Exploring the impact of somatic instability in Huntington's disease on tissue microstructure using in vivo MRI

Estevez Velez A (1,2), van Rijswijk J (1,2) , van Audekerke J (1,2), Van Spilbeeck I (1,2), Adhikari M H (1,2), Verhoye M (1,2), Bertoglio D (1,2)

1) Bio-Imaging Lab, University of Antwerp, Belgium.
2) µNeuro Research Center of Excellence, University of Antwerp, Belgium.

Huntington disease (HD) is a genetic neurodegenerative disorder characterized by a triad of motor, cognitive and psychiatric symptoms. It is caused by a CAG repeat expansion in the Huntingtin (HTT) gene, leading to the production of a misfolded protein, mutant huntingtin (mHTT). As a result, the pathological hallmark of HD is the aggregation of mHTT, which initiates in the striatum leading to neuronal dysfunction and death. Even before the onset of visible brain changes, subtle microstructural damage to white matter pathways occur, potentially 15 years prior to symptoms.

The temporal course of neurodegeneration in HD is largely determined by somatic instability (SI), the progressive somatic expansion of CAG repeats, rather than solely by the inherited CAG repeat length of ~40 which ensures HD onset. Recently, the Msh3 gene has emerged as a regulator of SI and its suppression leads to reduced mHTT protein aggregation in striatal neurons, making it a promising therapeutic target.

However, the precise effects of SI on brain structure remains unclear. To address this, we will explore the spatiotemporal structural changes in the Q111 mouse model of HD. This will be achieved by high-resolution anatomical 3D MRI and advanced multi-shell diffusion MRI to capture the macro- and microstructural deficits along with the novel inhomogeneous magnetization transfer (ihMT) MRI contrast, to dissect white matter integrity. This technique enhances the visualization of myelin rich tissues by isolating interactions of the restricted macromolecules in the myelin sheath and surrounding water.

By integrating in vivo MRI with myelin histology, this project will be the first one to explore how targeting SI impacts brain structure. The results will provide crucial insights for developing innovative therapies for HD and other trinucleotide repeat disorders.