Characterizing neurodegeneration in the human connectome: a network science study of hereditary diffuse leukoencephalopathy with spheroids.

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Abstract

The effect of white matter neurodegeneration on the human connectome and its functional implications is an important topic with clinical applicability of advanced brain network analysis. The aim of this study was to evaluate integration and segregation changes in structural connectivity (SC) that arise as consequence of white matter lesions in hereditary diffuse leukoencephalopathy with spheroids (HDLS). Also, we assessed the relationship between HDLS induced structural changes and changes in resting-state functional connectivity (rsFC).

HDLS is a rare autosomal dominant neurodegenerative disorder caused by mutations in the CSF1R gene. HDLS is characterized by severe white matter damage leading to prominent subcortical lesions detectable by structural MRI. Spheroids, an important feature of HDLS, are axonal swellings indicating damage. HDLS causes progressive motor and cognitive decline. The clinical symptoms of HDLS are often mistaken for other diseases such as Alzheimer’s disease, frontotemporal dementia, atypical Parkinsonism or multiple sclerosis. Our study is focused on the follow-up of two siblings, one being a healthy control (HC) and the other one being an HDLS patient.

In this study, deterministic fiber-tractography of diffusion MRI with multi-tensor modeling was used in order to obtain reliable and reproducible SC matrices. Integration changes were measured by means of SC shortest-paths (including distance and number of edges), whereas segregation and community organization were measured by means of a multiplex modularity analysis on the SC matrices. Additionally, rsFC was modeled using state of the art preprocessing methods including motion regressors and scrubbing. This allowed us to characterize functional changes associated to the disease.

Major integration disruption involved superior frontal (L,R), caudal middle frontal (R), precentral (L,R), inferior parietal (R), insula (R) and paracentral (L) regions. Major segregation changes were characterized by the disruption of a large bilateral module that was observed in the HC that includes the frontal pole (L,R), medial orbitofrontal (L,R), rostral middle frontal (L), superior frontal (L,R), precentral (L,R), paracentral (L,R), rostral anterior cingulate (L,R), caudal anterior cingulate (L,R), posterior cingulate (L,R), postcentral (L), precuneus (L,R), lateral orbitofrontal (R) and parsorbitalis (R).

The combination of tractography and network analysis permitted the detection and characterization of profound cortical to cortical changes in integration and segregation associated with HDLS white matter lesions and its relationship with rsFC. Our preliminary findings suggest that advanced network analytic approaches show promising sensitivity to known white matter pathology and progression. Further
research is needed to address the specificity of network profiles for differentiation among white matter pathologies and diseases.