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Abstract:

Despite the advancements in neuroimaging for understanding brain organization, its application in mental health has been minimal due to the lack of established normative reference frameworks for neuroimaging measures. This contrasts sharply with other medical fields where diagnoses and prognoses are aided by comparing biological measures to normative ranges. The absence of these standardized frameworks hinders the identification of reliable biomarkers and the translation of neuroimaging findings into clinical practice and public health policies.

This grant R01 aims to address the limited translational application of neuroimaging to mental health by developing internationally applicable normative models for MRI measures of brain structure, microstructure, and functional connectivity across the lifespan. This initiative will establish CentileBrain, a publicly accessible web-based platform hosting these normative models derived from a large dataset of approximately 50,000 healthy individuals with diverse ethnoracial backgrounds. The project will also quantify the influence of genetic and non-genetic factors (polygenic scores, BMI, socioeconomic status, cognition) on normative brain variation. Furthermore, it will map multivariate deviations from these normative models within and across five major psychiatric disorders: schizophrenia (SCZ), bipolar disorder (BD), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and substance use disorders (SUD). By providing a quantitative framework for identifying individuals with the greatest neural vulnerability, this project seeks to enhance our understanding of mental illness and facilitate the identification of novel therapeutic targets for personalized interventions.

The grant will establish and disseminate CentileBrain as the largest public access platform of normative models of multimodal neuroimaging measures. This involves generating sex-specific lifespan models of regional brain morphometry, white matter (WM) microstructure, and resting-state network (RCN) functional connectivity using large datasets of healthy individuals and longitudinal data to estimate normative inter-individual change. The grant will also quantify the influence of genetic and non-genetic features on normative models of brain morphometry, WM microstructure, and RSN connectivity. This includes testing the association of polygenic scores (PGS and PRS) and non-genetic factors like body mass index (BMI), socioeconomic status (SES), and cognitive ability with normative variation in these neuroimaging measures. In addition, the grant will map multivariate deviations from normative lifespan brain charts within and across 5 major psychiatric disorders. This aim focuses on demonstrating the translational value of normative modeling by identifying significant deviations in neuroimaging measures in individuals with SCZ, BD, MDD, PTSD, and SUD, and exploring their correlation with symptom severity and medication exposure.

Dr. Zhu will be instrumental in ensuring the statistical validity and robustness of the normative modeling approach for this grant project. With expertise in machine learning and normative modeling, Dr. Zhu has already made significant contributions by developing a novel framework for site harmonization of diffusion MRI (dMRI) data. This framework has been implemented in eHarmonize, an open-source Python package for dMRI data harmonization, which will be utilized in the project. Specifically, the grant outlines the plan to use eHarmonize (Zhu 2024) for the crucial task of data harmonization for dMRI measures across the diverse datasets included in the study. Furthermore, Dr. Zhu will contribute to ensuring the statistical validity and robustness of the overall approach alongside Dr. Marquand.

Collaboration with University of Southern California

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