A Longitudinal Diffusion Tensor Imaging Study of White Matter Changes in a Transgenic Huntington's Disease Monkey Model

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Target audience : Researchers in the MRI research field, particularly those who are interested in the neurodegenerative diseases.

Introduction Huntingtin Disease (HD) is an autosomal dominant neurodegenerative disorder caused by the expansion of CAG trinucleotides at the exon1 of Huntingtin (*HTT*) gene located at chromosome 4, [1] and to date remains incurable. Prior Diffusion Tensor Imaging (DTI) studies have demonstrated decreased fractional anisotropy (FA) in both presymptomatic and early stage HD individuals. [2, 3] HD monkeys recapitulate the progression similar to HD patient and constitute a unique model to study the structural and pathological changes in brain. The purpose of the present study is to examine longitudinal changes of brain white matter (WM) integrity in a cohort of transgenic HD monkeys [4] during their first 48 months of life by using DTI.

Methods Our group has developed four transgenic HD monkeys consisted of four males generated through a lentiviral-mediated protocol,[4] along with four age-matched wild-type controls. MRI scans were performed starting at six months of age with a six- month interval on a Siemens 3T scanner with an eight-channel phase array volume coil. A double spin-echo EPI sequence was used for DTI data acquisition with the parameters: TR = 5700 ms, TE=89 ms, FOV = 83 mm×83 mm, data matrix = 64×64, b-values = 0, 1000 s/cm^2, 30 gradient directions, voxel size=1.3×1.3×1.3 mm^3. FA maps were calculated through DTI studio. Left super frontal (LSF), right super frontal (RSF), left middle frontal (LMF) and right middle frontal (RMF) were selected for ROI analysis based on prior studies in HD patients. [3, 5] The FA values of selected ROIs were measured by image J and student t-test was applied for the statistic analysis.

Results FA map calculated from one of the control monkeys is illustrated in Figure 1. Distinct trend in progressive changes of FA in each ROI between HD monkeys and WT-control monkeys is demonstrated in Figure 2. Divergence in FA values was observed between the two groups as early as in 24 months in LMF and RMF (Figure 2c and 2d) while distinct trend in LSF and RSF was observed after 36 months of age. In particular, FA in each ROI was decreased progressively after 36 months for the HD monkeys.

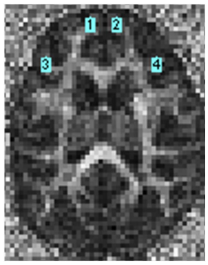

Figure 1. ROIs illustrated on a FA map.1. Left super frontal; 2. Right super frontal; 3. Left middle frontal;

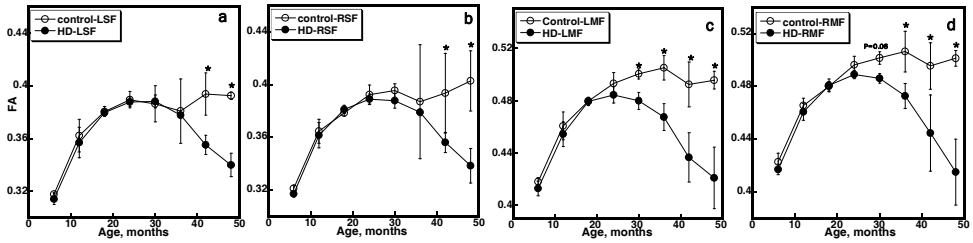

Figure 2. FA changes from 6 to 48 months in the selected ROIs. **(a):**LSF**,(b):** RSF,**(c)**: LMF,**(d)**: RMF. Control-empty circle. HD-solid circle. *: P<0.05.

Discussion and Conclusion As shown in Fig 2, longitudinal changes in WM integrity of HD monkeys are demonstrated in the 48 months study. Although it is unrevealed whether the changes of WM is global or more regionally restricted, Fennema and Rosas et.al have reported similar phenomenon by neuroimaging of symptomatic HD patients. [6, 7] Especially, a distinct trend between the HD monkeys and controls can be observed as early as 24 months of age in the LMF and RMF, while divergence in LSF and RSF can be observed at around 36 months of age, indicating the myelination process is disrupted in HD monkeys and the alteration becomes manifest as early as at 36 months of age. Our findings of FA reduction in HD monkeys are consistent with that in cross-sectional studies of HD patients, which suggest the potential of using DTI as a diagnostic tool for monitoring the WM abnormality associated with the neurodegenerative disorder in HD patients. [3, 8, 9]

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