Tissue Volume Fraction as a biomarker of genetically-determined disease burden in Huntington's disease

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Target audience: *Clinicians and researchers interested in neurodegeneration, white matter microstructure and diffusion MRI applications.*

Background Huntington's disease (HD) is a progressive neurodegenerative disease caused by a genetic mutation within the *Huntingtin* gene. At the beginning of the *Huntingtin* gene there is a repetitive stretch of 3 DNA bases (CAG); when this repetitive stretch exceeds the normal, stable threshold (>36 repeats), the protein malfunctions, resulting in HD. Above this threshold, the CAG repeat length predicts the age of symptom onset and the rate of clinical decline in the cognitive and motor domain[1,2]. HD neuropathology includes cell loss in the striatum, cortical thinning and white matter microstructural changes. In a degenerative disease such as HD, cerebrospinal fluid (CSF) fills the spaces left by atrophied tissue, which can lead to increased CSF-based partial volume artefacts in diffusion MRI metrics. The Tissue Volume Fraction (TVF), which is the fraction of the signal assigned to tissue after eliminating the CSF-partial volume component, can be mapped on a voxel-by-voxel basis by separating the diffusion properties of brain tissue from surrounding free water[3]. The aim of this study was to compare the relative sensitivity of TVF and diffusion tensor imaging (DTI) indices in predicting disease burden in HD, using the Disease Burden Index[4], which is a genetic marker of disease severity. To the best of our knowledge, this is the first application of TVF as a microstructural metric in a neurodegenerative disease.

Methods 13 gene-positive HD participants (7 male, mean age = 46.47±11.9 SEM) and 13 age, gender, and education-matched healthy control participants underwent MRI scanning on a 3T GE-HDx system. A T_1-weighted FSPGR scan (1 x 1 x 1 mm^3 , TR/TE = 7.9/3.0 ms) and 2 diffusion MRI acquisitions (twice-refocused spin-echo EPI with 60 axial slices, resolution =1.8 x 1.8 x 2.4 mm, matrix = 96 x 96, cardiac-gated = variable TR) were collected: a sequence optimised for DTI (b=1000 s/mm^2, TE = 84.6 ms, 30 isotropic gradient directions) , and a HARDI-based sequence (b=2000 s/mm^2, TE = 97.3 ms, 45 isotropic gradient directions) more suited for recovering fibre orientations through spherical deconvolution approaches. Pre-processing of both diffusion images involved motion and eddy current correction[5], tensor estimation (RESTORE [6]), EPI correction (non-rigid registration of FA map to T_1 map) and partial volume correction[3]. Deterministic whole-brain tractography was performed on the HARDI-based sequence (damped Richardson Lucy algorithm[7]; 0.5mm steps, 5-500mm length, fODF threshold=0.1, angle threshold=45°, α =1, 400 iterations, η =0.06, ν =8). ROI's were drawn manually according to published protocol[8] to delineate the subdivisions of the corpus callosum (Fig.1) and mean TVF and DTI indices were obtained along the tracts calculated from the DTI sequence (b=1000 s/mm^2). The Disease Burden Index was calculated according to the formula (age × [CAG-35.5]), where CAG is the number of CAG repeats[4]. A non-biological measure of disease severity and functional disability, the Total Functional Capacity (TFC) scale, was collected (*low score = more disability).*

Results The Disease Burden Index, a genetic measure of disease severity in HD, was selectively and negatively correlated with TVF in the 3rd segment of the corpus callosum (r = -.69, p < 0.05 FDR-corrected, *Fig.1*) which contains interhemispheric connections to the primary motor cortex. Tensor indices fractional anisotropy (FA) and mean diffusivity (MD) were not significantly related to disease burden in any segment (p > 0.05 FDR-corrected, *Fig.1*). In contrast, a non-biological measure of disease severity, the Total Functional Capacity (TFC) scale, was selectively positively correlated with TVF in the 2nd and 5th callosal segment (p < 0.05 FDR-corrected*, data not shown*), which contain interhemispheric connections to the premotor and supplementary motor areas, and parietal, occipital and temporal areas respectively. FA and MD were not significantly related to TFC in any segment (p > 0.05 FDR-corrected). There was no difference in TVF between HD and control participants (all p > 0.05), whereas MD was significantly higher in HD participants collapsed across corpus callosum segments (p < 0.05 FDR-corrected).

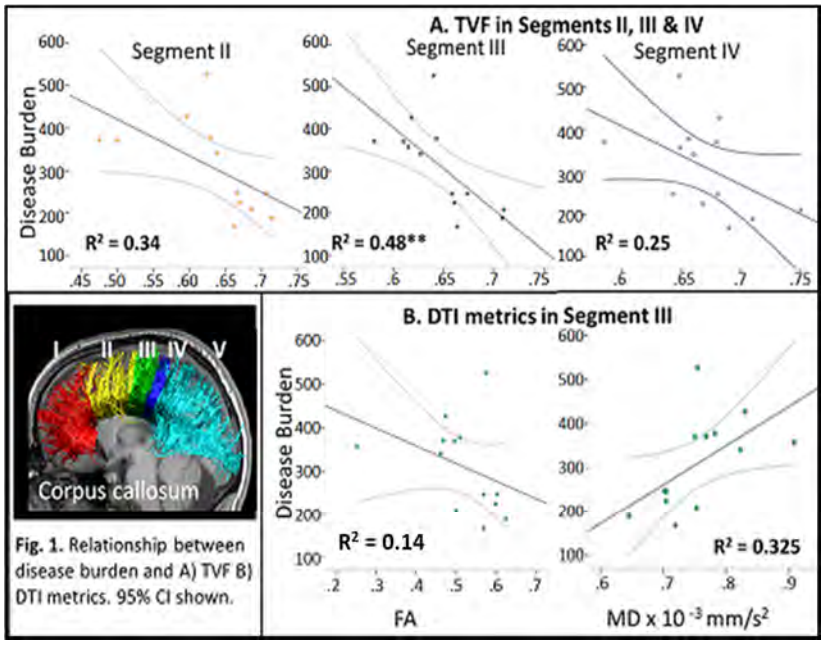

Fig. 1. Relationship between disease burden and A) TVF B) DTI metrics. 95% CI shown.

Discussion Tissue volume fraction (TVF), a relatively under-explored metric of tissue microstructure, was more sensitive to a genetic marker of disease severity in HD compared to DTI metrics. Segmenting the corpus callosum into sub-divisions revealed selective sensitivity: TVF served as a microstructural index of genetically-determined disease severity in the callosal segment containing primary motor cortex connections, in line with the HD phenotype of increased motor symptoms with increased disease severity. In contrast, TVF in the callosal segments containing premotor, supplementary motor and parietal, occipital and temporal connections was sensitive to a metric of functional capacity, likely to capture multiple symptom domains.

Conclusion Tissue Volume Fraction (TVF) is a clinically relevant microstructural metric, provides added value as a biomarker of disease severity, and should be adopted as a microstructural metric alongside tensor metrics in diffusion MRI studies of neurodegenerative diseases.

References **1**. Andrew et al. (1993). *Nature Genetics*, 4, 398–4. **2**. Brandt et al. (1996). *Neurology*, 46, 527–531. 3. Pasternak et al. (2009). *MRM,* 62(3), 717-30. **4**. Penney et al. (1997). *Ann. Neurol*. 41, 689–692**. 5.** Leemans et al. (2009) *ISMRM.* **6.** Chang et al. (2005). *MRM*, *53*(5), 1088-1095. **7.**Dell'acqua et al. (2010). *Neuroimage,* 49,2, 1446-48. **8.** Hofer & Frahm (2006). *Neuroimage,* 32,3, 989-94.