**Structural connectivity distinguishes prodromal from clinical Huntington’s disease**

Cristina Sánchez-Castañeda¹,², Hugo C Baggio¹, Alexandra Abos¹, Umberto Sabatini², Ferdinando Squitieri³,⁴, Carme Junqué i Plaja¹

¹Department of Psychiatry and Clinical Psychobiology, University of Barcelona, IDIBAPS, Barcelona, Spain, ²Radiology Department, IRCCS Santa Lucia Foundation, Rome, Italy, ³IRCSS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, ⁴Lega Italiana Ricerca Huntington (LIHR) Foundation, Rome, Italy

**Background:** Huntington disease (HD) is a neurodegenerative autosomal-dominant disease determined by a CAG expansion mutation. Graph theory analysis represents anatomical brain regions as nodes linked by edges representing the structural connections of white matter tracts. We can define a node by its degree of connectivity, centrality, efficiency and clustering coefficient. Mapping these structural networks may contribute to understand how the neurodegenerative process spreads across structurally interconnected brain regions. We aim to test the differences in structural connectivity between presymptomatic, clinical HD patients and controls to find preclinical markers of disease evolution.

**Methods:** 84 mutation carriers (31 at presymptomatic stage (PreHD) and 53 with clinical symptoms (HD, stage I-II)) and 76 matched control subjects underwent MR imaging (MDEFT sequence: TR/TE=7.92/2.4ms, voxel-size=1mm³) and Diffusion-weighted imaging (spin-echo EPI sequence: TE/TR=89/8500ms, voxel size=1.8mm³, 30 b=1000 and 6 b=0 images) on a 3T Siemens scan. The details of image processing and network computation can be found in Baggio et al. (2015). Briefly, Freesurfer v5.2 was used to parcellate the cortex into 68 regions and FSL 5.0.6. and Diffusion Toolkit/Trackvis to reconstruct the WM tracts. Individual 68×68 connectivity matrices were generated. Global network parameters were analyzed by the Brain Connectivity Toolbox. Differences in global measures between groups were assessed by ANCOVA models, including the clinical group as factor and age as covariate. We used the CAP index (Age*CAG-33.66) to test the effect of the mutation toxicity corrected by the length of exposure to the mutation toxicity.

**Results:** PreHD subjects show no significant differences compared to controls in global measures. HD patients, however, have impairment in all general measures of structural connectivity compared to both PreHD and control subjects. Patients have less strength (p<0.0001) and degree of connectivity (p=0.0002), worse efficiency (p<0.0001), longer path length (p<0.0001), reduced clustering coefficient (controls: p<0.0001; PreHD: p=0.003), and higher modularity (controls: p=0.021; PreHD: p=0.004). All general measures of structural connectivity correlated with the CAP index (p<0.005) and disease evolution (p<0.02).

**Conclusions:** HD patients have impairment in structural connectivity in all general measures. They have impairment in network integration, segregation and traffic. PreHD subjects, however, have relatively preserved connectivity compared to controls. These results also provide evidence that the number of CAG repeats together with the time of exposure to the mutation (CAP index) determine the integrity of structural connectivity. Also, structural connectivity measures are correlated with disease evolution.