Evidence of Antagonistic Pleiotropy: Somatomotor and Frontoparietal Network Corticostriatal Hyper-Connectivity in Huntington's Disease Gene-Expanders

Huntington's disease (HD) is traditionally defined by neurodegeneration, yet recent evidence suggests a neurodevelopmental phase characterized by early-life structural and cognitive advantages. This phenomenon supports the theory of antagonistic pleiotropy, where HTT gene expansion confers a biological benefit before the onset of pathology. However, the functional signatures of this early advantage remain poorly understood. Using functional neuroimaging data from the ChANGE-HD dataset (N = ~1,000), we investigated changes in striatal resting-state functional connectivity (rsFC) across the disease trajectory. We employed a "years-to-onset" (YTO) model to map striatal rsFC as a function of estimated time until motor symptom manifestation. Our results reveal a dynamic shift in connectivity: gene-expanded (GE) individuals exhibit significant hyper-corticostriatal connectivity with canonical motor and frontoparietal 30–20 regions years before estimated motor symptom onset, followed by a decrease in connectivity closer to onset. We found no evidence of hyper-corticostriatal rsFC between the striatum and any other cortical regions. These findings provide the first functional evidence that striatal connectivity differences emerge decades before neurodegeneration, aligning with observed structural brain advantages in early life. This study highlights the importance of characterizing the HD "pre-manifest" period not just as a decline, but as a complex developmental trajectory.