Resting-state functional network connectivity differences between prodromal Huntington’s disease and healthy control subjects

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Background: Huntington’s disease (HD) is a rare, neurodegenerative, heritable disorder that affects muscle coordination, leads to mental decline, and presents behavioral symptoms. Subjects are usually genetically tested for the CAG-repeat counts before disease onset. Generally, subjects with >36 CAG-repeats (CAG) are classified as prodromal HD (pro-HD). Those with ≥40 CAG develop HD during a normal lifespan. Previous structural brain studies have shown that HD progress is characterized by striatal (caudate and putamen) degradation and cortical changes. Also, functional seed-based approaches have demonstrated that alterations in functional network connectivity (FNC) exist in HD before the clinical presentation of symptoms. In this study, using a data-driven approach and resting-state functional magnetic resonance imaging (rsfMRI), we tested for within network (voxels) and among network (FNC) connectivity differences between pro-HD and healthy control (HC) subjects.

Methods: We selected a sample of 261 subjects (183 pro-HD (53M/130F) and 78 HC (25M/53F)) from the PREDICT-HD study. Group independent component analysis (ICA) was used to decompose the rsfMRI data into 100 maximally spatially independent components (ICs) and associated time-courses (TCs), of which 46 ICs were identified as meaningful resting-state networks (RSNs). Then, the FNC matrices were generated as the pairwise correlations among the 46 RSN TCs categorized into eight functional domains. Finally, multiple regression analysis with age, gender, CAG, age*CAG, translation and rotation as regressors was applied to identify the best FNC correlations model, and a CAG univariate test was performed to identify group differences.

Results: The reduced FNC correlation model only discarded the age*CAG regressor term. Next, since subcortical (SC) brain regions have been widely implicated in HD, we first compared the two ICs from the SC domain (putamen and insular cortex) to the remaining ICs. After accounting for false discovery rates (FDR), our results showed a negative correlation between CAG and the SC domain connectivity. We found evidence that higher CAG repetition rates are associated with diminished connectivity between
putamen and insular cortex. Next, we conducted a whole FNC brain analysis, considering connectivity between all 46 RSNs. At the whole-brain level, we identified a negative effect of CAG repetition rate on connectivity involving networks in three functional domains: default mode, auditory and visual. Pro-HD presented negative effects on the FNC of precuneus and superior temporal gyrus; lingual gyrus and cuneus, middle occipital gyrus; fusiform gyrus and lingual gyrus; inferior occipital gyrus and middle occipital gyrus, lingual gyrus, fusiform gyrus. We also tested each component voxelwise (within network connectivity) and the basal ganglia component was significant showing a decrease in connectivity associated with pro-HD.

**Conclusions:** The results show significant functional connectivity differences between pro-HD and HC subjects in specific networks. In particular, the negative effect of CAG on connectivity between putamen and insular cortex could be a functional correlate of symptom severity in HD. Further, the captured connectivity differences in the visual domain need more in-depth exploration in future analyses.