R01 MH133903 (PI: Odile, Simpson, Thompson) 07/01/2023-06/20/2028 (funded)

NIMH
Total Award Amount (including Indirect Costs): $3,201,605
Global Imaging Genetics Approach in Obsessive-Compulsive Disorder (GIGA-OCD), on diversity and predictive modeling
Role: Site-PI

Abstract: Obsessive-compulsive disorder (OCD) is a leading cause of disability worldwide, with symptoms emerging in childhood for nearly half of those affected. Despite the availability of first-line treatments, only about 50% of individuals respond effectively, leaving many to endure a chronic course of illness. Multimodal neuroimaging provides a powerful tool to uncover the neural mechanisms underlying OCD and treatment response, yet existing studies are hindered by small sample sizes, clinical heterogeneity, and underrepresentation of diverse populations. To address these limitations, the GIGA-OCD Initiative integrates data from two leading global consortia—ENIGMA-OCD and Global-OCD—in the most comprehensive neuroimaging study of OCD to date. The R01 grant aims to establish reproducible neurobiological markers of OCD, refine diagnostic frameworks, and enhance personalized treatment approaches.

Through a multimodal neuroimaging approach, combining structural MRI (sMRI), diffusion MRI (dMRI), and resting-state fMRI (rsfMRI) data from over 4,000 individuals across five continents, the grant will analyze ENIGMA-OCD's large dataset to identify brain-based signatures linked to OCD, accounting for factors such as age, symptom severity, disease onset, medication status, and comorbidities. These findings will be validated in Global-OCD's deeply phenotyped, unmedicated adult OCD cohort, allowing for controlled replication and deeper insights into the disorder's neurobiology. Additionally, a subset of ENIGMA-OCD participants will undergo task-based fMRI to investigate functional brain alterations in emotion regulation, response inhibition, and executive function, clarifying how these circuits contribute to OCD across developmental stages.

To refine diagnostic classification and improve treatment predictions, the grant will implement machine learning and deep learning models trained on multimodal neuroimaging data. These models will classify OCD subtypes based on distinct neurobiological patterns and predict treatment response. By analyzing brain circuit dysfunction—particularly in fronto-striatal and fronto-limbic pathways—this approach aims to identify individuals most likely to benefit from specific therapeutic interventions.

Furthermore, the R01 grant will explore OCD's neurogenetic underpinnings by integrating neuroimaging with transcriptomics and cytoarchitectonic atlases. Structural and functional brain gradients will be examined across OCD patients, their unaffected siblings, and healthy controls to reveal inherited neurobiological traits. These differences will be mapped onto gene expression profiles, identifying molecular pathways and cell types, such as glial cells involved in immune function, that may contribute to OCD. Comparing these gradients in patients and their siblings will provide insights into genetic risk factors and potential early markers of the disorder.

Collaboration with USC, Columbia U, University of Amsterdam

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