Longitudinal assessment of changes in the BBB water permeability in a mouse model of Huntington's disease using multi-TE ASL MRI

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Huntington's disease (HD) is a neurodegenerative disorder with neuropsychiatric, cognitive, and motor symptoms, lacking a disease-modifying treatment. It is caused by a mutation in the Huntingtin (HTT) gene, leading to the production of toxic mutant HTT (mHTT) aggregates. Investigating clearance of these aggregates from the brain via the blood-brain barrier (BBB) can potentially lead to the discovery of new biomarkers that can be used to test the efficacy of novel HD treatments. Neuroimaging studies have demonstrated BBB abnormalities in several neurodegenerative disorders, however not yet in HD. We investigated longitudinally the integrity of the BBB water permeability in the zQ175DN HD mouse model using multi-echo time (TE) arterial spin labeling (ASL) MRI, which offers the estimation of blood–tissue water exchange dynamics.

We acquired longitudinal MRI data under isoflurane anesthesia using a 9.4T Biospec MRI scanner in 15 WT and 15 HD zQ175DN mice at 3, 6 and 9 months of age. Within 3 regions of interest, the cerebral blood flow (CBF), arterial transit time (ATT) and the water exchange time were extracted and statistically analyzed using a mixed-effects model.

We observed a progressive reduction in CBF and an increased ATT with age within the somatosensory cortex, independent of genotype. Interestingly, the lack of significant genotype differences in CBF and ATT suggests preservation of the vascular architecture which therefore does not bias the estimation of the water exchange time. Finally, we observed a significantly reduced water exchange time, in both the somatosensory and the cingulate cortex in 9 month old HD mice compared to WT mice.

Due to the absence of significant findings at the younger ages, the multi-TE ASL method may not yield promising biomarkers in this mouse model. However, the results suggests an increased BBB water permeability in cortical regions of the HD mice at 9 months of age that are not caused by changes in the vascular architecture.