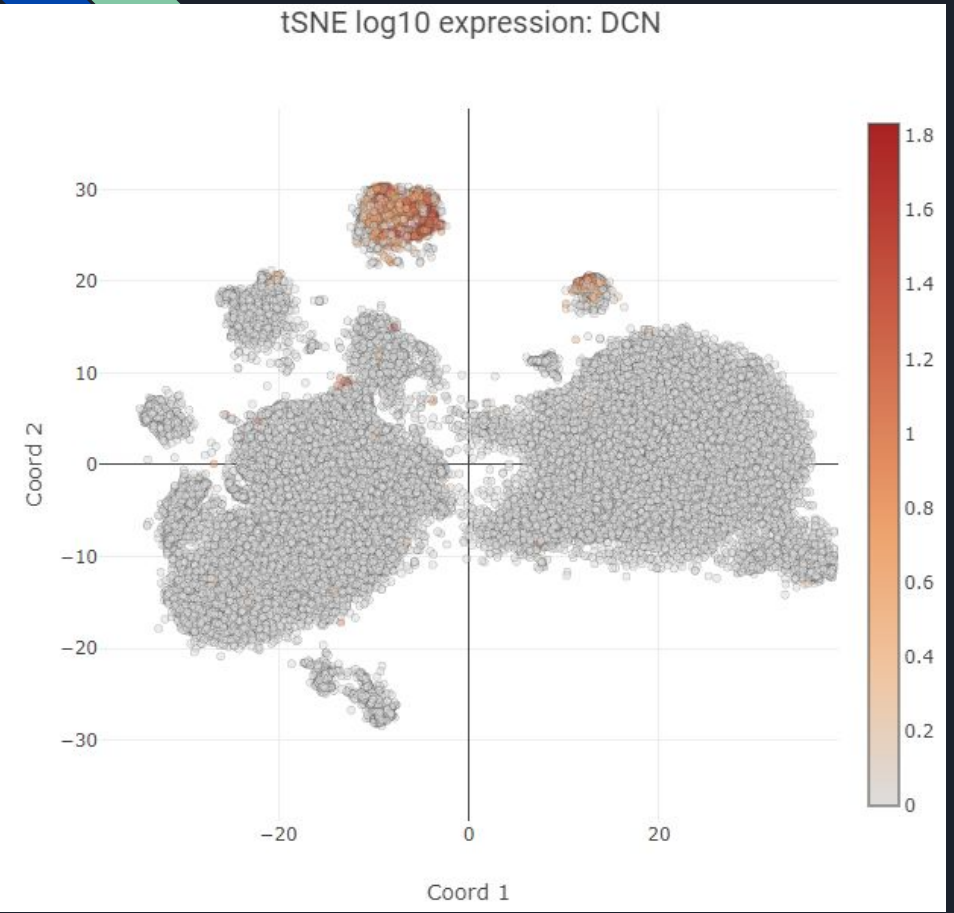


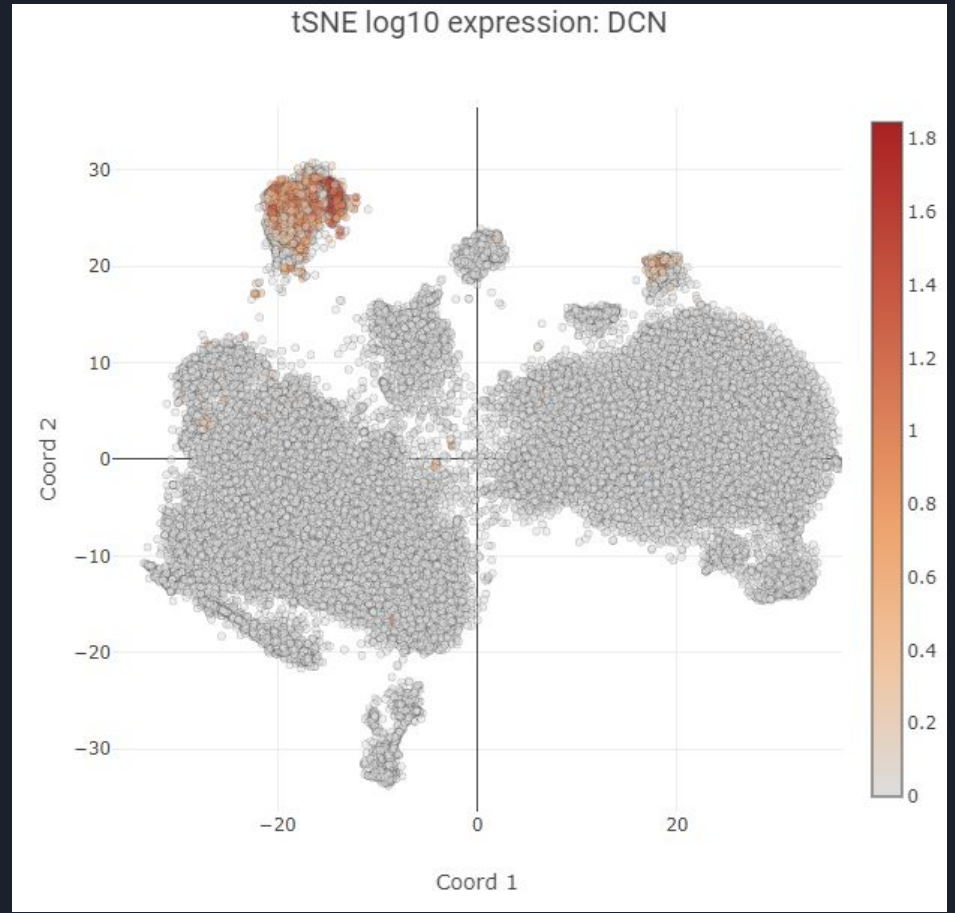


Village 1

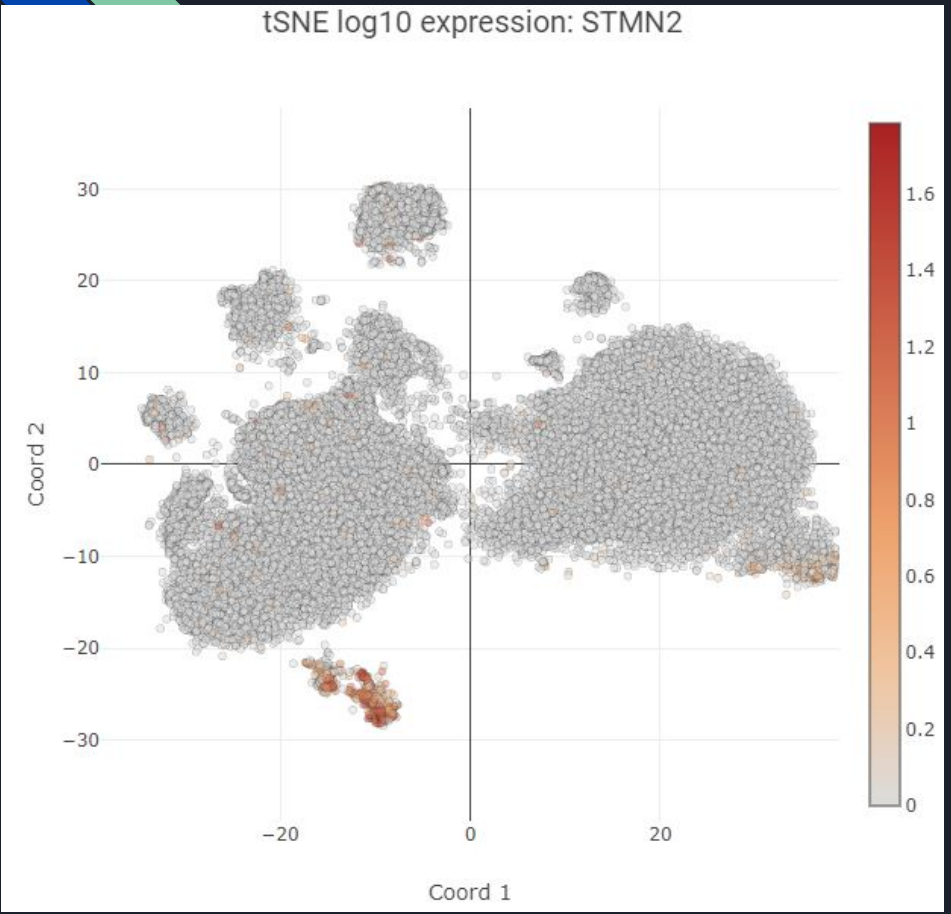
Neural Crest Marker (DCN)

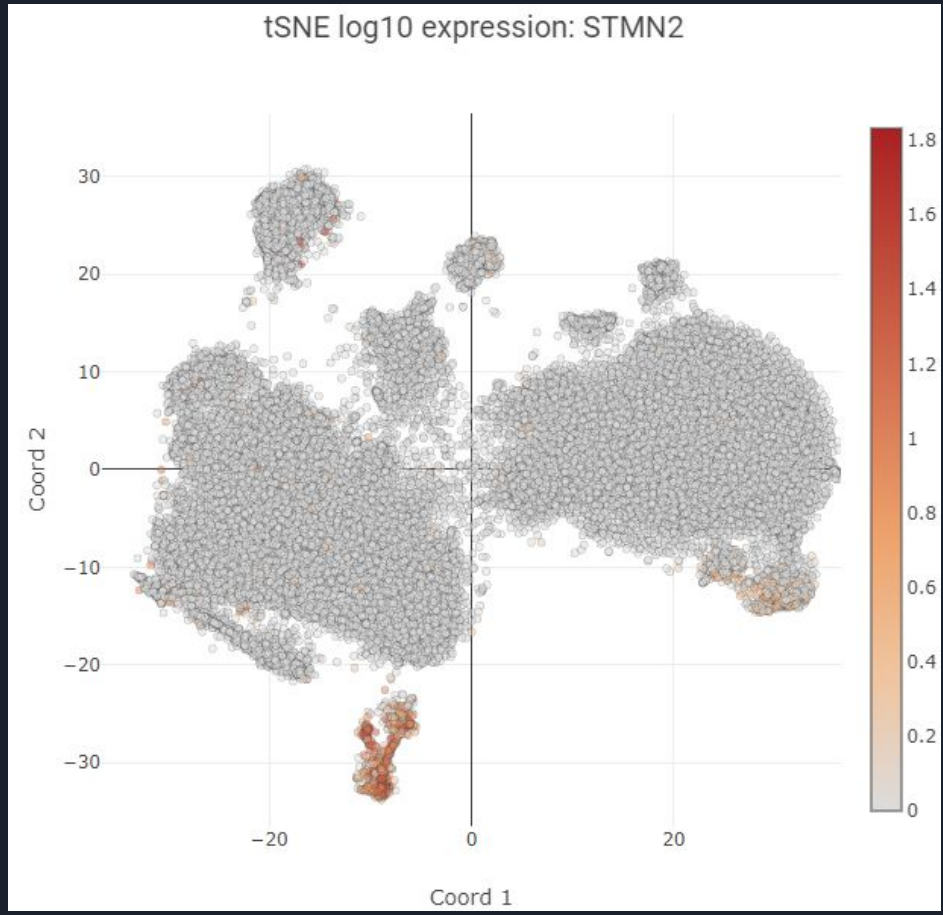
Array 1





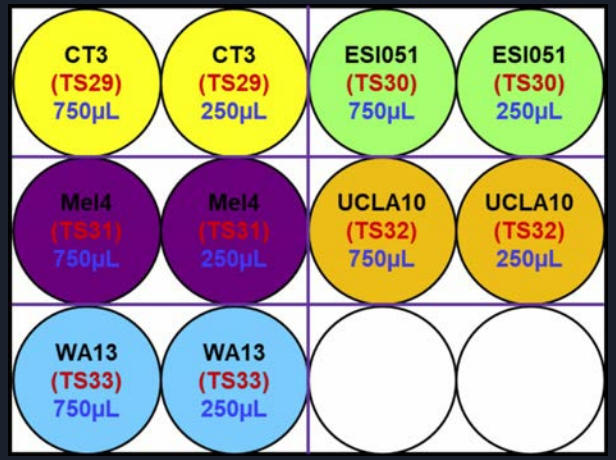
Village 1 Neuron Marker (STMN2) Array 1





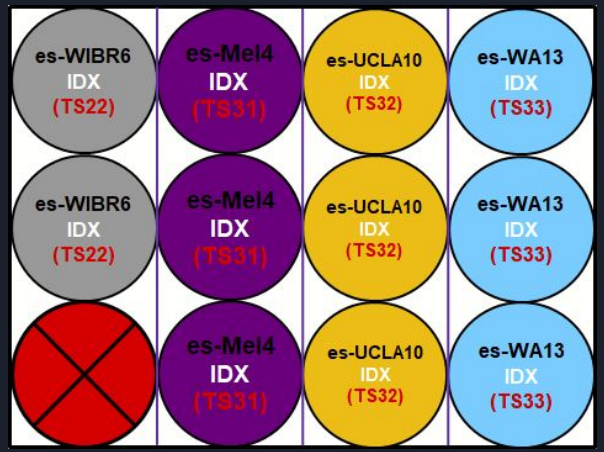
Ana ESC NGN2 Transductions and SNaP Inductions

1. Initially, 5 ESC lines
2. Transduced 4 lines, CT3 dropped out, failed again before transduction



1. Ended, 4 total ESC lines Induced.
2. 3 original (TS31-33), 1 new added to transductions (transduced separately by Ana)

TS22	es-WIBR6
TS31	es-Mel4
TS32	es-UCLA10
TS33	es-WA13



Future Directions

1. Cross-disorder/transdiagnostic molecular investigation of ADHD, ASD, SCZ, BP etc
    a. Village integration with CRISPR screens and more complex in-vitro models, such as: Modular Neuronal Networks (MoNNets), assembloids, organoids?
2. High-throughput neuropsych drug/therapeutic screening , “Clin-trial” in a dish (villages to prioritize candidate drugs and conserve time/money running actual trials by screening out less promising drugs, uncertain of suitable and compatible readouts)
3. What other readouts could be compatible with the village 2.0 platform (i.e. epigenomic, proteomic, cytological/cellular/macrophenotypic, e-phys)?
4. Pooled vs scRNA-Seq experimental designs tradeoff between RNA transcript sensitivity and cell-specific transcriptional effects when using . How could this be integrated with villages?

Cooper’s Rotation Project Update

Geschwind Lab

Winter Quarter Rotation

March 7th 2024

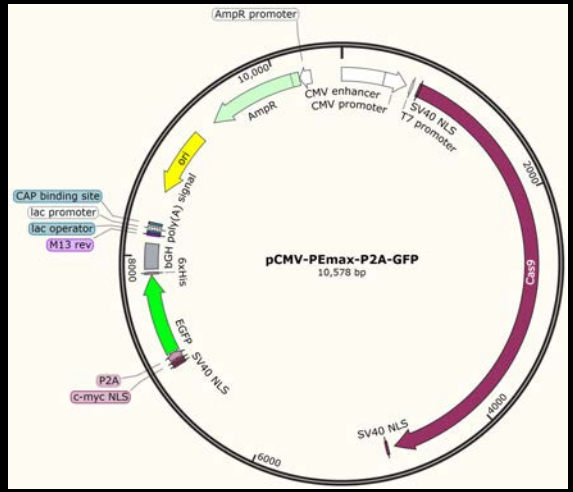
Overview

1. HEK-293T PEmax Line
    A. Generation
    B. Validation
2. NGN2 PEmax iPSC Line
    A. Generation
    B. Validation
3. Future Directions
    A. High-throughput functional validation project ideas
    B. Technical challenges and goals
4. Other Updates

HEK-293T PEmax Line - Generation

Retroviral delivery FACS enrichment:

1. Packaged GFP-PEmax fusion protein into retrovirus
2. Transduced GFP-PEmax fusion protein construct (random integration)
3. Enriched the population via FACS for GFP fluorescence as a proxy of PEmax expression
4. Cells were then expanded, banked, and used for further comparison with iPSC editing efficiencies, and for Christian and Le's future experiments

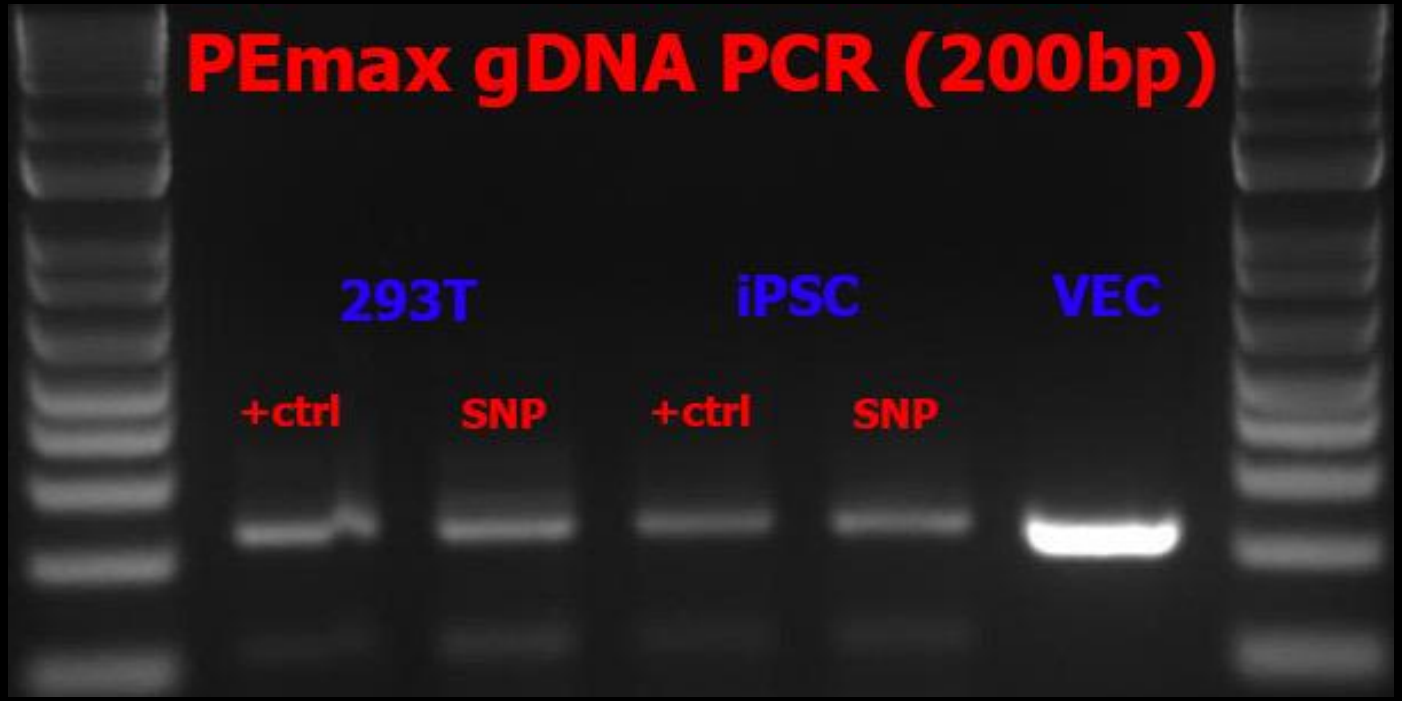


HEK-293T PEmax Line - Validation

- PCR confirming PEmax expression will be completed today
- PEmax integration also confirmed during FACS sorting (based on GFP expression) by Le
- One round of TA cloning was performed to assess editing efficiencies in this line using two pegRNAs (positive control from original PEmax publication: PRNP; finemapped SNP for Le's project: rs111972148), but the sanger sequences were not as we expected
    - pegRNAs were delivered via standard transient transfection, and cells were propagated 2-3 additional days to allow sufficient time for editing to occur
- Round two TA cloning with several adjustments and further QC is underway

Presentation will be updated with additional data as it is generated over the next 1-2 weeks

HEK-293T PEmax Line - Validation



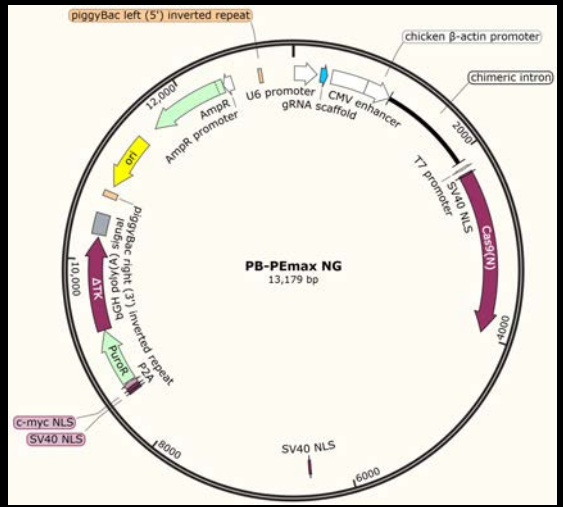
NGN2 PEmax iPSC Line - Generation

Retroviral delivery and FACS enrichment:

1. Retroviral delivery using the same approach as was used for HEK293T cells, was attempted for the NGN2 iPSC line
2. Transduction failed completely, and no GFP cells were visible during FACS

Piggybac delivery and puromycin enrichment:

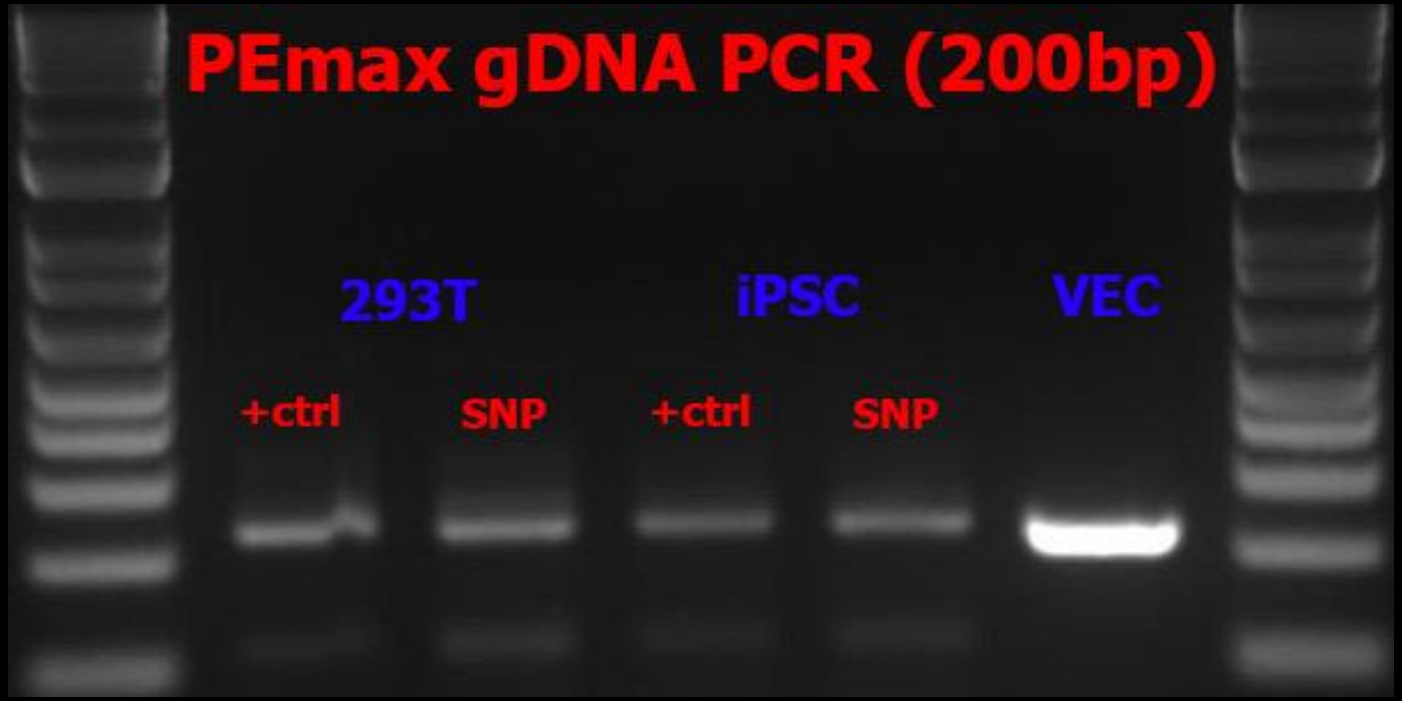
1. Alternative Piggybac delivery of a puromycin selection PEmax vector was then attempted using lipofectamine transient transfection
2. Edited cells were enriched under puromycin selection
3. Cells were then expanded, banked, and used for further validation, and for Christian and Le's future experiments



NGN2 PEmax iPSC Line - Validation

1. PCR confirming PEmax expression will be completed today
2. Optical confirmation of PEmax integration not possible, as this plasmid's PEmax construct was not fused to a fluorescent reporter
3. One round of TA cloning was performed to assess editing efficiencies in this line using two pegRNAs (positive control from original PEmax publication: PRNP; finemapped SNP for Le's project: rs111972148), but the sanger sequences were not as we expected
    a. pegRNAs were delivered via standard transient transfection, and cells were propagated 2-3 additional days to allow sufficient time for editing to occur
4. Round two TA cloning with several adjustments and further QC is underway

NGN2 PEmax iPSC Line - Validation



Future Directions

1. PEmax and other high-throughput functional validation project ideas:
    a. Intersecting Leanna and similar group's genetic results with the functional validation potential of prime editing and other high-throughput approaches
        i. Disorder agnostic, complex trait, PheWAS functional validation (organoids and other models)
    b. Functional characterization of noncoding GWAS vars associated with ASD and SCZ
    c. Cross-disorder research to identify and characterize existing convergent genetic drivers of atypical neurodevelopmental phenotypes (ASD, SCZ, BP, ADHD).
2. High-throughput validation technical challenges and goals
    a. Editing efficiencies
        i. Transgene silencing
            1. AAV delivery overcomes at the expense of lower transgene copy numbers
        ii. Guide and loci dependent effects on editing efficiencies
    b. Neurobiologically relevant screen design
    c. High throughput confirmation of editing without Sanger
    d. ASD and complex trait relevant readouts for screen design
        i. Protein interaction reporters
        ii. Cellular morphology
        iii. 3D and more sophisticated in vitro systems
    e. Clonal selection

Other Updates

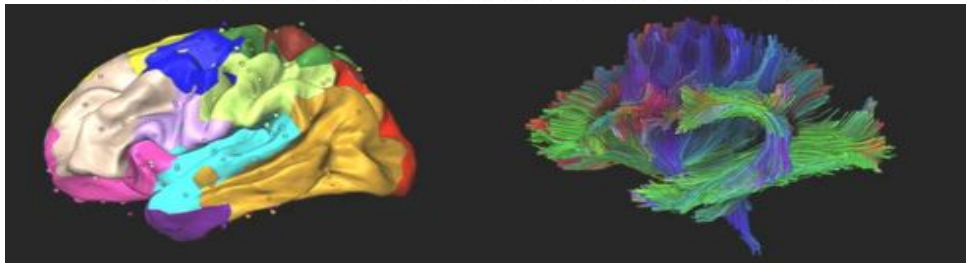
1. Now rotating with Dr. Hernandez in the Spring
2. Would be very interested in collaborating on the wetlab side assuming I join her lab.
    a. In vitro validation of variants, genes, loci we identify, following novel large scale association projects.
3. Last day in lab will likely be 3/21 or 3/22

Subcortical Volume Rate of Change GWAS

Hernandez Lab

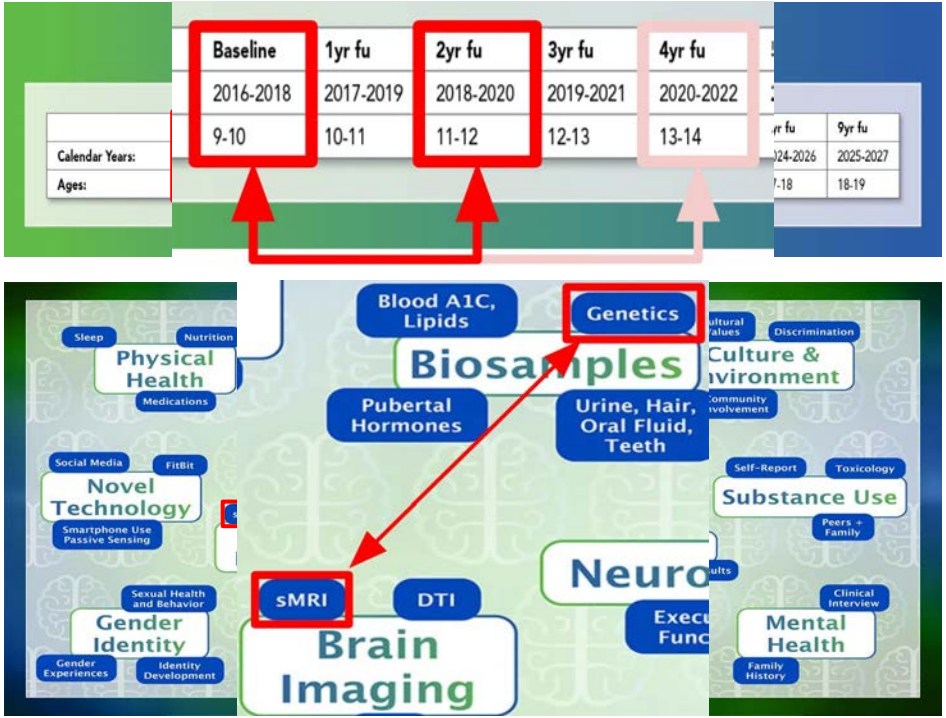
Cooper Beaman

6/6/24



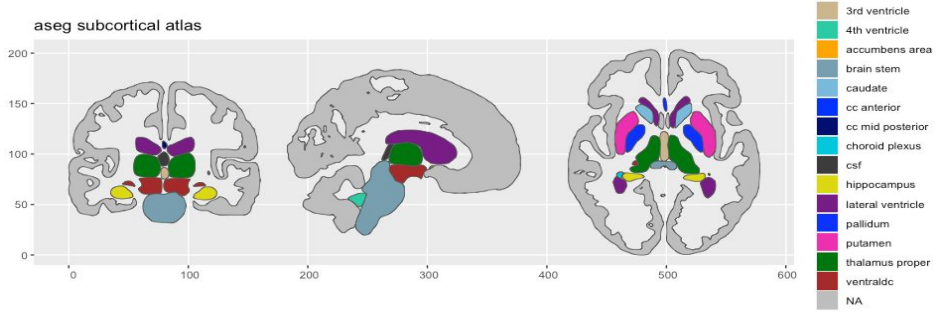
ABCD Subcortical Volume Rate of Change GWAS

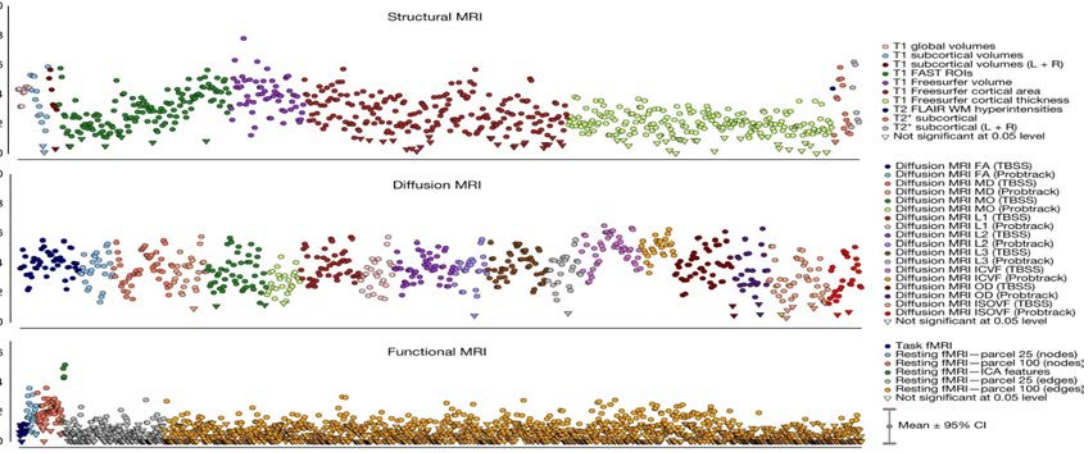
Adolescent Brain Cognitive Development (ABCD) Study



ABCD Study

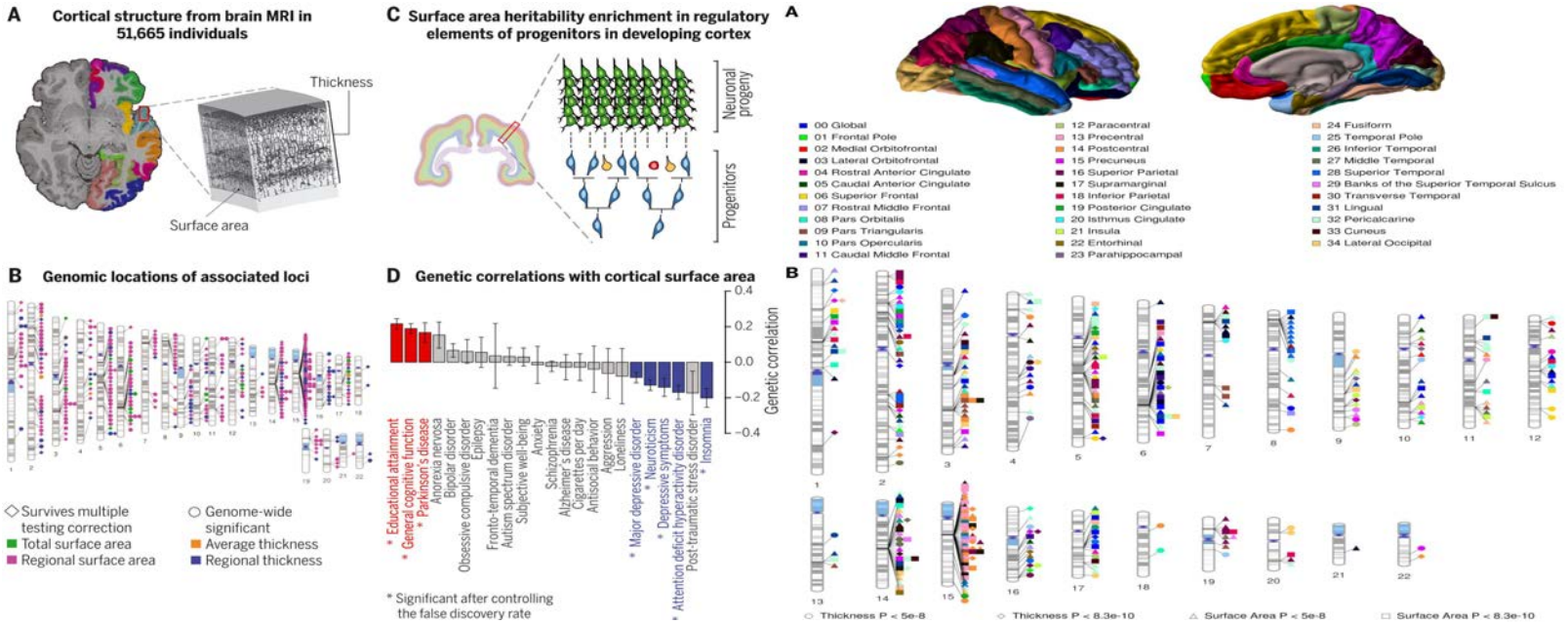
Background





	Final Phenotype List		
	ASEG Subcortical Region	ROI	Example % ROC
1	Accumbens	smri_vol_scs_aa_ROC0_2	-4.27675179
2	Amygdala	smri_vol_scs_amygdala_ROC0_2	3.21407755
3	Caudate	smri_vol_scs_caudate_ROC0_2	1.21853058
4	Cerebral White Matter	smri_vol_scs_cbwmatter_ROC0_2	1.42869447
5	Anterior Corpus Callosum	smri_vol_scs_ccat_ROC0_2	1.50748116
6	Central Corpus Callosum	smri_vol_scs_ccct_ROC0_2	-1.72962649
7	Mid-Anterior Corpus Callosum	smri_vol_scs_ccmidat_ROC0_2	2.54587156
8	Mid-Posterior Corpus Callosum	smri_vol_scs_ccmidps_ROC0_2	-0.59142435
9	Posterior Corpus Callosum	smri_vol_scs_ccps_ROC0_2	4.07221665
10	Cerebellum Cortex	smri_vol_scs_crbcortex_ROC0_2	2.04550786
11	Cerebellum White Matter	smri_vol_scs_crbwmatter_ROC0_2	-3.35290482
12	Hippocampus	smri_vol_scs_hpus_ROC0_2	0.64882091
13	Intracranial (Covariate)	smri_vol_scs_intracranialv_ROC0_2	1.06787494
14	Pallidum	smri_vol_scs_pallidum_ROC0_2	1.24972594
15	Putamen	smri_vol_scs_putamen_ROC0_2	1.81281542
16	Thalamus	smri_vol_scs_tp_ROC0_2	-0.84263414
17	Ventral Diencephalon	smri_vol_scs_vedc_ROC0_2	2.49121069

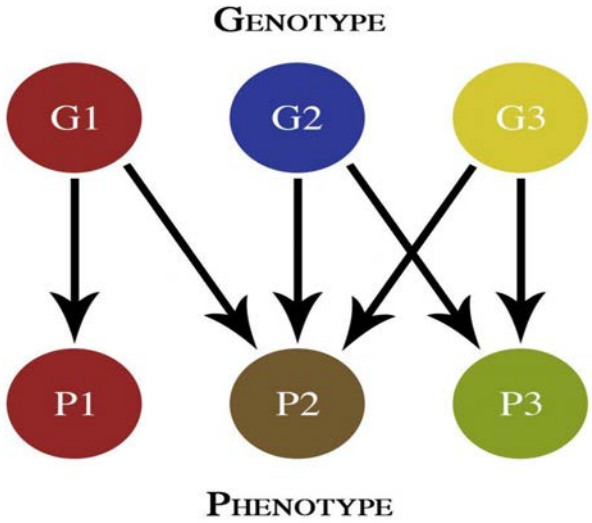
Genetic Influences on Brain Structure and Function



To date, the largest GWAS of regional brain morphological features, based on brain scans obtained from up to 50,000 individuals, identified almost 200 genetic variants, which together explained only a fraction of the reported narrow-sense heritability. These studies primarily investigate each region of interest individually, compounding the multiple-comparisons correction problem.

Katrina L. Grasby et al., The genetic architecture of the human cerebral cortex. Science (2020).

Genetic Pleiotropy

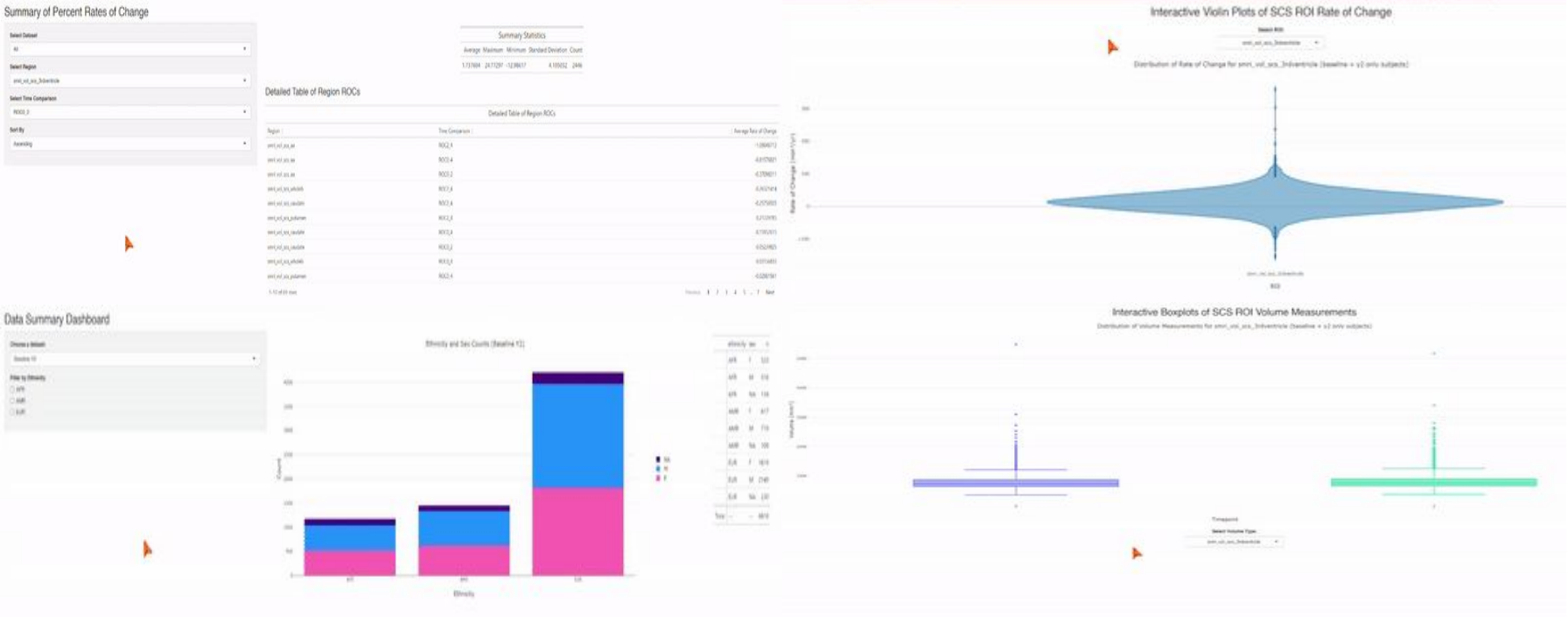


- The investigation of genetic influences via genome-wide association studies (GWAS) has demonstrated that **most loci and genes are associated with multiple traits**, which is referred to as statistical pleiotropy.

- **Previously** characterized pleiotropic genes and loci have been discovered to mediate their effects across brain phenotypes **within** a single neuroimaging modality.
- However, **most** pleiotropic loci act **across** rather than **within** phenotype domains, indicating that the genes associated within these loci may also exhibit pleiotropic effects across neuroimaging phenotypes.
- Investigating genetic associations with brain imaging phenotypes may elucidate mechanisms underlying alterations in **brain morphology, activity, connectivity, and tissue composition** that co-occur in heritable psychiatric disorders.

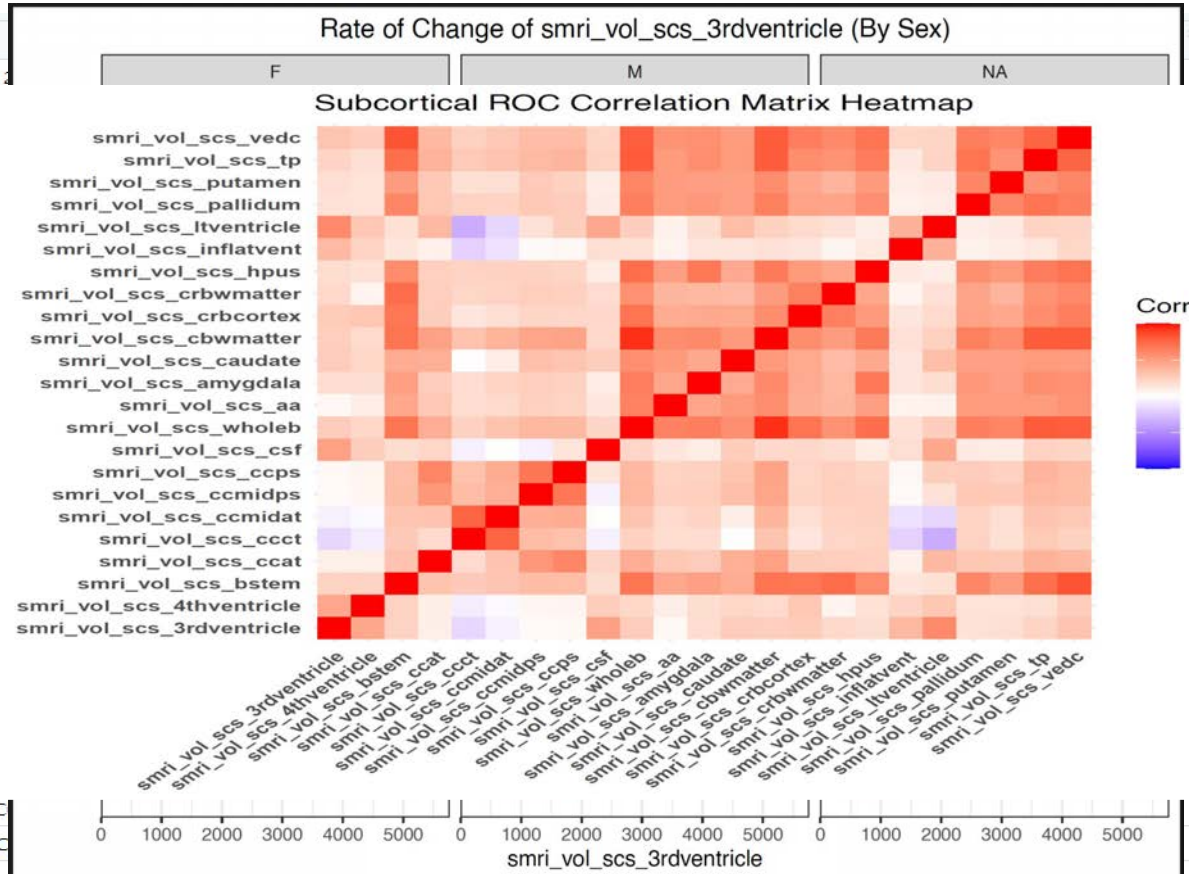
Quality Control Data Characterization - part 1

Percent ROC statistics, Sample sizes, Volume and ROC Distributions

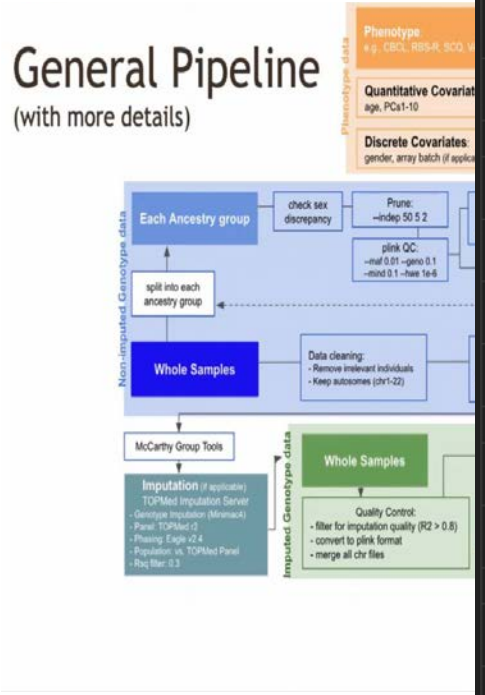


Quality Control Data Characterization - Part 2

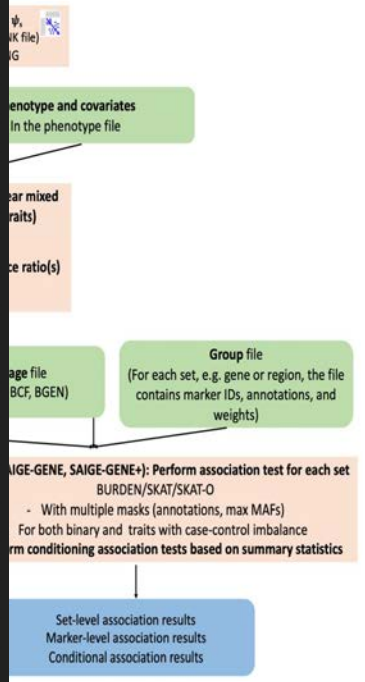
	phenotype	sufficient_power_EUR
1	smri_vol_scs_bstem_ROC0	TRUE
2	smri_vol_scs_ccps_	
3	smri_vol_scs_whole	
4	smri_vol_scs_cbwn	
5	smri_vol_scs_crbco	
6	smri_vol_scs_hpus_	
7	smri_vol_scs_vedc_	
8	smri_vol_scs_ccmic	
9	smri_vol_scs_tp_RC	
10	smri_vol_scs_3rdve	
11	smri_vol_scs_4thve	
12	smri_vol_scs_ccat_	
13	smri_vol_scs_ccct_	
14	smri_vol_scs_ccmic	
15	smri_vol_scs_csf_R	
16	smri_vol_scs_aa_RC	
17	smri_vol_scs_amyg	
18	smri_vol_scs_cauda	
19	smri_vol_scs_crbwr	
20	smri_vol_scs_inflat	
21	smri_vol_scs_ltvent	
22	smri_vol_scs_pallidum_ROC	FALSE
23	smri_vol_scs_putamen_ROC	FALSE



GWAS Prep



Method	Metric	AFR Samples (n=1100)	EUR Samples (n=4500)
Full GRM SAIGE	Runtime	2-4 hours per phenotype	6-12 hours per phenotype
	Type I Error Control	Robust	Robust
	Statistical Power	High	High
	Heritability Estimates	Accurate and reliable	Accurate and reliable
	Use Case Suitability	Detailed relationship modeling	Detailed relationship modeling
Sparse GRM SAIGE	Runtime	1-2 hours per phenotype	3-6 hours per phenotype
	Type I Error Control	Robust	Robust
	Statistical Power	High	High
	Heritability Estimates	Efficient for large-scale studies	Efficient for large-scale studies
	Use Case Suitability	Efficient, handles population structure	Efficient, handles population structure
GCTA MLMA	Runtime	4-8 hours per phenotype	24-48 hours per phenotype
	Type I Error Control	Robust	Robust
	Statistical Power	High	High
	Heritability Estimates	Precise, detailed genetic relationships	Precise, detailed genetic relationships
	Use Case Suitability	Precise modeling with high computational cost	Suitable for detailed analysis with sufficient resources



GCT

Next Steps

1. Run GCTA MLMA and SAIGE GWASes for each subcortical ROI Rate of Change
2. Compare hits to those of existing adult psychiatric GWAS
    a. Condition existing Neuropsychiatric PRS on imaging auxiliary phenotype GWAS results to improve predictive accuracy
    b. Perform Structural equation modeling GWAS using summary statistics to investigate joint-genetic architectures

Acknowledgements

To the entire Hernandez lab for their generous guidance, code sharing, and converting me into a computational geneticist!

Thank you!

```r
library(dplyr);
library(tidyr);
library(ggplot2);
library(rlang);
library(lme4);
library(plotrix);
library(ggrepel);
library(gt);
library(ggridges);

source('/u/project/lhernand/cobeaman/ABCD_Longitudinal_Subcortical_Imaging_GWAS/Analysis/releaseS_external_functions.R');

#### LOAD DATA AND RECODE TIMEPOINT ####
base_dir <- '/u/project/lhernand/cobeaman/ABCD_Longitudinal_Subcortical_Imaging_GWAS/Analysis/';
load('/u/project/lhernand/cobeaman/ABCD_Longitudinal_Subcortical_Imaging_GWAS/ABCD.Release.5.1.C4.Merged.Data.Rda');

# recode timepoint data
abcdData.R5.1$timepoint <- lapply(
  X = abcdData.R5.1$eventname,
  FUN = recode.timepoint
  );

abcdData.R5.1$sex <- lapply(
  X = abcdData.R5.1$sex,
  FUN = recode.sex
  );
abcdData.R5.1$sex <- sapply(abcdData.R5.1$sex, paste, collapse = ",");

samples <- unique(abcdData.R5.1$src_subject_id);
id.timepoint.fields <- c('src_subject_id', 'eventname', 'timepoint');
print(colnames(abcdData.R5.1)); # variable names
print(length(unique(abcdData.R5.1$src_subject_id))); # number of samples
# extract C4 data
C4.expr <- abcdData.R5.1 %>%
  #filter(!is.na(c4a_expression) & is.finite(c4a_expression)) %>%
  dplyr::select(matches('src_subject_id|eventname|timepoint|c4'), -pc4);

#### PLOT C4 EXPRESSION ####
# plot histogram of C4A expression
pdf('/u/project/lhernand/cobeaman/ABCD_Longitudinal_Subcortical_Imaging_GWAS/Analysis/plots/C4A_expression.pdf');
plot <- ggplot(data = C4.expr, mapping = aes(x = c4a_expression)) +
  geom_histogram(bins = 10, fill = 'skyblue', color = 'black', alpha = 0.7) +
  labs(title = "Histogram of C4a Expression",
       x = "C4a Expression Level",
       y = "Frequency") +
  theme_bw() +
  theme(plot.title = element_text(hjust = 0.5),
        panel.grid.major = element_blank(),
```

Accelerated Biological Aging in Bipolar Disorder

Cooper Beaman

Tuesday August 27th 2024

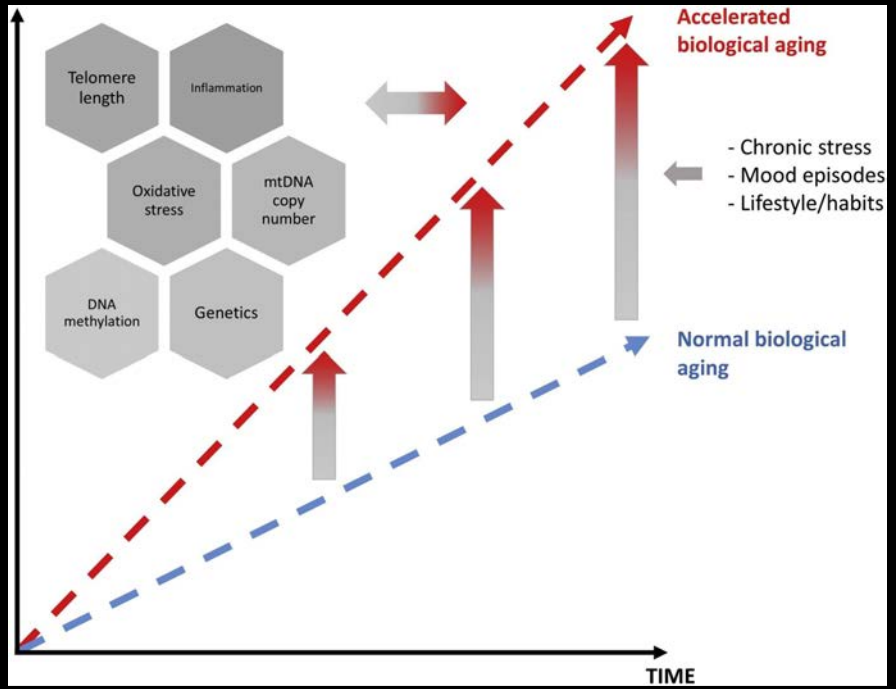
https://gitfront.io/r/Lowestprime/vZoNWtdBm7oP/BP-DNAm/

Agenda

1. Background - Existing Literature
2. Results - Preliminary Findings
3. Conclusions

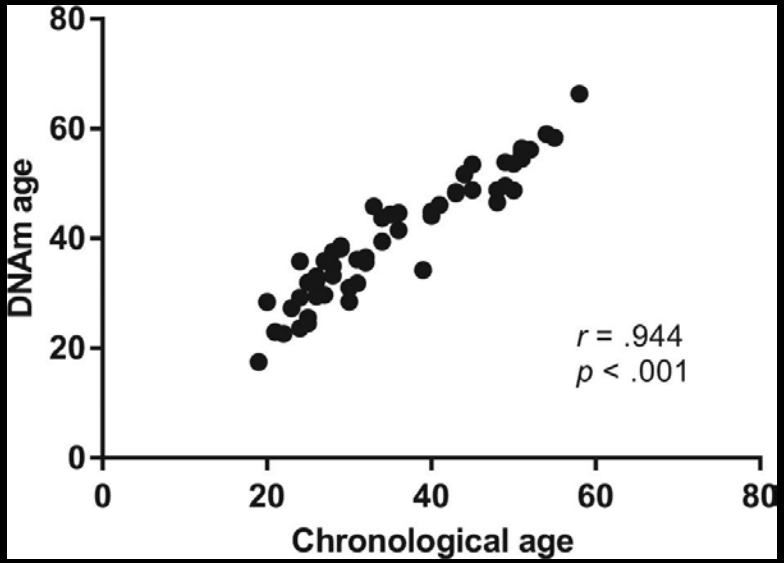
Background

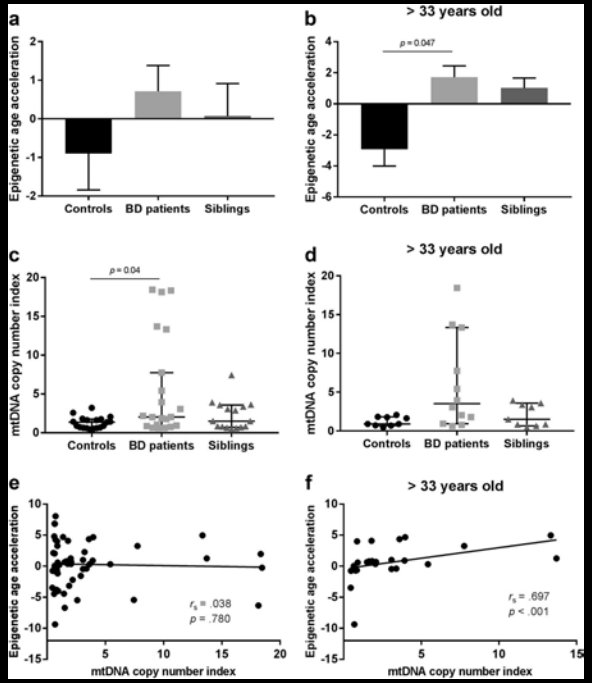
Accelerated aging in bipolar disorder: A comprehensive review of molecular findings and their clinical implications



Background
Accelerated epigenetic aging and mitochondrial DNA copy number in bipolar disorder

	Controls (n = 20)	BD I (n = 22)	Siblings (n = 16)	P-value
Age (years), mean ± SD	34.75 ± 10.0	33.95 ± 9.3	39 ± 10.6	0.325[a]
Sex (F/M)	12/8	15/7	10/6	0.852[b]

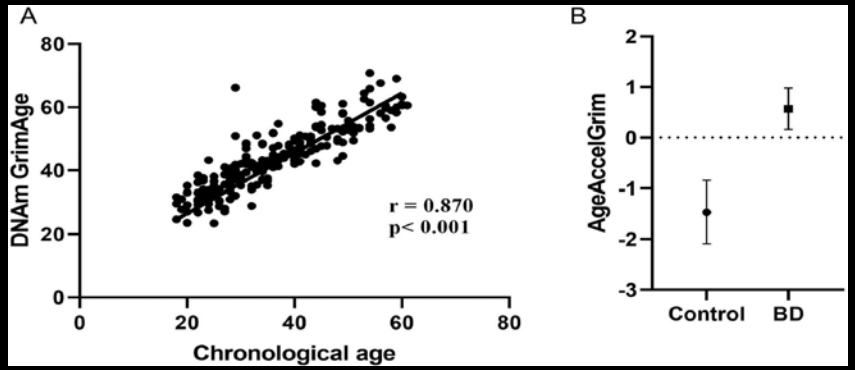




Background
Epigenetic GrimAge acceleration and cognitive impairment in bipolar disorder

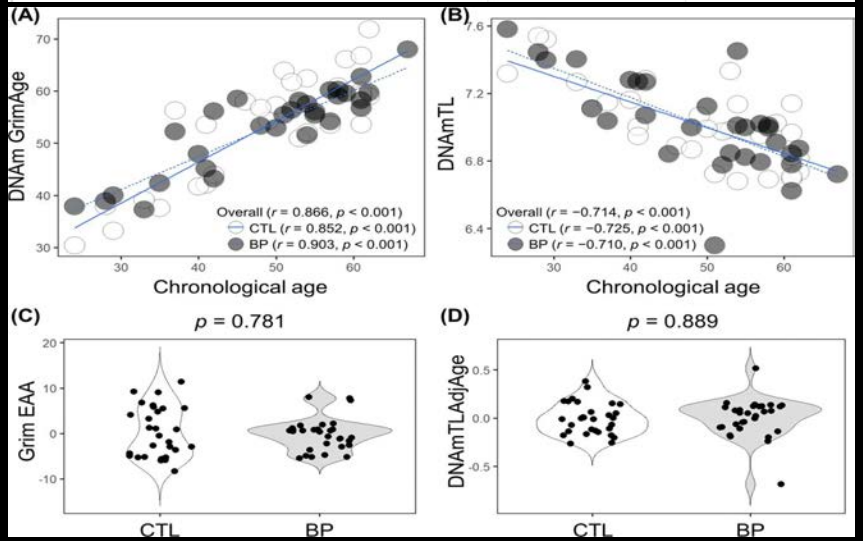
Table 1. Sample demographics.

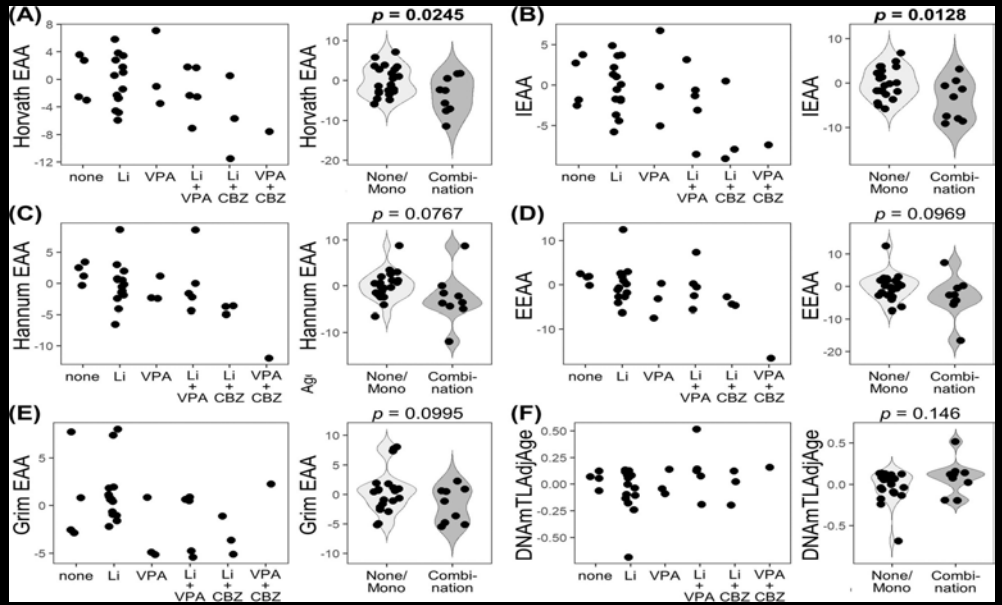
	Bipolar disorder (n=153)	Controls (n=50)	p-value
Age (years), mean (SD)	37.0 (11.2)	35.5 (10.4)	0.404[†]
Sex (%)			
Female	71.9	68.0	0.360[‡]
Male	28.1	32.0	



Background
Decelerated epigenetic aging associated with mood stabilizers in the blood of patients with bipolar disorder

	Control (n = 30)	Bipolar disorder (n = 30)
Bipolar type, I/II	–	20/10
Sex, male/female	16/14	16/14
Age (years), mean±SD	48.8 ± 11.3	49.0 ± 11.4

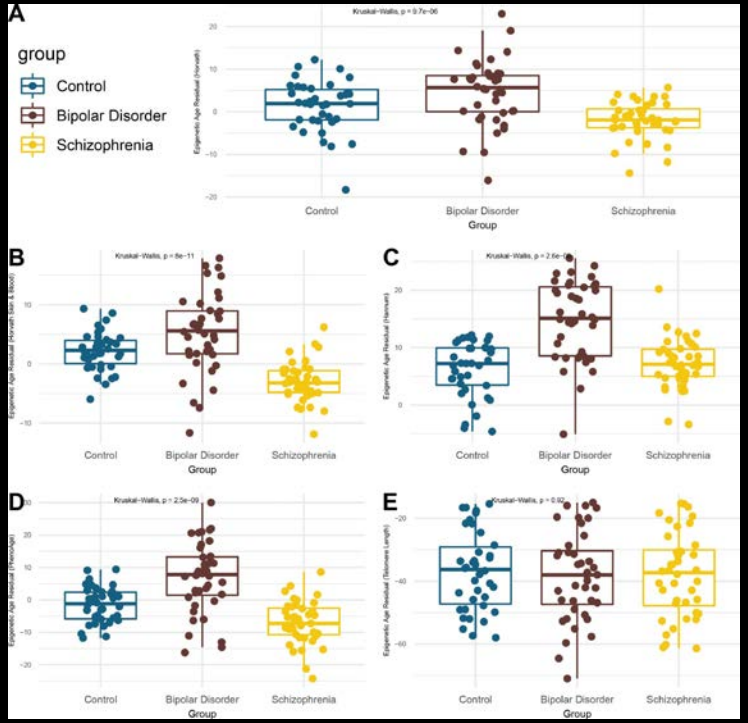




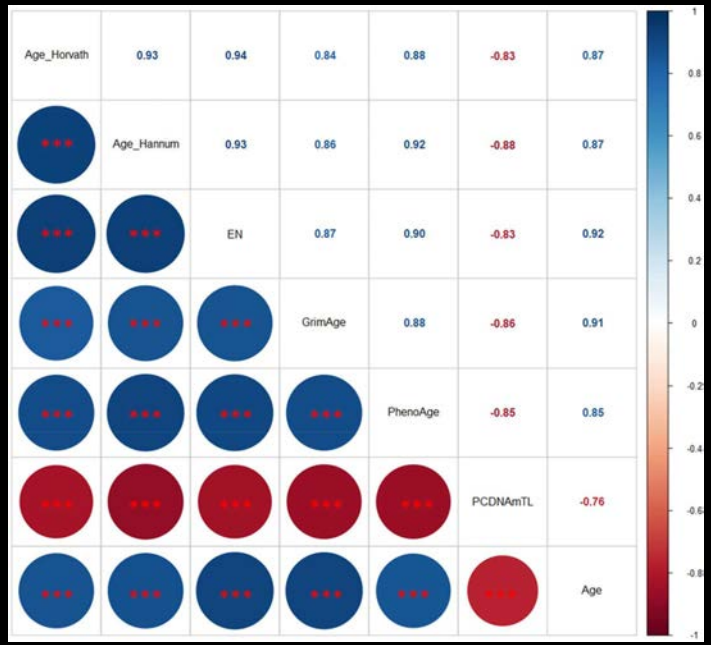
Background
Epigenetic age dysregulation in individuals with bipolar disorder and schizophrenia

Table 1. Participant demographics (*n*=number in group, SD=standard deviation).

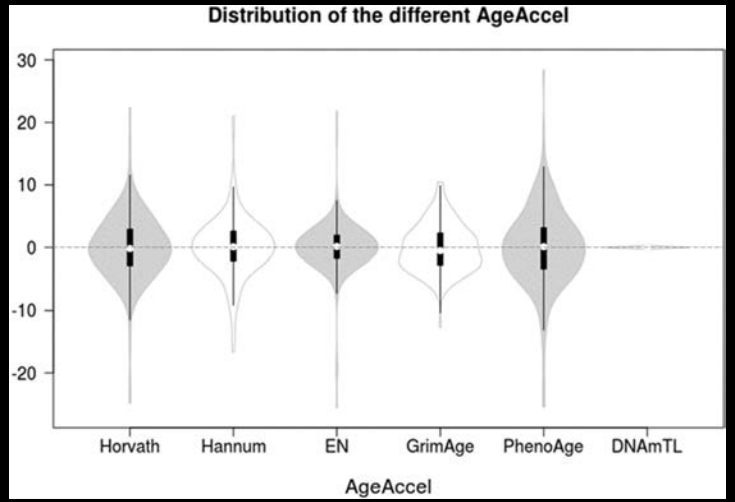
	Controls (n=38)	Bipolar Disorder (n=40)	Schizophrenia (n=40)
Female sex, *n* (%)	21(55.26%)	22(55%)	23(42%)
Mean age (SD) in years	44.11(12.39)	46.03(14.11)	45.28(13.23)
Age at Onset	N/A	22.4(9.9)	22.5(6.8)



Background
Accelerated aging in bipolar disorders: An exploratory study of six epigenetic clocks

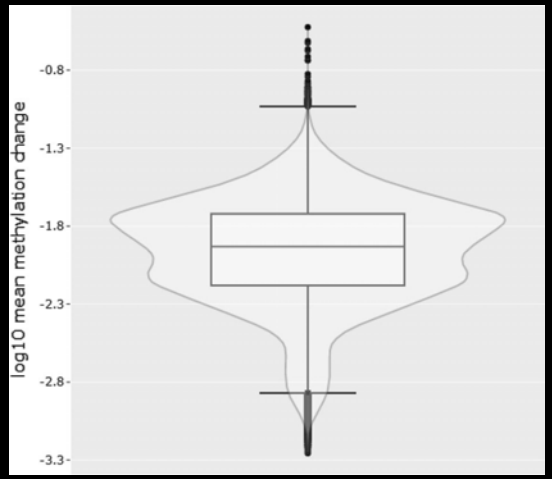


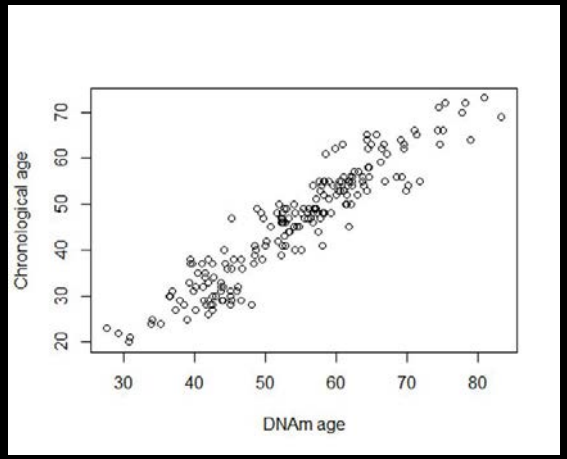
Characteristics	Mean (or number) of each variable
Age	38.82 (SD: 9.89)
Sex	110 women (59.8%) - 74 men
Bipolar disorder type	126 type I (68.5%) - 55 type II - [3 missing]



Background
The role of environmental stress and DNA methylation in the longitudinal course of bipolar disorder

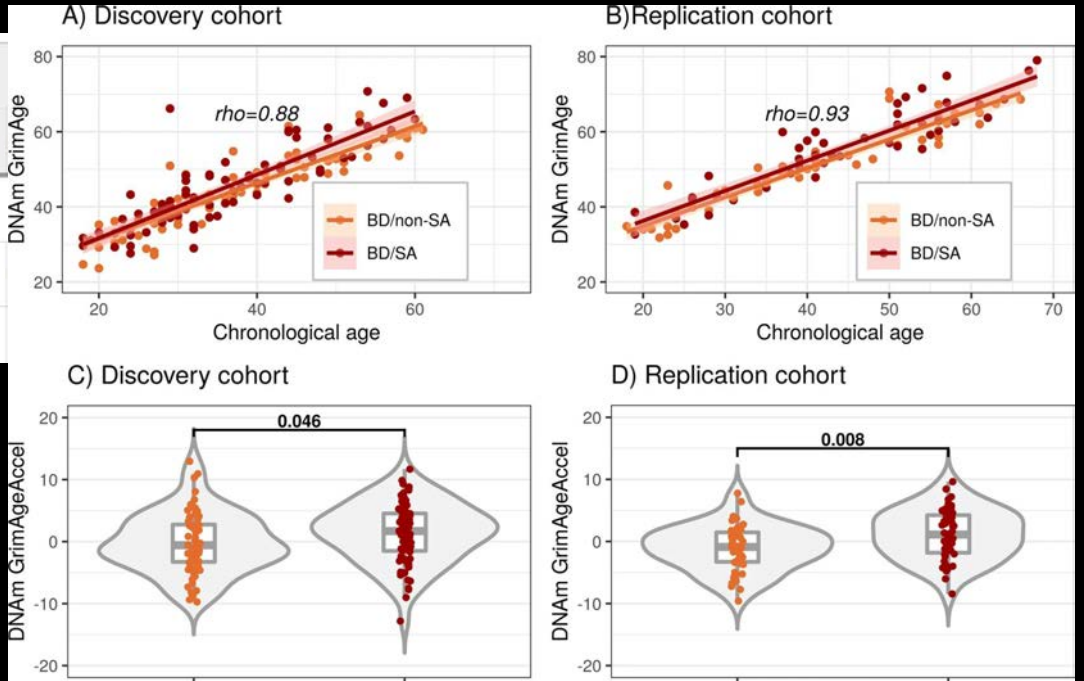
	Baseline (n = 96)	1-year follow-up (n = 95)
Sex		
Female	50	50
Age, mean ± SD	45.2 ± 12.4	46.17 ± 12.4





Background
Association between the epigenetic lifespan predictor GrimAge and history of suicide attempt in bipolar disorder

	Discovery cohort		
	CON (*n* = 50)	BD/non-SA (*n* = 67)	BD/SA (*n* = 77)
Demographic characteristics			
Female Sex, *n* (%)	34 (68.0%)	48 (71.6%)	55 (71.4%)
Age, median (IQR)	34.0 (16.0)	34.0 (18.5)	34.0 (15.0)



Background
Lithium response in bipolar disorder: Epigenome-wide DNA methylation signatures and epigenetic aging

Table 1. Socio-demographic and clinical data were split by excellent responders (Ex-Rp) and non-responders (N-Rp).

	Excellent responders (n = 26)	Non-responders (n = 37)	Comparison between groups
Age, mean (SD)	44.88 (11.95)	47.97 (12.13)	$T_{61\ d.f.}$ = 1.00; p-value = 0.321

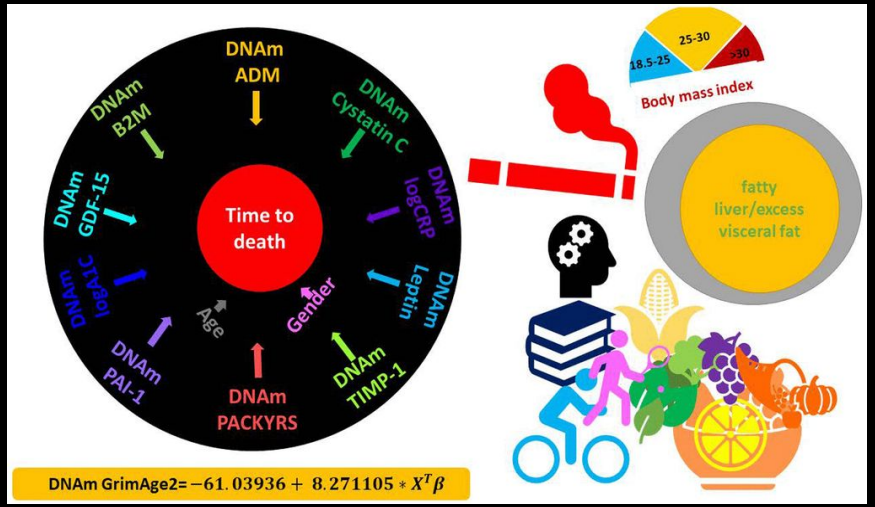
Clock	Ex-Rp (n=26)	N-Rp (n=37)	Test Results
DunedinPACE Mean (SD)	1.09 (0.1)	1.11 (0.12)	$t_{63\ d.f.}$=1.37; p-value=0.176
Horvath AgeAccel Mean (SD)	-1.21 (4.0)	0.85 (4.74)	$U_{63\ d.f.}$=422; p-value=0,410
Skin and blood AgeAccel Mean (SD)	-0.351 (2.63)	0.246 (2.05)	$t_{63\ d.f.}$=1.129; p-value=0.263
Hannum AgeAccel Mean (SD)	-0.151 (2.67)	0.106 (4.44)	$U_{63\ d.f.}$=456; p-value=0.727
PhenoAgeAccel Mean (SD)	-0.793 (4.79)	0.558 (5.70)	$t_{63\ d.f.}$=1.479; p-value=0.144
GrimAgeAccel Mean (SD)	0.194 (4.76)	-0.137 (4.14)	$t_{63\ d.f.}$=0.932; p-value=0.355
GrimAgeAccel2 Mean (SD)	0.276 (4.76)	-0.194 (4.60)	$t_{63\ d.f.}$=0.932; p-value=0.355
IEAA (Hannum) Mean (SD)	-0.123 (2.58)	0.086 (3.20)	$U_{63\ d.f.}$=480; p-value=0.989
EEAA-like (Hannum) Mean (SD)	-0.362 (2.75)	-0.362 (2.75)	$U_{63\ d.f.}$=440; p-value=0.567

*Data corrected by linear regression analysis for age and sex.

		Chronological age	DNAm Horvath	DNAm Skin and Blood	DNAm Hannum	DNAm PhenoAge	DNAm GrimAge	DNAm GrimAge2	DunedinPACE
Mean (SD)		46.78 (11.988)	43.91 (11.76)	50.19 (11.92)	42.18 (10.92)	31.34 (13.17)	62.09 (10.07)	70.21 (9.77)	1.10 (0.11)
Correlations with chronological age	r	_	0.923	0.981	0.938	0.914	0.909	0.881	0.115
	p-value	_	$5.96x10^{-27}$	$3.18x10^{-32}$	$9.47x10^{-30}$	$1.37x10^{-25}$	$7.48x10^{-25}$	$1.89x10^{-21}$	0.37
	FDR adjusted p-value	_	$1.39x10^{-26}$	$2.22x10^{-31}$	$3.31x10^{-29}$	$2.39x10^{-25}$	$1.05x10^{-24}$	$2.20x10^{-21}$	0.37

Methods

- Grimage2 (AgeAccelGrim2)
- Pyaging

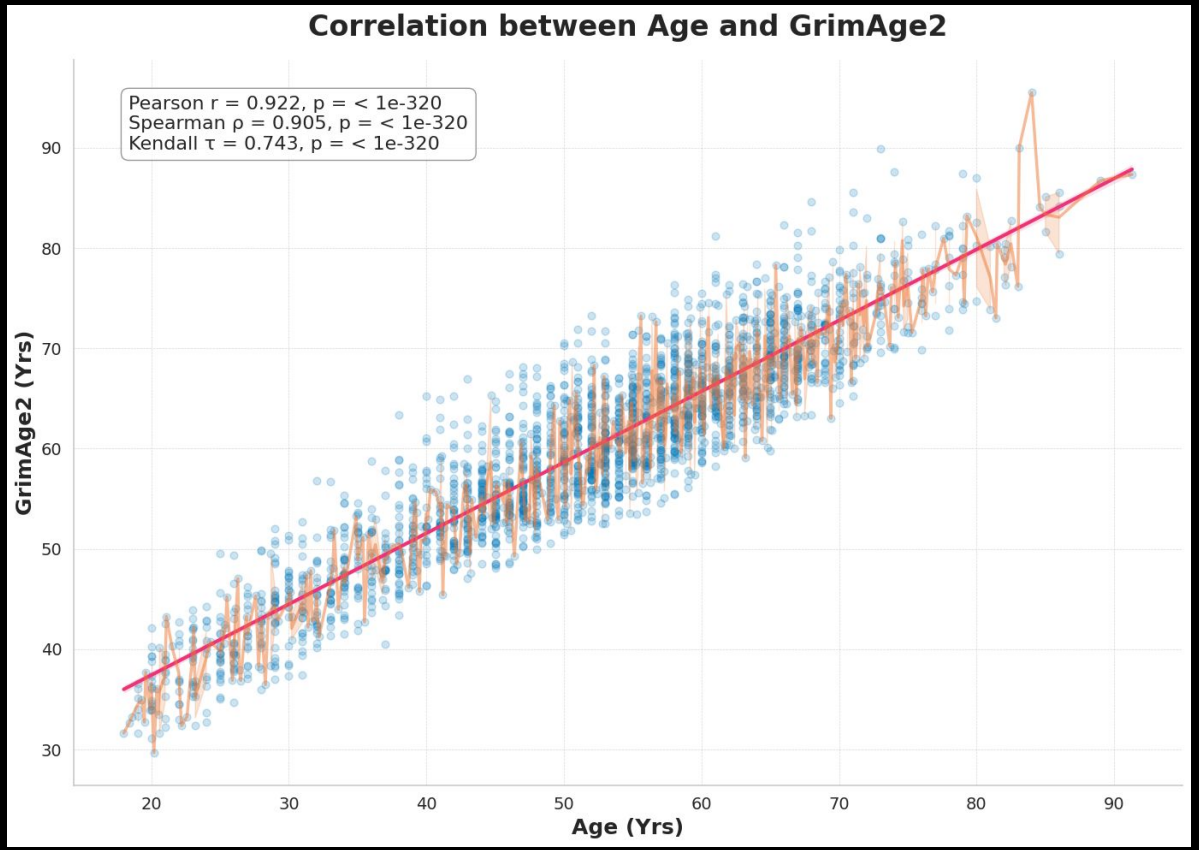


Results - Cohort Characteristics

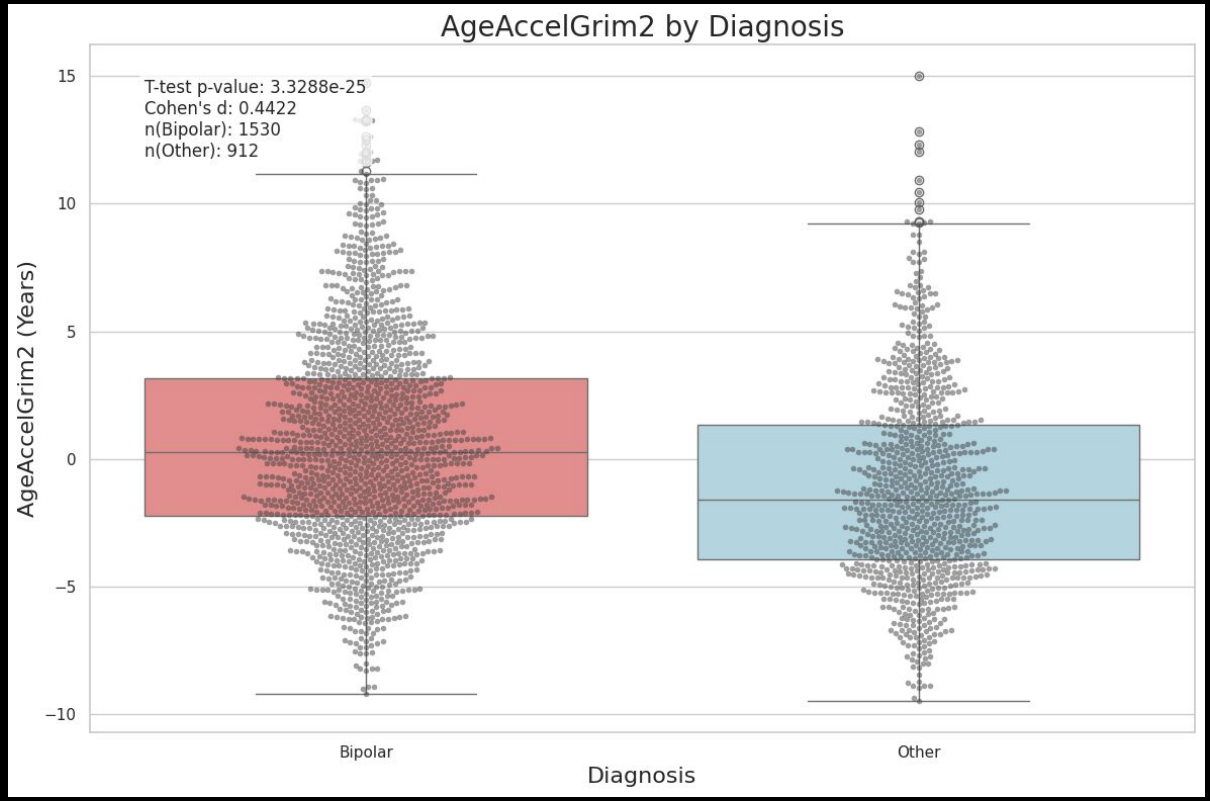
	Characteristic	Bipolar (n=1530)	Other (n=912)
0	Age	50.191568627450984 (SD: 12.39)	53.450986842105266 (SD: 15.53)
1	Female	875 (57.2%)	530 (58.1%)
2	Male	655 (42.8%)	382 (41.9%)

	Diagnosis	Count	Age_Mean	Age_SD	Age_Median	GrimAge2_Mean	GrimAge2_SD	GrimAge2_Median	AgeAccelGrim2_Mean	AgeAccelGrim2_SD	AgeAccelGrim2_Median
0	Bipolar	1530	50.191569	12.389986	51.0	59.433587	9.661698	59.791795	0.656173	4.093261	0.272248
1	Other	912	53.450987	15.532425	56.0	59.982916	11.880574	61.554658	-1.100816	3.850500	-1.610269

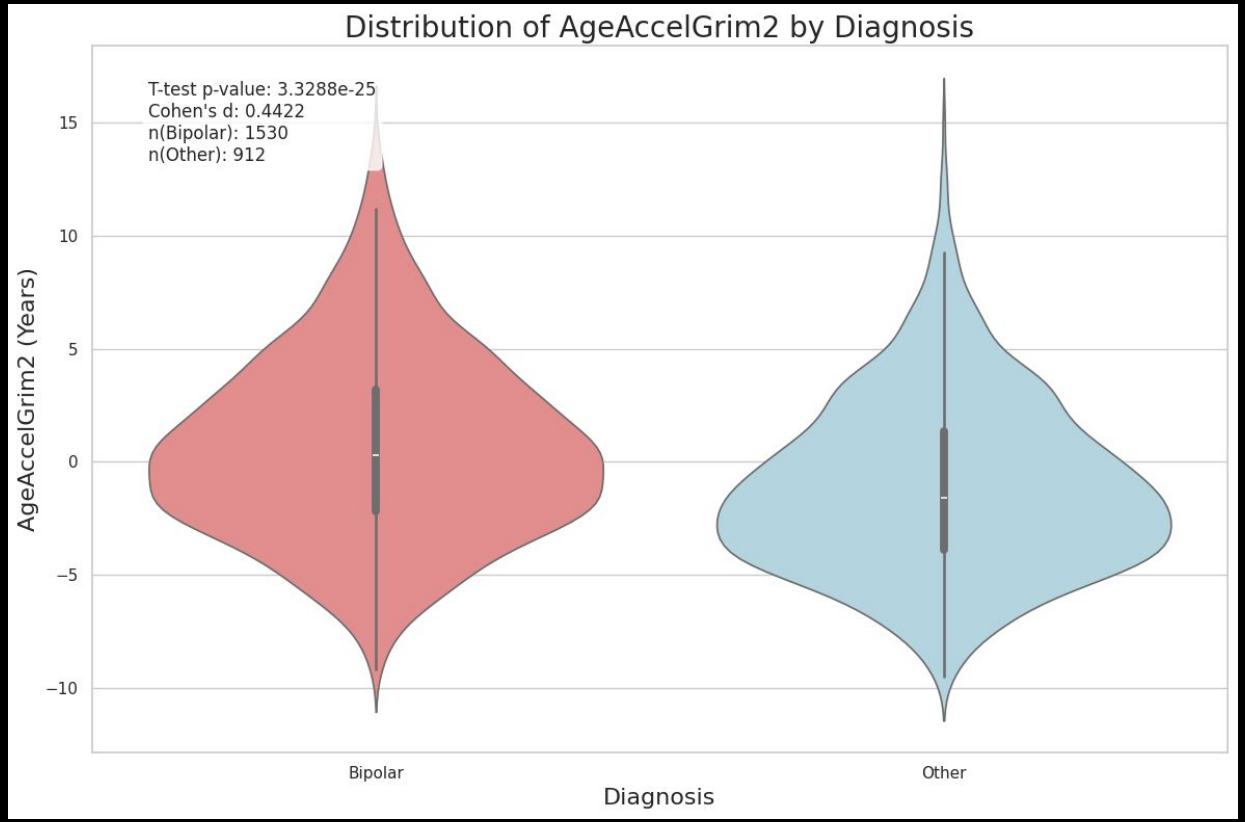
Results


Correlation between Age and GrimAge2
Pearson r = 0.922, p = < 1e-320
Spearman ρ = 0.905, p = < 1e-320
Kendall τ = 0.743, p = < 1e-320
GrimAge2 (Yrs)
Age (Yrs)
30
40
50
60
70
80
90
20
30
40
50
60
70
80
90

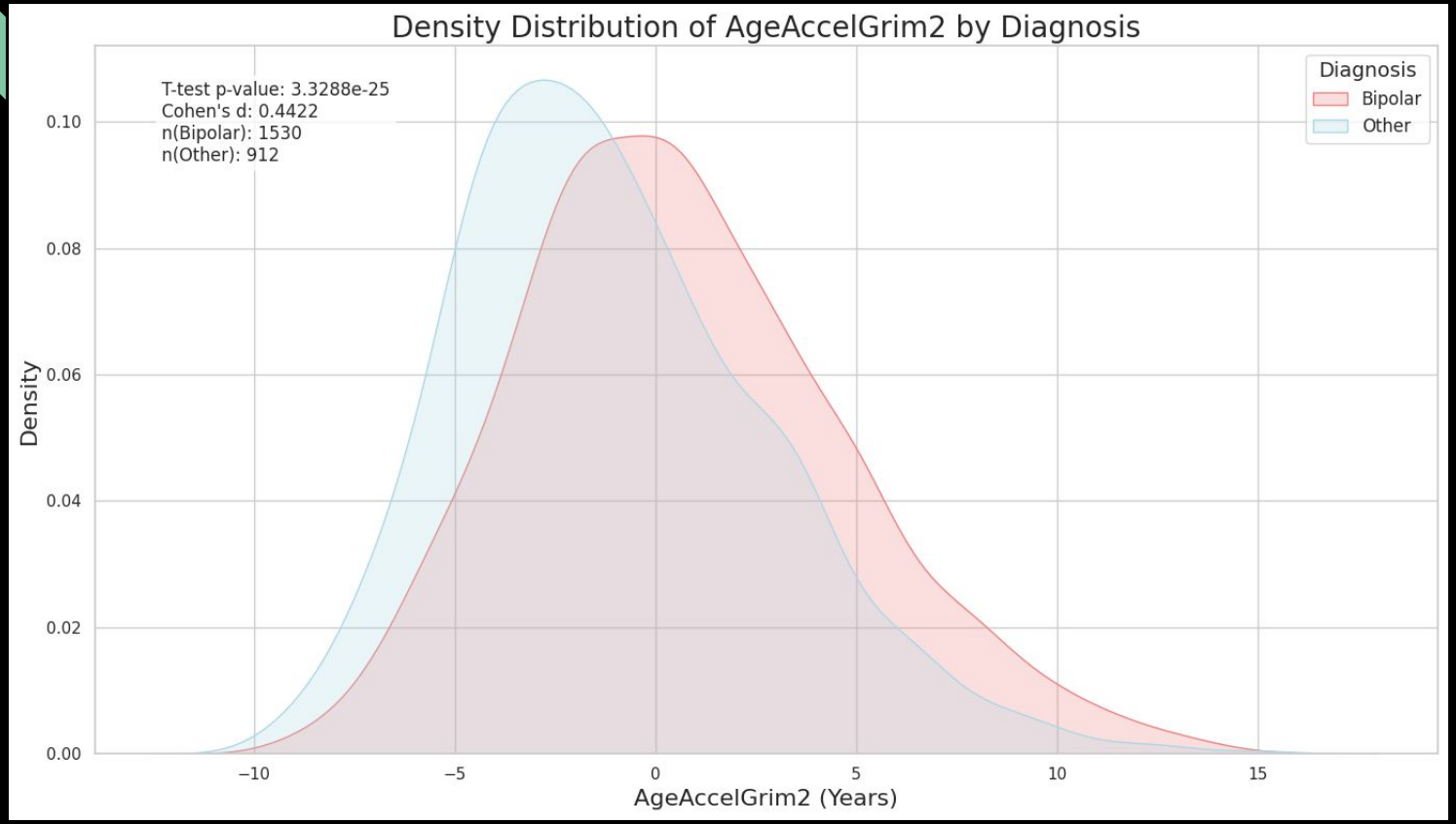
Results

- 
AgeAccelGrim2 by Diagnosis
T-test p-value: 3.3288e-25
Cohen's d: 0.4422
n(Bipolar): 1530
n(Other): 912
AgeAccelGrim2 (Years)
15
10
5
0
−5
−10
Bipolar
Other
Diagnosis

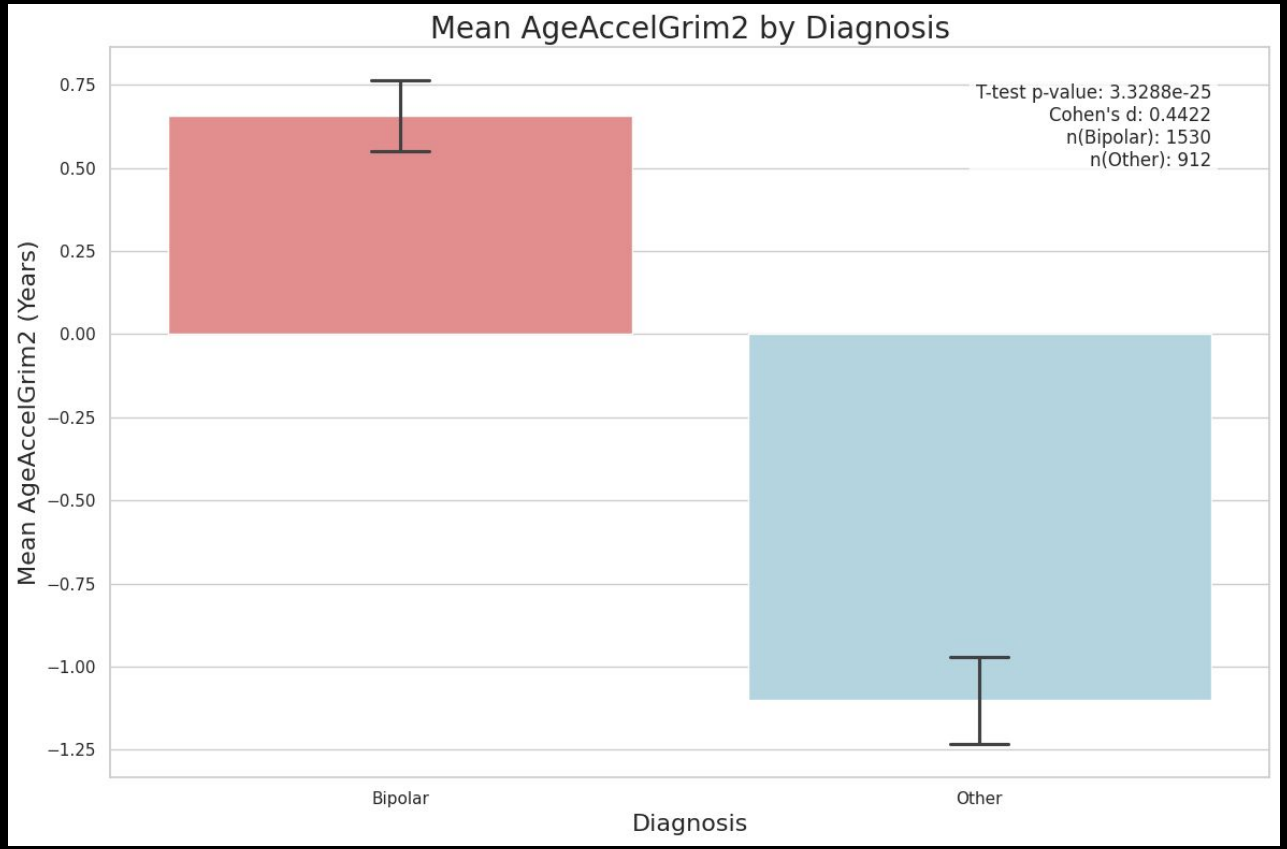
Results


Distribution of AgeAccelGrim2 by Diagnosis
T-test p-value: 3.3288e-25
Cohen's d: 0.4422
n(Bipolar): 1530
n(Other): 912
AgeAccelGrim2 (Years)
15
10
5
0
−5
−10
Bipolar
Other
Diagnosis

Results


Density Distribution of AgeAccelGrim2 by Diagnosis
T-test p-value: 3.3288e-25
Cohen's d: 0.4422
n(Bipolar): 1530
n(Other): 912
Diagnosis
Bipolar
Other
Density
0.00
0.02
0.04
0.06
0.08
0.10
−10
−5
0
5
10
15
AgeAccelGrim2 (Years)

Results


Mean AgeAccelGrim2 by Diagnosis
T-test p-value: 3.3288e-25
Cohen's d: 0.4422
n(Bipolar): 1530
n(Other): 912
Mean AgeAccelGrim2 (Years)
0.75
0.50
0.25
0.00
−0.25
−0.50
−0.75
−1.00
−1.25
Bipolar
Other
Diagnosis

Conclusions

- Tentative highly significant accelerated aging signal in individuals diagnosed with BP relative to individuals without a BP diagnosis

Thank you!

Future Directions

-

NAPLS 3 Genomic Data Processing Updates, and the Integration of Polygenic Profiling with Normative Modeling to Characterize Psychosis Resilience in CHR Youth

Cooper Beaman
Doctoral Student, Neuroscience Interdepartmental Program

Agenda

1. Introduction & Background
2. Overview of NAPLS 3 and Genomic Data Processing
3. Polygenic Profiling: Global vs. Partitioned Approaches
4. Normative Modeling of Brain Development
5. Integration Strategy: Linking Genetics & Neuroimaging
6. Anticipated Outcomes and Resilience Biotyping
7. Discussion, Challenges, and Future Directions
8. Q&A

Background & Rationale

- CHR (Clinical High Risk) youth: Only 15–25% convert to full-blown psychosis.
- The unmet need: Distinguishing resilience from risk despite high genetic liability.

Precision Psychiatry & Integration Imperative

- Emerging consensus: Multimodal integration (genomics + neuroimaging) is the goal.
- Our approach: Combine advanced polygenic risk profiling with individualized normative modeling.
- Translational potential: Inform early intervention and stratified treatment strategies.

Overview of NAPLS 3 Cohort

- Key Points:
- Approximately 700 CHR youth with extensive clinical, genomic, and longitudinal neuroimaging data.

Genomic Data Processing Updates

1. Status and Remaining goals
2. Caveats and Differences vs ENIGMA-DTI pre-imputation (e.g. ancestry handling)
3. Harmonization Approach to merge NAPLS 2 and 3 genomic datasets
4. Additional relevant details for lab members/collaborators considering incorporating this data into their projects.

Polygenic Risk Score (PRS) Generation Approaches

- Global PRS vs. Partitioned PRS (pPGS): Why partitioning is critical.
- Rationale for using curated gene sets (synaptic, excitatory–inhibitory, neurodevelopmental, immune).
- Methods: Genomic Structural Equation Modeling (gSEM) and GWAS-by-Subtraction.

Detailed Methods for pPGS Construction

- Data Sources: GWAS summary statistics from PGC (for SCZ, BIP, MDD) and available raw files.
- Gene Set Curation: Using databases like SynGO and GO categories.
- Processing Steps: SNP filtering (MAF > 0.01, HWE p > 1e-6), clumping thresholds, and Bayesian shrinkage (LDpred2).
- Validation: Using time-to-event models (Cox proportional hazards) to test prediction of psychosis conversion.

Normative Modeling of Brain Development

- Objective: To quantify individual deviations from normative brain trajectories.
- Dataset: Leverage the ABCD study's large normative sample (~11,000 youths).
- Methodology: Apply Gaussian Process Regression or hierarchical Bayesian models to develop "brain growth charts."
- Outcome: Generate individualized z-deviation maps (e.g., for cortical thickness, subcortical volumes, functional connectivity).

Integration Strategy: Linking pPGS with Normative Modeling

- Conceptual Framework:
  – pPGS represent pathway-specific genetic risk.
  – Normative modeling yields personalized deviation scores.

- Statistical Integration: Use regression analyses (e.g., linear models, Cox PH, canonical correlations) to link genetic risk with brain deviations.

- Key Hypothesis: CHR youth with high pPGS in specific pathways (e.g., synaptic signaling) will show corresponding neurodevelopmental red flags.

Anticipated Outcomes: Genetic & Neuroimaging Associations

- Genomic Insights:
  – Expect that partitioned PRS will provide better risk stratification than global PRS.
- Neuroimaging Findings:
  – Anticipate identifying specific deviation patterns (e.g., accelerated cortical thinning) associated with high pPGS.
- Resilience Biotypes:
  – Predict the emergence of a “resilient” subgroup: high pPGS yet normative brain profiles.

Specific Planned Analyses & Statistical Models

- Analysis of Conversion Risk:
  – Cox proportional hazards models using pPGS as predictors.
- Linking Brain Deviations and Genetics:
  – Univariate regressions and multivariate canonical correlation analyses to identify gene–brain associations.
- Subgroup Identification:
  – Two-dimensional classification (high genetic risk vs. brain deviation burden) to detect resilient vs. at-risk profiles.
- Handling Confounds:
  – Incorporate age, sex, site, and medication status; test for sex interactions.

Anticipated Translational Impact & Future Applications

- Clinical Utility:
  – Refined biomarkers for early psychosis prediction that can inform personalized interventions.
- Risk Calculator Enhancement:
  – Integration of pPGS and normative modeling to improve existing CHR risk calculators.
- Guiding Preventive Strategies:
  – Identification of resilience biotypes may point to protective factors and targeted therapies.

Discussion: Challenges & Contingency Plans

- Potential Challenges:
  – Data heterogeneity across sites; power limitations in detecting small effects.
- Contingency Strategies:
  – Use of ComBat for harmonization; combining gene sets for sufficient power; iterative cross-validation.
- Iterative Improvement:
  – Plans for future incorporation of additional environmental moderators (e.g., trauma metrics).

Thank You!

ABCD Subcortical Volume Rate of Change GWAS

Motivation and Background

A Genome-Wide Association Study (GWAS) is performed on the rate of change (ROC) of subcortical volumes in Adolescent Brain Cognitive Development (ABCD) study participants. The primary goal is to identify genetic variants associated with the longitudinal changes in 17 subcortical brain regions, covarying for interview_age, `bigsnpr` top 10 PCs, smri_vol_scs_intracranialv (except for smri_vol_scs_wholeb), sex, batch, and mri_info_deviceserialnumber. The project leverages existing pre-processed imaging and genotype data from ABCD Release 5.1. The computational workflow involves: **1) Data Characterization and Preparation:** including data cleaning, quality control, calculation of ROCs for each region between baseline and year 2, generating summary statistics, and visualization of phenotype distributions (histograms, boxplots, violin plots) using R and Shiny for interactive exploration. Normality of the ROC data is assessed, and rank-based inverse normal transformation is applied. **2) GWAS Execution:** The prepared data is split by sex and ancestry (European, African, and American). `GCTA-MLMA` is employed to perform GWAS for each phenotype, covarying for age, sex, genotyping batch, top 10 ancestry principal components, and intracranial volume (except for whole brain volume). Parallel job submission scripts are used to efficiently execute multiple GWASes on the `Hoffman2` cluster. **3) Post-GWAS Analysis:** This involves generating Manhattan, QQ, `trumpet`, and locuszoom plots for each GWAS result. Meta-analysis across ancestries using tools like `METAL` and `others` will be conducted. Further analyses include genetic correlation, polygenic risk score (PRS) conditioning with `PleioPGS`, gene-based tests (`MOSTtest`), and investigation of joint genetic architectures using `GenomicSEM` and `GSMR2`.

Computational Overview

- **R:** Extensive use of R for data manipulation, statistical analysis, and visualization (`dplyr` , `tidyr` , `ggplot2` , `data.table` , `qqman` , etc.).
- **GCTA:** `GCTA-MLMA` is employed to conduct GWAS analyses.
- **PLINK:** PLINK binary files are prepared for genotype data.
- **Shell Scripting:** Bash scripts are created for job submission and data processing on Hoffman2.
- **Shiny:** Shiny plots are generated for interactive data exploration and visualization.
- **Other Tools:** `Ensembl` `BioMart` , `METAL` , `LDSC` , `PleioPGS` , `GenomicSEM` , `GSMR2` , and `SAIGE` .

1. Relevant Literature+
    i. Genomic analysis of intracranial and subcortical brain volumes yields polygenic scores accounting for variation across ancestries | Nature Genetics
2. Overview Presentation

Investigation Overview

Stage 1 - Data Acquisition and Preprocessing

- **Data Retrieval:** Accessing and downloading relevant datasets from the ABCD Study (Release 5.1) including imaging (structural MRI - sMRI) and genetic data.
- **Data Integration:** Merging multiple data files from ABCD based on subject IDs and timepoints.
- **Quality Control (QC):** Applying established QC procedures to filter out subjects and/or data points based on imaging quality metrics (e.g., `imgincl_t1w_include`), missing data, and other relevant criteria.
- **Subcortical Volume Extraction:** Utilizing pre-processed subcortical volume data derived using FreeSurfer's automated segmentation procedure (`ASEG`).
- **Rate of Change Calculation:** Calculating the percent rate of change (ROC) of subcortical volumes between baseline and subsequent time points (year 2 and/or year 4). Implementing formulas for calculating and normalizing ROCs.
- **Descriptive Statistics:** Generating summary tables and descriptive statistics for subcortical volumes, ROCs, sample sizes stratified by sex, ancestry, and timepoint.
- **Data Visualization:** Creating histograms, box plots, and violin plots to visualize the distributions of subcortical volumes and ROCs.
- **Correlation Analysis:** Calculating correlation matrices to assess relationships between different subcortical volume ROCs.
- **Normality Assessment:** Evaluating the normality of ROC distributions using statistical tests (e.g., Shapiro-Wilk test) and visualizations (Q-Q plots).

Summary Tables

- Overview Table and Barplots of Sample Sizes by Timepoint Ethnicity and Sex
- Overview Table of Subcortical Volume ROCs

Master dataframe Overview

```
> colnames(merged_data_no_na)
 [1] "FID"                                 "IID"
 [3] "sex"                                 "mri_info_deviceserialnumber"
 [5] "interview_age"                       "ethnicity"
 [7] "smri_vol_scs_aa_ROC0_2"              "smri_vol_scs_amygdala_ROC0_2"
 [9] "smri_vol_scs_caudate_ROC0_2"         "smri_vol_scs_cbwmatter_ROC0_2"
[11] "smri_vol_scs_ccat_ROC0_2"            "smri_vol_scs_ccct_ROC0_2"
[13] "smri_vol_scs_ccmidat_ROC0_2"         "smri_vol_scs_ccmidps_ROC0_2"
[15] "smri_vol_scs_ccps_ROC0_2"            "smri_vol_scs_crbcortex_ROC0_2"
[17] "smri_vol_scs_crbwmatter_ROC0_2"      "smri_vol_scs_hpus_ROC0_2"
[19] "smri_vol_scs_intracranialv_ROC0_2"   "smri_vol_scs_pallidum_ROC0_2"
[21] "smri_vol_scs_putamen_ROC0_2"         "smri_vol_scs_tp_ROC0_2"
[23] "smri_vol_scs_vedc_ROC0_2"            "smri_vol_scs_wholeb_ROC0_2"
[25] "batch"                               "PC1"
[27] "PC2"                                 "PC3"
[29] "PC4"                                 "PC5"
[31] "PC6"                                 "PC7"
[33] "PC8"                                 "PC9"
[35] "PC10"                                "PC11"
[37] "PC12"                                "PC13"
[39] "PC14"                                "PC15"
[41] "PC16"                                "PC17"
[43] "PC18"                                "PC19"
[45] "PC20"
> summary(factor(merged_data_no_na$sex))
   F    M
3041 3471

> summary(factor(merged_data_no_na$ethnicity))
 AFR  AMR  EAS  EUR  SAS
1035 1329  150 3955   43

# Interview age summary (months > years)
> summary(merged_data_no_na$interview_age / 12)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  10.58   11.42   11.92   11.96   12.50   13.83
```

Phenotype Distributions

- Violin Plots of Subcortical Volume ROCs
- Box Plots of Subcortical Volumes

Stage 2 - Longitudinal Subcortical Volume GWAS Preparation and Execution

- **Data Splitting:** Splitting the dataset into subsets based on sex and ancestry (European, African, American) to perform ancestry-specific GWAS.
- **Covariate Preparation:** Creating files containing covariate information including age, sex, genotyping batch, and the top 10 ancestry principal components. Handling both discrete and quantitative covariates. Excluding intracranial volume as a covariate in the whole brain volume GWAS.
- **Phenotype Preparation:** Formatting phenotype data (ROCs) into the required format for GCTA-MLMA.
- **GWAS Execution with GCTA-MLMA:** Running GWAS using GCTA-MLMA on the Hoffman2 cluster. This involves:
    - Writing shell scripts for job submission and management on a high-performance computing cluster.
    - Managing large genomic datasets (PLINK files, GRMs) on a cluster environment.
    - Optimizing job scripts for parallel execution and efficient resource utilization (memory, CPU).
    - Implementing appropriate quality control steps for genotype data, including filtering by minor allele frequency (MAF).
    - MLMA
    - SAIGE

Stage 3 - Post-GWAS Analysis and Visualization

- **Manhattan Plots:** Creating Manhattan plots to visualize GWAS results across the genome.
- **QQ Plots:** Generating QQ plots to assess the genomic inflation factor and potential biases in the GWAS. Optimizing QQ plot generation for large datasets using techniques like point pruning.
- **Trumpet Plots:** Creating trumpet plots to visualize the relationship between effect size, allele frequency, and statistical power.
- **LocusZoom Plots:** Generating LocusZoom plots for regions of interest to visualize association signals and nearby genes.
- **CMplot (Circular Manhattan Plots):** Generating circular Manhattan plots for visualizing GWAS results.
- **Hudson Plots:** Creating Hudson plots for comparing GWAS results across different phenotypes or datasets.

- **Annotation of Significant SNPs:** Annotating significant SNPs using resources like Ensembl BioMart to identify associated genes and functional consequences.
- **Meta-Analysis:** Performing meta-analysis across ancestry groups using tools like METAL to combine GWAS results.
- **Post-GWAS Analyses:** Implementing:
  - Genetic correlation analysis (e.g., LDSC).
  - Polygenic risk score (PRS) analysis and conditioning existing neurodevelopmental disorder PRS on ROCs using `PleioPGS`.
  - Gene-based association tests (e.g., MOSTtest).
  - Perform Genomic structural equation modeling (`GenomicSEM`) to investigate joint-genetic architectures and ROC mediation.
  - Perform Generalised Summary-data-based Mendelian Randomisation v2 (`GSMR2`).

Tasks

- [ ] Find out if/how relatedness needs to be accounted for in GCTA setup
- [ ] Finalize parallel job script
- [ ] Optional Phenotype Splitting Functionality
  - [ ] Add histogram/transformed phenotype data QC as toggleable arg in save_split_data function to be called within split txt prep script function.
- [ ] Optional Additional Normalization QC
  - [ ] Add Correlation Analysis
  - [ ] Pairwise Comparisons
  - [ ] Linear Models and Covariance Checks
  - [ ] Analysis of Covariance (ANCOVA)
  - [ ] Phenotypes-Covariate Relationship Visualizations
  - [ ] Phenotypes-Coefficient Association Analsyses and Rates of Change Comparisons

Accelerated Biological Aging in Bipolar Disorder

Motivation and Background

This project investigates accelerated biological aging in the largest bipolar disorder DNA methylation cohort to date, aiming to identify epigenetic age acceleration differences, drivers, and modifiers between individuals with bipolar disorder and controls. Preprocessing and quality control of DNA methylation data from Illumina EPIC arrays is performed, specifically addressing missing probes and data normalization. GrimAge2 and other epigenetic aging algorithms from the `pyaging` Python package are applied. Statistical analyses, including t-tests, ANCOVA, and correlation analysis, are conducted in R and Python to assess differences in GrimAge2 age acceleration between diagnostic groups while covarying for age and sex. Data visualization is employed using Python libraries including `seaborn` and `matplotlib` to generate informative plots for data exploration and presentation. The R packages `minfi`, `BioAge`, `dnaMethyAge`, and `methylclock` are applied to prepare for epigenetic clock analysis. Finally, data wrangling and manipulation is performed using R's `data.table` and Python's `pandas` to prepare, clean, and transform the raw data for analysis. Future research will compare across multiple methylation aging clocks, characterize the individual contributions of GrimAge2 subcomponents, and explore the effects of lithium treatment and other environmental modifiers on epigenetic age acceleration in bipolar disorder.

1. Relevant Literature+
2. Meta-analysis of epigenetic aging in schizophrenia reveals multifaceted relationships with age, sex, illness duration, and polygenic risk

Computational Overview

- **Programming Languages:** R and Python.
- **R Packages:** `minfi`, `BioAge`, `dnaMethyAge`, `methylclock`, `dplyr`, `tidyr`, `data.table`, `purrr`, `ggplot2`, `plotly`, `RColorBrewer`, `reshape2`, `GenomicRanges`, `SummarizedExperiment`, `qs`, `bigmemory`, `doParallel`, `parallel`, `arrow`.
- **Python Packages:** `pyaging`, `pandas`, `numpy`, `scipy`, `seaborn`, `matplotlib`, `sklearn` (specifically `KMeans`, `StandardScaler`), `statsmodels`, `pygam`, `pyarrow`.
- **High-Performance Computing (HPC):** Conducted in the Hoffman2 HPC environment utilizing SGE job scheduling and parallel processing in R for computationally intensive tasks.
- **Data Management:** Data cleaning, transformation, merging, and subsetting across both R and Python is performed. Efficiently procssed large datasets using packages including `bigmemory` and `pyarrow`. Generated reproducible analysis workflows by logging key data characteristics (e.g. data dimensions, timestamps) to filenames.
- **Statistical Analysis:** Conducted various statistical analyses, including descriptive statistics, correlation analysis, t-tests, ANCOVA, and planned for GAMs.
- **Data Visualization:** Created a wide range of static visualizations for exploratory data analysis and presentation of results.
- **Version Control:** Utilized GitHub for code sharing and version control.
- **Workflow Design:** Designed and implemented a multi-stage analysis pipeline involving data preprocessing, clock calculation, statistical analysis, visualization, and reporting, including integration of R and Python components.

Results

- Overview Presentation

Stage 1 - Data Acquisition and Preparation

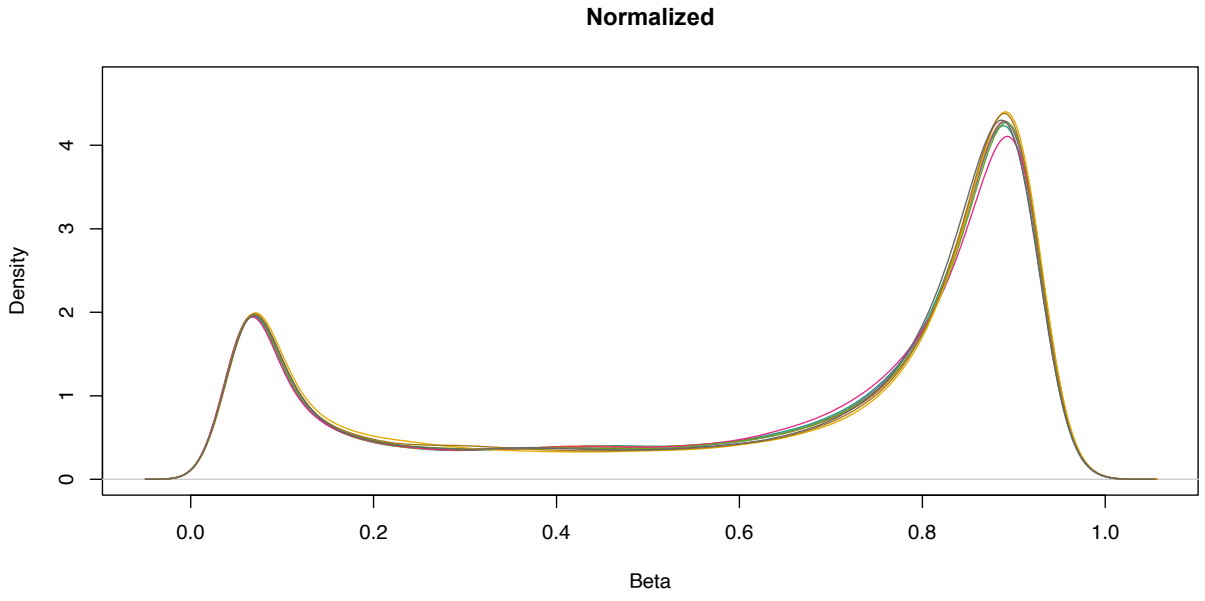
- **Data Acquisition:** Acquired raw DNA methylation data (likely IDAT files) from Illumina EPIC arrays along with accompanying sample sheets containing demographic and diagnostic information. Potentially integrated data from multiple sources (e.g., "Bipolar 2023 Sample Sheet", "2000_sample_covariates", "highcov_technical_covariates", "Complete BIG Data").
- **Data Import and Formatting:** Imported data into R and converted to appropriate formats (e.g., `GenomicRatioSet`) for downstream analysis using `minfi`. Used R's `read.csv`, `read_excel`, and `read.table` for sample sheet information. Employed Python's `pyarrow.feather` for efficient loading of preprocessed and saved data subsets.
- **Data Cleaning and Quality Control (QC):** Performed quality control procedures, including:
  - Checking for missing data in both methylation and sample annotation data.

    - Addressing missing probe information using external resources like the `mepylome` package and manifest files.
    - Removal of duplicate probe data.
    - Compared predicted and reported sex.
- **Data Wrangling and Transformation:** Manipulated and transformed data using `dplyr`, `tidyr`, `data.table` in R and `pandas` in Python. This included renaming columns, recoding variables (e.g., Gender), handling "_REP" sample duplicates, merging datasets, calculating age in months/years from date data, and summarizing missing data patterns.
- **Data Subsetting:** Created subsets of data for specific analyses (e.g., selecting samples with complete data, extracting specific CpG sites related to GrimAge2).

Cohort Demographics

Characteristic	Bipolar	Other
Count	1530	912
Male	655 (42.8%)	382 (41.9%)
Female	875 (57.2%)	530 (58.1%)

Density Plot of Normalized Beta Values



Stage 2 - Epigenetic Clock Analysis

- **GrimAge2 Calculation:** Calculated GrimAge2 and AgeAccelGrim2 using custom R functions leveraging `bigmemory` for efficient handling of large matrices and `doParallel` for parallel processing of subcomponents. This included loading pre-trained GrimAge2 model weights and reference values.

- **Other Clock Calculations:** Calculated various epigenetic clocks using R packages (`DNAmAge` , `DunedinPoAm` , `DunedinPACE`) and Python package (`pyaging`). This required handling missing CpG sites for each clock and managing compatibility between R and Python data structures.
- **Probe Analysis and Verification:** Compared the CpG sites required by GrimAge2 with the available CpG sites in the methylation data and reference array annotations (`IlluminaHumanMethylationEPICv2anno.20a1.hg38`). Identified and documented missing probes.
- **Descriptive Statistics:** Computed descriptive statistics (e.g., mean, standard deviation, median, quartiles) for age, GrimAge2, and AgeAccelGrim2, stratified by diagnosis, using `data.table` and `pandas` .
- **Correlation Analysis:** Calculated Pearson, Spearman, and Kendall correlations between chronological age and GrimAge2 using R's `stats` package.
- **Comparative Analysis:** Performed t-tests and ANCOVA to compare AgeAccelGrim2 between bipolar and control groups, considering age as a covariate, using R's `stats` and `statsmodels` packages in Python.
- **Data Visualization:** Generated various plots, including density plots, box plots, violin plots, scatter plots, bar plots, and pie charts, to visualize data distributions, correlations, and group differences using `ggplot2` , `plotly` in R and `seaborn` , `matplotlib` in Python. This involved customizing plot aesthetics, adding statistical annotations (p-values, effect sizes), and creating multi-panel figures.
- **Data Export and Reporting:** Exported results and summary tables to CSV and Excel files using R's `fwrite` and Python's `pandas.to_csv` for reporting and sharing.

BPDNAm GrimAge2 Source Code Variables

1. **DNAmGrimAge2** and **AgeAccelGrim2**
2. Seven DNAm-based plasma protein estimates
3. DNAm-based pack years (**DNAmPACKYRS**)

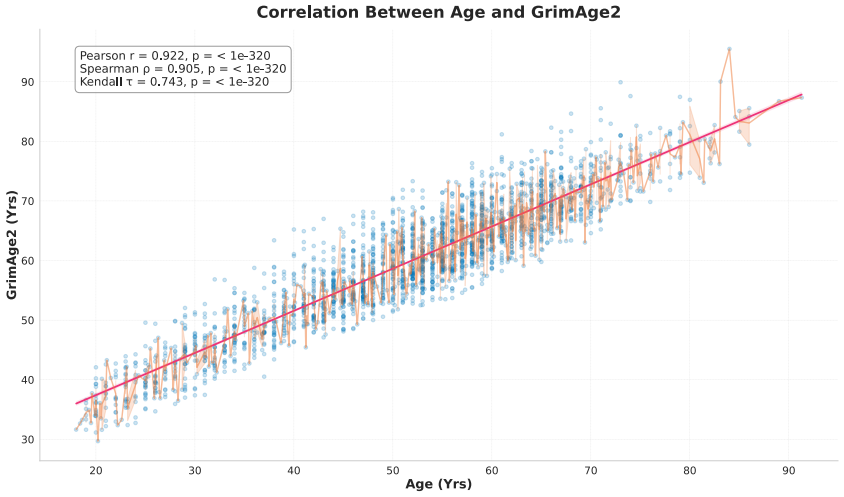
Name	Variable	Unit
DNAm GrimAge2	**DNAmGrimAge2**	year
GrimAge2 age acceleration	**AgeAccelGrim2**	year
DNAm Growth differentiation factor 15	**DNAmGDF15**	pg/mL
DNAm Beta-2-microglobulin	**DNAmB2M**	pg/mL
DNAm Cystatin-C	**DNAmCystatinC**	pg/mL
DNAm Tissue Inhibitor Metalloproteinases 1	**DNAmTIMP1**	pg/mL
DNAm Adrenomedullin	**DNAmADM**	pg/mL

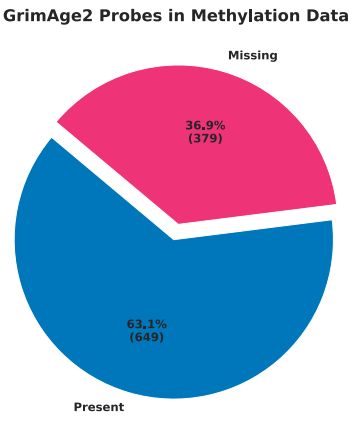
Name	Variable	Unit
DNAm Plasminogen activator inhibitor 1	DNAmPAI1	pg/mL
DNAm Leptin	DNAmLeptin	pg/mL
DNAm log C-reactive protein	DNAmlogCRP	mg/L (in CRP)
DNAm log hemoglobin A1C	DNAmlogA1C	% (in A1C)
DNAm smoking pack years	DNAmPACKYRS	

Summary Statistsics

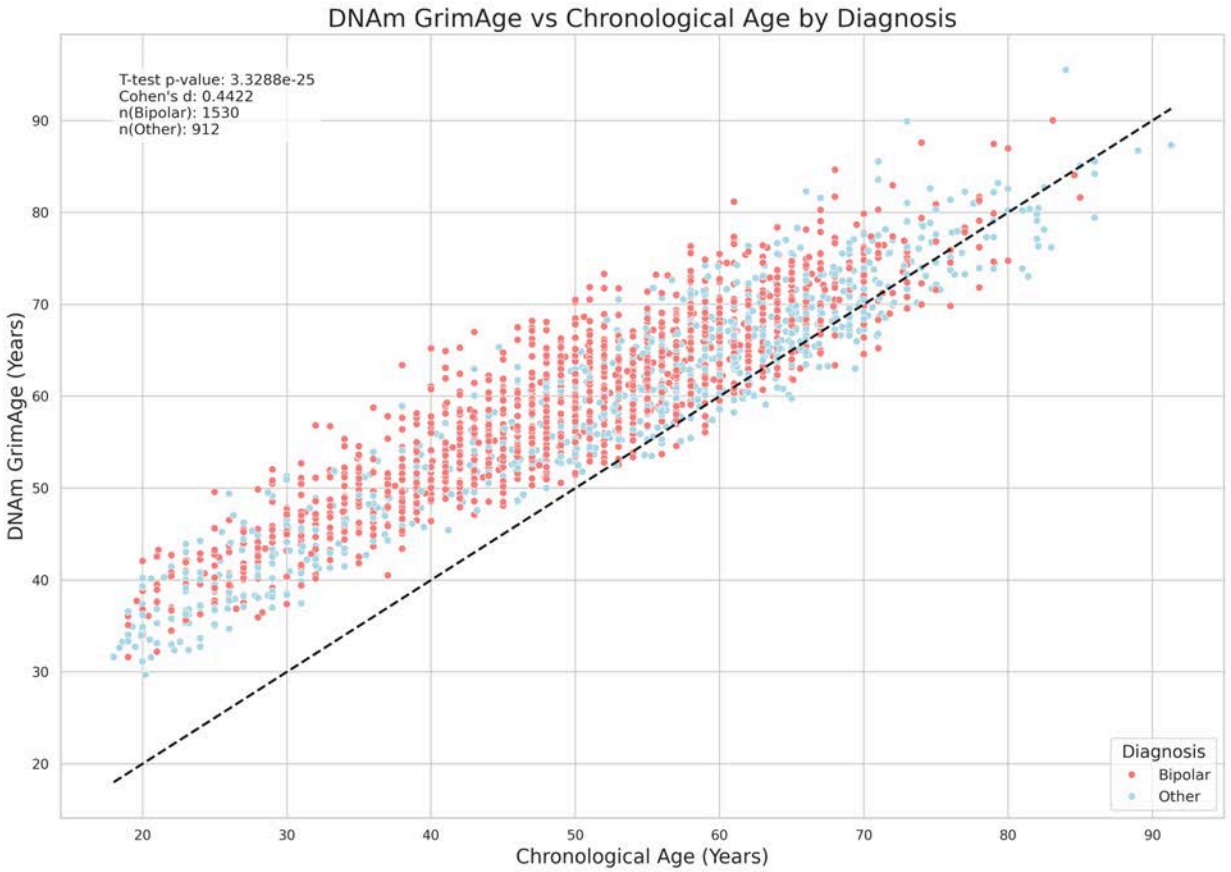
	Chronological Age		DNAmGrimAge2		AgeAccelGrim2	
Metric	Bipolar	Other	Bipolar	Other	Bipolar	Other
Mean	50.19	53.45	59.43	59.98	0.66	-1.10
SD	12.39	15.53	9.66	11.88	4.09	3.85
Min	19.00	18.00	31.61	29.69	-9.18	-9.49
Max	85.00	91.30	90.03	95.51	3.18	1.35
Q_1	42.00	44.35	53.00	52.85	14.75	15.00
Q_2	51.00	56.00	59.79	61.55	-2.21	-3.91
Q_3	59.00	65.00	66.37	68.38	0.27	-1.61

Correlation Between Age and GrimAge2 with Missing Probes Summary

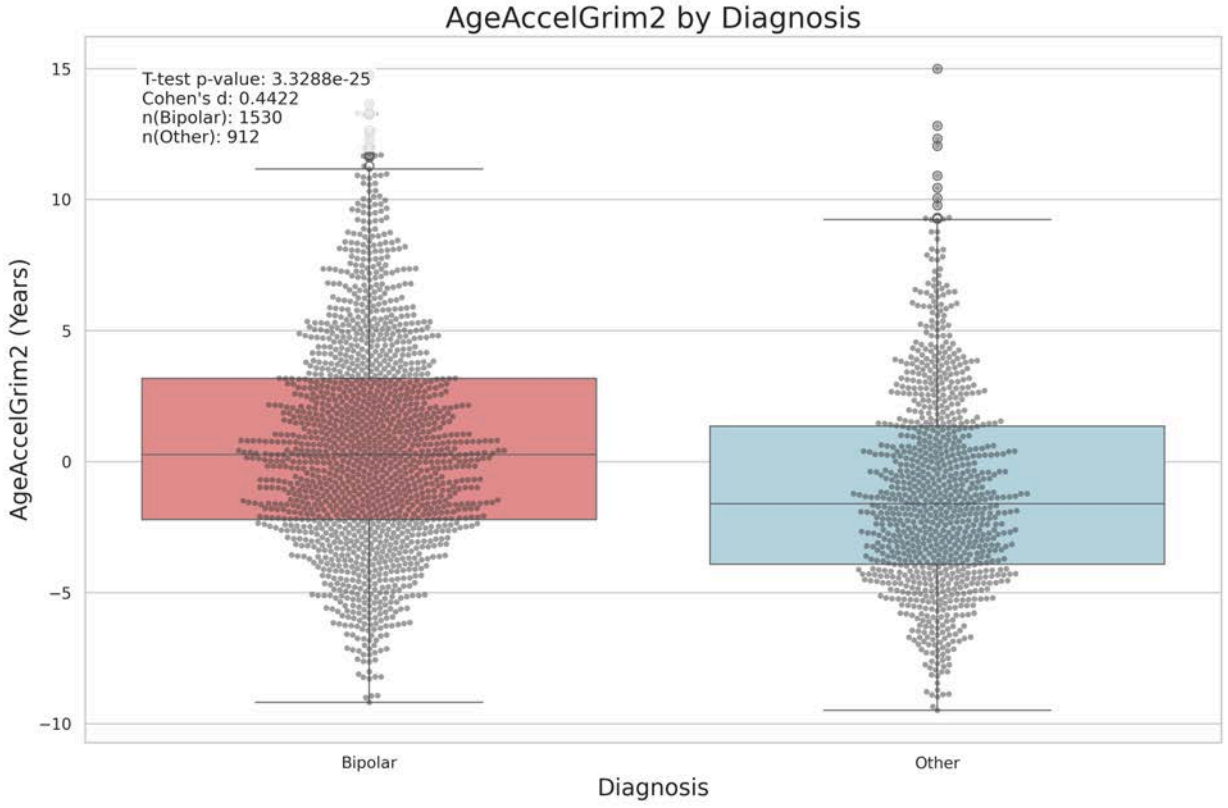




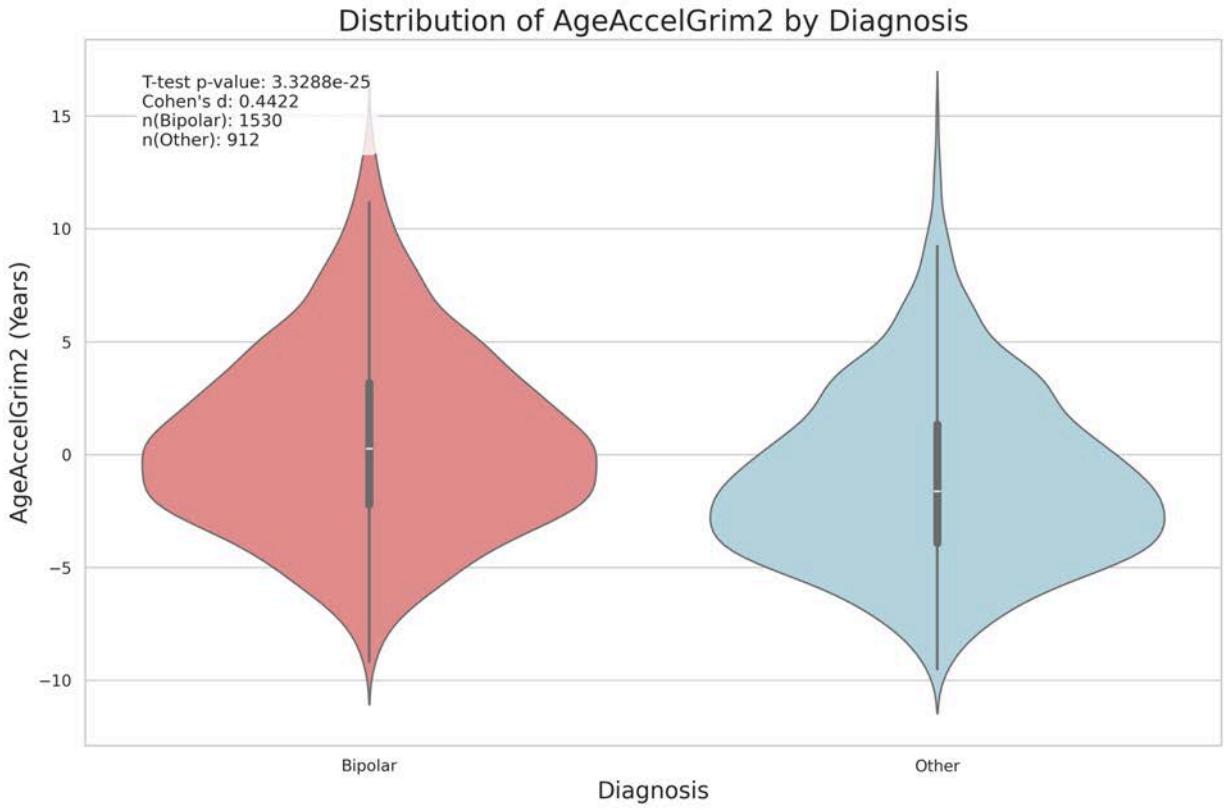
DNAm GrimAge2 vs Chronological Age by Diagnosis



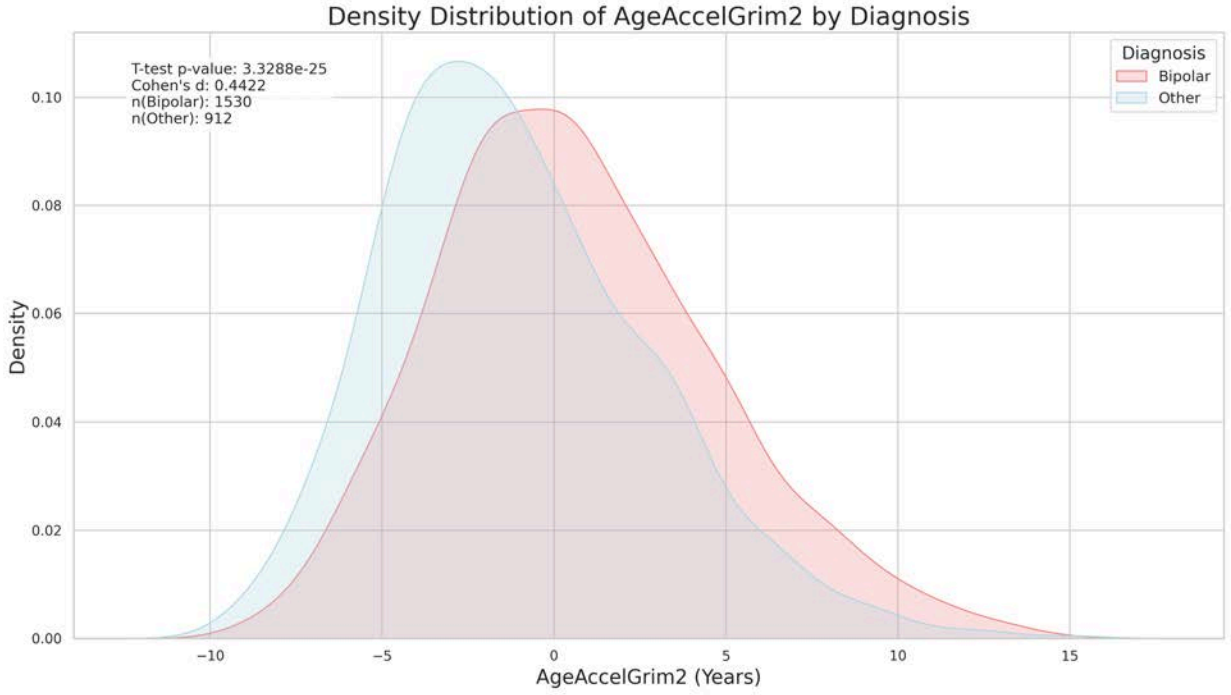
AgeAccelGrim2 by Diagnosis



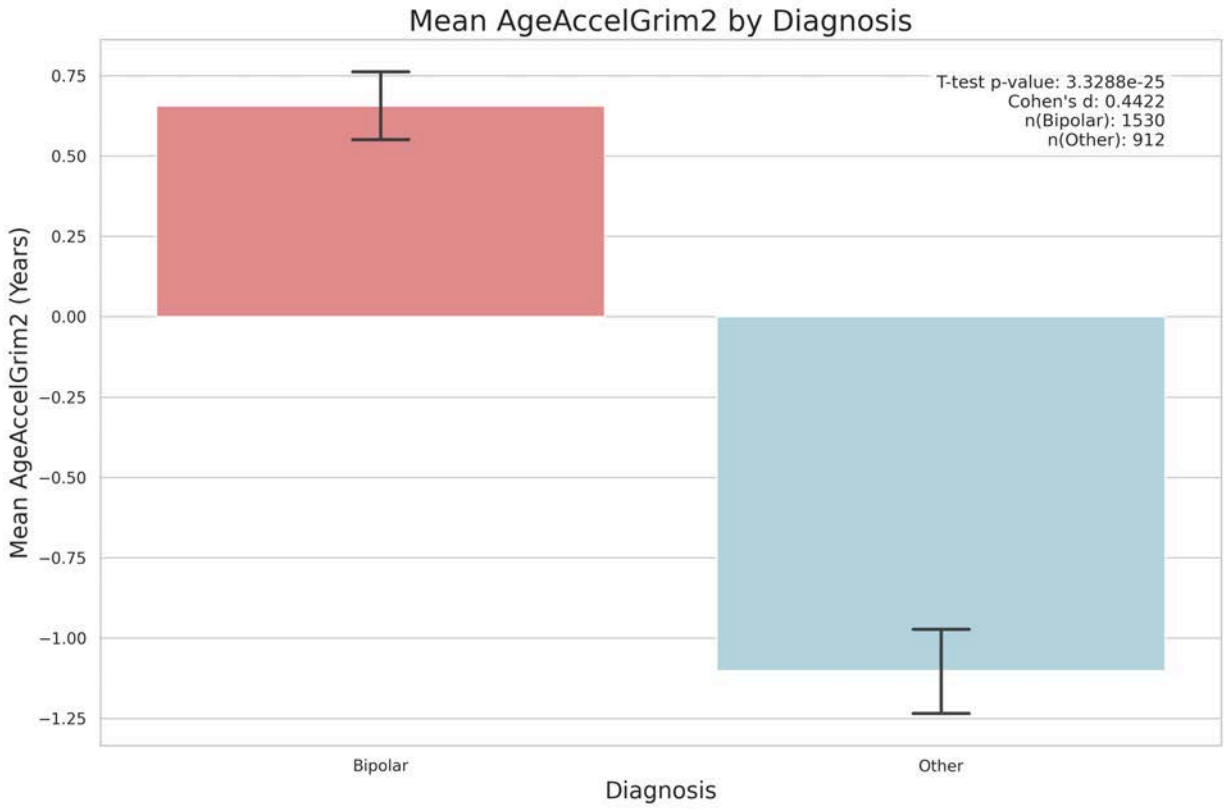
Distribution of AgeAccelGrim2 by Diagnosis



Density Distribution of AgeAccelGrim2 by Diagnosis



Mean AgeAccelGrim2 by Diagnosis



BPDNAm All Calculated GrimAge2 Variables

SampleID	Female	Age	Diagnosis	DNAmGrimAge2	AgeAccelGrim
431-BG00001	1.0	51.0	BipolarI	56.85389522787445	-2.4955535070
431-BG00002	1.0	33.0	BipolarI	44.49051949954246	-2.1223872026
431-BG00003	0.0	49.0	BipolarI	57.901584527482825	-0.0326928704
431-BG00004	0.0	41.0	BipolarI	58.85398316038897	6.5803911103
431-BG00006	0.0	64.0	BipolarI	67.78206206165513	-0.7660003635

Stage 3 - Additional Analysis

Tasks

- [ ] Double check QC steps below and search for missing ~180 probes
  - [ ] Complete A cross-package Bioconductor workflow for analysing methylation array data vignette for cohort DNAm data

- [ ] compare predicted vs reported sex
- [ ] Perform other analyses on the dataset
  - [ ] DMR and standard analyses with this cohort to replicate prior work
  - [ ] See Methylcheck and Methylize
- [ ] Compare _REP vs non _REP sample pair methylation data and acquire missing information for these samples if it differs
- [ ] Split "Other" non-bipolar samples with higher granularity
  - [ ] Ensure age and sex matching between groups and covariate/controlling for other vars; see publications in Overview Presentation for qc guidance
- [ ] Compute biological age acceleration using other methylation clocks in pyaging: a Python-based compendium of GPU-optimized aging clocks and compare with grimage2
- [ ] Establish plasma protein estimate and other clock output's for outsized influence on ageaccelgrim2 and other measures of accelerated biological aging
  - [ ] Compare lithium effects on aging in bipolar; see Methylcheck

NAPLS Genomic Data Processing Pipeline (ENIGMA-DTI QC)

Overview

This document describes the pre-imputation Quality Control (QC) pipeline applied to the North American Prodrome Longitudinal Study (NAPLS) Phase 3 (NAPLS3) genomic data. The pipeline follows the ENIGMA-DTI Quality Control (QC) Protocol and is implemented via a series of shell scripts designed to run on the Hoffman2 cluster.

The primary goal is to prepare the raw NAPLS3 genotype data (Genome Build: hg19/GRCh37) for subsequent imputation by performing SNP renaming and rigorous QC prior to imputation.

The workflow consists of the following stages:

1. **(Optional Setup)** Creation of dbSNP binary files for efficient SNP mapping.
2. **SNP Renaming:** Standardizing variant identifiers to rsIDs or `chr:pos:ref:alt`.
3. **ENIGMA-DTI QC Part 1:** Initial filtering, sex/phenotype updates, and sex checks.

4. **ENIGMA-DTI QC Part 2:** Duplicate/relatedness checks, HapMap3 merging, and MDS analysis for ancestry outlier removal.
5. **ENIGMA-DTI QC Part 3:** PCA covariate generation, summary statistics calculation, and final results packaging.

Prerequisites

Software

- **PLINK v1.9:** (`/u/project/cbearden/hughesdy/software/plinkv1.9/plink`)
- **PLINK v2.0:** (`/u/project/cbearden/hughesdy/software/plink2`)
- **rsid_tools:** (`$HOME/apps/rsid_tools/bin/rsid_tools`) - Installation required, see rsid_tools GitHub.
- **R:** (v4.2.2+ recommended) with packages: `data.table` , `ggplot2` , `calibrate` , `rmarkdown` , `tinytex` , `knitr` , `xfun` . (Loaded via module `R/4.2.2-BIO` in scripts).
- **Hoffman2 Modules:** `parallel` , `bcftools` , `htslib` , `aria2` .

Input Data

- **Raw NAPLS3 Genotypes:** Located at `/u/project/cbearden/hughesdy/NAPLS/raw_genotype/NAPLS3/NAPLS3_n710.{bed,bim,fam}` . Genotyped on Illumina Infinium Global Screening Array-24 (`GSAMD-24v1-0_20011747_A1`).
- **Phenotype/Sample Information:** Located in `processed_genotype/enigma/DTIgenetics/info/` :
  - `NAPLS3_Terra_samplestab_phenofile.txt` : Contains subject IDs, sex, and case/control status.
  - `napls3_MS_diffusion.csv` : Contains list of subjects with DTI data.
- **dbSNP VCF (for Stage 0):** dbSNP build 156 for GRCh37 (`GCF_000001405.25.gz` and `.tbi`). Can be downloaded automatically or provided locally.

Environment

- Scripts are designed for the Hoffman2 cluster environment.
- Access to project directories (`/u/project/cbearden/` , `/u/home/c/cobeaman/`) and `$SCRATCH` space is required.

Workflow Steps

The pipeline can be executed using the master script `run_napls_qc.sh` or by running the individual scripts sequentially.

Detailed NAPLS3 Genomic Data Pre-Imputation QC Workflow (ENIGMA-DTI Protocol Implementation)

Stage 0: Create rsID Binaries (Optional - `processed_genotype/01_create_rsid_binaries.sh`)

- **Purpose:** Generates binary index files from a dbSNP VCF. These files allow `rsid_tools` (used in Stage 1) to quickly map variant coordinates to rsIDs.
- **Execution:** This is typically a **one-time setup**. The master script: `run_napls_qc.sh` checks for existing binaries in `$RS_BIN_DIR` (defined as `$HOME/scratch/GRCh37_dbSNP156_Binaries/Standard`) and skips this step if found.
- **Inputs:** dbSNP VCF file (e.g., `GCF_000001405.25.gz`) and its index (`.tbi`).
- **Outputs:** Binary `.bin` files (e.g., `GRCh37_1.hash2rsid.bin`, `GRCh37_1.rsid2pos.bin`, etc.) placed in `$OUTPUT_DIR` (defined as `$HOME/project-cbearden/napls/binaries` in the script, but the master script expects them in `$RS_BIN_DIR`).

Stage 1: SNP Renaming (`processed_genotype/01_rename_snps_direct.sh`)

- **Purpose:** Renames variant identifiers in the raw NAPLS3 `.bim` file. It attempts to find the corresponding rsID using the dbSNP binaries created in Stage 0. If an rsID is not found, it uses a composite ID format (`chr:pos:ref:alt`).
- **Inputs:**
  - Raw NAPLS3 PLINK files (`/u/project/cbearden/hughesdy/NAPLS/raw_genotype/NAPLS3/NAPLS3_n710.*`).
  - rsID binary files (from Stage 0, located via `$RS_BIN_DIR`).
- **Outputs:**
  - Renamed PLINK fileset: `processed_genotype/NAPLS3_n710_renamed*.{bed,bim,fam}`.
  - Renaming map file: `processed_genotype/final_snp_rename*.txt`.
  - Log files in `processed_genotype/logs/<jobid>_rename_snps_direct/`.

Stage 2: ENIGMA-DTI QC Part 1 (`processed_genotype/02_enigma_dti_qc_napls3_part1.sh`)

- **Purpose:** Implements ENIGMA-DTI QC Steps 1-3. Filters subjects, updates sex and phenotype information, performs initial SNP/sample QC, splits the X chromosome, and performs sex checks.
- **Inputs:**
  - Renamed PLINK files from Stage 1 (`processed_genotype/NAPLS3_n710_renamed*.{bed,bim,fam}`).

    - Phenotype file (`processed_genotype/enigma/DTIgenetics/info/NAPLS3_Terra_samplestab_phenofile.txt`).
    - DTI subject list (`processed_genotype/enigma/DTIgenetics/info/napls3_MS_diffusion.csv`).
- **Outputs (in `processed_genotype/enigma/DTIgenetics/<jobid>_enigma_dti_qc_napls3_part1/`):**
    - QC'd PLINK fileset: `*_QC1.{bed,bim,fam}`.
    - Sex mismatch list: `sex_mismatches.txt`.
    - Summary files and logs.

Stage 3: ENIGMA-DTI QC Part 2 (`processed_genotype/02_enigma_dti_qc_napls3_part2.sh`)

- **Purpose:** Implements ENIGMA-DTI QC Steps 4-6. Checks for duplicates and relatedness, merges data with HapMap3 reference, performs MDS analysis to identify and remove ancestry outliers (targeting European ancestry based on CEU/TSI cluster).
- **Inputs:** Output directory from Stage 2 (`processed_genotype/enigma/DTIgenetics/<jobid>_enigma_dti_qc_napls3_part1/`).
- **Outputs (in `processed_genotype/enigma/DTIgenetics/<jobid>_enigma_dti_qc_napls3_part2/`):**
    - QC'd PLINK fileset after outlier removal: `*_QC3.{bed,bim,fam}`.
    - MDS plots (before and after outlier removal): `mdsplot_*.pdf`.
    - Outlier lists: `*_pop_strat_mds.outlier.txt`, `*_pop_strat_mds.eur.txt`.
    - Duplicate/Relatedness counts.
    - Summary files and logs.

Stage 4: ENIGMA-DTI QC Part 3 (`processed_genotype/02_enigma_dti_qc_napls3_part3.sh`)

- **Purpose:** Implements ENIGMA-DTI QC Steps 8-9 and final packaging. Generates PCA covariates, calculates pre- and post-QC summary statistics, creates summary reports (text and PDF), and packages essential results into a zip archive for submission.
- **Inputs:** Output directories from Stage 2 and Stage 3.
- **Outputs (in `processed_genotype/enigma/DTIgenetics/<jobid>_enigma_dti_qc_napls3_part3/`):**
    - PCA results: `*_PCACovariates.{eigenval,eigenvec,log}`.
    - PCA scree plot: `screeplot_*.pdf`.

- Summary statistics files: `*_basic_stats_preQC.txt`, `*_basic_stats_postQC.txt`, `*_qc_summary.txt`.
- Summary reports: `*_QC3_summary.txt`, `summary_report.pdf`.
- Final submission archive: `*_ENIGMA-DTI_FilesToSend.zip` (contains logs, stats, plots).
- `output_all/` directory containing intermediate and final files.
- `output_final/` directory containing files included in the zip archive.

Running the Pipeline

Using the Master Script (Recommended)

The entire pipeline can be run using the master orchestration script `run_napls_qc.sh`.

1. **Review Configuration:** Check the environment variables defined within `run_napls_qc.sh` (e.g., `NAPLS3_DIR`, `WORK_DIR`, `SCRATCH_DIR`, tool paths) and adjust if necessary for your environment.
2. **Submit Job:** Submit the script to the Hoffman2 scheduler:

```
qsub run_napls_qc.sh
```

3. **Monitoring:**
   - The main pipeline log is written to `$LOG_DIR/napls3_qc_run.log` (where `$LOG_DIR` is defined in the script, e.g., `processed_genotype/logs/<jobid>_napls_qc_master`).
   - Individual script logs are stored within their respective output directories (e.g., `processed_genotype/enigma/DTIgenetics/<jobid>_partX/logs/`).
   - The pipeline uses a checkpoint file (`$LOG_DIR/napls3_qc_checkpoint.txt`) to track completed steps, allowing resumption if interrupted.

Running Individual Scripts

Alternatively, the scripts (`01_create_rsid_binaries.sh`, `01_rename_snps_direct.sh`, `02_enigma_dti_qc_napls3_part1.sh`, etc.) can be run sequentially via `qsub` or directly in an interactive session. Ensure the necessary inputs from the previous step are available and correctly located. The master script uses `cached_find` to locate outputs dynamically, which would need manual replication or hardcoding if running scripts individually.

Output Structure

- **SNP Renaming:** Renamed files (`NAPLS3_n710_renamed*`) are placed directly in `processed_genotype/` .
- **ENIGMA QC:** Each part of the ENIGMA QC creates a timestamped/job-ID-based directory within `processed_genotype/enigma/DTIgenetics/` .
  - `..._part1/` : Contains `*_QC1.*` files, logs, sex mismatch info.
  - `..._part2/` : Contains `*_QC3.*` files (final QC'd dataset), MDS plots, outlier lists, logs.
  - `..._part3/` : Contains PCA results, summary stats/reports, logs, and the final `*_ENIGMA-DTI_FilesToSend.zip` archive.
- **Logs:** Overall pipeline logs are in `processed_genotype/logs/<jobid>_napls_qc_master/` . Logs specific to each step are within the step's output directory.
- **Final Summary:** A comprehensive summary of the pipeline run is generated at `processed_genotype/napls3_qc_pipeline_summary.txt` .

Troubleshooting

- **Job Failures:** Check the `.log` file corresponding to the `qsub` job ID in the relevant log directory (master log or step-specific log).
- **Prerequisite Errors:** Ensure all required software is installed/loaded and input files exist and are accessible. The master script performs checks at the start.
- **File Not Found:** Verify that output files from previous steps were generated correctly and that paths used in subsequent scripts are accurate. The master script attempts to find these dynamically.
- **R Script Errors:** Check the R script output within the main log file (`*_run.log`) for specific error messages, often related to missing packages or data format issues.
- **PLINK Errors:** Consult the PLINK `.log` files generated within the step's output directory for detailed error messages.

References

ENIGMA Resources

- ENIGMA-DTI QC Protocol Summary (Aug 2024)
- ENIGMA-DTI Quality Control (QC) Protocol
- ENIGMA_DTI_GWAS GitHub Repository
- ENIGMA Genetics Protocols Overview
- ENIGMA Genetics GitHub Repository

Imputation Servers

1. Michigan Imputation Server 2
2. TOPMed Imputation Server
3. Sanger Imputation Service
4. Kiel EagleImp-web Imputation Server
    i. EagleImp: fast and accurate genome-wide phasing and imputation in a single tool
        a. "*For common variants investigated in typical genome-wide association studies, EagleImp provided same or higher imputation accuracy than the Sanger Imputation Service, Michigan Imputation Server and the newly developed TOPMed Imputation Server, despite larger (not publicly available) reference panels.*"
    ii. EagleImp Github
5. Helmholtz Munich Imputation Server (HMIS)
    i. Toward GDPR compliance with the Helmholtz Munich genotype imputation server

Tools & Formats

- PLINK 1.9 Documentation
- PLINK 2.0 Documentation
- rsid_tools GitHub

History

1. The ENIGMA group had wanted access to our genotyped data for NAPLS to perform a diffusion imaging GWAS.
2. We initially identified an older ENIGMA Genetics processing pipeline, which has since been updated to the current version specified below.
    i. **ENIGMA Genetics Protocols**
    ii. **ENIGMA Protocols for Imputation and Genetic Associations**

ENIGMA-DTI Quality Control (QC) Protocol - Pre Imputation Tasks/Info

1. The NAPLS3 data has been downloaded
    i. NAPLS2 data will be downloaded soon, and processed after a pipeline has been established and validated for NAPLS3
    ii. **Start with N3**
    iii. The data is already formatted in ENIGMA's required genome build: **hg19/grch37**
    iv. The data was genotyped using the **Illumina Infinium Global Screening Array-24** chip referred to as `GSAMD-24v1-0_20011747_A1` in the raw data

v. **bed**, **bim**, and **fam** files are located here `/u/project/cbearden/hughesdy/NAPLS/raw_genotype/NAPLS3/NAPLS3_n710*`

2. Before starting [ENIGMA-DTI Quality Control (QC) Protocol - Pre Imputation] SNP names must be changed:
   i. If you look in the .bim file, you'll see 6 columns: https://www.cog-genomics.org/plink/1.9/formats#bim
   ii. Convert to `rs` format
      a. ENIGMA may request `chr:bp` format [chrom # : base-pair location]
      b. `rs` is a good place to start and will make things cleaner
      c. Most of them are already in `rs` format already
         a. Some have `GSA-` prefix
   iii. Make a new text file with two columns
      a. old variant name [currently in the bim file]
      b. new variant name
   iv. Remove `GSA-` prefix from variant names and transfer the rs # to the new (second) column.
   v. There are a couple wonky ones with that are in `chr:bp` format or some other format.
      a. For these, you can honestly probably get away with keeping them like that
      b. Otherwise you can look here [list of `rs` ids linked to their `chr:bp` format for build `hg19`]: `/u/project/cbearden/hughesdy/NAPLS/rsDict/hg19/noDups/AllChr_Sorted_Tabdelim_nochr.txt`
3. Because the base-pair location is listed after the chromosome in the first column of this file, you can use that information to match it to the corresponding SNP in chr:bp format in the NAPLS data.
4. Then add the new name to the renaming file
   i. More information on renaming [--update-name documentation]: https://www.cog-genomics.org/plink/1.9/data#update_map
   ii. Path for plinkv1.9 `/u/project/cbearden/hughesdy/software/plinkv1.9/plink`
   iii. Path for plinkv2.0 `/u/project/cbearden/hughesdy/software/plink2`
   iv. They're pretty much the same, but plink2 can work with more efficient versions of the bed/bim/fam files.
   v. Should only need v1.9 though

NAPLS3 Genomic Data Pre-Imputation QC Workflow (ENIGMA-DTI Protocol Implementation)

1. Overview

This document provides a comprehensive, step-by-step explanation of the pre-imputation Quality Control (QC) workflow applied to the North American Prodrome Longitudinal Study Phase 3 (NAPLS3) genomic dataset. This implementation, executed via shell scripts on the Hoffman2 cluster, meticulously follows the **ENIGMA-DTI Quality Control (QC) Protocol (v1.1, July 2024)**.

Goal: To rigorously prepare the raw NAPLS3 genotype data (Genome Build: hg19/GRCh37) for subsequent imputation by standardizing variant identifiers (SNP renaming) and applying the specific QC filters mandated by the ENIGMA-DTI protocol.

Orchestration: The entire pipeline is managed by the master script `run_napls_qc.sh`. This script coordinates the execution of several modular scripts, each responsible for a specific stage of the workflow. It manages directories, handles job submission parameters for Hoffman2's SGE scheduler, verifies prerequisites, uses checkpointing (`naples3_qc_checkpoint.txt`) for resumability, and logs progress.

2. Workflow Stages

The pipeline is divided into distinct stages, each implemented by a dedicated script:

Stage 0: Create rsID Binaries (Optional Setup)

- **Script:** `01_create_rsid_binaries.sh`

- **Protocol Relevance:** This is a preparatory step, not explicitly part of the ENIGMA-DTI protocol document, but necessary for the chosen SNP renaming tool (`rsid_tools`).
- **Purpose:** To generate efficient binary index files from a comprehensive dbSNP VCF (Build 156 for GRCh37). These binaries allow the `rsid_tools annotate` command (used in Stage 1) to rapidly map variant coordinates (chromosome, position, alleles) to their corresponding reference SNP cluster IDs (rsIDs).
- **How it Works (Hoffman2 Implementation):**
  i. **Environment Setup:** Loads necessary Hoffman2 modules (`parallel`, `bcftools`, `htslib`). Defines directories, including `$SCRATCH` for intensive I/O and `$OUTPUT_DIR` for final binaries.
  ii. **dbSNP Acquisition (`get_dbsnp_files`):**
    - Checks `$SCRATCH` for existing dbSNP VCF (`GCF_000001405.25.gz`) and index (`.tbi`). If found, creates symbolic links.
    - Checks `EXISTING_VCF_DIR` (if specified) and copies files if found.
    - If not found locally, downloads the VCF and index from the NCBI FTP site using `curl`.
  iii. **VCF Verification (`verify_vcf`):** Uses `bcftools view -h` to quickly check if the downloaded/linked VCF header is readable, ensuring the file is not corrupted before processing.
  iv. **Parallel Chromosome Extraction:** Uses `parallel` and `bcftools view -r <region>` to extract data for each chromosome (1-22, X, Y, M) from the main dbSNP VCF into separate compressed VCF files (`chr{}.vcf.gz`) within `$TEMP_DIR`. This breaks down the large VCF for parallel processing. NCBI contig names (e.g., `NC_000001.10`) are mapped to simple chromosome numbers/letters.
  v. **Parallel Binary Creation:** Uses `parallel` again to process each chromosome's extracted VCF:
    - `bcftools query`: Extracts relevant fields (CHROM, ID, POS, REF, ALT).
    - `awk`: Replaces the NCBI chromosome name with the simple name (e.g., '1', 'X').
    - `sed 's/rs//g'`: Removes the 'rs' prefix from rsIDs, as expected by `rsid_tools make_bin`.
    - `sort`: Sorts the data numerically by position.
    - `bgzip`: Compresses the sorted TSV file.
    - `rsid_tools make_bin`: Creates the `.hash2rsid.bin` and `.rsid2pos.bin` files for the chromosome from the compressed TSV.
  vi. **Transfer & Cleanup:** Moves the generated `.bin` files from `$TEMP_DIR` to the final `$OUTPUT_DIR`. Optionally cleans up temporary files in `$SCRATCH`.
- **Why this Stage:** Pre-generating these binaries significantly speeds up the SNP renaming process in the next stage, which would otherwise involve much slower

lookups in the large text-based dbSNP VCF. Parallelization leverages Hoffman2's multi-core nodes.

Stage 1: SNP Renaming

- **Script:** `01_rename_snps_direct.sh`
- **Protocol Relevance:** Addresses the implicit requirement for standardized variant IDs before merging with reference panels (like HapMap3 in Stage 3). While the protocol doesn't mandate a specific tool, consistent naming (preferably rsIDs) is crucial.
- **Purpose:** To update the variant identifiers in the NAPLS3 `.bim` file. It prioritizes mapping variants to rsIDs using the dbSNP binaries created in Stage 0. If a variant cannot be mapped to an rsID, it assigns a composite key in the format `chr:pos:ref:alt`. This ensures every variant has a unique and informative identifier.
- **How it Works (Hoffman2 Implementation):**
  i. **Environment Setup:** Loads `parallel` module. Defines paths to tools (`plink2`, `rsid_tools`), input/output directories, and the location of the dbSNP binaries (`$RS_BIN_DIR`). Uses `$SCRATCH` for intermediate files.
  ii. **Input Copying:** Copies the raw NAPLS3 `.bed`, `.bim`, `.fam` files to a job-specific `$SCRATCH_DIR`.
  iii. **Binary Linking (`setup_links`):** Creates symbolic links in `$SCRATCH_DIR/bin_links` pointing to the actual binary files in `$RS_BIN_DIR`. This avoids potential issues with `rsid_tools` path length limits or special characters.
  iv. **BIM Preprocessing:** Uses `awk` to read the input `.bim` file. It filters for valid SNPs (numeric position, ACGT alleles), handles chromosome names (mapping PAR1/PAR2 to X), creates a composite key (`chr:pos:ref:alt` using REF:ALT alleles), and outputs a temporary map (`preprocessed_map.txt`) containing `OriginalID <tab> CompositeKey`. `!seen[$2]++` ensures only the first occurrence of a variant ID is kept.
  v. **Parallel Annotation (`annotate_chromosome` function called by `parallel`):**
    - For each chromosome (1-22, X, Y):
      - `awk` : Extracts the composite keys belonging to that chromosome from `preprocessed_map.txt` into `chr{}_ids.txt`.
      - `rsid_tools annotate` : Uses the dbSNP binaries (via links) to find rsIDs for the composite keys in `chr{}_ids.txt`. Outputs results to `chr{}/annotated/hash2rsid*.tsv`.
      - `awk` : Merges the `rsid_tools` output (CompositeKey, FoundID, rsID/.) with the `preprocessed_map.txt` to create a chromosome-specific map (`chr{}_map.txt`) containing `OriginalID <tab> FinalID` (where FinalID is the rsID if found, otherwise the OriginalID).

vi. **Map Combination:** Concatenates all `chr{}_map.txt` files. Uses `awk '!seen[$1]++'` to remove potential duplicate OriginalIDs introduced during parallel processing. Appends any OriginalIDs from `preprocessed_map.txt` that were *not* present in the concatenated map (these are variants that `rsid_tools` couldn't process or map), ensuring all original variants are accounted for, using their OriginalID as the FinalID. Saves this complete map as `final_snp_rename.txt`.

vii. **PLINK Renaming:** Uses `plink2 --update-name` with the `final_snp_rename.txt` file (specifying columns 1 and 2 for old and new IDs) to create the new, renamed PLINK fileset (`NAPLS3_n710_renamed*.{bed,bim,fam}`). `--merge-par` handles the PAR regions correctly. `--rm-dup force-first list` removes variants with duplicate positions, keeping the first one encountered and listing removed duplicates. `--not-chr MT` excludes the mitochondrial chromosome.

viii. **Output Comparison:** Uses `awk` to compare the original `.bim` and the newly created renamed `.bim`. It reconstructs the composite key from the original BIM and checks if it exists in the renamed BIM, listing any variants present in the original but missing in the renamed output (`missing_variants*.txt`).

ix. **Result Transfer:** Copies the final renamed PLINK fileset, the final map, the duplicate list, and the missing variants list from `$SCRATCH` back to the `$WORK_DIR`.

- **Why this Stage:** Standardizes variant IDs for compatibility with reference datasets (HapMap3) and downstream tools. Using rsIDs where possible is standard practice. Composite keys provide unique identifiers for unmapped variants. `rsid_tools` + `parallel` offers an efficient way to perform the mapping on Hoffman2. `plink2` is used for the actual file update.

Stage 2: ENIGMA-DTI QC Part 1 (Protocol Steps 1-3)

- **Script:** `02_enigma_dti_qc_napls3_part1.sh`
- **Protocol Relevance:** Directly implements the initial QC steps outlined in the ENIGMA-DTI protocol: filtering for DTI availability, ensuring correct sex/phenotype coding, splitting the X chromosome, applying basic SNP/sample filters, and performing a sex check.
- **Purpose:** To perform initial data cleaning and filtering specific to the ENIGMA-DTI project requirements, focusing on sample selection, data consistency, and basic quality thresholds before more intensive checks.
- **How it Works (Hoffman2 Implementation):**
  i. **Environment Setup:** Loads `parallel`. Defines paths, including input files (renamed PLINK set from Stage 1, phenotype/DTI info files) and output directories (`$TEMP_DIR` , `$FINAL_DIR`). Sets the output prefix (`ANC_DATA`). Copies input PLINK files to `$TEMP_DIR`.

  ii. **Phenotype/Sex Update:**

- Reads the main phenotype file (`NAPLS3_Terra_samplestab_phenofile.txt`) using `awk` to create a map (`sex_map.txt`) of internal ID to sex code (1=Male, 2=Female).
- Uses `awk` again to update the 5th column (sex) in the input `.fam` file (`input.fam`) based on the `sex_map.txt` , saving as `input_sex_updated.fam` .

iii. **DTI Subject Filtering:**

- Creates an ID map (`id_map.txt`) linking internal IDs to subject IDs (`awk` on `PHENO_FILE`).
- Extracts subject IDs with DTI data from `napls3_MS_diffusion.csv` (`awk` on `DTI_FILE` , saving as `dti_ids_raw.txt`).
- Uses `join` to find the intersection between the `id_map.txt` and `dti_ids_raw.txt` , outputting a list of internal IDs (FID and IID) for subjects with DTI data (`dti_fid_list.txt`).
- Uses `plink1.9 --keep` with `dti_fid_list.txt` on the sex-updated input data to create a dataset (`*_dti.*`) containing only individuals with DTI data. **(Protocol Step: "Very important Please remove individuals who do not have DTI data available...")**

iv. **Phenotype Recoding:**

- Creates a phenotype map (`pheno_map.txt`) from `PHENO_FILE` mapping internal ID to case/control status (1=Control, 2=Case) (`awk`).
- Uses `awk` to update the 6th column (phenotype) in the `*_dti.fam` file based on `pheno_map.txt` . Defaults to 1 (Control) if not found in the map. **(Protocol Step: "assign phenotype... coding controls... as 1 and cases as 2")**

v. **X Chromosome Splitting:**

- Uses `plink1.9 --split-x b37 no-fail` on the `*_dti` dataset to handle pseudo-autosomal regions (PARs) correctly, creating `*_splitx.*` . It attempts `hg19` if `b37` fails. **(Protocol Step: "Split-X to deal with pseudo-autosomal regions")**

vi. **Initial Filtering & Pruning:**

- Applies basic SNP/sample QC filters to the `*_splitx` dataset using `plink1.9` : `--mind 1` (no missing per-sample call rate filter applied here, differs slightly from protocol example's `--mind 1` in pre-sexcheck filtering), `--geno 0.01` (removes SNPs missing >1% calls), `--maf 0.05` (removes SNPs with MAF < 5%), `--hwe 1e-06` (removes SNPs failing HWE test at p < 1e-6, likely in controls only if cases exist). Creates `*_filtered.*` . **(Protocol Step: Implicit in filtering before sex check, though thresholds differ slightly from the protocol example's pre-sexcheck filter)**
- Performs LD pruning using `plink1.9 --indep-pairphase 20000 2000 0.5` (window 20kb, step 2000 SNPs, r2 > 0.5) in parallel across chromosomes

(`run_parallel_pruning` function) on the `*_filtered` dataset. Creates `*_pruned.prune.in`. **(Protocol Step: Uses `--indep-pairphase` as in protocol example)**
    - Extracts the pruned SNPs using `plink1.9 --extract` to create the `*_pruned.*` dataset.
vii. **Sex Check:**
    - Performs sex check on the `*_splitx` dataset using `plink1.9 --check-sex 0.2 0.8`. This compares reported sex (from `.fam`) with genetic sex inferred from X chromosome homozygosity (F-statistic). Thresholds 0.2/0.8 define boundaries for female/male calls. Creates `*_sexcheck.sexcheck`. **(Protocol Step: "plink --bfile ${datafile}_splitX --check-sex 0.2 0.8")**
    - Uses `grep PROBLEM` to extract individuals with conflicting sex information into `sex_mismatches.txt`.
viii. **Sex Mismatch Removal:**
    - If `sex_mismatches.txt` is not empty, uses `plink1.9 --remove` to exclude these individuals from the `*_splitx` dataset, creating the final `*_QC1.*` dataset for this stage. **(Protocol Step: "plink --bfile ${datafile} --remove sex.drop --make-bed --out ${datafile}_QC1")**
    - If no mismatches, `*_QC1.*` is simply a copy of `*_splitx.*`.
ix. **Reporting:** Calculates final counts (cases, controls, X SNPs) and generates summary files.

- **Why this Stage:** This stage enforces initial data quality and consistency according to ENIGMA's requirements. Filtering by DTI availability focuses the analysis. Correct sex/phenotype coding is essential for checks and association studies. Splitting X is crucial for accurate sex inference. Basic filtering removes unreliable data points. The sex check identifies and removes sample mix-ups or incorrect reporting.

Stage 3: ENIGMA-DTI QC Part 2 (Protocol Steps 4-7)

- **Script:** `02_enigma_dti_qc_napls3_part2.sh`
- **Protocol Relevance:** Implements ENIGMA-DTI steps for identifying and removing duplicate samples, assessing relatedness, merging with the HapMap3 reference panel, performing Multi-Dimensional Scaling (MDS) for ancestry visualization, and removing ancestry outliers.
- **Purpose:** To refine the dataset by removing technical duplicates, assessing cryptic relatedness, and ensuring the sample consists of individuals with the target ancestry (European, in this case) by comparing against a standard reference panel (HapMap3).
- **How it Works (Hoffman2 Implementation):**
    i. **Environment Setup:** Loads `aria2`, `parallel`, `R`. Defines paths, including the input directory (output of Part 1), `$TEMP_DIR`, `$FINAL_DIR`, HapMap3 URL/directory. Copies the `*_QC1.*` files from Part 1 input to `$TEMP_DIR`.

ii. **Duplicate/Relatedness Pruning:**
   - Applies basic filtering (`--mind 0.1` , `--geno 0.01` , `--maf 0.05`) to `*_QC1` creating `*_QC1tmp` . Note `--mind 0.1` is looser than later filters.
   - Performs LD pruning (`plink1.9 --indep-pairwise 100 5 0.2`) on `*_QC1tmp` creating `*_QC1pruned.*` . **(Protocol Step: Uses `--indep-pairwise` as in protocol)**

iii. **Duplicate Check & Removal:**
   - Calculates pairwise Identity-By-Descent (IBD) using `plink1.9 --genome --min 0.9` on the pruned data (`*_QC1pruned`), outputting pairs with PI_HAT > 0.9 to `pihat_duplicates.genome` . **(Protocol Step: "plink --bfile ${datafile}_QC1pruned --genome --min 0.9")**
   - Uses `awk` to extract one individual (FID, IID) from each duplicate pair found in `pihat_duplicates.genome` , *excluding* known monozygotic twin pairs specified in the script (`mz_twins` array). Saves this list to `pihat_duplicates.txt` .
   - Counts the number of individuals to be removed (`dup_count`) and saves it.
   - If `dup_count > 0` , uses `plink1.9 --remove` with `pihat_duplicates.txt` on the *unpruned* `*_QC1` dataset to create `*_QC2.*` . **(Protocol Step: "plink --bfile ${datafile}_QC1 --remove pihat_duplicates.txt --make-bed --out ${datafile}_QC2")**
   - If `dup_count == 0` , links `*_QC1.*` files to `*_QC2.*` .

iv. **Relatedness Check:**
   - Calculates pairwise IBD using `plink1.9 --genome --min 0.25 --max 0.9` on the pruned data (`*_QC1pruned`), outputting pairs with 0.25 < PI_HAT < 0.9 to `pihat_relatedness.genome` . **(Protocol Step: "plink --bfile ${datafile}_QC1pruned --genome --min 0.25 --max 0.9")**
   - Counts the number of related pairs (`rel_count`) and saves it. These individuals are *not* removed per the protocol.

v. **HapMap3 Preparation:**
   - Downloads HapMap3 reference data (`HM3_b37.{bed,bim,fam}.gz`) using `aria2c` if not already present in `$HAPMAP_DIR` . Uses `flock` for safe concurrent downloads if multiple jobs run. Decompresses using `pigz` . Creates `HM3_b37.snplist.txt` . **(Protocol Step: "Download the following 3 files...")**

vi. **MDS Filtering & Preparation:**
   - Applies stricter QC filters to `*_QC2` for MDS: `plink1.9 --mind 1` (no sample missingness filter), `--hwe 1e-6` , `--geno 0.05` , `--maf 0.01` . Creates `*_QC2_filtered.*` . **(Protocol Step: "plink --bfile ${datafile}_QC2 --mind 1 --hwe 1e-6 --geno 0.05 --maf 0.01")**
   - Extracts SNPs present in HapMap3 from `*_QC2_filtered` using `plink1.9 --extract HM3_b37.snplist.txt` , creating `*_QC2local.*` . **(Protocol Step:**

"plink --bfile ${datafile}_QC2_filtered --extract HM3_b37.snplist.txt")

- Uses `awk` to identify and exclude ambiguous SNPs (A/T, C/G) from `*_QC2_filtered.bim`, saving the list of unambiguous SNPs to `local.snplist.txt`. **(Protocol Step: "awk '{ if (($5=="T" && $6=="A")...")**
- Extracts these unambiguous SNPs from the HapMap3 data using `plink1.9 --extract local.snplist.txt`, creating `HM3_b37_external.*`. **(Protocol Step: "plink --bfile HM3_b37 --extract local.snplist.txt")**
- Identifies and excludes multi-allelic SNPs found within the local data (`*_QC2local.bim`) before merging.
- Uses `plink1.9 --flip-scan` to identify potential strand flips between local data and reference. Flips necessary SNPs using `plink1.9 --flip`.

vii. **Merging:**

- Attempts to merge the prepared local data (`*_QC2local_flipped` or `*_QC2local_no_multi`) with the prepared HapMap3 data (`HM3_b37_external_no_multi`) using `plink1.9 --bmerge`. **(Protocol Step: "plink --bfile ${datafile}_QC2local --bmerge HM3_b37_external...")**
- If merging fails due to mismatching SNPs (`-merge.missnp` file created), it excludes these problematic SNPs (`plink1.9 --exclude`) and retries the merge. **(Protocol Step: Handles merge errors similar to protocol alternatives)**

viii. **MDS Calculation:**

- Performs MDS on the successfully merged dataset (`*_QC2local_HM3b37merge`) using `plink1.9 --cluster --mind .05 --mds-plot 10 --extract local.snplist.txt`. Calculates 10 MDS components. **(Protocol Step: "plink --bfile ${datafile}_QC2local_HM3b37merge --cluster --mind .05 --mds-plot 10")**
- Formats the MDS output (`.mds`) into TSV and CSV formats for R.

ix. **Outlier Identification & Plotting (R Script):**

- Executes the R script `mds_plot.R`.
- Loads MDS data (`.csv`). Assigns population labels (NAPLS3 cohort vs. HapMap3 populations).
- Generates a PDF plot (`mdsplot_*_outliersincluded.pdf`) showing MDS components C1 vs C2, color-coded by population.
- Defines specific thresholds for C1 (`-0.06` to `-0.04`) and C2 (`0.055` to `0.07`) to isolate the CEU/TSI (European) cluster, as specified in the script comments reflecting ENIGMA guidance.
- Flags individuals from the NAPLS3 cohort falling *outside* these C1/C2 boundaries as outliers.
- Writes lists of outliers (`*_pop_strat_mds.outlier.txt`) and non-outliers/Europeans (`*_pop_strat_mds.eur.txt`).

- Generates a second PDF plot (`mdsplot_*_outliersexcluded.pdf`) showing only the HapMap3 reference and the non-outlier NAPLS3 individuals. **(Protocol Step: R code section for plotting and outlier identification)**

x. **Outlier Removal:**
- If outliers were identified, uses `plink1.9 --keep` with the `*_pop_strat_mds.eur.txt` list on the `*_QC2_filtered` dataset (the dataset *before* merging with HapMap3) to create the final `*_QC3.*` dataset for this stage. **(Protocol Step: "plink --bfile ${datafile}_QC2 --keep ${datafile}_pop_strat_mds.eur.txt --make-bed --out ${datafile}_QC3")**
- If no outliers were found, links `*_QC2_filtered.*` to `*_QC3.*` .

xi. **Summary Report:** Generates a text file summarizing removals during this stage.

- **Why this Stage:** Removes technical artifacts (duplicates). Assesses sample structure (relatedness, ancestry). Ensures the final dataset used for imputation and association testing primarily consists of the target ancestry (European), minimizing confounding due to population stratification, by comparing to HapMap3 and removing individuals distant from the CEU/TSI cluster in MDS space.

Stage 4: ENIGMA-DTI QC Part 3 (Protocol Steps 8-9 & Packaging)

- **Script:** `02_enigma_dti_qc_napls3_part3.sh`
- **Purpose:** Finalizes the QC process by generating PCA covariates for downstream association analyses, calculating comprehensive pre- and post-QC summary statistics, creating summary reports, and packaging the essential output files required by ENIGMA.
- **Protocol Alignment:** Directly implements ENIGMA-DTI Steps 8 ("Get genetic principal components") and 9 ("Cohort QC summary data"), plus the final data packaging instructions.
- **Execution Details:**

i. **Setup:** Creates necessary directories (`TEMP_DIR` , `ANC_DIR` , `FINAL_DIR` , `OUTPUT_ALL` , `OUTPUT_FINAL` , `SCRIPT_DIR` , `LOG_DIR`). Defines constants and paths, including locating the output directories from Part 1 and Part 2 using `ls -t` and `grep` . Creates R scripts (`pca_plot.R` , `summary_report.Rmd`) dynamically in `$SCRIPT_DIR` . Sets up a `trap cleanup EXIT INT TERM` to ensure results are saved even if the script is interrupted. Initializes log files.

ii. **Copy Inputs:** Uses `find` and `transfer_files` (an `rsync` wrapper) to copy required files from Part 1 (`*_QC1.fam` , `*_QC1.bim` , `sex_mismatches.txt` renamed to `sexcheck_PROBLEM.txt` , `*_QC_summary.txt` renamed to `snp_count_X.txt`) and Part 2 (`mdsplot*.pdf` , `*duplicates_count.txt` , `*relatedness_count.txt` , `*QC2_filtered.fam/log` , `*pop_strat_mds.outlier.txt` , `*QC3.bed/bim/fam` , `local.snplist.txt`) into the temporary `ANC_DIR` . This centralizes inputs for this stage.

iii. **Step 8: Generate PCA Covariates:**

- Runs `plink1.9 --pca` on the final QC'd dataset (`*_QC3`) using the common SNP list (`local.snplist.txt`) generated in Part 2. This calculates the top 20 principal components by default, outputting `.eigenval` and `.eigenvec` files to `ANC_DIR` .
- Executes the `pca_plot.R` script using `Rscript` . This script reads the `.eigenval` file, calculates the variance explained by each PC, and uses `ggplot2` to generate a scree plot (`screeplot_*.pdf`), saving it to `ANC_DIR` .

iv. **Step 9: Generate Summary Statistics:**

- Calls `generate_stats` function for pre-QC stats: Reads the `*_QC1.fam` file (copied from Part 1), uses `awk` to count cases/controls and males/females within each group, calculates proportions using `bc` , and writes the results to `*_basic_stats_preQC.txt` in `ANC_DIR` .
- Calls `generate_stats` function for post-QC stats: Reads the `*_QC3.fam` file (copied from Part 2), performs the same counts and calculations as above, and writes results to `*_basic_stats_postQC.txt` in `ANC_DIR` .
- Calls `generate_snp_summary` : Creates `*_qc_summary.txt` in `ANC_DIR` . It populates this file by:
  - Counting lines (`wc -l`) in `*_QC1.bim` and `*_QC1.fam` for pre-QC SNP/sample counts.
  - Grepping specific lines from the `*_QC2_filtered.log` (copied from Part 2) to extract counts of SNPs/samples removed due to missingness (`--geno` , `--mind`), MAF (`--maf`), and HWE (`--hwe`). Uses `awk` to get the numeric count. Handles cases where counts might be zero or missing (`0` is output).
  - Calculating the number of samples removed as MDS outliers by subtracting the line count of `*_QC3.fam` from `*_QC2_filtered.fam` .
  - Counting lines in `*_QC3.bim` and `*_QC3.fam` for post-QC SNP/sample counts.
- Calls `generate_summary_report_txt` : Creates `*_QC3_summary.txt` in `ANC_DIR` . This provides a human-readable summary including initial/final sample counts, counts of removed duplicates and outliers, final case/control numbers, final SNP count, and the specific MDS outlier thresholds used (hardcoded in the script based on Part 2 R script).

v. **Generate PDF Summary Report:**

- Calls `generate_summary_report_pdf` . This function first copies the text summary (`*_QC3_summary.txt`) into the `$SCRIPT_DIR` as `summary_report.txt` .
- It then executes an `Rscript` command that uses the `rmarkdown` package to render the `summary_report.Rmd` file (created during setup). The Rmd file simply includes the content of `summary_report.txt` .

        - The R script includes logic to install `tinytex` (a LaTeX distribution) if needed and handles potential rendering errors.
        - The resulting `summary_report.pdf` is saved in `$SCRIPT_DIR` and then copied to `$OUTPUT_ALL`.
    vi. **Packaging and Cleanup:**
        - The `cleanup` function (triggered by the `trap` at the end of the script or on interruption) performs the final packaging.
        - It copies all generated files from `ANC_DIR` and `SCRIPT_DIR` into `$OUTPUT_ALL`. It also copies logs from Part 1 and Part 2 directories into `$OUTPUT_ALL` for a complete archive.
        - It then identifies the specific files required for ENIGMA submission (based on the protocol's list: specific logs, stats files, MDS plots) by searching `ANC_DIR` and `OUTPUT_ALL`.
        - It copies these required files into `$OUTPUT_FINAL`, renaming the MDS plots to include the `$ANC_DATA` prefix for consistency.
        - It checks if the number of files in `$OUTPUT_FINAL` matches the expected count (27, or 26 if `*QC2.log` wasn't generated) and logs a warning if there's a mismatch.
        - It logs any missing required files to `missing_submission_files.txt`.
        - Finally, it creates the `*_ENIGMA-DTI_FilesToSend.zip` archive containing the contents of `$OUTPUT_FINAL` using `zip -r -j` (the `-j` flag junks the paths, putting all files in the root of the zip).
- **Key Tools:** `plink1.9`, `R` (`data.table`, `ggplot2`, `rmarkdown`, `tinytex`, `knitr`, `xfun`), `bc`, `awk`, `find`, `grep`, `wc`, `rsync`, `zip`.

5. Prerequisites

5.1 Software & Tools

- **PLINK v1.9:** `/u/project/cbearden/hughesdy/software/plinkv1.9/plink` (Used for most QC steps)
- **PLINK v2.0:** `/u/project/cbearden/hughesdy/software/plink2` (Used in Stage 1 for `--update-name` and `--rm-dup`)
- **rsid_tools:** `$HOME/apps/rsid_tools/bin/rsid_tools` (Used in Stage 1 for SNP mapping; requires separate installation)
- **R:** v4.2.2+ (Loaded via module `R/4.2.2-BIO`)
    - Required R Packages: `data.table`, `ggplot2`, `calibrate` (for MDS plot), `rmarkdown`, `tinytex`, `knitr`, `xfun` (for PDF report). Scripts attempt installation via `install.packages` if missing.
- **Hoffman2 Modules:** `parallel`, `bcftools`, `htslib` (for Stage 0), `aria2` (for HapMap download in Stage 3).

- **Standard Unix Utilities:** `bash`, `awk`, `grep`, `sort`, `join`, `curl`, `zip`, `rsync`, `timeout`, `bc`, `find`, `tee`, `cat`, `mv`, `cp`, `ln`, `mkdir`, `rm`, `stat`, `tr`, `wc`, `pigz` (or `gunzip`), `tail`, `head`.

5.2 Input Data

- **Raw NAPLS3 Genotypes:** `/u/project/cbearden/hughesdy/NAPLS/raw_genotype/NAPLS3/NAPLS3_n710.{bed,bim,fam}` (Build hg19/GRCh37).
- **Phenotype/Sample Information:** Located in `processed_genotype/enigma/DTIgenetics/info/`:
  - `NAPLS3_Terra_samplestab_phenofile.txt`: Subject IDs (column 3), sex (column 7), case/control status (column 8). Used in Part 1 for updating `.fam` file and ID mapping.
  - `napls3_MS_diffusion.csv`: List of subjects with DTI data (column 1, format `SITE-S####`). Used in Part 1 for filtering individuals (`--keep`).
- **dbSNP VCF (for Stage 0):** dbSNP build 156 for GRCh37 (`GCF_000001405.25.gz` and `.tbi`). Downloaded automatically by `01_create_rsid_binaries.sh` if not found locally or specified via `EXISTING_VCF_DIR`.
- **HapMap3 Reference Data (for Stage 3):** `HM3_b37.{bed,bim,fam}`. Downloaded automatically by `02_enigma_dti_qc_napls3_part2.sh` from ENIGMA website (`aria2c`) if not present in temp directory (`$HAPMAP_DIR`).

5.3 Environment

- **Hoffman2 Cluster:** Scripts rely on SGE job scheduler syntax (`#$`) and module system (`module load`).
- **Directory Access:** Read access to input data directories (`/u/project/cbearden/hughesdy/NAPLS/raw_genotype/NAPLS3/`) and write access to working directories (`/u/home/c/cobeaman/project-cbearden/napls/gprep/processed_genotype/`, `$SCRATCH`).
- **Environment Variables:** The master script `run_napls_qc.sh` defines key paths (e.g., `WORK_DIR`, `SCRATCH_DIR`, `LOG_DIR`, tool paths) which are exported and inherited by the subscripts. Subscripts also define their own specific paths relative to these.

6. Execution

The pipeline is executed by submitting the master script `run_napls_qc.sh` to the Hoffman2 scheduler:

```
qsub run_napls_qc.sh
```

- **Configuration:** Review and adjust environment variables within run_napls_qc.sh if necessary (e.g., paths to software, base directories).
- **Monitoring:**
  - Overall pipeline progress and logs: `${LOG_DIR}/napls3_qc_run.log` (where `$LOG_DIR` is defined in run_napls_qc.sh).
  - Individual script logs: Stored within subdirectories corresponding to each stage (e.g., `${FINAL_DIR}/logs/` for Part 3). Check both the main SGE log (`$JOB_ID_*.log`) and the script-specific run log (`*_run.log`) within these directories.
  - SGE job output: `$HOME/project-cbearden/napls/gprep/processed_genotype/logs/$JOB_ID_napls_qc_master.log`.
- **Resumption:** The pipeline uses a checkpoint file (`${LOG_DIR}/napls3_qc_checkpoint.txt`) to track completed stages. If the job is interrupted, resubmitting run_napls_qc.sh will detect completed steps via `step_completed` function and skip them, resuming from the first incomplete stage.

7. Output Structure

- **SNP Renaming (Stage 1):**
  - Renamed PLINK files: `processed_genotype/NAPLS3_n710_renamed*.{bed,bim,fam}` (Timestamped)
  - Renaming map: `processed_genotype/final_snp_rename*.txt` (Timestamped)
  - Missing variants list: `processed_genotype/missing_variants*.txt` (Timestamped)
  - Logs: `processed_genotype/logs/<jobid>_rename_snps_direct/`
- **ENIGMA QC (Stages 2-4):** Each part creates a job-ID-based directory within DTIgenetics.
  - **Part 1 (`..._part1/`):**
    - `*_QC1.{bed,bim,fam}`: Dataset after initial filtering (DTI subjects), sex/phenotype update, X-split, and sex check removal.
    - `sex_mismatches.txt`: List of individuals removed due to sex mismatch (FID, IID).
    - `*_QC_summary.txt`: Basic counts (Total N, Cases, Controls, X SNPs) for the QC1 dataset.
    - Logs: logs subdirectory (includes `run.log`, PLINK logs).
  - **Part 2 (`..._part2/`):**
    - `*_QC3.{bed,bim,fam}`: Final QC'd dataset after duplicate removal and MDS outlier removal. **This is the primary input for Part 3's PCA.**
    - `mdsplot_*.pdf`: MDS plots (before and after outlier removal).
    - `*_pop_strat_mds.outlier.txt`: List of removed ancestry outliers (FID, IID).

        - `*_pop_strat_mds.eur.txt`: List of individuals kept (European ancestry cluster) (FID, IID).
        - `*_QC1pruned_duplicates_count.txt`, `*_QC1pruned_relatedness_count.txt`: Counts from duplicate/relatedness checks.
        - `*_QC2_summary.txt`: Text summary of removals in Part 2.
        - `local.snplist.txt`: List of non-ambiguous SNPs common between dataset and HapMap3, used for MDS and PCA.
        - Logs: logs subdirectory (includes `run.log`, PLINK logs, R script output).
    - **Part 3 (`..._part3/`):**
        - `*_PCACovariates.{eigenval,eigenvec}`: PCA results (eigenvalues and eigenvectors).
        - `screeplot_*.pdf`: PCA scree plot.
        - `*_basic_stats_preQC.txt`, `*_basic_stats_postQC.txt`: Case/control/sex counts before/after QC.
        - `*_qc_summary.txt`: Detailed SNP/sample removal counts across steps (missingness, MAF, HWE, MDS).
        - `*_QC3_summary.txt`: Text summary report of final counts and thresholds.
        - `summary_report.pdf`: PDF version of the summary report.
        - `output_all/`: Archive of most intermediate and final files from all QC steps (useful for debugging).
        - `output_final/`: Curated set of files required for ENIGMA submission (specific logs, stats, plots).
        - `*_ENIGMA-DTI_FilesToSend.zip`: Final zip archive containing `output_final` contents.
        - `missing_submission_files.txt`: List of expected submission files that were not found (if any).
        - Logs: logs subdirectory (includes `run.log`, PLINK logs, R script output).
- **Master Script Logs:** `processed_genotype/logs/<jobid>_napls_qc_master/` (includes overall run log `napls3_qc_run.log` and checkpoint file `napls3_qc_checkpoint.txt`).
- **Overall Summary:** `processed_genotype/napls3_qc_pipeline_summary.txt` (Generated at the end of the master script, summarizing runtime, outputs, and completion status).

8. Troubleshooting

- **Job Failure:** Check the SGE output log (`$HOME/project-cbearden/napls/gprep/processed_genotype/logs/$JOB_ID_*.log`) and the pipeline run log (`${LOG_DIR}/napls3_qc_run.log`). Also check logs within the specific stage's output directory (e.g., `${FINAL_DIR}/logs/`). Look for `ERROR:` messages in the logs.

- **Prerequisite Errors:** Ensure all software (PLINK, R, rsid_tools, etc.) is correctly installed/loaded and paths in run_napls_qc.sh are accurate. Verify input files (`NAPLS3_n710.*`, phenotype files) exist and are accessible. The master script's `verify_prerequisites` function checks most common issues.
- **File Not Found:** Check if the previous step completed successfully and generated the expected output files. The `cached_find` function in the master script relies on specific naming patterns and timestamps; ensure outputs exist in the expected locations (`WORK_DIR`, `ENIGMA_DIR/<jobid>_partX/`). Errors in `transfer_files` (rsync) might also cause issues.
- **PLINK Errors:** Consult the PLINK `.log` files generated within the relevant stage's output directory (often in `output_all` or logs subdirectories). Common errors involve memory limits, file format issues, or conflicting parameters.
- **R Script Errors:** Look for errors within the main run log (`*_run.log`) or specific R output files/logs. Common issues include missing packages (though scripts attempt installation), incorrect input file formats/paths, or problems with plotting libraries. PDF generation errors might relate to LaTeX (`tinytex`) setup; check `tinytex` installation and logs.
- **`rsid_tools` Errors:** Ensure `rsid_tools` is correctly installed and the path is set. Verify the dbSNP binary files (Stage 0) were created successfully and are accessible in `$RS_BIN_DIR` (or linked correctly in Stage 1's scratch space).
- **Permissions:** Ensure write permissions in `$WORK_DIR`, `$SCRATCH_DIR`, and their subdirectories. Check read permissions for input data.
- **Timeout Errors:** If a step times out (reported by the master script), it may require more resources (time `h_rt`, memory `h_data`, or cores `pe shared`) requested in the SGE header (`#$`) of the failing script or the master script.

9. References

- **ENIGMA-DTI QC Protocol:** GitHub Link, Summary HTML
- **PLINK 1.9:** Documentation
- **PLINK 2.0:** Documentation
- **rsid_tools:** GitHub Repository
- **R Project:** Homepage
- **GNU Parallel:** Documentation
- **Hoffman2 Cluster:** User Guide

lowestprime feat: Improve NAPLS3 QC pipeline script documentation 94c2941 · 3 months ago

Code Blame Raw

```
#!/bin/bash
# ==============================================================================
# NAPLS3 Genomic Data QC Pipeline - Master Orchestration Script
# Individual scripts in /gprep/processed_genotype can also be run sequentially
# ==============================================================================
# Purpose: Coordinates the complete QC workflow for NAPLS3 genomic data through
#          the ENIGMA-DTI pre-imputation QC pipeline (with SNP renaming).
#
# Workflow stages:
# 1. Create rsid binaries - One-time setup of dbSNP156 binary files for variant mapping
# 2. Rename SNPs - Convert variants to standard rsID naming
# 3. ENIGMA-DTI QC - Three-part QC protocol for DTI genetic analysis:
#    - Part 1: Initial filtering, sex checks, phenotype coding
#    - Part 2: Relatedness analysis, HapMap merging, MDS analysis for ancestry
#    - Part 3: PCA covariate generation, statistics collection, final packaging
#
# Usage:
#   qsub run_napls_qc.sh
#
# Required inputs:
#   - NAPLS3 genotype data (.bed/.bim/.fam) in $NAPLS3_DIR
#   - Phenotype and DTI data in $INFO_DIR (see subscripts)
#
# Dependencies:
#   - PLINK 1.9, PLINK 2.0
#   - rsid_tools (https://github.com/HTGenomeAnalysisUnit/rsid_tools)
#   - R with required packages (see part3 script)
# ==============================================================================

# --- Job parameters [adjust as needed]---
#$ -cwd
#$ -l h_rt=3:00:00,h_data=2G
#$ -N NAPLS_QC_Pipeline
#$ -j y
#$ -o "$HOME/project-cbearden/napls/gprep/processed_genotype/logs/$JOB_ID_napls_qc_master.

# --- Set up environment ---
# Base project directories [adjust as needed]
```

```
export NAPLS3_DIR="/u/project/cbearden/hughesdy/NAPLS/raw_genotype/NAPLS3"
export PLINK2="/u/project/cbearden/hughesdy/software/plink2/plink2"
export PLINK19="/u/project/cbearden/hughesdy/software/plinkv1.9/plink"
export RSID_TOOLS="$HOME/apps/rsid_tools/bin/rsid_tools"

# Job project directories [adjust as needed]
export WORK_DIR="/u/home/c/cobeaman/project-cbearden/napls/gprep/processed_genotype"
export SCRATCH_DIR="/u/scratch/c/cobeaman/napls_qc_$JOB_ID"
export LOG_DIR="${WORK_DIR}/logs/${JOB_ID}_napls_qc_master"
export ENIGMA_DIR="${WORK_DIR}/enigma/DTIgenetics"
export INFO_DIR="${ENIGMA_DIR}/info"
export RS_BIN_DIR="${HOME}/scratch/GRCh37_dbSNP156_Binaries/Standard"
export STATE_FILE="${LOG_DIR}/pipeline_state.txt"
export CHECKPOINT_FILE="${LOG_DIR}/napls3_qc_checkpoint.txt"
export SUMMARY_FILE="${WORK_DIR}/napls3_qc_pipeline_summary.txt"

# --- Functions ---
log() { echo "[$(date '+%Y-%m-%d %H:%M:%S')] - $1" | tee -a "${LOG_DIR}/napls3_qc_run.log"
err() { log "ERROR: $1"; return 1; }
warn() { log "WARNING: $1"; }
success() { log "SUCCESS: $1"; }
confirm_file() { [[ -s "$1" ]] || err "Required file not found or empty: $1"; }
set_state() { echo "$1" > "$STATE_FILE"; }
get_state() { [[ -f "$STATE_FILE" ]] && cat "$STATE_FILE" || echo "init"; }
step_completed() { grep -q "^COMPLETED: ${1}$" "${CHECKPOINT_FILE}" 2>/dev/null; }
mark_completed() { echo "COMPLETED: ${1}" >> "${CHECKPOINT_FILE}"; log "Checkpoint saved:

# Find function to cache results and avoid repetitive filesystem operations
cached_find() {
    local dir="$1" pattern="$2" type="$3" sort_opt="$4" count="$5"
    local cache_key="${dir//\//_}_${pattern//\//_}_${type}_${sort_opt}_${count}"
    local cache_file="${SCRATCH_DIR}/cache_${cache_key}"

    if [[ -f "$cache_file" ]]; then
        cat "$cache_file"
    else
        mkdir -p "$(dirname "$cache_file")"
        if [[ "$sort_opt" == "time" ]]; then
            find "$dir" -maxdepth 1 -name "$pattern" -type "$type" -printf '%T@ %p\n' 2>/d
        else
            find "$dir" -maxdepth 1 -name "$pattern" -type "$type" 2>/dev/null | head -"${
        fi
    fi
}

run_step() {
    local script="$1" description="$2" timeout="${3:-7200}" state_name="$4"
    local current_state=$(get_state)

    # Check if this step should be skipped
    if step_completed "$state_name"; then
        log "SKIPPING: $description (already completed)"
```

```
91              return 0
92          fi
93
94          # Mark step as in progress
95          set_state "${state_name}_in_progress"
96
97          # Run the step with timeout protection
98          log "STARTING: $description"
99          if timeout "$timeout" bash "$script" 2>&1 | tee -a "${LOG_DIR}/napls3_qc_run.log"; the
100             if [[ ${PIPESTATUS[0]} -eq 0 ]]; then
101                 log "COMPLETED: $description"
102                 set_state "${state_name}_completed"
103                 mark_completed "$state_name"
104                 return 0
105             else
106                 err "$description failed with exit code ${PIPESTATUS[0]}. See log for details.
107                 return 1
108             fi
109         else
110             local exit_code=$?
111             if [[ $exit_code -eq 124 ]]; then
112                 err "$description timed out after $timeout seconds"
113             else
114                 err "$description failed with exit code $exit_code"
115             fi
116             return 1
117         fi
118     }
119
120     verify_prerequisites() {
121         log "Verifying prerequisites..."
122         local missing=0
123
124         # Check required commands with specific version requirements where applicable
125         local cmds=("$PLINK19" "$PLINK2" "$RSID_TOOLS" "timeout" "bc")
126         for cmd in "${cmds[@]}"; do
127             command -v "$cmd" >/dev/null 2>&1 || { err "Command not found: $cmd"; missing=1; }
128         done
129
130         # Check input files (all 3 PLINK files must exist)
131         for ext in bed bim fam; do
132             confirm_file "${NAPLS3_DIR}/NAPLS3_n710.${ext}" || { missing=1; }
133         done
134
135         # Essential data files for ENIGMA QC
136         mkdir -p "$INFO_DIR"
137         for req_file in "${INFO_DIR}/NAPLS3_Terra_samplestab_phenofile.txt" "${INFO_DIR}/napls
138             if [[ ! -f "$req_file" ]]; then
139                 warn "Required file for ENIGMA QC not found: $req_file"
140                 warn "Please ensure this file exists before running the ENIGMA QC steps."
141             fi
142         done
```

```
143
144         return $missing
145     }
146
147     # Function to handle directory validation
148     verify_directory() {
149         local dir_var="$1" dir_name="$2" required="$3"
150         local dir_path="${!dir_var}"
151
152         if [[ ! -d "$dir_path" ]]; then
153             if [[ "$required" == "required" ]]; then
154                 err "$dir_name directory not found at: $dir_path"
155                 return 1
156             else
157                 warn "$dir_name directory not found at: $dir_path"
158                 if [[ "$required" == "create" ]]; then
159                     log "Creating $dir_name directory: $dir_path"
160                     mkdir -p "$dir_path" || { err "Failed to create $dir_name directory"; retu
161                     success "Created $dir_name directory: $dir_path"
162                 fi
163             fi
164         fi
165         return 0
166     }
167
168     # Create essential directories with error handling
169     setup_directories() {
170         log "Setting up directory structure..."
171         local dirs=(
172             "WORK_DIR:work:create"
173             "SCRATCH_DIR:scratch:create"
174             "LOG_DIR:log:create"
175             "ENIGMA_DIR:ENIGMA:create"
176             "INFO_DIR:phenotype info:create"
177         )
178
179         for dir_info in "${dirs[@]}"; do
180             IFS=':' read -r dir_var dir_name required <<< "$dir_info"
181             verify_directory "$dir_var" "$dir_name" "$required" || return 1
182         done
183
184         # Create checkpoint file
185         touch "$CHECKPOINT_FILE" || { err "Failed to create checkpoint file"; return 1; }
186         return 0
187     }
188
189     # Graceful handling of unexpected termination
190     cleanup() {
191         log "Pipeline interrupted or terminated. Saving state for resume capability."
192         # Don't delete anything - allow for resumption
193         exit 1
194     }
```

```
195
196     # --- Main workflow ---
197     main() {
198         # Set up traps for signal handling
199         trap cleanup SIGHUP SIGINT SIGTERM
200
201         log "Starting NAPLS3 Genomic Data QC Pipeline"
202
203         # Create directory structure
204         setup_directories || { err "Failed to setup directories"; exit 1; }
205
206         # Verify prerequisites
207         verify_prerequisites || {
208             err "Prerequisite check failed. Fix errors before proceeding."
209             log "TIP: Ensure all required software and input files are available and accessible
210             exit 1
211         }
212
213         # --- STAGE 1: Binary creation (one-time setup) ---
214         if ! step_completed "rsid_binaries"; then
215             log "Step 1 of 5: Creating RSID binaries (one-time setup)"
216             if [[ -d "$RS_BIN_DIR" && -f "${RS_BIN_DIR}/GRCh37_1.hash2rsid.bin" ]]; then
217                 log "RSID binaries already exist at ${RS_BIN_DIR} (skipping creation)"
218                 mark_completed "rsid_binaries"
219             else
220                 run_step "${WORK_DIR}/01_create_rsid_binaries.sh" "Creation of RSID binary file
221                     err "Failed to create RSID binaries. Please check logs at ${LOG_DIR}"
222                     exit 1
223                 }
224             fi
225         else
226             log "Step 1 of 5: RSID binaries creation already completed (skipping)"
227         fi
228
229         # --- STAGE 2: SNP Renaming ---
230         if ! step_completed "rename_snps"; then
231             log "Step 2 of 5: Renaming SNPs to standard rsIDs"
232             run_step "${WORK_DIR}/01_rename_snps_direct.sh" "SNP renaming process" 7200 "renam
233                 err "SNP renaming failed. Please check logs at ${LOG_DIR}"
234                 exit 1
235             }
236         else
237             log "Step 2 of 5: SNP renaming already completed (skipping)"
238         fi
239
240         # Find the most recent renamed genotype files more efficiently
241         RENAMED_PREFIX=$(cached_find "${WORK_DIR}" "NAPLS3_n710_renamed_*[0-9]*.bed" "f" "time
242         RENAMED_PREFIX="${RENAMED_PREFIX%.bed}"
243
244         if [[ -z "$RENAMED_PREFIX" ]]; then
245             err "No renamed genotype files found after SNP renaming step. Pipeline cannot cont
246             log "TIP: Check if the SNP renaming step completed successfully and produced outpu
```

```
247             exit 1
248         fi
249         log "Using renamed genotype files: ${RENAMED_PREFIX}"
250 
251         # --- STAGE 3: ENIGMA-DTI QC Part 1 ---
252         if ! step_completed "enigma_qc_part1"; then
253             log "Step 3 of 5: ENIGMA-DTI QC Part 1 (Initial filtering, sex checks, phenotype c
254             run_step "${WORK_DIR}/02_enigma_dti_qc_napls3_part1.sh" "ENIGMA-DTI QC Part 1" 360
255                 err "ENIGMA-DTI QC Part 1 failed. Please check logs and fix issues before cont
256                 exit 1
257             }
258         else
259             log "Step 3 of 5: ENIGMA-DTI QC Part 1 already completed (skipping)"
260         fi
261 
262         # Find Part 1 output directory with optimized search
263         PART1_DIR=$(cached_find "${ENIGMA_DIR}" "*_enigma_dti_qc_napls3_part1" "d" "time" 1)
264         if [[ -z "$PART1_DIR" ]]; then
265             err "Part 1 output directory not found. Cannot proceed to next step."
266             log "TIP: Check if Part 1 completed successfully and created its output directory.
267             exit 1
268         fi
269         log "Using Part 1 results from: $PART1_DIR"
270 
271         # Verify Part 1 outputs with a more efficient check
272         PART1_QC1_FILE=$(cached_find "${PART1_DIR}" "*_QC1.bed" "f" "" 1)
273         if [[ -z "$PART1_QC1_FILE" ]]; then
274             err "Critical Part 1 output files (*_QC1.bed) not found in ${PART1_DIR}"
275             log "TIP: Check Part 1 logs for errors that may have prevented output generation."
276             exit 1
277         fi
278         log "Found QC1 dataset: ${PART1_QC1_FILE%.bed}.[bed,bim,fam]"
279 
280         # --- STAGE 4: ENIGMA-DTI QC Part 2 ---
281         if ! step_completed "enigma_qc_part2"; then
282             log "Step 4 of 5: ENIGMA-DTI QC Part 2 (Relatedness checks, HapMap merging, MDS ana
283             run_step "${WORK_DIR}/02_enigma_dti_qc_napls3_part2.sh" "ENIGMA-DTI QC Part 2" 360
284                 err "ENIGMA-DTI QC Part 2 failed. Please check logs and fix issues before cont
285                 exit 1
286             }
287         else
288             log "Step 4 of 5: ENIGMA-DTI QC Part 2 already completed (skipping)"
289         fi
290 
291         # Find Part 2 output directory
292         PART2_DIR=$(cached_find "${ENIGMA_DIR}" "*_enigma_dti_qc_napls3_part2" "d" "time" 1)
293         if [[ -z "$PART2_DIR" ]]; then
294             err "Part 2 output directory not found. Cannot proceed to next step."
295             log "TIP: Check if Part 2 completed successfully and created its output directory.
296             exit 1
297         fi
298         log "Using Part 2 results from: $PART2_DIR"
```

```
299
300         # Verify Part 2 outputs
301         PART2_QC3_FILE=$(cached_find "${PART2_DIR}" "*_QC3.bed" "f" "" 1)
302         if [[ -z "$PART2_QC3_FILE" ]]; then
303             err "Critical Part 2 output files (*_QC3.bed) not found in ${PART2_DIR}"
304             log "TIP: Check Part 2 logs for errors that may have prevented output generation."
305             exit 1
306         fi
307         log "Found QC3 dataset: ${PART2_QC3_FILE%.bed}.[bed,bim,fam]"
308
309         # --- STAGE 5: ENIGMA-DTI QC Part 3 ---
310         if ! step_completed "enigma_qc_part3"; then
311             log "Step 5 of 5: ENIGMA-DTI QC Part 3 (PCA covariates, summary statistics, packag
312             run_step "${WORK_DIR}/02_enigma_dti_qc_napls3_part3.sh" "ENIGMA-DTI QC Part 3" 360
313                 err "ENIGMA-DTI QC Part 3 failed. Please check logs for details."
314                 log "TIP: Check Part 3 logs for specific error messages."
315                 exit 1
316             }
317         else
318             log "Step 5 of 5: ENIGMA-DTI QC Part 3 already completed (skipping)"
319         fi
320
321         # Find Part 3 output directory
322         PART3_DIR=$(cached_find "${ENIGMA_DIR}" "*_enigma_dti_qc_napls3_part3" "d" "time" 1)
323         if [[ -z "$PART3_DIR" ]]; then
324             err "Part 3 output directory not found. Final results may be missing."
325             log "TIP: Check if Part 3 completed successfully and created its output directory.
326             exit 1
327         fi
328         log "Using Part 3 results from: $PART3_DIR"
329
330         # --- Generate comprehensive pipeline summary ---
331         OUTPUT_ZIP=$(cached_find "${PART3_DIR}" "*_ENIGMA-DTI_FilesToSend.zip" "f" "" 1)
332         QC3_FILES=$(cached_find "${PART3_DIR}" "*_QC3.bed" "f" "" 1)
333
334         {
335             echo "================================================================="
336             echo "NAPLS3 QC PIPELINE SUMMARY ($(date))"
337             echo "================================================================="
338
339             # Calculate runtime more efficiently
340             START_TIME=$(stat -c %Y "${LOG_DIR}/napls3_qc_run.log" 2>/dev/null || echo $(date
341             END_TIME=$(date +%s)
342             TOTAL_MINS=$(( (END_TIME - START_TIME) / 60 ))
343             HOURS=$(( TOTAL_MINS / 60 ))
344             MINS=$(( TOTAL_MINS % 60 ))
345
346             echo "Total runtime: ${HOURS}h ${MINS}m (${TOTAL_MINS} minutes)"
347             echo ""
348
349             # Document pipeline versions and parameters
350             echo "Pipeline Configuration:"
```

```
            echo "- Build: GRCh37"
            echo "- dbSNP version: 156"
            echo "- Ancestry filtering: European (EUR)"
            echo "- Input subjects: $(wc -l < "${NAPLS3_DIR}/NAPLS3_n710.fam") individuals"

            # Get final subject count more robustly
            STATS_FILE=$(find "${PART3_DIR}/output_all/" -name "*_basic_stats_postQC.txt" -typ
            if [[ -f "$STATS_FILE" ]]; then
                FINAL_COUNT=$(tail -1 "$STATS_FILE" | awk '{print $2+$3}')
                echo "- Final subjects: $FINAL_COUNT individuals"
            else
                echo "- Final subjects: Unknown (stats file not found)"
            fi
            echo ""

            echo "Output Locations:"
            echo "- SNP Renamed Files: ${RENAMED_PREFIX}.[bed,bim,fam]"
            echo "- QC Part 1 Results: ${PART1_DIR}"
            echo "- QC Part 2 Results: ${PART2_DIR}"
            echo "- QC Part 3 Results: ${PART3_DIR}"
            [[ -n "$OUTPUT_ZIP" ]] && echo "- Final ZIP Package: $OUTPUT_ZIP"
            [[ -n "$QC3_FILES" ]] && echo "- Final QC3 Files: $(dirname "$QC3_FILES")/$(basena
            echo ""

            echo "Final QC Summary:"
            QC3_SUMMARY=$(find "${PART3_DIR}/output_all/" -name "*_QC3_summary.txt" -type f 2>
            if [[ -f "$QC3_SUMMARY" ]]; then
                cat "$QC3_SUMMARY"
            else
                echo "QC3 summary file not found."
            fi
            echo ""

            echo "Pipeline Completion Status:"
            for step in "rsid_binaries" "rename_snps" "enigma_qc_part1" "enigma_qc_part2" "eni
                if step_completed "$step"; then
                    echo "- ${step}: COMPLETED"
                else
                    echo "- ${step}: NOT COMPLETED"
                fi
            done
            echo "================================================================="
        } | tee "${SUMMARY_FILE}" | tee -a "${LOG_DIR}/napls3_qc_run.log"

        # --- Clean up scratch directory if requested ---
        if [[ -d "$SCRATCH_DIR" && "${AUTO_CLEANUP:-no}" == "yes" ]]; then
            log "Cleaning up scratch directory: $SCRATCH_DIR"
            rm -rf "$SCRATCH_DIR" && success "Scratch directory removed"
        else
            log "Scratch directory preserved at: $SCRATCH_DIR"
            log "To clean up manually, run: rm -rf $SCRATCH_DIR"
        fi
```

```
403
404         success "NAPLS3 Genomic Data QC Pipeline Completed Successfully"
405         return 0
406     }
407
408     # Execute main workflow
409     main "$@"
410     exit $?
```

lowestprime feat: Add ENIGMA-DTI QC protocol and fix log filename typo

05aa395 · 3 months ago

Code Blame Raw

```
#!/bin/bash
# ==============================================================================
# Script: 01_create_rsid_binaries.sh
# Description: Acquires latest dbSNP VCF and Index (GCF_000001405.25.gz and .tbi),
#              generates rsid_tools binary files (parallelized by chromosome),
#              and transfers completed binaries to OUTPUT_DIR (I/O performed in $SCRATCH).
# ==============================================================================
set -euo pipefail

# ----------------------------
# Job Parameters
# ----------------------------
#$ -cwd
#$ -l h_rt=2:00:00,h_data=4G,highp
#$ -pe shared 32
#$ -N create_rsid_binaries
#$ -j y
#$ -o "$HOME/project-cbearden/napls/gprep/processed_genotype/logs/$JOB_ID_create_binaries/(

# ----------------------------
# Modules
# ----------------------------
. /u/local/Modules/default/init/modules.sh
for mod in parallel bcftools htslib; do
    module load $mod || exit 1
done

# ----------------------------
# Constants
# ----------------------------
readonly BUILD="GRCh37"
readonly DBSNP_VERSION="156"
readonly DBSNP_VCF_FILE="GCF_000001405.25.gz"
readonly DBSNP_TBI_FILE="${DBSNP_VCF_FILE}.tbi"
readonly DBSNP_FTP_BASE="https://ftp.ncbi.nih.gov/snp/latest_release/VCF"
# Optional Parameters
readonly EXISTING_VCF_DIR=""  # Specify directory path to copy pre-existing dbNSP files
```

```
readonly CLEANUP_TEMP="no"    # Set "yes" to cleanup temp files

# ----------------------------
# Directories
# ----------------------------
SCRATCH_DIR="$SCRATCH/napls_qc_${JOB_ID}"
TEMP_DIR="${SCRATCH_DIR}/temp_chr_files_createbin"
LOG_DIR="$HOME/project-cbearden/napls/gprep/processed_genotype/logs/${JOB_ID}_create_binar
OUTPUT_DIR="$HOME/project-cbearden/napls/binaries"
RSID_TOOLS="$HOME/apps/rsid_tools/bin/rsid_tools"
DBSNP_VCF="${SCRATCH_DIR}/${DBSNP_VCF_FILE}"
DBSNP_TBI="${SCRATCH_DIR}/${DBSNP_TBI_FILE}"

mkdir -p "$LOG_DIR" "$SCRATCH_DIR" "$OUTPUT_DIR" "$TEMP_DIR"

# ----------------------------
# Functions
# ----------------------------
# Function to verify VCF before processing
verify_vcf() {
    echo "$(date) - Verifying VCF file..."
    if ! bcftools view -h "$DBSNP_VCF" &>/dev/null; then
        echo "$(date) - ERROR: Invalid or corrupted VCF file" >&2
        return 1
    fi
    # Skip index check since we have valid contig definitions
    return 0
}

# Function to acquire dbSNP files
get_dbsnp_files() {
    local vcf_found
    if vcf_found=$(find "$SCRATCH" -maxdepth 2 -name "$DBSNP_VCF_FILE" -type f -print -qui
       [[ -f "$vcf_found" ]] && [[ -f "${vcf_found}.tbi" ]]; then
        ln -sf "$vcf_found" "$DBSNP_VCF"
        ln -sf "${vcf_found}.tbi" "$DBSNP_TBI"
        return 0
    fi

    if [[ -n "$EXISTING_VCF_DIR" ]] && [[ -f "$EXISTING_VCF_DIR/$DBSNP_VCF_FILE" ]]; then
        cp -f "$EXISTING_VCF_DIR/$DBSNP_VCF_FILE" "$DBSNP_VCF"
        cp -f "$EXISTING_VCF_DIR/$DBSNP_TBI_FILE" "$DBSNP_TBI"
        return 0
    fi

    curl -sL --compressed "${DBSNP_FTP_BASE}/${DBSNP_VCF_FILE}" > "$DBSNP_VCF" &&
    curl -sL --compressed "${DBSNP_FTP_BASE}/${DBSNP_TBI_FILE}" > "$DBSNP_TBI" &&
    [[ -s "$DBSNP_VCF" && -s "$DBSNP_TBI" ]]
}

# ----------------------------
# dbSNP VCF and Index File Aquisition
```

```
    # ----------------------------
    echo "$(date) - Acquiring dbSNP files..."
    get_dbsnp_files || { echo "$(date) - ERROR: Failed to acquire dbSNP files" >&2; exit 1; }
    verify_vcf || exit 1
    echo "$(date) - dbSNP VCF and index ready."

    # ----------------------------
    # Create Binary Files (Parallelized by chromosome)
    # ----------------------------
    # Step 1: Pre-extract chromosome data
    echo "$(date) - Pre-extracting chromosome data..."
    printf "%s\n" {1..22} X Y M | \
    parallel --will-cite --jobs 32 \
        --joblog "${LOG_DIR}/parallel_extract.log" \
        --halt now,fail=1 \
        "ncbi_chr=\$(case {} in
            1) echo NC_000001.10;; 2) echo NC_000002.11;; 3) echo NC_000003.11;;
            4) echo NC_000004.11;; 5) echo NC_000005.9;;  6) echo NC_000006.11;;
            7) echo NC_000007.13;; 8) echo NC_000008.10;; 9) echo NC_000009.11;;
            10) echo NC_000010.10;; 11) echo NC_000011.9;; 12) echo NC_000012.11;;
            13) echo NC_000013.10;; 14) echo NC_000014.8;; 15) echo NC_000015.9;;
            16) echo NC_000016.9;; 17) echo NC_000017.10;; 18) echo NC_000018.9;;
            19) echo NC_000019.9;; 20) echo NC_000020.10;; 21) echo NC_000021.8;;
            22) echo NC_000022.10;; X) echo NC_000023.10;; Y) echo NC_000024.9;;
            M) echo NC_012920.1;; *) echo {};;
        esac) && \
        echo Pre-extracting chromosome {} && \
        bcftools view -r \$ncbi_chr '$DBSNP_VCF' -o '$TEMP_DIR/vcf_per_chr/chr{}.vcf.gz' -Oz"

    # Step 2: Create binary files in parallel
    echo "$(date) - Creating binary files..."
    printf "%s\n" {1..22} X Y M | \
    parallel --will-cite --jobs 32 \
        --joblog "${LOG_DIR}/parallel.log" \
        --halt now,fail=1 \
        --line-buffer \
        "simple_chr={} && \
        echo Processing chromosome {} && \
        bcftools query -f '%CHROM\t%ID\t%POS\t%REF\t%ALT\n' '$TEMP_DIR/vcf_per_chr/chr{}.vcf.g
        awk -v chr=\"\$simple_chr\" 'BEGIN{OFS=\"\\t\"} {\$1=chr; print}' | \
        sed 's/rs//g' | sort -S 4G --parallel=2 -T '$TEMP_DIR' -k1,1V -k2,2n | \
        bgzip -@ 2 > '$TEMP_DIR/${BUILD}_dbSNP${DBSNP_VERSION}.chr{}.tsv.gz' && \
        '$RSID_TOOLS' make_bin -b '$BUILD' -v '$DBSNP_VERSION' -o '$TEMP_DIR' \
        '$TEMP_DIR/${BUILD}_dbSNP${DBSNP_VERSION}.chr{}.tsv.gz'" || exit 1

    # ----------------------------
    # Binary File Transfer and Optional Cleanup
    # ----------------------------
    echo "$(date) - Moving binary files..."
    find "$TEMP_DIR" -name "*.bin" -type f -exec mv -t "$OUTPUT_DIR" {} +

    if [[ "$CLEANUP_TEMP" == "yes" ]]; then
```

```
142         echo "$(date) - Cleaning up..."
143         rm -rf "$TEMP_DIR" "$DBSNP_VCF" "$DBSNP_TBI"
144     fi
145 
146     echo "$(date) - Binary file creation complete!"
147     exit 0
```

lowestprime Optimize genomic QC pipeline performance and robustness 5cab931 · 3 months ago

Code Blame Raw

```
#!/bin/bash
# ==============================================================================
# Script: 01_rename_snps_direct.sh
# Description: Efficiently renames SNPs to rsIDs or CHR:POS:REF:ALT composite keys.
# ==============================================================================
set -euo pipefail

# Job Parameters
#$ -cwd
#$ -l h_rt=2:00:00,h_data=4G,highp
#$ -pe shared 32
#$ -N rename_snps_direct
#$ -j y
#$ -o "$HOME/project-cbearden/napls/gprep/processed_genotype/logs/$JOB_ID_rename_snps_dire

# Load Modules
. /u/local/Modules/default/init/modules.sh
module load parallel || { echo "$(date) - Error: Failed to load parallel module" >&2; exit

# Constants
readonly BUILD="GRCh37"
readonly PLINK2="/u/project/cbearden/hughesdy/software/plink2"
readonly RSID_TOOLS="$HOME/apps/rsid_tools/bin/rsid_tools"
readonly RS_BIN_DIR="$SCRATCH/GRCh37_dbSNP156_Binaries/Standard"
readonly NAPLS3_DIR="/u/project/cbearden/hughesdy/NAPLS/raw_genotype/NAPLS3"
readonly CHROMOSOMES=(1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y)
readonly PLINK_CHROM="MT"
readonly WORK_DIR="$HOME/project-cbearden/napls/gprep/processed_genotype"
readonly TIMESTAMP=$(date +"%m%d%Y_%I%M%S%p")
readonly SUFFIX="_[job-${JOB_ID:-unknown}]_[${TIMESTAMP}]"
readonly SCRATCH_DIR="$SCRATCH/napls_qc_rename_snps_direct${SUFFIX}"
readonly TEMP_DIR="$SCRATCH_DIR/temp_chr_files"
readonly LOG_DIR="$WORK_DIR/logs/${JOB_ID:-unknown}_rename_snps_direct"
readonly RSYNC_CMD="rsync -avW --no-compress --info=progress2"

# Functions
log() { echo "$(date) - $1" >&2; }
err() { log "Error: $1"; exit 1; }
```

```
make_filepath() { local lines=$(wc -l < "$2"); echo "${1}${SUFFIX}_[${lines}-lines].${3:-t
validate_file() { [[ ! -s "$1" ]] && err "$2 is empty or missing"; awk -F'\t' 'NF!=2 || $1

setup_links() {
    log "Setting up binary links..."
    mkdir -p "$SCRATCH_DIR/bin_links" || err "Failed to create bin_links directory"
    for chr in "${CHROMOSOMES[@]}"; do ln -sf "$RS_BIN_DIR/GRCh37_${chr}."{hash2rsid,rsid2
}

annotate_chromosome() {
    local chr="$1" chr_dir="$TEMP_DIR/chr$chr"
    mkdir -p "$chr_dir/annotated" || err "Failed to create $chr_dir/annotated"
    log "Annotating chromosome $chr..."
    "$RSID_TOOLS" annotate --build "$BUILD" --sep $'\t' --varid_column 0 --map_dir "$SCRAT
        --out "$chr_dir/annotated" --no_missing --chrom "$chr" "$TEMP_DIR/chr${chr}_ids.tx
    [[ -s "$chr_dir/annotated/hash2rsid_${BUILD}-chr${chr}_ids.tsv" ]] || err "Annotated f
    awk -F'\t' 'NR==FNR {map[$2]=$1; next} {print map[$1]"\t"($3~/^rs[0-9]+$/ ? $3 : $1)}'
        "$TEMP_DIR/preprocessed_map.txt" "$chr_dir/annotated/hash2rsid_${BUILD}-chr${chr}_
        || err "Failed to create map for chr$chr"
}

export -f annotate_chromosome log err
export BUILD RSID_TOOLS SCRATCH_DIR TEMP_DIR

# Main Execution
log "Copying input files to scratch..."
mkdir -p "$SCRATCH_DIR" "$TEMP_DIR" "$LOG_DIR" || err "Failed to create directories"
time for f in bed bim fam; do $RSYNC_CMD "$NAPLS3_DIR/NAPLS3_n710.$f" "$SCRATCH_DIR/" || e

setup_links

log "Preprocessing BIM file..."
time awk -F'\t' '$4~/^[0-9]+$/ && $5~/^[ACGT]+$/ && $6~/^[ACGT]+$/ && !seen[$2]++ {
    chr=($1=="PAR1"||$1=="PAR2")?"X":$1; print $2"\t"chr":"$4":"toupper($6)":"toupper($5)
}' "$SCRATCH_DIR/NAPLS3_n710.bim" > "$TEMP_DIR/preprocessed_map.txt" || err "Failed to pre
validate_file "$TEMP_DIR/preprocessed_map.txt" "preprocessed map"

log "Splitting and annotating in parallel..."
time printf '%s\n' "${CHROMOSOMES[@]}" | parallel -j 24 --line-buffer --eta --progress --n
    --halt now,fail=1 --workdir "$SCRATCH_DIR" --results "$LOG_DIR/parallel_output" \
    "awk -F'\t' -v chr={} '\$2~\"^\"chr\":\" {print \$2}' \"$TEMP_DIR/preprocessed_map.txt
    || err "Parallel annotation failed"

log "Combining maps and adding unmapped variants..."
ALL_MAPPED="$TEMP_DIR/all_mapped.txt"
FINAL_MAP="$SCRATCH_DIR/final_snp_rename.txt"
time {
    awk -F'\t' '!seen[$1]++ {print}' "$TEMP_DIR"/chr*_map.txt > "$ALL_MAPPED" || err "Fail
    awk -F'\t' 'NR==FNR {mapped[$1]; next} !($1 in mapped) {print}' "$ALL_MAPPED" "$TEMP_D
    mv "$ALL_MAPPED" "$FINAL_MAP" || err "Failed to move all_mapped.txt to final_snp_renam
}
validate_file "$FINAL_MAP" "final map"
```

```
    FINAL_MAP_RENAMED=$(make_filepath "$SCRATCH_DIR/final_snp_rename" "$FINAL_MAP")
    mv "$FINAL_MAP" "$FINAL_MAP_RENAMED" || err "Failed to rename final map"
    log "Final map has $(wc -l < "$FINAL_MAP_RENAMED") lines; original BIM has $(wc -l < "$SCR

    log "Renaming SNPs with PLINK..."
    time "$PLINK2" --bfile "$SCRATCH_DIR/NAPLS3_n710" --merge-par --update-name "$FINAL_MAP_REI
        --not-chr "$PLINK_CHROM" --make-bed --threads 32 --silent --rm-dup force-first list \
        --out "$SCRATCH_DIR/NAPLS3_n710_renamed${SUFFIX}" || err "PLINK renaming failed"

    log "Renaming output files..."
    for ext in bed bim fam; do
        OLD_PATH="$SCRATCH_DIR/NAPLS3_n710_renamed${SUFFIX}.$ext"
        NEW_PATH=$(make_filepath "$SCRATCH_DIR/NAPLS3_n710_renamed" "$OLD_PATH" "$ext")
        mv "$OLD_PATH" "$NEW_PATH" || err "Failed to rename $ext"
        [[ "$ext" == "bim" ]] && RENAMED_BIM="$NEW_PATH"
    done

    log "Comparing BIM files..."
    MISSING_VARIANTS="$SCRATCH_DIR/missing_variants${SUFFIX}.txt"
    time awk -F'[ \t]+' 'FNR==NR {key[$1":"$4":"$6":"$5]=1; next} {
        chr=($1=="PAR1"||$1=="PAR2")?"X":$1; k=chr":"$4":"toupper($6)":"toupper($5);
        if (!(k in key)) print
    }' "$RENAMED_BIM" "$SCRATCH_DIR/NAPLS3_n710.bim" > "$MISSING_VARIANTS" || err "Comparison
    log "Found $(wc -l < "$MISSING_VARIANTS") missing variants; see $MISSING_VARIANTS"

    log "Transferring results..."
    time $RSYNC_CMD "$SCRATCH_DIR/"*"${SUFFIX}"* "$WORK_DIR/" || err "Failed to transfer resul

    log "Completed successfully"
```

lowestprime style: update QC flow comment for clarity add3aef · 3 months ago

Code Blame Raw

```
#!/bin/bash
# ================================================================================
# Script: 02_enigma_dti_qc_napls3_part1.sh
# Description: Performs ENIGMA-DTI QC Steps 1-3 for NAPLS3 dataset
# ================================================================================
set -euo pipefail

# Job Parameters
#$ -cwd
#$ -l h_rt=1:00:00,h_data=4G,highp
#$ -pe shared 24
#$ -N enigma_dti_qc_part1
#$ -j y
#$ -o "$HOME/project-cbearden/napls/gprep/processed_genotype/enigma/DTIgenetics/$JOB_ID_en

# Load Modules
. /u/local/Modules/default/init/modules.sh
module load parallel || { echo "$(date) - ERROR: Failed to load module parallel" >&2; exit

# Constants
readonly HOME_DIR="$HOME/project-cbearden/napls"
readonly PROJECT_DIR="${HOME_DIR}/gprep/processed_genotype"
readonly DATE_STAMP=$(date +%Y%m%d)
readonly ANALYST="CB"
readonly COHORT="NAPLS3"
readonly PLINK19="/u/project/cbearden/hughesdy/software/plinkv1.9/plink"
readonly INFO_DIR="${PROJECT_DIR}/enigma/DTIgenetics/info"
readonly PHENO_FILE="${INFO_DIR}/NAPLS3_Terra_samplestab_phenofile.txt"
readonly DTI_FILE="${INFO_DIR}/napls3_MS_diffusion.csv"
readonly INPUT_BED=$(ls "${PROJECT_DIR}"/NAPLS3_n710_renamed_*.bed | head -1)
readonly INPUT_BIM=$(ls "${PROJECT_DIR}"/NAPLS3_n710_renamed_*.bim | head -1)
readonly INPUT_FAM=$(ls "${PROJECT_DIR}"/NAPLS3_n710_renamed_*.fam | head -1)
readonly JOB_ID=${JOB_ID:-"local_$$"}
readonly THREADS=24
readonly PARALLEL_JOBS=8
readonly THREADS_PER_JOB=$((THREADS / PARALLEL_JOBS))
```

```
readonly RSYNC_CMD="rsync -avW --no-compress --info=progress2"
readonly ANCESTRY="EUR"
readonly ANC_DATA="${COHORT}_${ANCESTRY}_${ANALYST}_${DATE_STAMP}"

# Directory Structure
readonly TEMP_DIR="${TMPDIR:-/tmp}/enigma_dti_${JOB_ID}"
readonly FINAL_DIR="${PROJECT_DIR}/enigma/DTIgenetics/${JOB_ID}_enigma_dti_qc_napls3_part1
readonly LOG_DIR="${TEMP_DIR}/logs"

# Functions
log() { echo "$(date) - $1" | tee -a "${LOG_DIR}/run.log"; }
err() { log "ERROR: $1"; exit 1; }
warn() { log "WARNING: $1"; }

transfer_files() {
    local src="$1"
    local dst="$2"
    $RSYNC_CMD "${src}" "${dst}" > /dev/null 2>&1 || warn "Failed to transfer ${src} to ${
}

setup() {
    mkdir -p "${TEMP_DIR}" "${LOG_DIR}" "${FINAL_DIR}/logs" || err "Failed to create direc
    trap 'cleanup' EXIT INT TERM
}

cleanup() {
    log "Syncing results to ${FINAL_DIR}"
    $RSYNC_CMD "${LOG_DIR}/" "${FINAL_DIR}/logs/" || warn "Failed to sync logs"
    [[ -f "${TEMP_DIR}/${COHORT}_Combined_${ANALYST}_${DATE_STAMP}_summary.txt" ]] && \
        transfer_files "${TEMP_DIR}/${COHORT}_Combined_${ANALYST}_${DATE_STAMP}_summary.tx
    if [[ -f "${TEMP_DIR}/${ANC_DATA}_QC1.bed" ]]; then
        for ext in bed bim fam; do
            transfer_files "${TEMP_DIR}/${ANC_DATA}_QC1.${ext}" "${FINAL_DIR}/${ANC_DATA}_(
        done
        [[ -f "${TEMP_DIR}/${ANC_DATA}_QC_summary.txt" ]] && \
            transfer_files "${TEMP_DIR}/${ANC_DATA}_QC_summary.txt" "${FINAL_DIR}/${ANC_DA
        # Copy essential logs
        find "${TEMP_DIR}" -name "${ANC_DATA}*.log" -exec $RSYNC_CMD {} "${FINAL_DIR}/" \;
    fi
    # Also copy the sex check file and sex mismatches file
    [[ -f "${TEMP_DIR}/${ANC_DATA}_sexcheck.sexcheck" ]] && \
        transfer_files "${TEMP_DIR}/${ANC_DATA}_sexcheck.sexcheck" "${FINAL_DIR}/${ANC_DAT
    [[ -f "${TEMP_DIR}/sex_mismatches.txt" ]] && \
        transfer_files "${TEMP_DIR}/sex_mismatches.txt" "${FINAL_DIR}/sex_mismatches.txt"
}

run_plink() {
    local out="$1"; shift
    local cmd_args="$*"
    log "PLINK: $cmd_args"
    if [[ "$cmd_args" == *"--check-sex"* || "$cmd_args" == *"--split-x"* || "$cmd_args" ==
        $PLINK19 --out "${TEMP_DIR}/${out}" --threads ${THREADS} "$@" > /dev/null
```

```
        else
            $PLINK19 --out "${TEMP_DIR}/${out}" --threads ${THREADS} --set-hh-missing "$@" > /
        fi
        local status=$?
        [[ $status -ne 0 ]] && err "PLINK failed with exit code $status"
        return 0
    }

    run_parallel_pruning() {
        local bfile="$1" out="$2"
        local temp_dir="${TEMP_DIR}/${out}_temp"
        mkdir -p "${temp_dir}"
        log "Running parallel pruning for ${bfile}"
        local cmd_file="${temp_dir}/cmds.txt"
        for chr in $(seq 1 23); do
            echo "$PLINK19 --bfile ${TEMP_DIR}/${bfile} --chr ${chr} --indep-pairphase 20000 2
        done
        parallel --halt soon,fail=1 --jobs ${PARALLEL_JOBS} < "${cmd_file}" || err "Parallel p
        cat "${temp_dir}"/chr*.prune.in 2>/dev/null > "${TEMP_DIR}/${out}.prune.in" || true
        cat "${temp_dir}"/chr*.prune.out 2>/dev/null > "${TEMP_DIR}/${out}.prune.out" || true
        rm -rf "${temp_dir}"
    }

    has_xy_region() {
        local bimfile="$1"
        [[ $(awk '{if ($1==25) print $1}' "${bimfile}" | wc -l) -gt 0 ]]
    }

    create_sex_mismatch_report() {
        local mismatch_file="$1"
        local output_file="$2"
        {
            echo "FID IID subID Reason"
            awk 'BEGIN { OFS=" " }
                 NR==FNR { subject_ids[$1]=$2; next }
                 { if ($1 in subject_ids) { sub_id = subject_ids[$1]; } else { sub_id = $1; }
                   print $1, $2, sub_id, "Sex mismatch detected" }' "${LOG_DIR}/id_map.txt" "$
        } > "${output_file}"
    }

    # QC flow: dti filter -> sex and phenotype recode -> X-chrom split -> filtering and pruning
    perform_qc() {
        log "Performing QC steps on the entire dataset labeled as EUR"

        # Step 1: Update sex information from phenotype data
        awk -F'\t' 'NR>1 { gsub(/\r/,"",$7); print $3, ($7=="Male"?1:2) }' "${PHENO_FILE}" > "
        awk 'BEGIN { OFS=" " }
             NR==FNR { sex[$1]=$2; next }
             { if ($1 in sex) $5=sex[$1]; print }' \
             "${LOG_DIR}/sex_map.txt" "${TEMP_DIR}/input.fam" > "${LOG_DIR}/input_sex_updated.

        # Step 2: Create DTI ID mapping and filter list
```

```
        awk -F'\t' 'NR>1 {
             sub(/NAPLS3-/,"",$4);
             match($4,/^([0-9]{2})(.*)$/);
             print $3, substr($4,RSTART,2) "-S" substr($4,RSTART+2)
        }' "${PHENO_FILE}" | sort -k2,2 > "${LOG_DIR}/id_map.txt"

        # Step 3: Extract DTI subject IDs
        awk -F',' 'NR>1 { sub(/_.*/,"",$1); print $1 }' "${DTI_FILE}" | sort -u > "${LOG_DIR}/
        log "DTI file contains $(wc -l < "${LOG_DIR}/dti_ids_raw.txt") unique individuals"

        # Step 4: Find overlap between genetic and DTI data
        join -1 2 -2 1 "${LOG_DIR}/id_map.txt" "${LOG_DIR}/dti_ids_raw.txt" | \
             awk '{ print $2, $2 }' | sort -u > "${LOG_DIR}/dti_fid_list.txt"
        log "Identified $(wc -l < "${LOG_DIR}/dti_fid_list.txt") individuals with DTI data"

        # Step 5: DTI Filter: Create _dti dataset (full variant list) from raw input
        run_plink "${ANC_DATA}_dti" \
            --bed "${TEMP_DIR}/input.bed" \
            --bim "${TEMP_DIR}/input.bim" \
            --fam "${LOG_DIR}/input_sex_updated.fam" \
            --keep "${LOG_DIR}/dti_fid_list.txt" \
            --make-bed

        # Step 6: Phenotype Recode: Update phenotypes on the _dti dataset
        awk -F'\t' 'NR>1 {
             gsub(/\r/,"");
             is_control = ($8 ~ /^Control$/ ? 1 : 2);
             print $3, is_control;
        }' "${PHENO_FILE}" | sort -u > "${LOG_DIR}/pheno_map.txt"
        awk 'BEGIN { OFS=" " }
             NR==FNR { pheno[$1]=$2; next }
             { if ($1 in pheno) $6=pheno[$1]; else $6=1; print }' \
             "${LOG_DIR}/pheno_map.txt" "${TEMP_DIR}/${ANC_DATA}_dti.fam" > "${TEMP_DIR}/${ANC_
        mv "${TEMP_DIR}/${ANC_DATA}_dti.fam.new" "${TEMP_DIR}/${ANC_DATA}_dti.fam"

        # Step 7: X-chrom Split: Recode pseudoautosomal regions on the _dti dataset
        run_plink "${ANC_DATA}_splitx" \
            --bfile "${TEMP_DIR}/${ANC_DATA}_dti" \
            --split-x b37 no-fail \
            --make-bed
        local xy_count
        xy_count=$(awk '{if ($1==25) print $1}' "${TEMP_DIR}/${ANC_DATA}_splitx.bim" | wc -l)
        if [[ $xy_count -eq 0 ]]; then
            log "Split-X with b37 didn't create XY region; trying hg19"
            run_plink "${ANC_DATA}_splitx" \
                --bfile "${TEMP_DIR}/${ANC_DATA}_dti" \
                --split-x hg19 no-fail \
                --make-bed
            xy_count=$(awk '{if ($1==25) print $1}' "${TEMP_DIR}/${ANC_DATA}_splitx.bim" | wc
            if [[ $xy_count -eq 0 ]]; then
                log "Split-X with hg19 also didn't create XY region; please verify input data"
            else
```

```
            log "Split-X succeeded with hg19; XY region count: ${xy_count}"
        fi
    else
        log "X chromosome PAR splitting status: ${xy_count} variants in XY region"
    fi

    # Step 8: Filtering and Pruning: Apply SNP filtering and LD pruning on the _splitx data
    run_plink "${ANC_DATA}_filtered" \
        --bfile "${TEMP_DIR}/${ANC_DATA}_splitx" \
        --mind 1 \
        --geno 0.01 \
        --maf 0.05 \
        --hwe 1e-06 \
        --make-bed
    run_parallel_pruning "${ANC_DATA}_filtered" "${ANC_DATA}_pruned"
    run_plink "${ANC_DATA}_pruned" \
        --bfile "${TEMP_DIR}/${ANC_DATA}_filtered" \
        --extract "${TEMP_DIR}/${ANC_DATA}_pruned.prune.in" \
        --make-bed

    # Step 9: Sex Check and Filter: Perform sex check on the _splitx dataset and remove mis
    local x_count
    x_count=$(awk '$1=="23" || $1=="X"' "${TEMP_DIR}/${ANC_DATA}_splitx.bim" | wc -l)
    if [[ $x_count -gt 0 ]]; then
        log "Performing sex check for EUR with ${x_count} X chromosome variants"
        run_plink "${ANC_DATA}_sexcheck" \
            --bfile "${TEMP_DIR}/${ANC_DATA}_splitx" \
            --check-sex 0.2 0.8
        grep -w "PROBLEM" "${TEMP_DIR}/${ANC_DATA}_sexcheck.sexcheck" > "${TEMP_DIR}/sex_m
        local sex_drop_count
        sex_drop_count=$(wc -l < "${TEMP_DIR}/sex_mismatches.txt")
    else
        log "No X chromosome variants for sex check in EUR"
        touch "${TEMP_DIR}/sex_mismatches.txt"
        local sex_drop_count=0
    fi

    if [[ $sex_drop_count -gt 0 ]]; then
        log "Removing ${sex_drop_count} sex-mismatched individuals"
        create_sex_mismatch_report "${TEMP_DIR}/sex_mismatches.txt" "${TEMP_DIR}/sex_drop_
        run_plink "${ANC_DATA}_QC1" \
            --bfile "${TEMP_DIR}/${ANC_DATA}_splitx" \
            --remove "${TEMP_DIR}/sex_mismatches.txt" \
            --make-bed
    else
        log "No sex mismatches found"
        run_plink "${ANC_DATA}_QC1" \
            --bfile "${TEMP_DIR}/${ANC_DATA}_splitx" \
            --make-bed
    fi

    # Step 10: Collect metrics for reporting from the final QC dataset (_QC1)
```

```
        local x_count_final
        x_count_final=$(awk '$1=="23" || $1=="X"' "${TEMP_DIR}/${ANC_DATA}_QC1.bim" | wc -l)
        local case_count
        case_count=$(awk '$6==2' "${TEMP_DIR}/${ANC_DATA}_QC1.fam" | wc -l)
        local control_count
        control_count=$(awk '$6==1' "${TEMP_DIR}/${ANC_DATA}_QC1.fam" | wc -l)
        local final_count
        final_count=$(wc -l < "${TEMP_DIR}/${ANC_DATA}_QC1.fam")

        # Create summary report
        cat > "${TEMP_DIR}/${ANC_DATA}_QC_summary.txt" << EOF
    ENIGMA-DTI QC Summary for NAPLS3 ($(date))
    --------------------------------
    Total individuals: ${final_count}
    Cases: ${case_count}
    Controls: ${control_count}
    X chromosome SNPs: ${x_count_final}
    --------------------------------
    EOF

        log "ENIGMA-DTI QC completed for NAPLS3"
    }

    main() {
        setup
        cd "${TEMP_DIR}" || err "Failed to cd to ${TEMP_DIR}"
        touch "${LOG_DIR}/run.log"
        log "Starting ENIGMA-DTI QC processing"

        for f in "${INPUT_BED}" "${INPUT_BIM}" "${INPUT_FAM}" "${PHENO_FILE}" "${DTI_FILE}"; d
            [[ -f "$f" ]] || err "Input file not found: $f"
        done

        $RSYNC_CMD "${INPUT_BED}" "${TEMP_DIR}/input.bed" > /dev/null 2>&1 || err "Failed to c
        $RSYNC_CMD "${INPUT_BIM}" "${TEMP_DIR}/input.bim" > /dev/null 2>&1 || err "Failed to c
        $RSYNC_CMD "${INPUT_FAM}" "${TEMP_DIR}/input.fam" > /dev/null 2>&1 || err "Failed to c

        perform_qc

        {
            echo "ENIGMA-DTI QC Summary ($(date))"
            echo "==================================="
            echo "Total individuals in genotype data: $(wc -l < "${TEMP_DIR}/input.fam")"
            echo "Total individuals with DTI data: $(wc -l < "${LOG_DIR}/dti_fid_list.txt")"
            echo ""
            echo "Samples breakdown:"
            echo "-----------------------------------"
            local count=$(wc -l < "${TEMP_DIR}/${ANC_DATA}_QC1.fam")
            local case_count=$(awk '$6==2' "${TEMP_DIR}/${ANC_DATA}_QC1.fam" | wc -l)
            local control_count=$(awk '$6==1' "${TEMP_DIR}/${ANC_DATA}_QC1.fam" | wc -l)
            echo "NAPLS3: ${count} individuals (${case_count} cases, ${control_count} controls
            echo "-----------------------------------"
```

```
            echo "Total across all samples: ${count} individuals"
            echo "Cases: ${case_count}"
            echo "Controls: ${control_count}"
            echo "================================="
        } > "${TEMP_DIR}/${COHORT}_Combined_${ANALYST}_${DATE_STAMP}_summary.txt"

        log "ENIGMA-DTI QC completed successfully"
    }

    main
```

lowestprime feat: Exclude header line in duplicate handling script f97a9f0 · 3 months ago

Code Blame Raw

```
#!/bin/bash
# ================================================================================
# Script: 02_enigma_dti_qc_napls3_part2.sh
# Description: Performs Steps 4-6 of ENIGMA-DTI QC protocol for NAPLS3 dataset.
#              Handles duplicate/relatedness checks, MDS analysis, and outlier
#              identification/removal, producing _QC3 dataset. Generates a
#              summary report of removals for Part 3. Thresholds are set to
#              isolate the CEU/TSI cluster per ENIGMA protocol.
# ================================================================================
set -euo pipefail

# Job Parameters
#$ -cwd
#$ -l h_rt=1:00:00,h_data=4G,highp
#$ -pe shared 24
#$ -N enigma_dti_qc_part2
#$ -j y
#$ -o "$HOME/project-cbearden/napls/gprep/processed_genotype/enigma/DTIgenetics/$JOB_ID_en

# Load Modules
. /u/local/Modules/default/init/modules.sh
module load aria2 parallel R/4.2.2-BIO || { echo "$(date) - ERROR: Failed to load modules"

# Constants
HOME_DIR="/u/home/c/cobeaman/project-cbearden/napls"
PROJECT_DIR="${HOME_DIR}/gprep/processed_genotype"
DATE_STAMP=$(date +%Y%m%d)
ANALYST="CB"
COHORT="NAPLS3"
ANCESTRY="EUR"
PLINK19="/u/project/cbearden/hughesdy/software/plinkv1.9/plink"
JOB_ID=${JOB_ID:-"local_$$"}
THREADS=24
HAPMAP_URL="https://enigma.ini.usc.edu/website_downloads/ENIGMA_DTI_downloads/HapMap3"
INPUT_DIR="${PROJECT_DIR}/enigma/DTIgenetics/$(ls -t ${PROJECT_DIR}/enigma/DTIgenetics/ |
TEMP_DIR="${TMPDIR:-/tmp}/enigma_dti_${JOB_ID}"
```

```
    FINAL_DIR="${PROJECT_DIR}/enigma/DTIgenetics/${JOB_ID}_enigma_dti_qc_napls3_part2"
    LOG_DIR="${FINAL_DIR}/logs"
    HAPMAP_DIR="${TEMP_DIR}/hapmap3"
    SCRIPT_DIR="${TEMP_DIR}/scripts"
    SUMMARY_TXT="${FINAL_DIR}/${JOB_ID}_summary_report.txt"
    ANC_DATA="${COHORT}_${ANCESTRY}_${ANALYST}_${DATE_STAMP}"
    ANC_DIR="${TEMP_DIR}"
    RSYNC_CMD="rsync -avW --no-compress --info=progress2"

    # Functions
    log() { echo "$(date) - $1" >> "${LOG_DIR}/${JOB_ID}_run.log"; }
    err() { log "ERROR: $1"; exit 1; }
    transfer_files() { $RSYNC_CMD "$1" "$2" 2>/dev/null || log "WARNING: Failed to transfer $1

    setup() {
        [[ ! -d "${INPUT_DIR}" ]] && err "Cannot find input directory: ${INPUT_DIR}"
        log "Using input from: ${INPUT_DIR}"
        mkdir -p "${TEMP_DIR}" "${LOG_DIR}" "${HAPMAP_DIR}" "${FINAL_DIR}" "${SCRIPT_DIR}" "${
        trap 'cleanup' EXIT INT TERM
        touch "${LOG_DIR}/${JOB_ID}_run.log" "${LOG_DIR}/${JOB_ID}_plink_cmds.log"
        create_mds_r_script
    }

    create_mds_r_script() {
        # R script for MDS plotting and outlier detection
        # Adjusted thresholds target the CEU/TSI cluster:
        #   Dimension 1 between -0.06 and -0.04
        #   Dimension 2 between 0.055 and 0.07
        cat > "${SCRIPT_DIR}/mds_plot.R" << 'EOF'
    suppressWarnings({
        if (!require("calibrate", quietly = TRUE)) {
            install.packages("calibrate", repos="https://cloud.r-project.org", quiet=TRUE)
        }
        library(calibrate, quietly=TRUE)

        anc_data <- Sys.getenv("ANC_DATA")
        anc_dir  <- Sys.getenv("ANC_DIR")
        cohort   <- Sys.getenv("COHORT")

        # Input CSV from PLINK MDS
        mds_csv <- file.path(anc_dir, paste0(anc_data, "_QC2_HM3b37mds2R.mds.csv"))
        outlier_file <- file.path(anc_dir, paste0(anc_data, "_pop_strat_mds.outlier.txt"))
        eur_file <- file.path(anc_dir, paste0(anc_data, "_pop_strat_mds.eur.txt"))

        # Output PDFs
        pdf_included <- file.path(anc_dir, paste0("mdsplot_", anc_data, "_QC2_outliersincluded
        pdf_excluded <- file.path(anc_dir, paste0("mdsplot_", anc_data, "_QC2_outliersexcluded

        # 1) Read and label MDS data
        mds.cluster <- read.csv(mds_csv, header=TRUE)

        # Assign population labels
```

```
        mds.cluster$POP <- rep(cohort, nrow(mds.cluster))
        hapmap_pops <- c("CEU","CHB","YRI","TSI","JPT","CHD","MEX","GIH","ASW","LWK","MKK")
        color_map <- c("CEU"="lightblue","CHB"="brown","YRI"="yellow","TSI"="green",
                       "JPT"="purple","CHD"="orange","MEX"="grey50","GIH"="black",
                       "ASW"="darkolivegreen","LWK"="magenta","MKK"="darkblue")
        for (pop in hapmap_pops) {
            mds.cluster$POP[mds.cluster$FID == pop] <- pop
        }

        # Color each population; use "darkturquoise" for cohort samples (NAPLS3)
        colors <- rep("darkturquoise", nrow(mds.cluster))
        for (pop in hapmap_pops) {
            colors[mds.cluster$POP == pop] <- color_map[[pop]]
        }

        # More descriptive HapMap legend names
        hapmap_names <- c("CEU (European)", "CHB (Han Chinese)", "YRI (Yoruba)",
                          "TSI (Tuscans)", "JPT (Japanese)", "CHD (Chinese)",
                          "MEX (Mexican)", "GIH (Gujarati)", "ASW (African American)",
                          "LWK (Luhya)", "MKK (Maasai)")

        # 2) Plot: Outliers Included
        pdf(pdf_included, width=10, height=10, paper="special", useDingbats=FALSE)
        # Increase right margin to 14 so the legend is fully visible
        par(mar=c(5,5,4,14))
        plot(rev(mds.cluster$C2), rev(mds.cluster$C1),
             col=rev(colors),
             ylab="Dimension 1", xlab="Dimension 2",
             pch=19, cex=1.2,
             main=paste("MDS Plot for", cohort, "Samples (Outliers Included)"))
        legend("topright",
               legend=c(paste(cohort, "(All)"), hapmap_names),
               fill=c("darkturquoise", unlist(color_map[hapmap_pops])),
               xpd=TRUE, inset=c(-0.35,0), bty="n", cex=1.0)
        dev.off()

        # 3) Define outlier thresholds for CEU/TSI
        # Based on provided coordinates:
        #   C1 between -0.06 and -0.04
        #   C2 between 0.055 and 0.07
        c1_min <- -0.06
        c1_max <- -0.04
        c2_min <- 0.055
        c2_max <- 0.07
        cat("Outlier thresholds (to isolate CEU/TSI per ENIGMA protocol):\n")
        cat(sprintf("C1 < %.3f & C1 > %.3f, C2 < %.3f & C2 > %.3f\n",
                    c1_min, c1_max, c2_min, c2_max))

        # 4) Flag outliers in the cohort
        MDS_mySample <- mds.cluster[mds.cluster$POP == cohort, ]
        MDS_mySample$outlier <- 0
        MDS_mySample$outlier[
```

```
            MDS_mySample$C1 < c1_min | MDS_mySample$C1 > c1_max |
            MDS_mySample$C2 < c2_min | MDS_mySample$C2 > c2_max
        ] <- 1

        # Write outlier vs. inlier files
        MDS_mySample_outliers <- MDS_mySample[MDS_mySample$outlier == 1, c("FID","IID")]
        MDS_mySample_european <- MDS_mySample[MDS_mySample$outlier == 0, c("FID","IID")]
        write.table(MDS_mySample_outliers, outlier_file, sep="\t", quote=FALSE, row.names=FALSE
        write.table(MDS_mySample_european, eur_file, sep="\t", quote=FALSE, row.names=FALSE)

        # 5) Plot: Outliers Excluded
        MDS_ref <- mds.cluster[mds.cluster$POP != cohort, ]
        MDS_ref$outlier <- 0
        MDS_mySample_inliers <- MDS_mySample[MDS_mySample$outlier == 0, ]
        MDS_noOutliers <- rbind(MDS_ref, MDS_mySample_inliers)

        colors_noOut <- rep("darkturquoise", nrow(MDS_noOutliers))
        for (pop in hapmap_pops) {
            colors_noOut[MDS_noOutliers$POP == pop] <- color_map[[pop]]
        }

        pdf(pdf_excluded, width=10, height=10, paper="special", useDingbats=FALSE)
        par(mar=c(5,5,4,14))
        plot(rev(MDS_noOutliers$C2), rev(MDS_noOutliers$C1),
             col=rev(colors_noOut),
             ylab="Dimension 1", xlab="Dimension 2",
             pch=19, cex=1.2,
             main="MDS Plot after Outlier Removal")
        legend("topright",
               legend=c(paste(cohort, "(EUR)"), hapmap_names),
               fill=c("darkturquoise", unlist(color_map[hapmap_pops])),
               xpd=TRUE, inset=c(-0.35,0), bty="n", cex=1.0)
        dev.off()
    });
    EOF
    }


    download_hapmap3_reference() {
        if [[ ! -f "${HAPMAP_DIR}/HM3_b37.snplist.txt" ]]; then
            log "Downloading HapMap3 reference data"
            mkdir -p "${HAPMAP_DIR}"
            cd "${HAPMAP_DIR}"
            (
                flock -w 60 9 || err "Failed to acquire lock for HapMap3 download"
                if [[ ! -f "HM3_b37.snplist.txt" ]]; then
                    aria2c --max-connection-per-server=16 --file-allocation=none --continue=tru
                    aria2c --max-connection-per-server=16 --file-allocation=none --continue=tru
                    aria2c --max-connection-per-server=16 --file-allocation=none --continue=tru
                    pigz -d -p ${THREADS} *.gz
                    awk '{print $2}' HM3_b37.bim > HM3_b37.snplist.txt
                fi
```

```
193             ) 9>"${HAPMAP_DIR}/download.lock"
194             log "HapMap3 reference data downloaded and prepared"
195         fi
196     }
197
198     process_data() {
199         local qc1_base="${INPUT_DIR}"/*_QC1
200         for ext in bed bim fam; do
201             file=$(find "${INPUT_DIR}" -maxdepth 1 -name "*_QC1.${ext}" | head -n 1)
202             [[ -z "${file}" ]] && { log "WARNING: Missing QC1 file with extension ${ext}, exit
203             transfer_files "${file}" "${ANC_DIR}/${ANC_DATA}_QC1.${ext}"
204         done
205
206
207         # Step 4: Check duplicates and relatedness
208         log "Step 4: Checking duplicates and relatedness"
209         run_plink "${ANC_DATA}_QC1tmp" \
210             --bfile "${ANC_DIR}/${ANC_DATA}_QC1" \
211             --mind 0.1 \
212             --geno 0.01 \
213             --maf 0.05 \
214             --make-bed
215
216         run_plink "${ANC_DATA}_QC1pruned" \
217             --bfile "${ANC_DIR}/${ANC_DATA}_QC1tmp" \
218             --indep-pairwise 100 5 0.2
219
220         run_plink "${ANC_DATA}_QC1pruned" \
221             --bfile "${ANC_DIR}/${ANC_DATA}_QC1tmp" \
222             --extract "${ANC_DIR}/${ANC_DATA}_QC1pruned.prune.in" \
223             --make-bed
224
225         run_plink "pihat_duplicates" \
226             --bfile "${ANC_DIR}/${ANC_DATA}_QC1pruned" \
227             --genome --min 0.9
228
229         # Define confirmed monozygotic twin pairs (IID only, assuming FID is consistent)
230         declare -a mz_twins=("204127370086_R10C01" "204127370145_R11C02" "204127370105_R08C02"
231         echo "${mz_twins[@]}" | tr ' ' '\n' > "${ANC_DIR}/mz_twins.txt"
232
233         # Extract FID1 IID1 for pairs with PI_HAT >= 0.9 and exclude confirmed MZ twins in one
234         awk 'NR > 1 && $10 >= 0.9 {print $1, $2}' "${ANC_DIR}/pihat_duplicates.genome" | grep
235                 > "${ANC_DIR}/pihat_duplicates.txt" 2>/dev/null || touch "${ANC_DIR}/pihat_dup
236
237         # Log individuals to be removed for verification
238         log "Individuals to remove as duplicates (PI_HAT > 0.9, excluding confirmed mz twins):
239         cat "${ANC_DIR}/pihat_duplicates.txt" >> "${LOG_DIR}/${JOB_ID}_run.log"
240
241         dup_count=$(wc -l < "${ANC_DIR}/pihat_duplicates.txt")
242         echo "${dup_count}" > "${ANC_DIR}/${ANC_DATA}_QC1pruned_duplicates_count.txt"
243         log "Identified and counted ${dup_count} individuals to remove as duplicates"
244
```

```
245         if [[ ${dup_count} -gt 0 ]]; then
246             run_plink "${ANC_DATA}_QC2" \
247                 --bfile "${ANC_DIR}/${ANC_DATA}_QC1" \
248                 --remove "${ANC_DIR}/pihat_duplicates.txt" \
249                 --make-bed
250             log "Removed ${dup_count} duplicates"
251         else
252             for ext in bed bim fam; do
253                 ln -sf "${ANC_DIR}/${ANC_DATA}_QC1.${ext}" "${ANC_DIR}/${ANC_DATA}_QC2.${ext}"
254             done
255             log "No duplicates found (excluding confirmed mz twins); linking QC1 to QC2"
256         fi
257
258         # Check for relatedness (PI_HAT 0.25-0.9)
259         run_plink "pihat_relatedness" \
260             --bfile "${ANC_DIR}/${ANC_DATA}_QC1pruned" \
261             --genome --min 0.25 --max 0.9
262
263         # Count related pairs, excluding header
264         rel_count=$(tail -n +2 "${ANC_DIR}/pihat_relatedness.genome" | wc -l 2>/dev/null || ec
265         echo "${rel_count}" > "${ANC_DIR}/${ANC_DATA}_QC1pruned_relatedness_count.txt"
266         log "Detected ${rel_count} related pairs (PI_HAT 0.25-0.9); not removed per ENIGMA pro
267
268         # Step 5: MDS Analysis
269         log "Step 5: Performing MDS per ENIGMA protocol"
270         run_plink "${ANC_DATA}_QC2_filtered" \
271             --bfile "${ANC_DIR}/${ANC_DATA}_QC2" \
272             --mind 1 \
273             --hwe 1e-6 \
274             --geno 0.05 \
275             --maf 0.01 \
276             --make-bed
277
278         run_plink "${ANC_DATA}_QC2local" \
279             --bfile "${ANC_DIR}/${ANC_DATA}_QC2_filtered" \
280             --extract "${HAPMAP_DIR}/HM3_b37.snplist.txt" \
281             --make-bed
282
283         awk '{ if(($5=="T" && $6=="A")||($5=="A" && $6=="T")||($5=="C" && $6=="G")||($5=="G" &&
284             "${ANC_DIR}/${ANC_DATA}_QC2_filtered.bim" > "${ANC_DIR}/local.snplist.txt"
285
286         awk '{print $2}' "${ANC_DIR}/${ANC_DATA}_QC2local.bim" | sort | uniq -d > "${ANC_DIR}/
287
288         run_plink "${ANC_DATA}_QC2local_no_multi" \
289             --bfile "${ANC_DIR}/${ANC_DATA}_QC2local" \
290             --exclude "${ANC_DIR}/multiallelic.snps" \
291             --make-bed
292
293         run_plink "HM3_b37_external_no_multi" \
294             --bfile "${HAPMAP_DIR}/HM3_b37" \
295             --extract "${ANC_DIR}/local.snplist.txt" \
296             --exclude "${ANC_DIR}/multiallelic.snps" \
```

```
297             --make-bed
298
299         run_plink "${ANC_DATA}_QC2local_flipscan" \
300             --bfile "${ANC_DIR}/${ANC_DATA}_QC2local_no_multi" \
301             --flip-scan
302
303         awk '$8 == "FLIP" {print $2}' "${ANC_DIR}/${ANC_DATA}_QC2local_flipscan.flipscan" \
304             > "${ANC_DIR}/flip.snps" 2>/dev/null || touch "${ANC_DIR}/flip.snps"
305
306         if [[ -s "${ANC_DIR}/flip.snps" ]]; then
307             run_plink "${ANC_DATA}_QC2local_flipped" \
308                 --bfile "${ANC_DIR}/${ANC_DATA}_QC2local_no_multi" \
309                 --flip "${ANC_DIR}/flip.snps" \
310                 --make-bed
311             merge_base="${ANC_DIR}/${ANC_DATA}_QC2local_flipped"
312         else
313             merge_base="${ANC_DIR}/${ANC_DATA}_QC2local_no_multi"
314         fi
315
316         if ! run_plink "${ANC_DATA}_QC2local_HM3b37merge" \
317              --bfile "${merge_base}" \
318              --bmerge "${ANC_DIR}/HM3_b37_external_no_multi" \
319              --make-bed
320         then
321             log "Initial merge failed, attempting to flip and exclude SNPs"
322             run_plink "${ANC_DATA}_QC2local_final" \
323                 --bfile "${merge_base}" \
324                 --exclude "${ANC_DIR}/${ANC_DATA}_QC2local_HM3b37merge-merge.missnp" \
325                 --make-bed
326             if ! run_plink "${ANC_DATA}_QC2local_HM3b37merge" \
327                  --bfile "${ANC_DIR}/${ANC_DATA}_QC2local_final" \
328                  --bmerge "${ANC_DIR}/HM3_b37_external_no_multi" \
329                  --make-bed
330             then
331                 log "WARNING: Merge failed after flipping and exclusion, skipping MDS"
332                 for ext in bed bim fam; do
333                     ln -sf "${ANC_DIR}/${ANC_DATA}_QC2_filtered.${ext}" "${ANC_DIR}/${ANC_DATA
334                 done
335                 return
336             else
337                 log "Merge succeeded after flipping and exclusion"
338             fi
339         else
340             log "Initial merge succeeded"
341         fi
342
343         run_plink "${ANC_DATA}_QC2_HM3b37mds" \
344             --bfile "${ANC_DIR}/${ANC_DATA}_QC2local_HM3b37merge" \
345             --cluster --mind 0.05 --mds-plot 10 \
346             --extract "${ANC_DIR}/local.snplist.txt"
347
348         cat "${ANC_DIR}/${ANC_DATA}_QC2_HM3b37mds.mds" | tr -s ' ' '\t' > "${ANC_DIR}/${ANC_DA
```

```
        awk 'BEGIN{OFS=","}{print $1,$2,$3,$4,$5,$6,$7}' "${ANC_DIR}/${ANC_DATA}_QC2_HM3b37mds
            > "${ANC_DIR}/${ANC_DATA}_QC2_HM3b37mds2R.mds.csv"

        # Step 6: Identify Outliers
        log "Step 6: Identifying ancestry outliers (refining to European ancestry)"
        unset R_HOME
        ANC_DATA="${ANC_DATA}" ANC_DIR="${ANC_DIR}" COHORT="${COHORT}" \
        Rscript "${SCRIPT_DIR}/mds_plot.R" || log "WARNING: R script failed"

        # Step 7: Remove Outliers
        if [[ -s "${ANC_DIR}/${ANC_DATA}_pop_strat_mds.outlier.txt" ]]; then
            local outlier_lines=$(wc -l < "${ANC_DIR}/${ANC_DATA}_pop_strat_mds.outlier.txt")
            local num_ind=$(wc -l < "${ANC_DIR}/${ANC_DATA}_QC2_filtered.fam")
            if [[ $outlier_lines -ge $num_ind ]]; then
                log "All individuals marked as outliers; using QC2_filtered as QC3"
                log "WARNING: No NAPLS3 samples align with CEU/TSI. Check MDS analysis (e.g., 
                for ext in bed bim fam; do
                    ln -sf "${ANC_DIR}/${ANC_DATA}_QC2_filtered.${ext}" "${ANC_DIR}/${ANC_DATA
                done
            else
                run_plink "${ANC_DATA}_QC3" \
                    --bfile "${ANC_DIR}/${ANC_DATA}_QC2_filtered" \
                    --keep "${ANC_DIR}/${ANC_DATA}_pop_strat_mds.eur.txt" \
                    --make-bed
                log "Removed ${outlier_lines} ancestry outliers"
            fi
        else
            log "No outliers identified, linking QC2_filtered to QC3"
            for ext in bed bim fam; do
                ln -sf "${ANC_DIR}/${ANC_DATA}_QC2_filtered.${ext}" "${ANC_DIR}/${ANC_DATA}_QC
            done
        fi

        # Generate Summary Report
        local qc1_ind=$(wc -l < "${ANC_DIR}/${ANC_DATA}_QC1.fam")
        local qc2_ind=$(wc -l < "${ANC_DIR}/${ANC_DATA}_QC2_filtered.fam")
        local qc3_ind=$(wc -l < "${ANC_DIR}/${ANC_DATA}_QC3.fam")
        local dup_count=$(cat "${ANC_DIR}/${ANC_DATA}_QC1pruned_duplicates_count.txt")
        local rel_count=$(cat "${ANC_DIR}/${ANC_DATA}_QC1pruned_relatedness_count.txt")
        local outlier_count=$(wc -l < "${ANC_DIR}/${ANC_DATA}_pop_strat_mds.outlier.txt")
        local snp_count=$(wc -l < "${ANC_DIR}/${ANC_DATA}_QC3.bim")

        cat > "${ANC_DIR}/${ANC_DATA}_QC2_summary.txt" << EOF
    ENIGMA-DTI Part 2 Summary for ${COHORT} ($(date))
    --------------------------------
    Initial individuals (post-sex check): ${qc1_ind}
    Duplicates removed: ${dup_count}
    Individuals after duplicate removal: $((qc1_ind - dup_count))
    Related pairs detected (PI_HAT 0.25-0.9): ${rel_count}
    Outliers removed (MDS): ${outlier_count}
    Final individuals (post-MDS): ${qc3_ind}
    Final SNPs: ${snp_count}
```

```
    Outlier thresholds (to isolate CEU/TSI): C1 < -0.06 & C1 > -0.04, C2 < 0.055 & C2 > 0.07
    --------------------------------
    EOF

        transfer_files "${ANC_DIR}/${ANC_DATA}_QC2_summary.txt" "${FINAL_DIR}/"
        log "Part 2 summary generated: ${qc3_ind} individuals, ${snp_count} SNPs"
    }

    run_plink() {
        local out="$1"; shift
        local args="$@"
        echo "$(date) - PLINK: ${args}" >> "${LOG_DIR}/${JOB_ID}_plink_cmds.log"
        ${PLINK19} --out "${ANC_DIR}/${out}" --threads ${THREADS} ${args} > "${ANC_DIR}/${out}
            log "ERROR: PLINK failed for ${out}"
            return 1
        }
        log "PLINK succeeded for ${out}"
        [[ -f "${ANC_DIR}/${out}.log" ]] && transfer_files "${ANC_DIR}/${out}.log" "${FINAL_DI
    }

    cleanup() {
        log "Syncing results to ${FINAL_DIR}"
        for file in "${ANC_DATA}_QC3.bed" "${ANC_DATA}_QC3.bim" "${ANC_DATA}_QC3.fam" \
                    "mdsplot_${ANC_DATA}_QC2_outliersincluded.pdf" \
                    "mdsplot_${ANC_DATA}_QC2_outliersexcluded.pdf" \
                    "${ANC_DATA}_pop_strat_mds.outlier.txt" \
                    "${ANC_DATA}_pop_strat_mds.eur.txt" \
                    "${ANC_DATA}_QC1pruned_duplicates_count.txt" \
                    "${ANC_DATA}_QC1pruned_relatedness_count.txt" \
                    "${ANC_DATA}_QC2_HM3b37.mds.tsv" \
                    "${ANC_DATA}_QC2_filtered.fam" \
                    "${ANC_DATA}_QC2_filtered.log" \
                    "${ANC_DATA}_QC2_summary.txt" \
                    "local.snplist.txt"; do
            [[ -f "${ANC_DIR}/${file}" ]] && transfer_files "${ANC_DIR}/${file}" "${FINAL_DIR}
        done

        find "${TEMP_DIR}" -type f \( -name "*.log" -o -name "*.genome" -o -name "*.missnp" -o
             -o -name "*.prune.out" -o -name "*.mds" -o -name "*.csv" -o -name "*.flipscan" -o
             -exec $RSYNC_CMD {} "${FINAL_DIR}/logs/" \; > /dev/null 2>&1 || true

        log "Cleanup completed: Intermediate files saved for Part 3"
    }

    main() {
        local start_time=$(date +%s)
        setup
        download_hapmap3_reference
        process_data
        local duration=$(( $(date +%s) - start_time ))
        log "Completed Steps 4-6 in ${duration} seconds"
    }
```

```
453
454     main
```

lowestprime feat: Refactor cleanup process in QC script ab2fbef · 3 months ago

Code Blame Raw

```
#!/bin/bash
# ================================================================================
# Script: 03_enigma_dti_qc_napls3_part3.sh
# Description: Performs Steps 7-9 of ENIGMA-DTI QC protocol for NAPLS3 dataset.
#              Generates PCA covariates and summary statistics.
#              Archives all files in output_all and assembles submission files
#              into output_final, then zips them.
# ================================================================================
set -euo pipefail

# --- Job Parameters ---
#$ -cwd
#$ -l h_rt=1:00:00,h_data=4G,highp
#$ -pe shared 24
#$ -N enigma_dti_qc_part3
#$ -j y
#$ -o "$HOME/project-cbearden/napls/gprep/processed_genotype/enigma/DTIgenetics/$JOB_ID_en

# --- Load Modules ---
. /u/local/Modules/default/init/modules.sh
module load R/4.2.2-BIO || { echo "$(date) - ERROR: Failed to load modules" >&2; exit 1; }

# ----- Directories & Constants -----
readonly HOME_DIR="/u/home/c/cobeaman/project-cbearden/napls"
readonly PROJECT_DIR="${HOME_DIR}/gprep/processed_genotype"
readonly DATE_STAMP=$(date +%Y%m%d)
readonly ANALYST="CB"
readonly COHORT="NAPLS3"
readonly ANCESTRY="EUR"
readonly PLINK19="/u/project/cbearden/hughesdy/software/plinkv1.9/plink"
readonly JOB_ID=${JOB_ID:-"local_$$"}
readonly THREADS=24
readonly INPUT_DIR="${PROJECT_DIR}/enigma/DTIgenetics/$(ls -t "${PROJECT_DIR}/enigma/DTIge
readonly PART1_DIR="${PROJECT_DIR}/enigma/DTIgenetics/$(ls -t "${PROJECT_DIR}/enigma/DTIge
readonly TEMP_DIR="${TMPDIR:-/tmp}/enigma_dti_${JOB_ID}"
readonly ANC_DATA="${COHORT}_${ANCESTRY}_${ANALYST}_${DATE_STAMP}"
```

```
readonly ANC_DIR="${TEMP_DIR}/anc_files"
readonly FINAL_DIR="${PROJECT_DIR}/enigma/DTIgenetics/${JOB_ID}_enigma_dti_qc_napls3_part3
readonly OUTPUT_ALL="${FINAL_DIR}/output_all"
readonly OUTPUT_FINAL="${FINAL_DIR}/output_final"
readonly SCRIPT_DIR="${TEMP_DIR}/scripts"
readonly LOG_DIR="${FINAL_DIR}/logs"
readonly RSYNC_CMD=(rsync -avW --no-compress --info=progress2)
readonly ZIP_FILE="${FINAL_DIR}/${ANC_DATA}_ENIGMA-DTI_FilesToSend.zip"

# Input files from Part 1
readonly QC1_FAM=$(find "${PART1_DIR}" -maxdepth 1 -type f -name "*_QC1.fam" | head -1)
readonly QC1_BIM=$(find "${PART1_DIR}" -maxdepth 1 -type f -name "*_QC1.bim" | head -1)
readonly QC_SUMMARY=$(find "${PART1_DIR}" -maxdepth 1 -type f -name "*_QC_summary.txt" | h

# ----- Functions -----
log() { echo "$(date) - $1" >> "${LOG_DIR}/${JOB_ID}_run.log"; }
err() { log "ERROR: $1"; exit 1; }
transfer_files() { "${RSYNC_CMD[@]}" "$1" "$2" 2>/dev/null || log "WARNING: Failed to tran

setup() {
    command -v bc &>/dev/null || err "bc command not found"
    [[ ! -d "${INPUT_DIR}" ]] && err "Missing Part2 dir: ${INPUT_DIR}"
    [[ ! -d "${PART1_DIR}" ]] && err "Missing Part1 dir: ${PART1_DIR}"
    [[ -z "${QC1_FAM}" || -z "${QC1_BIM}" ]] && err "Missing QC1 files in Part1"
    log "Using inputs: Part1 (${PART1_DIR}), Part2 (${INPUT_DIR})"
    mkdir -p "${TEMP_DIR}" "${ANC_DIR}" "${LOG_DIR}" "${OUTPUT_ALL}" "${OUTPUT_FINAL}" "${
    trap cleanup EXIT INT TERM
    touch "${LOG_DIR}/${JOB_ID}_run.log" "${LOG_DIR}/${JOB_ID}_plink_cmds.log"
    create_r_scripts
    log "Setup complete"
}

create_r_scripts() {
    cat > "${SCRIPT_DIR}/pca_plot.R" << 'EOF'
options(warn=-1)
pkgs <- c("data.table", "ggplot2")
for(pkg in pkgs) {
  if (!require(pkg, quietly=TRUE, character.only=TRUE))
    install.packages(pkg, repos="https://cloud.r-project.org", quiet=TRUE)
}
library(data.table); library(ggplot2)
eigv <- fread(file.path(Sys.getenv("ANC_DIR"), paste0(Sys.getenv("ANC_DATA"), "_PCACovariat
var_explained <- (eigv$V1/sum(eigv$V1))*100
pdf(file.path(Sys.getenv("ANC_DIR"), paste0("screeplot_", Sys.getenv("ANC_DATA"), "_PCACova
print(qplot(1:20, var_explained[1:20]) + geom_line() +
      xlab("Principal Component") + ylab("Variance Explained (%)") +
      ggtitle("Scree Plot for PCA Covariates") + ylim(0,100))
dev.off()
EOF

    cat > "${SCRIPT_DIR}/summary_report.Rmd" << 'EOF'
---
```

```
    title: "ENIGMA-DTI QC3 Summary Report for NAPLS3"
    output: pdf_document
    ---
    ```{r, echo=FALSE}
    cat(readLines("summary_report.txt"), sep="\n")
    ```
    EOF
    }

    run_plink() {
        echo "$(date) - PLINK: $*" >> "${LOG_DIR}/${JOB_ID}_plink_cmds.log"
        log "PLINK: $*"
        "${PLINK19}" --out "${ANC_DIR}/${1}" --threads "${THREADS}" "${@:2}" > "${ANC_DIR}/${1
        transfer_files "${ANC_DIR}/${1}.log" "${OUTPUT_ALL}/"
    }

    process_data() {
        # Copy required files from Part 2 to ANC_DIR
        for pattern in "mdsplot_*outliersincluded.pdf" "mdsplot_*outliersexcluded.pdf" "*QC1pr
            file=$(find "${INPUT_DIR}" -maxdepth 1 -type f -name "$pattern" | head -1)
            [[-z "$file"]] && err "Missing Part2 file: $pattern"
            transfer_files "$file" "${ANC_DIR}/$(basename "$file")"
        done

        # Copy required files from Part 1 to ANC_DIR
        file=$(find "${PART1_DIR}" -maxdepth 1 -type f -name "sex_mismatches.txt" | head -1)
        [[-z "$file"]] && err "Missing Part1 file: sex_mismatches.txt"
        transfer_files "$file" "${ANC_DIR}/sexcheck_PROBLEM.txt"
        if [[-n "${QC_SUMMARY}"]]; then
            transfer_files "${QC_SUMMARY}" "${ANC_DIR}/snp_count_X.txt"
        else
            log "WARNING: QC summary file (for SNP count) not found in Part1"
        fi

        # Step 8: Generate PCA covariates
        log "Step 8: Generating PCA covariates"
        qc3_bed=$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*QC3.bed" | head -1)
        [[-z "$qc3_bed"]] && err "QC3.bed not found in ANC_DIR"
        qc3_prefix="$(dirname "$qc3_bed")/$(basename "$qc3_bed" .bed)"
        run_plink "${ANC_DATA}_PCACovariates" --bfile "${qc3_prefix}" --pca --extract "${ANC_D
        unset R_HOME
        env ANC_DATA="${ANC_DATA}" ANC_DIR="${ANC_DIR}" Rscript "${SCRIPT_DIR}/pca_plot.R" 2>>

        # Step 9: Generate cohort QC summary statistics
        log "Step 9: Generating cohort QC summary statistics"
        generate_stats "preQC" "${QC1_FAM}" "${ANC_DIR}/${ANC_DATA}_basic_stats_preQC.txt"
        qc3_fam=$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*QC3.fam" | head -1)
        generate_stats "postQC" "${qc3_fam}" "${ANC_DIR}/${ANC_DATA}_basic_stats_postQC.txt"
        generate_snp_summary
        generate_summary_report_txt
    }
```

```
generate_stats() {
    local type="$1" fam="$2" outfile="$3"
    echo "COHORTNAME N_CONTROLS N_CASES N_CONTROLS_M N_CONTROLS_F N_CASES_M N_CASES_F PROP_
    echo -n "${ANC_DATA} " >> "${outfile}"
    local stats
    stats=($(awk -v OFS='\t' 'BEGIN { nc=0; nca=0; ncm=0; ncf=0; ncam=0; ncaf=0 }
      { if ($6==1) { nc++; if ($5==1) ncm++; else if ($5==2) ncf++ }
        else if ($6==2) { nca++; if ($5==1) ncam++; else if ($5==2) ncaf++ } }
      END { print nc, nca, ncm, ncf, ncam, ncaf }' "${fam}"))
    local N_CONTROLS=${stats[0]} N_CASES=${stats[1]} N_CONTROLS_M=${stats[2]} N_CONTROLS_F=
    local PROP_CONTROLS_F; PROP_CONTROLS_F=$(echo "scale=4; ${N_CONTROLS_F:-0} / ${N_CONTR(
    local PROP_CONTROLS_M; PROP_CONTROLS_M=$(echo "scale=4; ${N_CONTROLS_M:-0} / ${N_CONTR(
    local PROP_CASES_F; PROP_CASES_F=$(if [[ ${N_CASES:-0} -eq 0 ]]; then echo 0; else ech(
    local PROP_CASES_M; PROP_CASES_M=$(if [[ ${N_CASES:-0} -eq 0 ]]; then echo 0; else ech(
    echo "${N_CONTROLS} ${N_CASES} ${N_CONTROLS_M} ${N_CONTROLS_F} ${N_CASES_M} ${N_CASES_
    log "Generated ${type} stats: $(basename "${outfile}")"
}

generate_snp_summary() {
    local summary_file="${ANC_DIR}/${ANC_DATA}_qc_summary.txt"
    echo "COHORTNAME N_SNPs_preQC N_samples_preQC SNPs_removed_>missingnessT Samples_remove
    echo -n "${ANC_DATA} " >> "${summary_file}"
    local vals=(
        "$(wc -l < "${QC1_BIM}")"
        "$(wc -l < "${QC1_FAM}")"
        "$(grep -im 1 "variants removed due to missing genotype data" "$(find "${INPUT_DIR
        "$(grep -im 1 "people removed due to missing genotype data" "$(find "${INPUT_DIR}"
        "$(grep -im 1 "variants removed due to minor allele threshold(s)" "$(find "${INPUT_
        "$(grep -im 1 "variants removed due to Hardy-Weinberg exact test" "$(find "${INPUT_
        "$(( $(wc -l < "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*QC2_filtered.fam"
        "$(wc -l < "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*QC3.bim" | head -1)")"
        "$(wc -l < "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*QC3.fam" | head -1)")"
    )
    echo "${vals[*]}" >> "${summary_file}"
    [[ -s "${summary_file}" ]] && log "Generated SNP summary: $(basename "${summary_file}"
}

generate_summary_report_txt() {
    local outfile="${ANC_DIR}/${ANC_DATA}_QC3_summary.txt"
    local n_samples_postQC n_snps_postQC N_CASES N_CONTROLS
    n_samples_postQC=$(wc -l < "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*QC3.fam" |
    n_snps_postQC=$(wc -l < "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*QC3.bim" | he
    N_CASES=$(awk '{if ($6==2) print $0}' "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "
    N_CONTROLS=$(awk '{if ($6==1) print $0}' "$(find "${ANC_DIR}" -maxdepth 1 -type f -nam
    local outlier_count=$(( $(wc -l < "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*pop_
    {
        echo "ENIGMA-DTI QC3 Summary for ${COHORT} ($(date))"
        echo "--------------------------------"
        echo "Initial individuals: $(wc -l < "${QC1_FAM}")"
        echo "Duplicates removed: $(cat "$(find "${ANC_DIR}" -maxdepth 1 -type f -name "*Q(
        echo "Related pairs detected (PI_HAT 0.25-0.9): $(cat "$(find "${ANC_DIR}" -maxdep
        echo "Outliers removed: ${outlier_count}"
```

```
            echo "Final individuals: ${n_samples_postQC}"
            echo "Cases: ${N_CASES}"
            echo "Controls: ${N_CONTROLS}"
            echo "SNPs: ${n_snps_postQC}"
            echo "Outlier thresholds: C1 between -0.06 and -0.04, C2 between 0.055 and 0.07"
            echo "--------------------------------"
        } > "${outfile}"
        log "Generated summary report text: $(basename "${outfile}")"
    }

    generate_summary_report_pdf() {
        log "Generating PDF summary report"
        cd "${SCRIPT_DIR}" || err "Cannot cd to ${SCRIPT_DIR}"

        # Transfer summary file
        transfer_files "${ANC_DIR}/${ANC_DATA}_QC3_summary.txt" "${SCRIPT_DIR}/summary_report.
        # Check file existence and render PDF
        if [[ ! -f "${SCRIPT_DIR}/summary_report.txt" ]]; then
            echo "ERROR: summary_report.txt not found in ${SCRIPT_DIR}" >&2
            exit 1
        fi
        cd "${SCRIPT_DIR}" || { echo "ERROR: Cannot cd to ${SCRIPT_DIR}" >&2; exit 1; }
        env Rscript -e "rmarkdown::render('summary_report.Rmd', output_dir='$SCRIPT_DIR')" ||
            echo "ERROR: PDF generation failed" >&2
            exit 1
        }
        # Run R script to generate the PDF with improved error handling
        unset R_HOME
        env Rscript -e "
        for(pkg in c('tinytex', 'rmarkdown', 'knitr', 'xfun')) {
          if(!require(pkg, quietly=TRUE, character.only=TRUE))
              install.packages(pkg, repos='https://cloud.r-project.org', quiet=TRUE)
        }
        library(tinytex); library(rmarkdown); library(knitr); library(xfun)
        if(!tinytex:::is_tinytex()) install_tinytex(force=FALSE)
        tryCatch({
          render('${SCRIPT_DIR}/summary_report.Rmd', output_file='${SCRIPT_DIR}/summary_report
        }, error=function(e){
          write(sprintf('Error: %s', e\$message), stderr())
          write('Check if LaTeX is installed and configured correctly.', stderr())
          quit(status=1)
        })" 2>>"${LOG_DIR}/${JOB_ID}_run.log" || {
            log "ERROR: PDF generation failed. Check logs for details."
            return 1
        }

        # Verify and transfer the generated PDF
        if [[ -f "${SCRIPT_DIR}/summary_report.pdf" ]]; then
            transfer_files "${SCRIPT_DIR}/summary_report.pdf" "${OUTPUT_ALL}/"
            log "PDF successfully generated and transferred to ${OUTPUT_ALL}"
        else
            log "ERROR: summary_report.pdf not generated"
```

```
            return 1
        fi

        # Transfer the Rmd and txt files for reference
        transfer_files "${SCRIPT_DIR}/summary_report.Rmd" "${OUTPUT_ALL}/"
        transfer_files "${SCRIPT_DIR}/summary_report.txt" "${OUTPUT_ALL}/"
        log "PDF summary report generation complete"
    }

    cleanup() {
        log "Starting cleanup and packaging"
        missing_files=()

        # Archive all files to OUTPUT_ALL once
        cp -r "${ANC_DIR}/"* "${OUTPUT_ALL}/" 2>/dev/null
        cp -r "${SCRIPT_DIR}/"* "${OUTPUT_ALL}/" 2>/dev/null
        cp -r "${PART1_DIR}/"* "${OUTPUT_ALL}/" 2>/dev/null
        cp "${PART1_DIR}/logs/"*.log "${OUTPUT_ALL}/" 2>/dev/null
        cp "${INPUT_DIR}/logs/"*.log "${OUTPUT_ALL}/" 2>/dev/null

        # Assemble submission files
        required_nonlog=(
            "*QC1pruned_duplicates_count.txt"
            "*QC1pruned_relatedness_count.txt"
            "sexcheck_PROBLEM.txt"
            "snp_count_X.txt"
            "${ANC_DATA}_basic_stats_preQC.txt"
            "${ANC_DATA}_qc_summary.txt"
            "${ANC_DATA}_basic_stats_postQC.txt"
        )

        # Handle MDS plot files
        if file=$(find "${ANC_DIR}" -maxdepth 1 -type f -name "mdsplot_*outliersincluded.pdf"
            cp "$file" "${OUTPUT_FINAL}/${ANC_DATA}_QC2_outliersincluded.pdf"
            log "Copied mdsplot (outliersincluded) as ${ANC_DATA}_QC2_outliersincluded.pdf"
        else
            missing_files+=("mdsplot_QC2_outliersincluded.pdf")
            log "WARNING: mdsplot file for outliersincluded missing"
        fi
        if file=$(find "${ANC_DIR}" -maxdepth 1 -type f -name "mdsplot_*outliersexcluded.pdf"
            cp "$file" "${OUTPUT_FINAL}/${ANC_DATA}_QC2_outliersexcluded.pdf"
            log "Copied mdsplot (outliersexcluded) as ${ANC_DATA}_QC2_outliersexcluded.pdf"
        else
            missing_files+=("mdsplot_QC2_outliersexcluded.pdf")
            log "WARNING: mdsplot file for outliersexcluded missing"
        fi

        # Copy required non-log files
        for expected in "${required_nonlog[@]}"; do
            file=$(find "${ANC_DIR}" -maxdepth 1 -type f -name "$expected" | head -1)
            if [[ -n "$file" ]]; then
                cp "$file" "${OUTPUT_FINAL}/$(basename "$file")"
```

```
            log "Found non-log file: $(basename "$file")"
        else
            missing_files+=("$expected")
            log "WARNING: Expected non-log file missing: $expected"
        fi
    done

    # Define required log files, conditionally including *QC2.log if it exists
    required_log=(
        "*enigma_dti_qc_napls3_part2.log"
        "*plink_cmds.log"
        "*run.log"
        "HM3_b37_external_no_multi.log"
        "*QC1pruned.log"
        "*QC1tmp.log"
        "*QC2_HM3b37mds.log"
        "*QC2_filtered.log"
        "*QC2local.log"
        "*QC2local_HM3b37merge.log"
        "*QC2local_final.log"
        "*QC2local_flipscan.log"
        "*QC2local_no_multi.log"
        "*QC3.log"
        "*PCACovariates.log"
        "pihat_duplicates.log"
        "pihat_relatedness.log"
    )
    if file=$(find "${OUTPUT_ALL}" -type f -name "*QC2.log" | head -1); then
        required_log+=("*QC2.log")
    fi

    # Copy required log files
    for pattern in "${required_log[@]}"; do
        file=$(find "${OUTPUT_ALL}" -type f -name "$pattern" | head -1)
        if [[ -n "$file" ]]; then
            cp "$file" "${OUTPUT_FINAL}/$(basename "$file")"
            log "Found log file: $(basename "$file")"
        else
            missing_files+=("$pattern")
            log "WARNING: Expected log file missing: $pattern"
        fi
    done

    # Calculate total files and adjust expected count
    total_files=$(find "${OUTPUT_FINAL}" -type f | wc -l)
    expected_count=$(( ${#required_nonlog[@]} + ${#required_log[@]} + 2 ))  # +2 for MDS p
    if [[ -z $(find "${OUTPUT_ALL}" -type f -name "*QC2.log" | head -1) ]]; then
        expected_count=$((expected_count - 1))
    fi
    log "Submission files count: ${total_files} (expected ${expected_count})"
    if [[ ${total_files} -ne ${expected_count} ]]; then
        log "WARNING: File count mismatch. Expected ${expected_count} files, found ${total
```

```
        fi

        # Log missing files if any
        if [[ ${#missing_files[@]} -gt 0 ]]; then
            {
                echo "Missing submission files:"
                for mf in "${missing_files[@]}"; do
                    echo "$mf"
                done
            } > "${FINAL_DIR}/missing_submission_files.txt"
            log "Missing submission files logged in missing_submission_files.txt"
        fi

        # Create zip archive
        zip -r "${ZIP_FILE}" -j "${OUTPUT_FINAL}/" || err "Failed to create zip archive"
        log "Created submission zip: ${ZIP_FILE}"
    }

    main() {
        local start_time=$(date +%s)
        setup
        process_data
        generate_summary_report_pdf
        local duration=$(( $(date +%s) - start_time ))
        log "Completed Steps 7-9 in ${duration} seconds"
        # Cleanup is handled by trap, no explicit call needed here
    }

    main
```

lowestprime Update README.md cb84dfe · 3 months ago

Preview Code Blame Raw

Disentangling Trauma and Genetic Predisposition: Isolating Disorder-Specific Polygenic Risks in the NAPLS Cohort

This project aims to elucidate why individuals exposed to similar traumatic experiences develop different psychiatric disorders. Trauma and adversity are established risk factors for a broad spectrum of psychopathologies, including schizophrenia, anxiety, depression, obsessive-compulsive disorder (OCD), and bipolar disorder. Notably, childhood adversities have been linked to an increased risk of psychosis and other mental health conditions.

The central question addresses why, given equivalent trauma exposure, one individual may develop schizophrenia while another develops depression without psychotic features. A prevailing hypothesis suggests that genetic predispositions interact with traumatic experiences, activating specific latent vulnerabilities that steer individuals toward particular psychopathological outcomes. This aligns with the concept of gene-environment correlation, where genetic factors influence an individual's exposure to certain environments, subsequently affecting their mental health outcomes.

Polygenic scores (PGS) offer a quantitative measure of an individual's genetic liability to various psychiatric disorders. However, these scores often capture a shared genetic "p factor", which encompasses risks for multiple disorders, complicating the isolation of disorder-specific genetic risks. For instance, a high PGS for schizophrenia may also reflect elevated risks for bipolar disorder and major depressive disorder.

Here, we isolate disorder-specific polygenic risk scores to asses the contribution of distinct genetic liability to divergent psychiatric outcomes following trauma exposure (e.g., developing schizophrenia vs bipolar disorder vs major depressive disorder). The study will utilize genomic data from the North American Prodrome Longitudinal Study (NAPLS) cohort, which provides a valuable resource for examining the interplay between trauma exposure and genetic risk in individuals at high risk for psychosis. By integrating refined polygenic risk assessments with detailed trauma histories within the NAPLS cohort, this study seeks to advance our understanding of the mechanisms that drive divergent psychiatric outcomes following trauma exposure.

Sum Stats

- `/u/project/cbearden/hughesdy/genetics/summary_statistics`
- SCZ/EUR, BIP, and MDD are in the corresponding folders.
- BIP and MDD are both derived from EUR samples.

Each have a file similar to:

- `MDD19_forPRSCS.txt`

These may have all required columns, but if not, check the raw files.

- MDD: `PGC_UKB_depression_genome-wide.txt`
- BIP: `daner_pgc4_bd_eur_no23andMe_neff75_dentrem_HRCfrq`
- SCZ: `PGC3_SCZ_wave3.european.autosome.public.v3.vcf.tsv`

Existing NAPLS Genetic and Phenotypic Data

- `/u/project/cbearden/hughesdy/NAPLS/pgs/napls3/EUR`
- `/u/project/cbearden/hughesdy/NAPLS/nice-data`

Planning

1. In theory, we can derive the SCZ-specific risk by subtracting the shared risk among SCZ, BIP, and MDD.
    i. For example, instead of subtracting EduA from Cog, we would subtract the combined risk (SCZ+BIP+MDD) from SCZ, from BIP, and from MDD.

    ii. We may need to generate the shared risk using a standard gSEM model before applying the gwas-sub model.
    iii. If this approach is not statistically justified, we might instead compare SCZ minus BIP.
    iv. Alternatively, we could start with standard gSEM to derive a common factor among all disorders.
2. Trauma/adversity is a broad risk factor for psychopathology.
    i. It is implicated in schizophrenia, anxiety, depression, OCD, bipolar disorder, and other conditions.
    ii. The key question is: given two individuals exposed to trauma, why does one develop schizophrenia while the other develops depression without psychotic features?
        a. One possibility is that genetic factors interact with trauma to activate an underlying predisposition for a specific form of psychopathology.
    iii. Although polygenic scores can measure this underlying propensity, they also capture risk for other disorders because of a shared genetic p factor.
        a. When measuring schizophrenia risk, we are also assessing risk for bipolar disorder, MDD, and more.
        b. By isolating the disorder-specific risk, we can determine whether genetic differences drive one individual with trauma toward schizophrenia versus another toward bipolar disorder.
3. Partitioned PGSs represent a promising addition within the gSEM framework.
    i. They are compatible with gSEM and integrate well with the overall analysis.
    ii. Although not yet fully validated, they offer a valuable exploratory extension to conventional PGS analyses.
    iii. This method is relatively easy to add at the end, minimizing the upfront work during genetic QC and gSEM syntax development.

Tools

1. `Bayesian polygenic score Probability Conversion (BPC)`
2. `CASTom-iGEx`
3. `DDx-PRS`
4. `Genomic Structural Invariance (GSI)`
5. `GenomicSEM`
6. `GenoPred`
7. `GSMR2`
8. `GSUB`
9. `GWAS-by-Subtraction`
10. `Local Standardized Root Mean-square Difference (localSRMD)`

11. `pathway-PRS`
12. `PleioPGS`
13. `PRSet`
14. `PRSice-2`
15. `SBayesRC`

References

1. A phenome-wide association study of cross-disorder genetic liability in youth genetically similar to individuals from European reference populations [14 October 2024]
2. Attention-mediated genetic influences on psychotic symptomatology in adolescence [28 October 2024]
3. Boosting Schizophrenia Genetics by Utilizing Genetic Overlap With Brain Morphology [August 15, 2022]
4. Bridging the scales: leveraging personalized disease models and deep phenotyping to dissect cognitive impairment in schizophrenia [February 27, 2025]
5. Comparison of the multivariate genetic architecture of eight major psychiatric disorders across sex [07 March 2025]
6. Distinct genetic liability profiles define clinically relevant patient strata across common diseases [July 01, 2024]
7. Distinguishing different psychiatric disorders using DDx-PRS [February 4, 2024]
8. Gene set enrichment analysis of pathophysiological pathways highlights oxidative stress in psychosis [21 September 2022]
9. Genetic analysis of psychosis Biotypes: shared Ancestry-adjusted polygenic risk and unique genomic associations [21 December 2024]
10. Genetic patterning for child psychopathology is distinct from that for adults and implicates fetal cerebellar development [18 May 2023]
11. Genetic, transcriptomic, metabolic, and neuropsychiatric underpinnings of cortical functional gradients [March 05, 2025]
12. Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction [07 January 2021]
13. Isolating transdiagnostic effects reveals specific genetic profiles in psychiatric disorders [April 11, 2024]
14. Splitting Schizophrenia: Divergent Cognitive and Educational Outcomes Revealed by Genomic Structural Equation Modelling [October 24, 2024]
15. Pathway Polygenic Risk Scores (pPRS) for the Analysis of Gene-environment Interaction [December 20, 2024]
16. Patterns of stressful life events and polygenic scores for five mental disorders and neuroticism among adults with depression [04 April 2024]

17. Polygenic Scores and Networks of Psychopathology Symptoms [June 12, 2024]
18. PRSet: Pathway-based polygenic risk score analyses and software [February 7, 2023]
19. Psychological trauma as a transdiagnostic risk factor for mental disorder: an umbrella meta-analysis [08 October 2022]
20. Using polygenic scores corrected for the general psychopathology factor to predict specific psychopathology [March 19, 2024]

NSIDP Written Qualifying Exams

NSIDP WQE Results Email

Date: Thu, Oct 17, 2024 at 3:16 PM
Subject: Results – Written Qualifying Exam
From: Lee, Jenny [BRI] JenniferL@mednet.ucla.edu
To: Cooper Beaman cobeaman@g.ucla.edu
Cc: Felix Schweizer felixs@g.ucla.edu

Dear Cooper,

The 2024 Neuroscience Written Qualifying Examination Committee would like to provide you with the following exam results:

Exam	**Result**
Molecular	High Pass
Cellular	High Pass
Systems	Pass

Individual exam feedback and comments, if any, will be available via the Bruin Learn site; please stand by for notification.

Congratulations on your successful completion of the exam!

Take care,
Jenny

cc: Faculty Mentor, Student File

Graduate Program Coordinator
UCLA Neuroscience Interdepartmental Program (NSIDP)
JenniferL@mednet.ucla.edu
Zoom ID: 569-756-2969
(310) 825-8153 p
She/Her/Hers

Grades

Exam	Due Date & Time	Score
Molecular	Sep 3, 2024 at 1:40 PM	100/100
Cellular	Sep 5, 2024 at 1:40 PM	100/100
Systems	Sep 10, 2024 at 2:50 PM	90/100

Molecular Exam

Date: Sep 3, 2024 at 1:40 PM
Professor: Stephanie White

Comments and Time

Oct 17, 2024 at 3:34 PM
Extremely well written and engaging paper. A major strength are the set of bullet points at the end that clearly lay out next questions and steps. Great job!

In-Text Annotations (9)

1. Thoughtful and engaging title!
2. Compelling intro!
3. Good synthesis of prior literature and the state of the field at the onset of the present work.
4. Good highlight
5. Good explanation of what the acronym stands for.
6. Well related!
7. Excellent point not often considered
8. Yes!
9. I'd love to see spatial transcriptomics ;-)

Cellular Exam

Date: Sep 5, 2024 at 1:40 PM
Professor: Thomas O'Dell

Comments and Time

Oct 17, 2024 at 3:33 PM
Excellent!

Systems Exam

Date: Sep 10, 2024 at 2:50 PM
Professor: Paul Mathews

Comments and Time

Oct 17, 2024 at 3:34 PM
Grading Rubric - 1 = Above average - 2 = Average - 3 = Below average - 4 = Not addressed

Focal Element	Score
Introduction	1
Methods	1
Limitations	2
Overall analytical depth	2

Molecular Section – Stephanie White:

Subtopic:

The neurobiological basis of social bonding. Recent transcriptional insights into social bond formation from study of voles

Exam Task:

Write a Journal of Neuroscience 'Journal Club' commentary on these two recent papers:

1. Nucleus accumbens dopamine release reflects the selective nature of pair bonds. Pierce et al. (2024)
2. Prolonged partner separation erodes nucleus accumbens transcriptional signatures of pair bonding in male prairie voles. Sadino et al. (2023)

Requirements:

Your article should be:

- Approximately 3 pages long
- Arial 11 pt
- Single-spacing
- 0.5-inch margins
- It's okay if it is shorter or a little longer

Your Journal Club article should include:

- Short overview of the topic and questions addressed in the two papers
- A brief discussion of their significance and how they build upon one another
- Your comments should include a brief discussion of the implications of the results reported
- You should describe at least one potential question that could be addressed in future experiments to expand on the findings reported in these papers

Additional Sources:

Review

3. Walum, H., Young, L.J. The neural mechanisms and circuitry of the pair bond. (2018)

Methods

4. Cell type-specific mRNA purification by translating ribosome affinity purification (TRAP) Heiman et al. (2014)

Background

5. Oxytocin receptor function regulates neural signatures of pair bonding and fidelity in the nucleus accumbens Links to an external site. Long et al. (2024)
6. Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles Liu and Wang et al. (2003)
7. RNAi knockdown of oxytocin receptor in the nucleus accumbens inhibits social attachment and parental care in monogamous female prairie voles Keebaugh et al. (2015)

Dopamine Signaling and Transcriptional Plasticity in the Nucleus Accumbens: Shaping Pair Bond Selectivity and Loss Adaptation in the Vole

Introduction

Elucidating the molecular underpinnings of behavioral variation is a central endeavor of neuroscience research. Yet the vast scale between genes and complex traits often necessitates investigation spanning multiple laboratories and subdomains to efficiently establish causal relationships and unifying theories. Molecular neuroscientists' decades-long effort to establish a robust neurobiological basis of social bonding in the vole model is no exception. Recently, Sadino et al. (2023) and Pierce et al. (2024), published novel findings elucidating transcriptional programs implicating glial-specific contributions to social bond formation and erosion during prolonged separation, and dopamine (DA) receptor subtype-specificity and role of nucleus accumbens (NAc) dopaminergic reward-mediated encoding of partner salience and preference, respectively. While these insights significantly advance the field's collective delineation of the molecular mechanisms underlying social bond formation and erosion, several important components of this framework continue to lack robust characterization. Among these, opportunities remain for researchers to investigate the most relevant specific cell types and molecular networks underlying social bond formation and erosion in voles, and to evaluate the interspecies generalizability and construct validity of transcriptional findings in voles to propose a more rigorous model of this intricate and dynamic process.

Social bonding, the formation of selective and enduring social attachments, is a fundamental process crucial for the survival and reproduction of many species (Walum, 2018). Pair- bonded animals exhibit a preference for their partner over unfamiliar conspecifics, display selective aggression towards non-partner individuals, and, in many cases, exhibit robust bi-parental care (Williams, 1992; Winslow et al., 1993; Carter et al., 1995; Insel and Young, 2001). Social bonding in the monogamous prairie vole (*Microtus ochrogaster*) is a well-established model system for understanding the neurobiological mechanisms underlying these behaviors. While an extended network of brain regions is involved in pair bonding, the

nucleus accumbens (NAc) – a critical hub for reward, motivation, and action selection – is thought to play a central role (Aragona and Wang, 2004; Lim and Young, 2004; Walum and Young, 2018). Previous research has demonstrated that both oxytocin and dopamine signaling within the NAc are crucial for the formation and maintenance of pair bonds in prairie voles (Liu and Wang, 2003; Keebaugh, 2015; Aragona, 2006).

Both Pierce et al. (2024) and Sadino et al. (2023) utilize the prairie vole as a model organism to investigate the neurobiological basis of pair bonding, but with distinct and complementary foci. Pierce et al. (2024) examines the role of dopamine signaling within the NAc in mediating partner preference, while Sadino et al. (2023) focuses on how the NAc transcriptional landscape changes as a function of pair bond formation, maintenance, and prolonged separation. More specifically, Pierce et al. (2024) employs fiber photometry, a technique that allows for real-time measurement of neurotransmitter release, to investigate how dopamine release dynamics in the NAc distinguish between interactions with a bonded partner and a novel vole. They hypothesize that “accumbal dopamine systems differentiate between interactions with a bonded partner and an unknown conspecific” and aim to determine if NAc dopamine signaling reflects and reinforces the selective nature of pair bonds. This study raises questions about how dopamine release might vary during different stages of partner interaction: seeking, anticipation, and actual social contact. They also investigate how these dynamics might change following bond devaluation via prolonged separation.

Sadino et al. (2023), on the other hand, utilizes RNAseq to compare gene expression in the NAc of opposite-sex paired males to their same-sex paired siblings, a clever control that allows for the isolation of pair bond-specific transcriptional changes from those associated with more general social housing or cohabitation, allowing them to more precisely investigate the molecular underpinnings of pair bonding. This study investigates whether pair bonding leads to a stable transcriptional signature in the NAc, and how this signature, if present, changes over time. The authors hypothesize that "extended partner separation diminishes pair bond-associated behaviors and causes pair bond transcriptional signatures to erode,” suggesting a dynamic transcriptional landscape that reflects the evolving state of the bond.

By combining behavioral analysis with real-time measurements of dopamine release, Pierce et al. (2024) provide compelling evidence that the NAc dopamine system plays a crucial role in shaping partner preference in prairie voles. Their study revealed that pair-bonded partners elicit enhanced dopamine release during partner seeking and during subsequent social interactions compared to novel voles. This finding, achieved through precise, real-time measurements of dopamine release using a genetically encoded dopamine sensor (GRABDA) and fiber photometry, suggests that the NAc encodes partner value, making the chosen mate uniquely rewarding and thus driving partner preference. The strength of this study lies in its multiple behavioral assays and use of fiber photometry to measure real-time dopamine dynamics, which allowed for a direct link between the NAc dopamine system and the behavioral expression of partner preference, strengthening the case for its role in shaping selective social attachments.

Sadino et al. (2023) complement this by investigating the longer-term, molecular-level mechanisms underlying these behavioral changes in the NAc. Their study utilizes RNAseq to provide a comprehensive snapshot of the NAc transcriptional landscape across different social contexts and time points, revealing a distinct transcriptional signature associated with pair bonding. This signature, which includes changes in genes related to gliogenesis, myelination, dopaminergic signaling, mitochondrial organization, and steroid hormone signaling, is maintained for at least six weeks while animals remain paired, but erodes following prolonged partner separation. This erosion, although not perfectly mirroring the behavioral persistence of partner preference, suggests that the NAc is actively involved in facilitating adaptation to loss, potentially “resetting” itself at the molecular level to enable the formation of new bonds. The strength of this study lies in its meticulous experimental design, which allowed for isolating pair-bond-specific transcriptional changes, and its use of RNAseq to thoroughly assess the transcriptional landscape.

Both Pierce (2024) and Sadino (2023) employed carefully designed controls to isolate the effects of pair bonding from those associated with more general social interaction. Pierce (2024) used both a traditional partner preference test and a social operant task in which voles could choose between interacting with their partner or a novel vole. The social operant task allowed them to control for effort, ensuring that the observed differences in dopamine release were not due to the amount of work required to access the partner. Sadino (2023) compared opposite-sex paired males to their same-sex paired siblings, an important control that allowed them to isolate transcriptional changes specific to the unique nature of pair bonds, as opposed to those associated with more general social housing. These controls strengthen the argument that the observed changes in dopamine signaling and gene expression are specifically related to the formation, maintenance, and disruption of pair bonds.

Implications

The findings of Pierce (2024) and Sadino (2023) have important implications for our understanding of

the neurobiology of social bonding and loss, particularly in the context of the NAc. By combining behavioral analysis with real-time dopamine measurements and transcriptional profiling, these studies illuminate the dynamic interplay between neurochemical signaling and gene expression in shaping the rewarding value of social partners and facilitating adaptation to partner loss.

Pierce's (2024) findings highlight the role of dopamine in encoding partner value and driving partner preference, suggesting that interventions aimed at enhancing dopamine signaling in the NAc, particularly in response to partner-related cues, might strengthen pair bonds. Conversely, Sadino's (2023) results raise the possibility that manipulating the NAc transcriptional signature, particularly after partner separation, might facilitate adaptation to loss and reduce the negative consequences of social isolation. These findings have potential implications for developing therapeutic interventions for disorders characterized by social dysfunction, such as autism spectrum disorder.

These studies also underscore the importance of considering the time course of both neurochemical and transcriptional changes in the NAc. Pierce's (2024) findings highlight the rapid and dynamic nature of dopamine signaling, while Sadino's (2023) work demonstrates that transcriptional changes can be both stable (in the context of maintained pair bonds) and dynamic (in response to separation). This suggests that interventions targeting the NAc, whether pharmacological or behavioral, might need to be carefully timed to be most effective.

Future Directions

Several important questions remain to be addressed in future research:

How do transcriptional changes in the NAc influence dopamine signaling and partner preference? While Pierce (2024) demonstrates the selective enhancement of dopamine release in response to partners, and Sadino (2023) reveals the erosion of the transcriptional signature after separation, the link between these two processes remains unclear. Do specific transcriptional changes, such as those identified in Sadino's study, directly influence the expression or function of dopamine receptors or transporters, thereby altering dopamine dynamics?

Future studies could combine fiber photometry with manipulations of gene expression (e.g., using viral vectors or CRISPR-Cas9 technology to overexpress or knockdown specific genes) to test causal links between transcriptional changes in the NAc and dopamine signaling dynamics during social interactions. This would provide a more direct understanding of how transcriptional regulation shapes dopamine signaling in the context of pair bonding.

What are the specific functions of the genes and pathways identified by Sadino et al. (2023) that change as a function of both pairing and separation? Sadino's study reveals a broad transcriptional signature associated with pair bonding, but the functional roles of many of these genes remain unknown. Are specific genes involved in encoding partner-specific information, regulating reward sensitivity, or modulating the stress response to separation? Answering these questions would provide a deeper understanding of how these transcriptional changes contribute to the behavioral and physiological changes observed during pair bond formation, maintenance, and disruption.

Future studies could use a combination of techniques, including in situ hybridization, immunohistochemistry, and optogenetics, to investigate the expression and function of these genes within specific NAc circuits and cell types. Examining the effects of manipulating these genes on partner preference, social behavior, and stress responses could provide insights into their specific roles in pair bonding.

What is the precise role of glia in pair bond formation and loss adaptation? Sadino (2023) found that genes associated with gliogenesis and myelination, processes primarily attributed to glial cells, were significantly affected by prolonged partner separation, suggesting a potential role for glia in bond dynamics. However, their RNAseq analysis could not distinguish between neuronal and glial contributions to these changes. This distinction is crucial, as it would reveal whether the erosion of the pair bond signature observed by Sadino is driven by changes primarily in neurons, in glia, or both.

Future studies could utilize cell type-specific techniques, such as Translating Ribosome Affinity Purification (TRAP) described by Heiman (2014), to isolate mRNA from neurons and glia separately, revealing the unique contributions of each cell type to the observed transcriptional changes. This approach would provide a more nuanced understanding of the complex interplay between neurons and glia in the NAc and its role in shaping pair bonding and loss.

By addressing these questions, researchers can gain a more comprehensive understanding of the NAc's intricate role in pair bonding and loss adaptation. This information could potentially inform the development of interventions aimed at addressing the negative consequences of social isolation and loss in humans.

Cellular Section – Tom O'Dell:

Subtopic:

Cellular and synaptic mechanisms underlying the antidepressant effects of ketamine.

- The non-competitive NMDA receptor antagonist ketamine has potent and rapid antidepressant effects in both rodents and humans.
- Although ketamine was approved by the FDA for use in humans in 2019, we still have a very rudimentary (and controversial) understanding of the cellular mechanisms underlying ketamine's antidepressant effects.

Exam Task:

1. Write a Journal of Neuroscience Journal Club article that provides an overview of the article by Ma et al. (Sustained antidepressant effect of ketamine through NMDAR trapping in the LHB. Nature 622: 802-809, 2023).
2. Your article should be approximately 3 pages long (Arial 11 pt, single-spacing, 0.5-inch margins, it's okay if it is shorter or a little longer). Do not indicate your name on the document.
3. Your Journal Club article should include a short overview of the topic and questions addressed in the paper as well as a brief discussion of the significance of the paper.
4. You should highlight how the findings in this paper compare to findings from other studies investigating the cellular mechanisms underlying the antidepressant effects of ketamine. Your comments here should include a brief discussion of the implications of the results reported by Ma et al. for current controversies in the field regarding how ketamine produces its antidepressant effects.
5. You should describe at least one potential question that could be addressed in future experiments to expand on the findings reported in the Ma et al. paper.

Reading List:

1. Autry et al. (2011) NMDA receptor blockade at rest triggers rapid behavioral antidepressant responses.
2. Miller et al. (2014) GluN2B-containg NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine.
3. Zanos et al. (2016) NMDAR inhibition-independent antidepressant actions of ketamine metabolites.
4. Suzuki et al. (2017) Effects of a ketamine metabolite on synaptic NMDAR function.
5. Yang et al. (2018) Ketamine blocks bursting in the lateral habenula to rapidly relieve depression.
6. Cui et al. (2018) Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression.
7. Ma et al. (2023) Sustained antidepressant effect of ketamine through NMDAR trapping in the LHB.

Novel Perspectives on Ketamine's Sustained Antidepressant Action: NMDAR Trapping in the Lateral Habenula

Introduction

The discovery of ketamine's rapid and potent antidepressant effects, often observed within hours of a single administration in both rodent models and humans (Autry et al., 2011), has significantly reshaped the landscape of depression treatment. Its rapid onset, standing in stark contrast to the weeks-to-months time frame typical of traditional antidepressants, has generated immense excitement, leading to the FDA's approval of ketamine for antidepressant use in 2019. However, the precise cellular and synaptic mechanisms driving ketamine's therapeutic effects, and particularly the sustained efficacy that extends far beyond the drug's short half-life in the system, remain an area of active investigation and ongoing debate. Recently, Ma et al. (2023) published a groundbreaking study in Nature, providing compelling evidence for a novel mechanism - NMDAR trapping in the lateral habenula (LHb) - to explain this long-lasting antidepressant action. The following commentary will delve into the findings of Ma et al. (2023), critically evaluating their significance in the context of existing research on ketamine's antidepressant actions and exploring potential implications for future research and therapeutic development.

Overview

Ma et al. (2023) focus their investigation on the LHb, a brain region increasingly recognized for its role in processing aversive stimuli, negative affect (Yang et al., 2018), and the pathophysiology of depression (Yang et al., 2018; Cui et al., 2018). The authors build upon a growing body of research suggesting that the LHb, often referred to as the "anti-reward center," represents a key target for ketamine's antidepressant effects (Yang et al., 2018). They hypothesize that ketamine's sustained antidepressant effects arise from its unique ability to become "trapped" within NMDARs in the LHb, resulting in prolonged blockade even after the drug itself has been cleared from the brain. Their study combines a series of meticulously designed behavioral assays, electrophysiological recordings, and pharmacological manipulations in a mouse model of depression to dissect the temporal dynamics of ketamine's action on LHb neurons.

Significance

The findings of Ma et al. (2023) constitute a significant advancement in the fields' understanding of ketamine's antidepressant actions to date. They provide a novel mechanistic framework for interpreting the

sustained effects, moving beyond the traditional focus on transient NMDAR blockade. This discovery of NMDAR trapping in the LHb, a phenomenon not previously considered in the context of ketamine's antidepressant effects, offers a new perspective on the drug's unique therapeutic properties and their long duration. It suggests that manipulating LHb activity, and consequently NMDAR opening, could be a novel strategy for optimizing ketamine treatment, potentially leading to the development of interventions that allow clinicians to fine-tune the duration of ketamine's antidepressant effects in individual patients.

Synthesis

Ma et al. (2023) began by meticulously mapping the time course of ketamine's antidepressant effects in a chronic restraint stress (CRS) mouse model of depression. Their results showed that a single systemic injection of ketamine (10 mg/kg, i.p.) produced sustained antidepressant-like effects, measured by both the forced swim test (FST) and sucrose preference test (SPT), lasting at least 24 hours, despite brain ketamine levels becoming nearly undetectable within an hour. This prolonged behavioral response, exceeding the drug's short half-life by a significant margin, mirrors previous research (Yang et al., 2018) and highlights the intriguing question of how a rapidly cleared drug can exert such long-lasting effects.

To address this question, the authors turned to electrophysiology, examining NMDAR currents in LHb brain slices prepared from CRS mice at 1 h, 24 h, and 3 days after a single ketamine injection. Even after extensive washing with ketamine-free ACSF, they observed significant and sustained reductions in NMDAR/AMPAR eEPSC ratios, indicating prolonged NMDAR blockade in LHb neurons. These results pointed toward a mechanism beyond simple receptor occupancy, one where ketamine remained functionally bound to NMDARs despite being cleared from the surrounding solution.

Further supporting this hypothesis, the authors performed a series of washout experiments comparing ketamine to memantine, an NMDAR inhibitor with a similar trapping mechanism but a faster off-rate compared with ketamine (Ma et al., 2023). Their findings revealed a stark contrast in recovery kinetics: memantine-blocked NMDAR-eEPSCs quickly recovered after washout, while the ketamine-blocked NMDAR-eEPSCs remained suppressed. This difference in recovery kinetics strengthened the case for ketamine's unique "trapping" properties, a phenomenon that had not been previously considered in explaining its sustained antidepressant effects.

To confirm the in vivo relevance of this trapping mechanism, they locally infused ketamine or memantine into the LHb of CRS mice and assessed for subsequent depressive-like behaviors. Local LHb infusion of ketamine, but not memantine, produced long-lasting antidepressant effects, mirroring the systemic effects, suggesting a causal link between prolonged LHb NMDAR blockade and sustained antidepressant action.

Implications and Insights

Ma et al. (2023) offer a compelling explanation for ketamine's sustained antidepressant effects by revealing the unique phenomenon of "NMDAR trapping" in the LHb. This mechanism, whereby ketamine becomes lodged within the channel pore of activated NMDARs, prolongs its inhibitory effects far beyond its presence in the brain. This is attributed to the relatively low baseline activity of NMDARs in the LHb, which keeps the channels predominantly closed, thereby reducing opportunities for ketamine to unbind. This highlights a crucial point: the pharmacological properties of NMDAR antagonists extend beyond their affinity for the receptor, with the trapping kinetics playing a critical role in determining their therapeutic efficacy.

These findings contribute to the ongoing debate regarding the cellular mechanisms driving ketamine's antidepressant effects. Autry et al. (2011) initially provided evidence that blocking NMDARs could trigger rapid antidepressant-like responses. Miller et al. (2014) further solidified the role of NMDARs by demonstrating that GluN2B-containing NMDARs are essential for both the expression of depression-like behavior and the rapid antidepressant effects of ketamine. Ma et al. (2023) build upon this foundation by providing a mechanism for the sustained action, explaining how this blockade can persist despite the drug's rapid clearance.

However, the discovery of NMDAR-independent antidepressant effects mediated by ketamine metabolites, particularly (2R,6R)-HNK, by Zanos et al. (2016) introduced a new dimension to the debate. Zanos et al. (2016) demonstrated that (2R,6R)-HNK, a key metabolite of ketamine, could exert its antidepressant effects independent of NMDAR inhibition. Their findings, corroborated by Suzuki et al. (2017) who showed that (2R,6R)-HNK can block synaptic NMDARs but at higher concentrations than those needed for its antidepressant effects, sparked a debate about the necessity of direct NMDAR blockade for ketamine's therapeutic benefits.

Ma et al. (2023) do not explicitly refute the findings of Zanos et al. (2016) or Suzuki et al. (2017). Rather, they provide a crucial piece to the puzzle by emphasizing the direct and persistent NMDAR blockade in the LHb as a key contributor to ketamine's sustained effects. The interplay between direct blockade by ketamine and the potential downstream effects of metabolites like (2R,6R)-HNK remains a critical area for future investigation.

The study by Ma et al. (2023) also provides a potential explanation for the lack of comparable clinical

efficacy observed with other NMDAR antagonists, such as MK-801 (Zanos et al., 2016). These antagonists, unlike ketamine, do not exhibit the same trapping kinetics, and this might be a key factor in their limited therapeutic success. The ability to manipulate the duration of ketamine's antidepressant effects by modulating LHb activity, as demonstrated by Ma et al. (2023), further suggests that the low intrinsic activity of NMDARs in the LHb, which facilitates trapping, might be a crucial factor in mediating the drug's sustained effects. This is particularly relevant given that other brain regions with higher NMDAR activity, such as the prefrontal cortex, have been proposed as targets for mediating ketamine's rapid antidepressant effects (Miller et al., 2014).

Future Directions

The findings of Ma et al. (2023) offer a new framework for understanding ketamine's sustained antidepressant actions and raise several compelling avenues for future research:

Investigate the molecular underpinnings of NMDAR trapping: A deeper understanding of the specific molecular interactions between ketamine and NMDARs, particularly those that influence its trapping and untrapping kinetics, is essential for developing drugs that could selectively target LHb NMDARs and induce prolonged blockade. Structural studies of ketamine bound to LHb NMDARs, combined with investigations into the effects of specific mutations on trapping kinetics and the potential role of allosteric modulators, could provide a path toward achieving this goal.

Explore NMDAR trapping in other brain regions and its interaction with metabolites: While Ma et al. (2023) focused on the LHb, further research is needed to determine if NMDAR trapping by ketamine occurs in other brain regions implicated in depression, such as the prefrontal cortex, which has been implicated in the rapid effects of ketamine (Miller et al., 2014), and to understand its contribution to ketamine's broader therapeutic profile. Comparative studies examining trapping kinetics across different regions, combined with investigations into the interplay between NMDAR trapping and the actions of ketamine metabolites like (2R,6R)-HNK, could provide a more comprehensive understanding of the drug's brain-wide effects.

Translate NMDAR trapping to human subjects: Translating the findings of Ma et al. (2023) to human subjects is critical for exploring their therapeutic implications. This would involve developing non-invasive methods to assess NMDAR occupancy and function in the LHb of living patients, potentially using PET imaging or MRS techniques. Additionally, investigating the possibility of modulating LHb activity and NMDAR opening in humans, perhaps using non-invasive brain stimulation techniques like TMS or focused ultrasound, could open new avenues for optimizing ketamine treatment and developing personalized therapeutic strategies.

By pursuing these lines of inquiry, researchers can move beyond the confines of transient NMDAR blockade and delve deeper into the complexities of ketamine's antidepressant actions, paving the way for a more comprehensive understanding of this remarkable drug and its potential for revolutionizing the treatment of mood disorders.

Systems Section – Paul Mathews
Subtopic:
How particular circuits and large brain networks control brain states and behavior.
Is the cerebellum directly involved in reward behavior?
Format:
Synthesis of literature and Journal of Neuroscience Journal Club article commentary on one of the papers.
Tasks:

1. **Select ONE of the six provided research articles**
    1. Washburn, S. *et al.* The cerebellum directly modulates the substantia nigra dopaminergic activity. *Nat. Neurosci.* 27, 497–513 (2024).
    2. Larry, N., Zur, G. & Joshua, M. Organization of reward and movement signals in the basal ganglia and cerebellum. *Nat. Commun.* 15, 2119 (2024).
    3. Garcia-Garcia, M. G. *et al.* A cerebellar granule cell-climbing fiber computation to learn to track long time intervals. *Neuron* (2024) doi:10.1016/j.neuron.2024.05.019.
    4. Ikezoe, K. *et al.* Cerebellar climbing fibers multiplex movement and reward signals during a voluntary movement task in mice. *Commun. Biol.* 6, 924 (2023).
    5. Wagner, M. J., Kim, T. H., Savall, J., Schnitzer, M. J. & Luo, L. Cerebellar granule cells encode the expectation of reward. *Nature* 544, 96–100 (2017).
    6. Heffley, W. & Hull, C. Classical conditioning drives learned reward prediction signals in climbing fibers across the lateral cerebellum. *eLife* 8, e46764 (2019).
2. **Write an analysis in the style of a *Journal of Neuroscience* Journal Club article.**
3. **Your analysis should focus on the following three elements:**
    1. **Introduction:**
        i. Critically evaluate how effectively the introduction frames the research question.
        ii. Discuss the extent to which the conducted experiments set out in the research article is supported by prior studies and relevant literature.
    2. **Methods:**
        i. Provide a comprehensive assessment of the methods used in the study.
        ii. Evaluate whether the descriptions are sufficiently detailed for replication and highlight any innovative techniques the researchers employed, especially those that push boundaries at the systems level.
    3. **Limitations:**
        i. Identify and discuss the limitations faced by the authors, whether technical, methodological, or related to foundational knowledge.
        ii. Consider how these limitations might affect the interpretation of the results and the overall significance of the study.
4. **Your article should be approximately 3 pages long (Arial 11 pt, single-spacing, 0.5-inch margins, it's okay if it is shorter or a little longer).**

Additional Sources:

7. Manto, M. *et al.* Consensus Paper: Cerebellum and Reward. *Cerebellum* 1–24 (2024) doi:10.1007/s12311-024-01702-0. [REVIEW]

Direct Cerebellar Modulation of Dopaminergic Activity: Unveiling a New Role for the Movement Hub

The cerebellum, long recognized for its role in fine-tuning motor control and coordination, has recently emerged as a potential operator involved in a significantly broader range of cognitive functions, including cognition, emotion, and reward processing. This shift in perspective has been driven by a growing body of evidence, from both animal models and human studies, suggesting that the cerebellum's influence extends far beyond the motor domain. However, the specific mechanisms underlying cerebellar contributions to reward-related behavior have remained elusive. Washburn et al. (2024), in their groundbreaking study published in Nature Neuroscience, provide compelling evidence for a direct, monosynaptic pathway from the cerebellum to the substantia nigra pars compacta (SNc), a key dopaminergic nucleus in the basal ganglia. This discovery of a direct cerebello-nigral pathway fundamentally challenges the traditional view of cerebellar function and opens up exciting new avenues for understanding the neural basis of reward, motivation, and movement.

Introduction

Washburn et al.'s Introduction section effectively frames the research question by highlighting the clinical significance of understanding motor control, particularly in the context of movement disorders like Parkinson's disease (PD). The authors vividly describe the debilitating motor impairments experienced by individuals with PD, emphasizing the urgent need for new therapeutic strategies. By specifically focusing on

the SNc, a key brain region involved in both motor control and reward-related behaviors, and its degeneration in PD, the authors establish the relevance of their investigation and its potential implications for developing new treatments.

The authors proceed to skillfully challenge the traditional view of cerebellar-basal ganglia interactions, as articulated in the consensus paper by Manto et al. (2024), that the cerebellum and basal ganglia primarily interact at the cortical level, with limited subcortical integration. This view, based on the anatomical segregation of their projections to distinct thalamic nuclei, suggests that the cerebellum's influence on the basal ganglia is primarily indirect, mediated through cortico-basal ganglia loops. Washburn et al. present compelling evidence from recent anatomical studies, using advanced viral tracing techniques, that suggests a more direct and rapid interaction between the cerebellum and basal ganglia. These studies reveal the existence of direct projections from the cerebellar nuclei to the SNc, challenging the traditional view and highlighting a potential alternative route for cerebellar influence on reward and motor control.

Washburn et al.'s (2024) findings challenge the traditional view, as articulated in the consensus paper by Manto et al. (2024), that the cerebellum and basal ganglia primarily interact at the cortical level, with limited subcortical integration. Their work provides compelling evidence that the cerebellum can exert a direct influence on the dopaminergic reward system, a finding that aligns with a growing body of research suggesting a more distributed and interactive model of reward processing.

For instance, Ikezoe et al. (2023) showed that individual climbing fibers in the cerebellum can multiplex movement and reward signals, suggesting a direct contribution to reward-related behavior beyond simply modulating motor output to the basal ganglia. Similarly, Garcia-Garcia et al. (2024) demonstrated that granule cells in the cerebellum can encode reward anticipation and learn to track time intervals related to reward, further supporting a role for the cerebellum in anticipating and predicting reward outcomes. These studies, alongside the findings of Washburn et al. (2024), describe the cerebellum as an active participant in the reward circuitry, not merely a passive relay station for motor commands. Wagner et al. (2017) and Heffley et al. (2019) further support this notion by demonstrating that granule cells and climbing fibers, respectively, can encode reward-related information, suggesting a rich and multifaceted representation of reward within the cerebellum.

However, the existence of a direct cerebello-nigral pathway does not negate the importance of indirect pathways or the complex interplay between the cerebellum and basal ganglia. Larry et al. (2024), in their comprehensive analysis of reward and movement signal organization in both structures, propose a compelling framework for understanding this interplay. They suggest a distributed model of reward processing, where the basal ganglia and cerebellum work in concert, with information flowing between them in a complex, non-hierarchical manner. Washburn et al.'s (2024) findings can be readily integrated into this model, suggesting that the cerebellum might provide the basal ganglia with real-time, cerebellar-specific information related to movement initiation, vigor, and reward value, potentially influencing the selection and execution of actions based on both internal predictions and external reward feedback.

This interplay between direct and indirect pathways underscores the need for a more nuanced understanding of the cerebellum's role in reward processing. While the direct cerebello-nigral pathway identified by Washburn et al. (2024) provides a mechanism for rapid and efficient modulation of dopaminergic activity, indirect pathways involving other brain regions, such as the thalamus and prefrontal cortex, might contribute to the cerebellum's broader influence on reward-related behaviors, including learning, motivation, and decision-making. It is conceivable that both direct and indirect pathways work synergistically to shape reward-related behaviors, with the relative contribution of each pathway potentially varying depending on the specific task, context, and timescale involved. Overall, Washburn et al.'s discovery of a direct cerebello-nigral pathway provides a compelling anatomical substrate for these functional observations, linking cerebellar activity to the modulation of the dopaminergic system, a key reward processing effector.

Methods

Washburn et al. (2024) employ a comprehensive suite of techniques to investigate the Cb-SNc pathway, each method providing complementary insights and allowing for a rigorous and multifaceted analysis. The study's methodological strength lies in its ability to combine these techniques, bridging the gap between anatomical connections, functional activity, and behavioral output.

The foundation of their investigation lies in electrophysiology, a technique that provides a direct measure of neuronal activity with high temporal precision. Using optrodes, the researchers combined optical stimulation of ChR2-expressing cerebellar axons in the SNc with simultaneous recordings of SNc neuronal activity in awake, head-fixed mice. This in vivo approach allowed them to assess the real-time effects of cerebellar stimulation on SNc firing, establishing a direct link between circuit activation and changes in neuronal activity. Complementing these in vivo experiments, the researchers also utilized whole-cell patch clamp recordings from SNc neurons in acute brain slices. This in vitro approach provided a controlled environment to dissect the synaptic properties of the Cb-SNc pathway, confirming its glutamatergic nature and revealing the involvement of both AMPA and NMDA receptors.

To establish a causal link between cerebellar activity and SNc dopaminergic signaling, Washburn et al. employed optogenetics, a powerful technique that allows for precise and selective activation or inhibition of specific neuronal populations using light. AAV vectors carrying ChR2 were injected into the deep cerebellar nuclei (DCN) to enable light-activated stimulation of cerebellar axons projecting to the SNc. This allowed for precise temporal and spatial control of cerebellar input to the SNc, ensuring that the observed effects were specifically due to the activation of the intended pathway. As a control, AAV vectors carrying the inhibitory opsin Jaws were injected into the SNc to reduce the excitability of SNc neurons, confirming that the observed effects of cerebellar stimulation on dopamine release were indeed mediated by the Cb-SNc pathway.

To gain further insight into the functional consequences of cerebellar modulation on the dopaminergic system, the researchers employed fiber photometry, a technique that allows for real-time monitoring of neuronal activity and neurotransmitter release in freely behaving animals using genetically encoded sensors. The dopamine sensor dLight1.1 was expressed in the dorsolateral striatum (DLS) to directly measure dopamine transients in response to cerebellar stimulation, providing a real-time readout of SNc dopaminergic activity. Additionally, calcium sensors (GCaMP7 and jRGECO1) were used to monitor the activity of both Cb-SNc projections and SNc neurons, respectively, during spontaneous locomotion and a lever manipulation task. These recordings provided valuable insights into the temporal dynamics of neuronal activity in both cerebellar inputs and SNc neurons, revealing a tight correlation between cerebellar activity and movement initiation.

To confirm the existence of a direct, monosynaptic pathway from the cerebellum to the SNc, the researchers employed anatomical tracing techniques using viral vectors. Anterograde tracing with AAV1-Cre virus injected into the DCN of Cre-dependent reporter mice allowed for the visualization and confirmation of the Cb-SNc pathway. Retrograde tracing, using both RetroAAV-Cre virus and a modified rabies virus (RVΔG-GFP) injected into the SNc, allowed for the identification of the specific cerebellar nuclei projecting to the SNc, confirming that all three deep cerebellar nuclei contribute to this pathway.

Finally, to link the activity of the Cb-SNc pathway to observable behaviors, Washburn et al. employed a range of behavioral assays, including locomotion on a head-fixed treadmill, a unilateral lever manipulation task, and a Pavlovian reward task. These assays provided a functional context for understanding the role of the Cb-SNc pathway in modulating motor output and reward-related behavior, revealing its involvement in promoting locomotion, encoding reward value, and potentially contributing to movement initiation.

The methods section of Washburn et al. (2024) is meticulously detailed, providing a clear and comprehensive account of the experimental procedures, making their findings highly replicable. The combination of these diverse techniques allows for a robust and multifaceted investigation of the Cb-SNc pathway, providing compelling evidence for its role in modulating dopamine release, influencing motor behavior, and encoding reward value.

The study's innovative use of techniques like optogenetics, viral tracing, and fiber photometry pushes the boundaries of systems-level neuroscience, enabling the investigation of specific neural circuits and their influence on behavior in unprecedented detail. The combined use of optogenetics and electrophysiology in vivo allows for both selective manipulation and real-time monitoring of specific neural pathways in awake, behaving animals, providing a powerful tool for dissecting the causal relationships between neural circuits and behavior. The use of Cre-dependent viral tracing enables highly specific labeling of neurons based on their genetic identity, allowing for precise mapping of neural pathways and differentiation between specific cell types within brain regions. Finally, fiber photometry with genetically encoded dopamine and calcium sensors allowed for real-time monitoring of dopamine dynamics and neuronal activity in freely behaving animals, providing a direct measure of the functional consequences of cerebellar modulation on the dopaminergic system.

Limitations

Washburn et al. (2024) acknowledge several limitations in their study, emphasizing the need for further research to refine our understanding of this novel circuit. Although these limitations warrant consideration, they do not diminish the study's overall significance, which provides a substantial advancement in our knowledge of cerebellar function and its influence on the dopaminergic system.

A primary limitation of the author’s approach stems from its reliance on viral vectors and optogenetics to manipulate specific neuronal populations. While these techniques offer high precision, the authors note the challenge of achieving complete specificity. Off-target effects, such as the unintended transduction of neighboring neurons or the activation of passing axons, may complicate the interpretation of behavioral outcomes and dopamine release. To address these concerns, future studies should explore alternative approaches, such as chemogenetics or optogenetic tools with improved spatial precision, to confirm the causal role of cerebellar-SNc (Cb-SNc) projections while minimizing unintended effects.

The study's behavioral assessments focus primarily on locomotion and basic lever manipulation tasks, which are informative but insufficient to capture the full complexity of reward-related behaviors. To extend the understanding of the Cb-SNc pathway, future research should examine its role in more intricate tasks, such as

decision-making, reward-based learning, goal-directed behavior, and social interaction. Investigating these behaviors would offer deeper insight into the pathway's contribution to cognitive and affective processes.

Another limitation concerns the investigation of cerebellar activity during unilateral motor tasks. The authors acknowledge the difficulty of ensuring purely unilateral movements, as subtle bilateral muscle activity for balance and posture may confound the observed bilateral activation patterns. Future research should use refined behavioral paradigms or bilateral muscle recordings to separate unilateral from bilateral motor command contributions to cerebellar activity, providing clearer insights into cerebellar lateralization.

The study also targets the entire deep cerebellar nuclei (DCN) without distinguishing between the dentate, interposed, and fastigial nuclei, each of which may have distinct roles in motor control and reward processing. This lack of specificity limits the ability to pinpoint the exact contributions of each nucleus to SNc modulation. Future research should focus on selectively targeting individual DCN nuclei to unravel their specific roles in modulating SNc activity and influencing behavior.

Furthermore, while the study demonstrates that Cb-SNc activation increases striatal dopamine levels, the precise mechanisms underlying this modulation remain unclear. It is uncertain whether this increase results from direct excitation of dopaminergic neurons in the SNc or involves local inhibitory circuits. Future investigations using techniques like electrophysiological recordings and optogenetic manipulation of specific neuronal subtypes within the SNc would provide a more detailed understanding of the cellular and synaptic mechanisms at play.

Finally, the study centers on the effects of Cb-SNc activation on the striatum, leaving unexplored its influence on other brain regions receiving SNc projections. Investigating how Cb-SNc activity affects additional basal ganglia structures and regions beyond would be crucial for understanding its broader impact on brain networks and behavior. Future research using tools like fiber photometry with region-specific dopamine or calcium sensors could help elucidate these effects.

By addressing these limitations, future researchers can achieve a more nuanced and comprehensive understanding of the cerebello-nigral pathway's roles in reward processing, motor control, and its therapeutic potential.

Conclusion

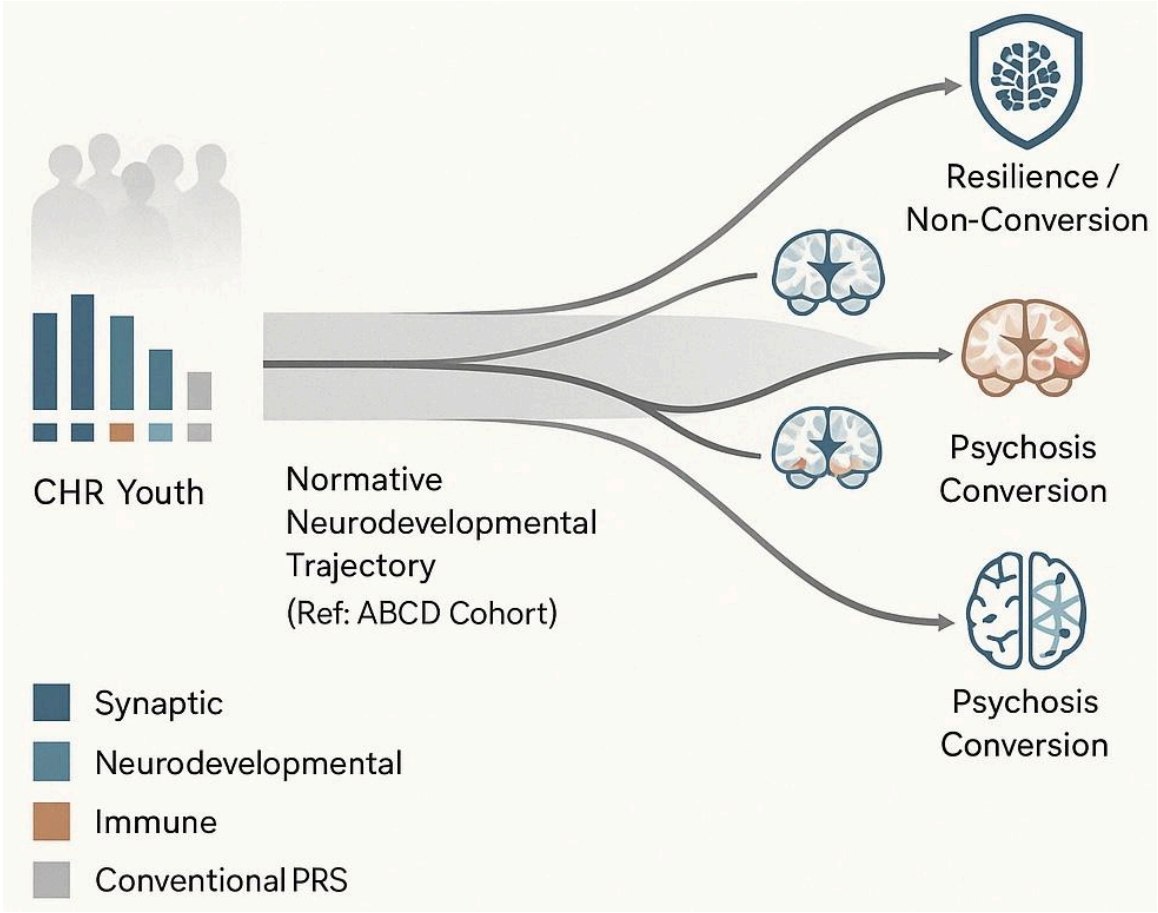
Washburn et al. (2024) make a groundbreaking contribution to our understanding of cerebellar function, providing the first direct evidence for a monosynaptic pathway from the cerebellum to the substantia nigra pars compacta (SNc). This discovery challenges the traditional view of the cerebellum as solely an indirect modulator of reward, highlighting its direct and rapid influence on the dopaminergic system. The study's findings have significant implications for understanding both healthy motor control and potential therapeutic strategies for movement disorders like Parkinson's disease.

By demonstrating that cerebellar activation of the SNc increases striatal dopamine levels and influences locomotion, the study provides a compelling link between the cerebellum, traditionally associated with motor learning and coordination, and the brain's reward circuitry. This finding opens up exciting possibilities for investigating the cerebellum's role in a wide range of motivated behaviors, including those related to reward-seeking, decision-making, and even potentially addiction and mood regulation.

The study's limitations, while important to acknowledge, do not diminish the significance of its findings. The identified limitations, rather, serve as a springboard for future research to further unravel the complexities of the Cb-SNc pathway and its broader influence on brain networks and behavior. Exploring the specific roles of different cerebellar nuclei, clarifying the precise mechanisms of dopamine modulation, investigating the pathway's influence on other brain regions, and using more complex behavioral paradigms will be crucial for gaining a more comprehensive understanding of this novel circuit.

This research, with its innovative use of techniques and its focus on a previously underappreciated pathway, represents a paradigm shift in our understanding of cerebellar function. The cerebellum can no longer be viewed solely as a motor control center; it is now recognized as an active participant in shaping reward-related behaviors and influencing dopaminergic signaling in the brain. This expanded view of cerebellar function holds great promise for developing new therapeutic strategies for disorders involving reward processing deficits, potentially leading to innovative treatments for conditions like Parkinson's disease and addiction.

Integrated Polygenic Profiling and Normative Neurodevelopmental Modeling to Dissect Psychosis Resilience in Youth at Clinical High Risk



Specific Aims

Overview: Psychotic disorders often first manifest in adolescence and early adulthood, causing profound disability. Identifying which at-risk youth will develop psychosis—and *why* others **resist** illness despite risk factors—remains a critical challenge. Clinical high-risk (CHR) youth can be identified based on subthreshold symptoms, but current risk prediction is only moderately accurate (only ~15–25% of CHR individuals convert to psychosis within 2 years). Genetic liability contributes substantially (schizophrenia is highly heritable), yet classical polygenic risk scores (PRS) offer limited predictive power in CHR cohorts and provide little biological insight. Similarly, neuroimaging studies reveal group-level brain differences in CHR, but averaging across individuals obscures person-specific deviations that might herald psychosis onset. **This project integrates polygenic profiling with normative brain modeling to pinpoint individualized risk and resilience biomarkers in CHR youth.** I will leverage the North American Prodrome Longitudinal Study (NAPLS) dataset (~700 CHR adolescents with genomic, neuroimaging, and clinical follow-up data) as the primary sample, with supplementary data drawn from ABCD (normative reference cohort) and ProNET (an international CHR consortium). **I propose three specific aims**:

1. **Aim 1: Construct and validate pathway-partitioned polygenic risk scores (pPGS) for psychosis in CHR youth.** I will decompose polygenic risk by biological pathways (e.g. synaptic function, neurodevelopmental processes, immune signaling) to create **partitioned PRS** for each individual. I hypothesize that certain pathway-specific scores will more accurately predict clinical outcomes (conversion to psychosis and symptom trajectories) than conventional genome-wide PRS. *Outcome:* Aim 1 aims to identify which molecular pathways confer the greatest genetic risk for psychosis in youth, providing a biologically informative genetic profile for each CHR individual.
2. **Aim 2: Link polygenic pathway risk to individualized neurodevelopmental brain trajectories via normative modeling.** I will apply **normative brain modeling** to quantify how each CHR youth's brain structure/function deviates from age-expected norms, using the ABCD study as a large healthy reference. I hypothesize that CHR youth with high pathway-specific polygenic risks will exhibit corresponding atypical brain development (e.g., accelerated cortical thinning or dysmaturation in specific networks) relative to normative reference biotypes. *Outcome:* Aim 2 seeks to link individual

genetic liability to personalized neuroimaging "fingerprints," potentially illuminating how variation within specific genetic pathways manifests to disrupt neurodevelopment prior to psychosis conversion.

3. **Aim 3: Identify "resilient" CHR individuals with high genetic risk but normative brain profiles (and vice versa) to uncover protective factors.** By integrating genetic risk (Aim 1) and brain deviation (Aim 2) profiles, I will identify **discordant risk cases**, for example: youth with high polygenic risk who nonetheless exhibit predominantly typical brain development and do *not* progress to psychosis (putative resilient individuals), and conversely those with low genetic risk but substantial brain deviations who do develop illness. I will compare these subgroups to discover factors associated with psychosis resilience. I hypothesize that resilient high-risk youth enjoy protective elements (e.g. enriching environments, cognitive reserve, or compensatory neurobiology) that differentiate them from those who become ill. *Outcome:* Aim 3 will isolate protective factors and alternative pathways that buffer against psychosis, informing novel preventive strategies.

Impact: Collectively, these aims will produce an integrated **"genotype-phenotype-environment"** model of psychosis risk and resilience in adolescence. This project directly addresses NIMH's strategic priority to leverage big data and novel analytics for the early identification of serious mental illness. The **innovation** lies in uniting genomics and normative neuroimaging to move beyond a risk-only paradigm while simultaneously capturing **why some high-risk youth remain well**. The findings will guide more precise risk stratification (e.g. pathway-specific risk scores) and highlight targets for early intervention (including enhancing protective factors), ultimately helping to preempt psychosis and improve youth outcomes.

Research Strategy

Significance

High-risk youth and the need for precise predictive markers: Psychotic disorders (like schizophrenia) emerge in adolescence, often after a **prodromal** period of subclinical symptoms. Early intervention during this CHR phase can be life-changing, but current tools cannot reliably distinguish which youths will transition to full psychosis. Even with specialized risk calculators, only about **15–25% of CHR individuals develop psychosis within 2 years**, meaning many false positives. This uncertainty limits the ability to target preventive interventions and causes undue stress for families. There is an urgent need for **more precise, biologically informed markers** to improve early psychosis prediction and to understand why some at-risk youth **resist progression** to illness.

Genomic information is underutilized in risk assessment: Psychosis risk is strongly influenced by genetics (heritability of schizophrenia ~80%). Polygenic risk score (PRS) approaches have shown that higher PRS for schizophrenia is associated with greater conversion risk in CHR samples. However, traditional PRS compute cumulative genetic liability across thousands of associated variants, offering **limited predictive power** and little insight into underlying biological mechanisms. A significant gap is that we do not know *which* biological pathways drive this polygenic risk (e.g., do risk genes disproportionately affect synaptic biology or Immune processes?) **Partitioning genetic risk by pathway** can enhance interpretability and potentially improve prediction by focusing on the most relevant gene sets.

Neurodevelopmental deviations can serve as early warnings: Converging evidence indicates that subtle brain changes precede psychosis onset. CHR youth, on average, show neuroimaging abnormalities (e.g. cortical thinning or dysconnectivity) compared to healthy peers. However, these findings are typically at the **group level**; they do not tell us what is happening in a specific individual's brain. **Normative modeling** is an emerging approach that addresses this by using large healthy reference data to define typical developmental trajectories for brain structure and function. By comparing a CHR youth's MRI measures to age- and sex-matched norms, we can derive **person-specific deviation scores** (like a Z-score for how far their brain metrics deviate from expected). This yields individualized biomarkers indicating if a given adolescent's brain development is atypical in a manner associated with progression to psychosis. Normative models effectively create **"neurodevelopmental charts"**, and flag extreme outliers. Applying this to CHR youth is highly significant: it can identify which youth have abnormal neurodevelopmental trajectories (potential "red flags" for illness) versus those developing typically *despite* risk factors. Such personalized neuroimaging markers represent a new frontier in computational psychiatry, emphasizing individual differences over group averages.

Resilience should not be discounted: Equally important as risk factors are the **protective factors** that allow some high-risk youth to thrive. In CHR cohorts, a majority do *not* convert to psychosis, even among those with high polygenic risk or worrisome signs. Why do some individuals remain well? Understanding this "psychosis resilience" could transform prevention: rather than only reducing risk, it might become feasible to bolster protective mechanisms. So far, resilience in CHR has received less attention than risk. Recent work

suggests factors like **supportive family environment, positive life events, and better cognitive reserve** correlate with resilient outcomes. However, we lack a framework to identify resilient individuals in advance. By integrating genetic and brain profiles, this project objectively highlights CHR youth who **defy the odds** (e.g. carrying high genetic risk without ill effect). Studying these cases in Aim 3 will uncover protective influences, including but not limited to: genetic variants that mitigate risk, robust neuroplasticity, or beneficial environmental factors (e.g. strong social support). These insights are directly translatable: for example, if high-risk non-converters are identified to consistently enjoy greater social support, this could underscore the importance of psychosocial interventions to foster resilience in CHR populations. In short, illuminating **why some high-risk youth stay well** is as significant as understanding why others become ill, filling a critical gap in early psychosis research.

This proposal addresses key NIMH priorities by leveraging **big data (genomics, multimodal imaging)** and innovative analytics to improve early identification of serious mental illness. It embodies a **precision psychiatry** approach, integrating multidimensional data (genes, brain, environment) to tailor risk assessment for individuals. The project is **ideally positioned** in Dr. Carrie Bearden's lab, which specializes in the investigation of psychosis neurodevelopment and holds decades of experience leading CHR-centered research. These include primary investigation of the **NAPLS** cohort, containing neuroimaging, genomic, and clinical follow-up data from ~700 CHR participants; ongoing participation in the **ProNET** consortium, which integrates multimodal biomarkers to dissect CHR heterogeneity and develop individualized risk-prediction and intervention-guidance algorithms; and leadership of a **22q11.2** deletion syndrome (22q11.2DS) study characterizing the neurobehavioral consequences of this high-penetrance psychosis risk CNV. These rich resources and mentorship comprise an exceptionally well suited environment to carry out the proposed research. The project's questions are deeply aligned with the lab's mission to understand youth at risk for psychosis and to identify biomarkers that can inform early intervention. This synergy ensures **feasibility** (data and expertise are in hand) and maximizes the likelihood of impactful discoveries that will be readily interpreted in a real-world clinical context.

Innovation

This proposal introduces a **novel integration** of *partitioned polygenic scores* with *normative neurodevelopmental modeling* to characterize psychosis risk and resilience. Key innovations include:

A. **Pathway-Specific Polygenic Risk Scores (pPGS):** *Moving beyond one-size-fits-all PRS.* Rather than a single polygenic score, I will compute **multiple scores each capturing a specific biological pathway** or gene set (e.g. genes for synaptic structure, for dopaminergic signaling, for immune function). Recent advances in psychiatric genomics demonstrate that stratifying genetic risk by functional categories can unmask relationships that are lost in global PRS. By isolating polygenic signals relevant to distinct mechanisms and biological pathways, pPGS adds biological interpretability to existing PRS. For example, a "synaptic plasticity score" might pinpoint neural circuitry risk, and potentially improve predictive power relative to global PRS if specific pathways are ultimately identified as top drivers of psychosis. This approach is distinct within statistical genetics, providing a biologically informed annotation of big GWAS data. Application of pPGS within the NAPLS participants dataset represents the first application of pathway-partitioned PRS in a CHR cohort, expanding on prior CHR studies that found overall PRS to have limited predictive utility. If successful, this innovation yields a **precision genomic profile** for each individual (which pathways are high-risk for *them*), opening the door to targeted interventions (e.g. modulation of a specific brain circuits or signalling pathways).

B. **Normative Brain Trajectories for Individualized Biomarkers:** *Shifting from group means to person-specific neuroimaging.* I will implement **normative modeling** using the unprecedented ABCD dataset (~11,000 youth) to establish representative typical neurodevelopmental trajectory from ages ~9–18. For each CHR youth in NAPLS, I will calculate how their brain measures deviate from these norms, yielding a **personalized deviation map** across dozens of brain regions. This approach is highly innovative, as it compares each individual as a *singular* reference relative to the typically-developing norm, in contrast to prevailing case-control *group* comparisons. Normative modeling has only recently become feasible with big data and advanced statistical tools. Large-scale "brain chart" projects have demonstrated the power of this approach to capture outlier individuals in developmental populations (e.g. identifying adolescents whose brain metrics are extreme for their age). Our group will be among the first to apply it to a CHR cohort. This enables the detection of subtle neurobiological warning signs *at participant resolution* (e.g., an adolescent may exhibit abnormally low hippocampal volume *for their age*, which could be a warning sign even if the group average difference is small). By integrating these differences with genetic information, our approach aligns with the concept of **computational**

psychiatry, leveraging quantitative models to yield clinically relevant, personalized biomarkers. It represents a conceptual shift towards *precision neuroimaging* in early psychosis.

C. **Integrated Risk-Resilience Spectrum Analysis:** *Not only identifying risk factors, but also why some individuals escape it.* A particularly **innovative aspect** is this design's explicit prioritization of **resilience biomarkers elucidation in CHR** over those associated with risk. By cross-referencing genetic risk with brain development profiles, I will identify CHR youth who defy typical risk correlations (e.g. high genetic risk *without* corresponding brain pathology, or vice versa). Studying these discordant cases is a novel strategy to uncover protective factors or alternate pathways to illness. Traditional studies focus on risk factors alone; our project is forward-looking in that it will capture **both ends of the spectrum**—risk *and* resilience—within the same framework. This dual focus can reveal, for example, that some youth remain well due to enriching environments or compensatory brain adaptations. Uncovering such factors (which might include psychosocial support, specific alleles that counteract risk, or enhanced cognitive networks) would break new ground in psychosis prevention. Ultimately, this integrative approach could inform a **"protective index"** analogous to risk scores, highlighting positive predictors of wellness in high-risk youth. I anticipate this strategy will yield novel insights and a more balanced understanding of the psychosis prodrome, viewing it not only as a trajectory of decline but as one that can be diverted or buffered by resilience. This is directly in line with modern prevention science, making the project highly innovative in scope and vision.

By uniting these elements—**biologically informed polygenic profiling, individualized brain deviation mapping, and a resilience emphasis**—our approach is distinctly **multidisciplinary and transformative**. The knowledge gained could aid in redefining the assessment and risk stratification of CHR youth, moving the field toward a more precise, personalized, and optimistic paradigm that identifies *both* risk *and* resilience factors to optimize interventions for the most vulnerable.

Approach

Overview: I will address the above aims using existing datasets and robust analytical pipelines. The **primary cohort** is NAPLS, comprising ~700 CHR adolescents who have genomic data (SNP genotyping), longitudinal clinical assessments, and MRI scans (structural and functional). I will integrate external data where needed: the **ABCD study** (to train normative models on a large healthy sample) and potentially the **ProNET** CHR cohort or Dr. Bearden's **22q11.2DS** cohort for exploratory validation. All analyses will account for relevant covariates (age, sex, site, etc.) and adhere to rigorous standards of reproducibility (pre-processing quality control, cross-validation, and correction for multiple comparisons).

Aim 1: Construct and Validate Pathway-Partitioned Polygenic Scores (pPGS) for Psychosis in CHR Youth

Rationale: Genome-wide PRS aggregate risk across all variants in the genome, potentially diluting signals from biologically-implicated pathways. By partitioning the PRS, specific hypotheses about **mechanisms** and outcome prediction can be evaluated (e.g., is polygenic risk enriched for genes in synaptic function? immune response?). This aim will establish a *genetic risk profile* for each individual decomposed by biological category, providing the foundation to link with brain and clinical data. Importantly, Aim 1 is analytically independent: even if partitioning yields no better prediction than a standard PRS, it will still inform us that psychosis genetic risk is diffusely distributed, and I will proceed to use the global PRS for subsequent aims.

Data and Sample: I will use the NAPLS cohort (~700 CHR individuals). About 15–25% convert to psychosis within 2 years, giving us a substantial number of outcomes (~100–150 converters) for analysis. Genotyping (genome-wide SNP array data) is already collected; I will use imputed SNP data to ensure comprehensive variant coverage. **Covariates** in all genetic analyses will include ancestry principal components (to control population stratification), age, sex, and study site. I will ensure all individuals meet standard quality control (QC) for genotyping (e.g. call rate > 98%, unrelatedness, etc.).

Generation of Pathway-Specific Polygenic Scores: I will obtain summary statistics from large psychiatric GWAS meta-analyses, primarily the latest **Psychiatric Genomics Consortium (PGC)** results for schizophrenia (and potentially bipolar disorder or major depression for shared risk loci). From these GWAS, I will **curate biologically relevant gene sets** to partition the SNPs. Candidate gene sets include:

A. *Synaptic plasticity, neuroinflammation and neurotransmission genes* (e.g. from SynGO database for synaptic genes),
B. *Neurodevelopmental processes* (genes involved in cortical development, axon guidance, etc., via Gene Ontology),
C. *Excitatory/Inhibitory neuron function* (e.g. genes regulating glutamatergic vs GABAergic signaling),
D. *Immune and inflammation pathways* (given evidence of immune involvement in schizophrenia),

E. Other relevant pathways like oxidative stress or hormone signaling as supported by literature.

For each gene set, I will extract SNPs within those genes (and perhaps regulatory regions) from the GWAS summary. I will then calculate a **polygenic score for each pathway** for every NAPLS individual. Scoring will be performed using standard tools (PLINK/PRSice-2) and/or Bayesian approaches (LDpred2) to incorporate linkage disequilibrium. Each score (pPGS) is essentially the sum of risk alleles in that pathway weighted by GWAS effect sizes. In addition to pathway scores, I will compute the conventional genome-wide PRS for baseline comparison. I will likely tune scores by P-value thresholding or other optimization, using an internal cross-validation approach within NAPLS (e.g., split into training/validation sets to avoid overfitting when selecting threshold parameters).

Clinical Outcome Analyses: Our primary outcome is **conversion to psychosis** (time-to-event within the follow-up period). I will use **Cox proportional hazards regression** to test if each pPGS is associated with hazard of psychosis onset, controlling for covariates (age, sex, ancestry PCs, etc.). This time-to-event framework makes use of the exact conversion timing and accounts for varying follow-up durations. Secondary outcomes include **symptom trajectories** and functional outcomes. NAPLS has serial symptom ratings (e.g. SOPS scale); I will fit linear mixed-effects models to determine if baseline pPGS predict the **trajectory of symptom severity** over time (for example, do individuals with high neurodevelopmental pPGS show steeper increase in negative symptoms?). I will also examine functional measures (social/role functioning scores) as outcomes. For all models, I will apply stringent **multiple comparison correction** since multiple scores are tested—likely controlling the false discovery rate (FDR) across all pathway score tests, or using Bonferroni if the number of scores is modest. This will ensure I identify the most robust associations.

Sex as a Biological Variable: I will explore whether polygenic effects differ by sex. Specifically, I will include **pPGS × sex interaction** terms in the models. This will test, for example, if a given pathway score is a stronger risk predictor in males versus females. If significant, I will stratify analyses by sex to interpret sex-specific genetic risk profiles. If no interactions are found, I will still report results adjusted for sex.

Anticipated Results: I expect to find that certain pathway-specific scores (e.g. those related to neuronal signaling or neurodevelopment) have a **significantly elevated hazard ratio** for conversion. For example, a high "synaptic gene PGS" might be associated with 2-fold higher risk of psychosis. Conversely, some scores (e.g. immune PGS) might show little to no predictive value, suggesting those pathways are less central in early psychosis. I also anticipate that combining top pathways or using them jointly in a multivariate model could improve prediction beyond the single PRS. Regardless of outcome, this aim will yield valuable insights: if successful, it identifies mechanistic genetic risks; if none outperform the global PRS, it indicates that risk is polygenic in a distributed way—an important finding in itself, guiding us to focus on aggregate risk or consider gene-environment interplay.

Potential Pitfalls and Alternatives:

A. *Pitfall 1:* **No pathway exhibits stronger prediction than the overall PRS.** It's possible that partitioning does not boost predictive power. **Plan:** Even in this case, the analysis is still informative (a negative finding that risk is not dominated by any one pathway). I would apply the standard PRS (or all pPGS collectively) in subsequent aims to examine gene-brain links. I can also refine our partitions (e.g. combine related gene sets to increase power, or examine alternative pathway definitions) to test if different grouping yields a signal.
B. *Pitfall 2:* **Limited power for rare pathway variants or small effect sizes.** Some gene sets might have very subtle effects that our sample can't detect. **Plan:** I will prioritize pathways with a strong a priori basis in psychosis biology to maximize chance of detectable effects. If certain scores are very weak, I may drop them or merge them with broader categories (increasing the polygenic scope to capture more variance). Our sample of ~700 is one of the largest CHR genetics cohorts, but if needed I could seek replication or aggregation (e.g. testing our pPGS in the independent ProNET sample if data become available, or earlier NAPLS waves) to validate findings.

Timeline (Aim 1): *Months 1–3:* Curate gene sets and acquire GWAS results; establish the computational pipeline for scoring. *Months 4–6:* Compute pPGS for all individuals across pathways; optimize scoring parameters. *Months 7–9:* Perform statistical analyses (Cox models for conversion, mixed models for symptoms); apply multiple comparisons correction. *Months 10–12:* Interpret results, refine partitions if needed, and prepare initial manuscript on pathway-specific genetic risk in CHR.

Aim 2: Link Polygenic Pathway Risks to Individualized Neurodevelopmental Trajectories via Normative Brain Modeling

Rationale: Aim 2 examines the **gene→brain relationship**: do youths with high genetic risk in certain pathways show abnormal brain development patterns? Many prior studies have compared average brain

measures between CHR and healthy controls, finding subtle differences (e.g. slightly thinner cortex in frontal regions). But CHR individuals are heterogeneous, thus group means may obscure those who have large deviations. **Normative modeling** is ideal here: it allows us to quantify brain aberrations at the single-subject level . By mapping each CHR youth's brain features to where they fall on an age-normative distribution, I can detect *who* has aberrant neurodevelopment. I will then test whether these person-specific brain deviations are linked to the polygenic scores from Aim 1. This aim is largely independent of Aim 1's outcomes: even if Aim 1 yields no standout pathways, I can still examine the global PRS or all pPGS in aggregate to test if polygenic burden correlates with brain changes. Conversely, even if no genetic associations emerge, describing the brain deviation profiles of CHR youth is itself a valuable contribution.

Data and Measures: I will utilize **longitudinal MRI data from NAPLS**. Most NAPLS participants have at least one structural MRI; many have multiple timepoints. Structural measures will include cortical thickness and surface area (parcellated by region, e.g. using FreeSurfer Desikan-Killiany atlas), and subcortical volumes (hippocampus, thalamus, etc.). If available, I will also incorporate resting-state fMRI-derived metrics (e.g. network connectivity strength) —NAPLS has some resting fMRI data, although structural MRI is the primary focus due to completeness. I will also leverage the **ABCD study** as our normative reference. ABCD provides a large sample of healthy children and adolescents (ages 9–18) with MRI data, which I will use to train normative models of brain development. I will ensure that MRI measures are harmonized between ABCD and NAPLS (accounting for scanner differences, e.g., *ComBat* to correct for site effects).

Normative Modeling Procedure: Using the ABCD dataset (which includes thousands of individuals, many with two or more scans), I will model the expected trajectory of each brain measure as a function of age (and other covariates). I will likely use a flexible nonlinear regression approach such as **Gaussian Process Regression (GPR)** or Bayesian hierarchical modeling (as implemented in the *PCNToolkit* for normative modeling). These methods can capture complex developmental curves and individual variance. I will include **covariates** like sex in the model to allow sex-specific norms if warranted (or include sex as a covariate to remove any gross sex differences in development). The output will be, for each brain feature (e.g. thickness of left dorsolateral prefrontal cortex), a mean and variance as a function of age (and sex) representing the normative population expectation.

For each CHR youth in NAPLS, at each MRI timepoint, I will compute a **deviation score** = (observed value – age/sex-expected mean) / SD. This results in a Z-score indicating how divergent that individual's brain measure is relative to peers of the same age. I will do this for all brain regional measures, potentially yielding a profile such as "Patient X has cortical thickness that is 2 SD below age-norm in the left superior frontal gyrus, and hippocampal volume 1.5 SD above norm," etc. I will especially focus on the **baseline scan** (or the scan prior to any conversion) for each CHR, though I can also examine change over time (e.g. does deviation get worse or improve at follow-up scans). Normative modeling will allow us to classify individuals as having **no significant deviations, moderate deviations, or extreme deviations** in various brain systems. I anticipate some CHR youth will show widespread deviations (multiple regions off-norm), whereas others look typical.

Linking Genetic Risk to Brain Deviations: Once each individual has polygenic scores (Aim 1) and brain deviation scores, I will statistically examine associations between the two. For example, I will test if a high **synaptic pPGS** correlates with greater deviation in cortical thickness in synaptic connectivity-related regions (frontal and temporal lobes). I will use regression models where brain deviation metrics are outcomes and pPGS are predictors (including covariates like sex, intracranial volume, and MRI site). Given the high dimensionality (many brain regions and several pPGS), I will start with targeted hypotheses: e.g., testing specific pairs like *neurodevelopmental pPGS vs. cortical thickness deviations* (hypothesizing that higher genetic risk in neurodevelopment genes predicts more negative deviation—thinner cortex than expected). I will correct for multiple tests across regions and scores, or use dimension reduction (such as summarizing deviations across regions into a global score or using principal components of the deviation map). Another approach is a **multivariate analysis** like canonical correlation analysis (CCA) or partial least squares (PLS) to characterize covariation patterns between the set of pPGS and the set of brain deviations. This could reveal, hypothetically, a mode where "high glutamatergic and neurodevelopmental genetic risk aligns with a pattern of widespread fronto-temporal brain deviations."

I will also evaluate if adding brain deviation measures improves prediction of outcomes beyond genetics. While this is more in Aim 3's territory, in Aim 2 I might do exploratory analyses like: does combining a particular pPGS and a particular brain deviation give a stronger prediction of conversion than either alone? This would hint at gene-brain interactions in determining outcomes.

Sex and Subgroup Analyses: As with Aim 1, I will examine **sex effects** by including sex interaction terms in gene→brain models: e.g., is the correlation between a given pPGS and brain deviation stronger in

males or females? Additionally, I might explore if gene-brain links are modulated by other factors (e.g., medication status or environmental exposures), although those interactions likely belong more to Aim 3's focus. All analyses will be conducted with rigorous cross-validation where feasible (though here I am primarily describing associations within one cohort, so cross-validation mainly applied in normative model fitting and pPGS training).

Anticipated Results: I expect to identify biologically sensible gene-brain relationships. I **hypothesize** that polygenic risk related to neuronal excitation/inhibition balance will be associated with deviations in cortical development of regions integral to those circuits (e.g., prefrontal or auditory cortex). Therefore, I might observe that CHR youth with high "neurodevelopmental gene PGS" have **accelerated cortical thinning** (i.e. negative deviation scores indicating thinner cortex than normal for their age) in frontal regions involved in executive function. Another possible finding: a high immune/inflammatory PGS could correlate with **abnormal volume** in subcortical structures (if neuroinflammation affects those areas) or perhaps show no effect, indicating that pathway isn't manifesting in brain structure changes. If our analyses do not yield significant associations, this could implicate alternative pathways for genetic risk might be influencing psychosis through pathways not captured by gross brain anatomy—or that environmental factors are needed to unmask genetic effects. However, given prior evidence that schizophrenia risk genes often affect brain structure (including known genetic overlap with brain morphology), I anticipate at least some detectable gene-brain links.

Potential Pitfalls and Alternatives:

A. *Pitfall 1:* **Normative model mismatch or technical issues.** The CHR sample (NAPLS) might differ from ABCD (scanners, demographics), potentially confounding deviation scores. **Plan:** I will harmonize data as much as possible (using identical MRI measures and statistical harmonization for site effects). I can also run a sensitivity analysis using a subset of ABCD matched on demographics to NAPLS or even use the healthy controls from NAPLS (if any) to build a smaller normative reference. If normative modeling proves complex, a simpler approach is to use **percentile norms** derived from ABCD or to compare CHR directly to matched controls (though that loses the individual-level resolution).
B. *Pitfall 2:* **Weak gene-brain correlations.** It's possible that polygenic scores do not show clear association with brain deviations due to limited effect sizes or noise. **Plan:** I will increase power by focusing on a few principal components of brain deviation (instead of hundreds of regions separately) to capture the major variance. I can also aggregate pPGS into a composite if needed (e.g., total polygenic load) to test overall genetic burden vs overall brain abnormality. If no associations are found, it suggests that genetics and brain might independently contribute to risk (or that timing is an issue, e.g., brain changes occur closer to conversion than our baseline genetic measure can capture). I would then proceed to Aim 3 using a broader definition of "risk" (e.g., top quartile PRS as "genetically high risk" and individuals with any significant brain deviation as "brain-atypical") to still define subgroups for resilience analysis.

Timeline (Aim 2): *Months 1–6:* Develop normative models with ABCD data (this can run in parallel with Aim 1). Validate that the model outputs sensible developmental trajectories for key measures. *Months 4–9:* Compute brain deviation scores for all NAPLS participants at baseline (and follow-up where possible). *Months 7–12:* Conduct gene-brain association analyses as described; iterate if needed for dimensionality reduction. By the end of Year 1, I expect initial gene-brain results; by mid-Year 2, finalize analyses and prepare a manuscript on polygenic risk and brain developmental deviations in CHR.

Aim 3: Identify Resilient vs. At-Risk Profiles by Integrating Genetic Risk and Brain Deviation to Uncover Protective Factors

Rationale: Aim 3 moves to an *integrative and translational* level. I will combine the genetic and neuroimaging dimensions to identify individuals who are **discordant** in risk markers—specifically **"resilient" cases** (high genetic risk but surprisingly normative brain development, who remain well) and **"unexpected converters"** (low genetic risk but large brain deviations, or vice versa). These outliers can reveal important protective or non-genetic risk factors. Studying why a high-risk person did *not* become ill can highlight protective influences that typical risk-factor analyses miss. By characterizing these subgroups, I aim to shift the focus from purely risk prediction to also understanding **mechanisms of resilience**. This aim ensures that even if earlier aims do not yield significant biomarkers, extreme cases are still examined in a meaningful way (e.g., an individual possessing all the risk indicators that did not convert). The analysis here will use outcomes (conversion or not, functional status) to define groups and then probe differences in environmental exposures, behavior, or additional biomarkers.

Subgroup Definition: I will create a 2-dimensional classification of CHR individuals based on **genetic risk level** and **brain deviation level**. For genetic risk, I can use the **composite polygenic risk** (if one

pathway stands out from Aim 1, I could use that, but more likely a composite or the top principal component of all pPGS). I will designate thresholds, for example the top ~25% of the PRS distribution as "Genetically High Risk" and bottom 25% as "Genetically Low Risk." Similarly, for brain deviation, I will derive an aggregate metric (like the number of brain measures with >2 SD deviation or perhaps the first principal component of the deviation profile indicating overall abnormality). The top ~25% most neuro-atypical individuals (those with the greatest overall deviation from norms) can be labeled "High Brain-Deviation," and the bottom 25% (closest to normative) as "Low Brain-Deviation." This yields four cells:

A. **High Genetic, High Brain risk**
B. **High Genetic, Low Brain risk**
C. **Low Genetic, High Brain risk**
D. **Low Genetic, Low Brain risk**

The group of greatest interest is **High-Genetic + Low-Brain**: these are youths who carry substantial genetic risk but who's brains appear typically developing—hypothesized *resilient* individuals. Conversely, **Low-Genetic + High-Brain** are those whose genetics alone wouldn't flag them, yet they show significant brain abnormalities; these might be driven by strong environmental or other factors (a different path to psychosis risk). The **High-High** group would represent those carrying multi-level risk (likely highest conversion rates), and **Low-Low** are low-risk on both fronts (expected to have best outcomes).

Using this stratification (with continuous measures available as well), I will examine **clinical outcomes** in each subgroup to validate the concept. I predict that the *High-Genetic + Low-Brain* group will have **better outcomes (lower conversion rate)** than the High-Genetic + High-Brain group—that exhibiting a normative neurodevelopmental trajectory predicts some degree of resilience to high genetic liability. Similarly, the Low-Genetic + High-Brain group might have worse outcomes than their genetics would suggest, perhaps due to non-genetic insults. These comparisons will tell us if mismatch profiles truly correspond to resilience or hidden risk.

Investigation of Protective and Risk Factors: Once subgroups are identified, I will compare them on various variables to search for factors that could explain why some are resilient. NAPLS collected rich **environmental and clinical data** that I will leverage:

A. **Life history of trauma and stress:** e.g., childhood trauma questionnaire scores, recent stressful life events. I predict resilient individuals may have *lower* trauma exposure or exceptional coping resources.
B. **Social support and family environment:** measures of perceived support or family functioning. Greater support might be a protective factor.
C. **Premorbid adjustment and cognitive reserve:** e.g., educational performance, IQ estimates. Resilient youth might have higher cognitive reserve (as suggested by better premorbid functioning in resilient CHR.
D. **Clinical management:** whether they received early treatment (therapy, low-dose antipsychotics) which might help prevent conversion.
E. **Neurocognitive performance:** NAPLS has cognitive testing (memory, attention). Better cognitive performance could be both an outcome and a resilience factor.
F. **Additional biomarkers:** If available, I will examine factors like baseline cortisol (stress hormone) or EEG measures to evaluate if resilient vs non-resilient differ.

I will perform statistical comparisons: for continuous variables (e.g., trauma score), an ANOVA or t-test between groups (e.g., resilient vs non-resilient); for categorical variables (e.g., sex distribution or medication), chi-square testing. I will particularly test interactions in regression models, such as **Genetic Risk × Environmental Factor** predicting outcome, to evaluate if high support nullifies genetic risk impact (a buffering effect).

I will also examine if resilient individuals show any **compensatory brain characteristics** despite being "normative" in standard metrics. For instance, perhaps resilient youth have *enhanced functional connectivity* in executive control networks (a protective neural adaptation) not captured by structural deviation alone. If resting-state data or other modality data are present, I will explore those.

Integration with External Cohorts: As a supplementary analysis, I will compare these findings with Dr. Bearden's 22q11.2DS cohort. In 22q11.2DS (a neurogenetic model population possessing the strongest genetic risk factor for psychosis), about 25–30% develop psychosis by adulthood. The remaining ~70–75% are resilient in a sense (possessing a high-penetrance psychosis genotype, but escaping psychosis conversion). I will examine available data for these individuals to identify known protective factors (e.g., does higher IQ or better family support distinguish 22q11.2DS youth who *don't* develop psychosis?) While 22q11.2DS is a distinct condition, any commonalities with CHR resilience (e.g., the importance of social engagement) would be

notable. Similarly, if ProNET (an ongoing CHR study) data becomes accessible during the project, I could attempt to replicate the subgroup approach in that independent sample to test if the same patterns hold.

Anticipated Outcomes: I expect the **High-Genetic + Low-Brain (resilient)** group to have significantly *lower conversion rates* and milder symptom trajectories compared to the High-Genetic + High-Brain group (who likely have the highest conversion). This would confirm that having a relatively normal brain development profile helps offset genetic risk. I anticipate identifying specific protective factors in the resilient group: for example, they may report significantly *greater family support and fewer childhood adversities* than their high-risk peers who converted. They might also have better baseline executive function or more gradual symptom onset. In contrast, the **Low-Genetic + High-Brain (unexpected converter)** group might show an enrichment of environmental risk factors like heavy cannabis use or trauma, indicating those factors pushed them toward illness despite low genetic loading. These findings will illustrate concrete scenarios of resilience (genetic risk buffered by environment or other factors) and risk (environment driving pathology even with low genetic predisposition).

Overall, Aim 3 should yield **actionable knowledge**: if resilient youth demonstrate positive social relationships, it reinforces that enhancing social support for CHR patients could improve outcomes. Or if resilient youth have unique neurocognitive strengths, interventions could aim to bolster cognitive remediation. Importantly, even if no protective factors (a possible outcome) are identified, this may support the hypothesis that resilience is simply the absence of risk factors or measurement noise (perhaps supporting deeper genetic or psychosocial investigation efforts).

Potential Pitfalls and Alternatives:

A. *Pitfall 1:* **Few Resilient Cases or Ambiguous Grouping.** If our criteria yield very small groups (e.g. only a handful of high-genetic/low-brain individuals), statistical comparisons lose power. **Plan:** I will adjust thresholds (use top 30% instead of 25%, etc.) to ensure sufficient group sizes. I could also treat genetic and brain risk as continuous and look for *continuous* interactions (e.g., does brain deviation modulate the effect of PRS on outcome). This would use regression to test if the relationship between PRS and conversion is weaker for those with low brain deviation (i.e., resilience effect).

B. *Pitfall 2:* **No clear protective differences found.** It's possible that our resilient vs non-resilient groups do not significantly differ on the measured factors (maybe due to unmeasured factors or small effect). **Plan:** I will report that result, as it suggests resilience might be due to factors outside what I measured (or that our definition needs refining). I would discuss other possibilities that require further investigation (e.g., contributions from benign genetic variants or brain network efficiency). However, given prior evidence in CHR and other high-risk populations, I expect at least some signals (for instance, the literature suggests resilience is often accompanied by better premorbid functioning and social support.

C. *Pitfall 3:* **Complex interplay hard to interpret.** Gene-brain-environment interactions may be multifaceted. **Plan:** I will employ *multivariate* statistical models to concurrently integrate genetic, neuroimaging, and environmental variables, thereby delineating their distinct and interactive contributions to clinical outcomes. This systems-level approach can handle complexity, albeit with caution on overfitting given sample size. Collaboration with the ENIGMA or other imaging genetics consortia may also provide external validation or larger meta-analyses to evaluate if the protective factors identified hold in combined datasets.

Timeline (Aim 3): *Year 2:* As Aim 1 and 2 results solidify, start defining subgroups and gathering relevant environmental data. By the end of Year 2, have preliminary subgroup outcomes analyzed. *Year 3:* Complete detailed comparisons of resilient vs non-resilient groups, including interaction models. If possible, integrate any external cohort analysis (22q11.2DS or ProNET) in parallel. Draft manuscript on resilience factors in CHR by mid-Year 3. Aim 3 analyses and manuscript writing will coincide with the latter part of the fellowship, ensuring time to interpret results in conjunction with mentors.

Timeline and Milestones

I anticipate the project spanning **~3 years**, with substantial parallel progress on aims (since Aim 2's normative modeling can begin while Aim 1's genomic work is underway, etc.). Below is an overview of the research timeline:

Months	Aim 1	Aim 2	Aim 3
1-3	Curate gene sets, acquire GWAS summary statistics, set up computational pipeline for pPGS calculation.	Begin development of normative models using ABCD data.	

4-6	Compute pPGS for all NAPLS individuals; optimize scoring parameters through internal cross-validation.	Validate normative models; ensure outputs produce sensible developmental trajectories for key brain measures.	
7-9	Perform statistical analyses (Cox models for psychosis conversion, mixed-effects models for symptom trajectories); apply multiple comparisons correction.	Compute brain deviation scores for all NAPLS participants at baseline (and follow-up timepoints where available).	
10-12	Interpret results; refine pathway partitions if needed based on initial findings; prepare a manuscript draft on pathway-specific genetic risk.	Conduct gene-brain association analyses (linking pPGS from Aim 1 to brain deviation scores from Aim 2); iterate with dimensionality reduction if needed.	
13-18		Finalize gene-brain association analyses; prepare a manuscript on polygenic risk and brain developmental deviations in CHR.	Begin defining subgroups (resilient, unexpected converter) based on integrated genetic and brain data.
19-24			Gather and prepare environmental, clinical, and cognitive data for subgroup comparisons. Conduct preliminary analyses of subgroup outcomes (conversion rates, symptom trajectories).
25-30			Complete detailed comparisons of resilient vs. non-resilient groups, including interaction models (gene x environment). Explore potential integration with external cohorts (22q11.2DS, ProNET).
31-36			Draft and revise manuscript on resilience factors in CHR. Prepare for submission to a peer-reviewed journal.

Rigor, Reproducibility, and Feasibility

I will leverage well-established datasets and methods, ensuring a high level of rigor. **Sample size/power:** NAPLS (n~700) provides adequate power for this analysis. For example, detecting a modest effect (Hazard Ratio ~1.5) for top vs. bottom PRS groups with ~100 converters is feasible, as shown in prior work. I will maximize power using efficient statistical models (time-to-event for conversion) and multi-site data integration (with covariate adjustments for site). **Data quality:** All genomic data undergo QC; imaging data will be quality-checked and harmonized. I will employ cross-validation and, where possible, replicate findings in independent data to ensure reproducibility. **Statistical rigor:** I will pre-plan our analyses to reduce data dredging, and adjust for multiple comparisons to control false positives. All code for computing scores and normative models will be documented and made available for transparency. **Feasibility:** The project is of **manageable scope** for a dissertation timespan. Aim 1 leverages existing genotype data and public GWAS summary statistics, Aim 2 employs advanced but established normative modeling approaches (Members of our lab have expertise applying this method), and Aim 3 largely involves data integration and statistical analysis of variables already collected. Mentorship from Dr. Bearden and statistical genetics collaborators will ensure the required expertise is available.

Importantly, the design is **flexible to yield meaningful results under various outcomes**. Even if some hypotheses are not borne out, the data-driven discoveries will still contribute significant knowledge to clinicians and researchers invested in alleviating the mental distress of individuals experiencing psychosis. The

project's multi-aim structure is designed such that the success of individual aims does not limit the success of the others. This complementary setup, combined with a strong mentoring environment and available resources, underpins the project's high likelihood of successful completion and significant scientific contribution.

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20. From Serendipity to Precision: Integrating AI, Multi-Omics, and Human-Specific Models for Personalized Neuropsychiatric Care
21.

Detailed Timeline

Time Period	Aim 1: Pathway-Partitioned Polygenic Scores (pPGS)	Aim 2: Normative Neurodevelopmental Modeling	Aim 3: Integrated Risk–Resilience Analysis	Training/Dissemination
Year 1 (Months 1–12)	**Months 1-3:** • Curate biologically relevant gene sets (e.g., synaptic, neurodevelopment, immune). • Acquire latest PGC GWAS summary statistics. • Establish the computational pipeline (e.g., PLINK, PRSice2, LDpred2).	**Months 1-6:** • Develop and validate normative modeling framework using ABCD data (Gaussian Process Regression/Bayesian Hierarchical Modeling). • Harmonize MRI measures between ABCD and NAPLS using ComBat.	**Months 10-12:** • Define initial criteria for resilience subgroups (based on preliminary pPGS and brain deviation scores). • Start exploratory analyses on environmental data from NAPLS.	**Ongoing:** • Attend advanced courses/workshops in statistical genetics, neuroimaging, and machine learning. • Present progress at internal lab meetings.
Year 2 (Months 13–24)	**Months 4-9 (Year 1 continuation/Year 2 start):** • Compute pPGS for the entire NAPLS cohort. • Optimize scoring thresholds via cross-validation. **Months 10-12 (Year 2):** • Run Cox proportional hazards models to test pPGS associations with conversion; conduct mixed-effects models for symptom trajectories. • Prepare initial manuscript for Aim 1 results.	**Months 7-12:** • Compute individualized brain deviation (Z-scores) for all available NAPLS scans (baseline & follow-up). • Begin targeted gene–brain association analyses using regression/CCA models. **Months 13-18:** • Refine models based on initial results; focus on key regions (e.g., fronto-temporal cortex). • Draft manuscript for Aim 2 findings.	**Months 13-18:** • Use combined pPGS and brain deviation metrics to stratify CHR subjects into four subgroups (High/Low Genetic Risk × High/Low Brain Deviation). • Begin preliminary analysis of clinical outcomes and environmental moderators across subgroups. **Months 19-24:** • Refine statistical analysis (ANOVAs, interaction models) to identify protective factors. • Prepare initial manuscript for Aim 3.	**Months 16-24:** • Present interim results at national conferences (e.g., Society of Biological Psychiatry). • Engage with mentors and collaborators (e.g., ENIGMA consortium) for feedback.
Year 3 (Months 25–36)	**Month 25-30:** • Finalize any remaining analyses for pPGS, update models based on additional data if needed. • Integrate any external replication data (e.g., ProNET) for validation.	**Months 25-30:** • Complete longitudinal modeling by integrating follow-up scans to assess trajectory changes over time. • Validate normative model predictions against clinical conversion events.	**Months 25-36:** • Complete full resilience analysis: compare outcomes (conversion, functional scores) among subgroups; test for environmental buffering effects. • Conduct additional sensitivity analyses and prepare final manuscript for Aim 3.	**Months 30-36:** • Consolidate dissertation findings; finalize manuscripts for peer-reviewed journals. • Present final project outcomes at national meetings and internal seminars. • Prepare for postdoctoral applications using the comprehensive interdisciplinary training acquired.