Structural and Resting-State Effective Connectivity in a Non-Human primate Model of Huntington's Disease

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Huntington's disease (HD) is a genetic neurodegenerative disorder caused by expanded CAG repeats in the huntingtin (HTT) gene leading to striatal atrophy that progresses to the cortex and white matter and results in motor dysfunction and cognitive decline. Recently, a non-human primate (NHP) model of HD was developed via injection of an adeno-associated viral vector expressing 85 CAG repeats into the striatum. This model captures several neuropathological changes and symptoms observed in people with HD (PwHD) including chorea and mild cognitive impairment. A longitudinal investigation using multimodal MRI in this model revealed volumetric and resting-state functional connectivity (rs-FC) changes in comparisons with a controls group, in key regions involved in HD over the course of 30 months post the virus injection.

We aimed to study longitudinal changes from baseline across 5 timepoints (3, 6, 9, 14, and 20 months) in structural connectivity (SC), obtained from the diffusion MRI (dMRI) scans acquired in the model primates (n=6, 4 males, 2 females) vis-à-vis the buffer group (n=5, 4 males, 1 female). Additionally, going beyond the correlative FC analyses, we aimed to analyse changes in causal, inter-regional interactions by estimating effective connectivity (EC) in each animal, from its rs-functional MRI scan, constrained to strong structural connections.

SC between basal ganglia regions and the cortex in the HTT85Q group – key regions involved in HD, was significantly reduced compared to the buffer group, at 14 months post-surgery. EC from the caudate and putamen to the motor cortex regions was reduced at 3-months post-surgery.

SC between basal ganglia regions and the cortex are affected in PwHD at the later stages of the disease, hence our results in this primate model, are in line with the pathological process observed in PwHD. Our EC findings provide valuable insights into the causal functional interaction changes occurring very early in this NHP model of HD.