Diffusion Tensor Imaging of 3T MRI of Huntington's Disease in Sheep

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Huntington's disease (HD) is a dominantly inherited progressive neurogenerative disorder that is often fatal and affects 4-5 people per 100,000 in the United States[1]. It is caused by an expansion of the nucleic acid sequence cytosine-adenine-guanine (CAG) located in exon 1 of chromosome 4 within the huntingtin (HTT) gene. The expansion of this sequence leads to an elongated huntingtin protein, causing it to break up and aggregate in neurons – leading to neuronal degeneration and loss of cell function[2]. This degeneration generates a loss of both connectivity and volume of white matter within the central nervous system. There is currently no clinical treatment or cure for HD and there is a critical need for biomarkers to track the progression of the disease and analyze the efficacy of novel treatments[3]. In 2008, a humanized HD sheep transgenic model was developed for study of HD and to provide a model that recapitulates adult onset HD. This model contains a clinically relevant HD genetic mutation, $(CAG)_{74}$--CAA-CAG, and expresses the expanded human-mutated huntingtin gene (mHTT) throughout the brain.

High-field (3T) magnetic resonance imaging (MRI) was utilized to determine if the HD sheep exhibit traditional neurodegenerative changes typically seen in humans with HD - a loss of connectivity and volume in white matter tracts of the brain. In previous studies, HD patients have exhibited lower values of fractional anisotropy (FA), higher values of apparent diffusion coefficient (ADC), and higher values of radial diffusivity (RD). Using diffusion tensor imaging (DTI), data were analyzed from normal and transgenic sheep using both a region of interest (ROI) analysis and a tract-based analysis to detect white matter alterations. It was predicted that the discrepancies between normal and transgenic sheep would recapitulate the differences typically seen within healthy and diseased humans.

The diffusion images were acquired on a 3T SIEMENS Skyra scanner (Siemens Healthcare, Germany) using a 2D EPI diffusion sequence. For each region segmented, the means of ADC, FA, RD, and axial diffusivity (AD) values were computed. A t-test was used to determine ten total statistically significant differences: one from the ROI-based analysis and nine from the tract-based analysis. For the ROI-based analysis, the difference was found in the ADC mean in the occipital cortex. For the tract-based analysis, the differences were found in the FA mean and RD mean in both the right and left internal capsules, the FA mean and RD mean in the left caudal internal capsule, the FA mean in the parietal cortex, and the ADC mean and RD mean in the occipital cortex. The values for these statistics are shown in Table 1.

While further studies are needed to validate these trends, these results suggest that the HD sheep model exhibits MR based changes that are consistent with human patients and these modalities may be objective measures for testing of novel therapeutics.

Statement of Research Advisor

Diffusion tensor imaging (DTI) is an imaging technique that measures how water diffuses in white matter tracts in the brain and can be used to study how the brain remodels in response to disease. Using DTI, Erin was the first to show that sheep with Huntington's Disease (HD) have differences in white matter that are consistent with HD in humans. She also established analysis protocols that will be used by other students.
– Thomas Denney, Jr., Electrical and Computer Engineering

Table 1. HD Sheep Significant Differences in Tract-Based and ROI-Based Analyses

Analysis	Statistic	Region	Transgenic	Normal	p
ROI	ADC	Occipital Cortex	0.86 ± 0.02	0.80 ± 0.01	0.039
Tract	ADC	Occipital Cortex	0.91 ± 0.01	0.85 ± 0.02	0.036
Tract	FA	Right IC	0.44 ± 0.01	0.49 ± 0.01	0.005
Tract	FA	Left IC	0.45 ± 0.00	0.48 ± 0.01	0.014
Tract	FA	Left Caudal IC	0.43 ± 0.03	0.47 ± 0.01	0.007
Tract	FA	Parietal Cortex	0.43 ± 0.01	0.47 ± 0.01	0.019
Tract	RD	Right IC	0.62 ± 0.01	0.56 ± 0.02	0.033
Tract	RD	Left IC	0.61 ± 0.01	0.56 ± 0.01	0.030
Tract	RD	Left Caudal IC	0.66 ± 0.01	0.61 ± 0.02	0.050
Tract	RD	Occipital Cortex	0.69 ± 0.02	0.63 ± 0.02	0.039

Values are mean ± standard error.

References

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[3] Nopoulos P. C. (2016). Huntington disease: a single-gene degenerative disorder of the striatum. *Dialogues in clinical neuroscience*, *18*(1), 91–98.