DTI reveals widespread white matter abnormalities in Myotonic Dystrophy Type 1 and Type 2 populations

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Introduction Myotonic Dystrophy Types 1 and 2 (DM1and DM2) are autosomal dominant multisystem diseases with an under-characterized brain pathology. In each disease expansion of a non-coding nucleotide repeat tract (CTG in DM1 and CCTG in DM2) results in pathological changes due to an affect on RNA processing (1). DM1 can have onset in adults (DM1ao) with a relatively less-severe phenotype or can result in developmental abnormalities noted congenitally or in childhood (DM1co), whereas DM2 is only known to begin in adulthood.

Although the most obvious pathologic signs of DM1 and DM2 include progressive muscle weakness and cardiac pathology, there is increasing evidence of central nervous system pathology within both DM types. Previous studies have linked both DM1 and DM2 with white matter hyperintensities in subcortical white matter (2, 3). Although a recent diffusion tensor imaging (DTI) study of the corpus callosum showed decreased fractional anisotropy (FA) in a Japanese DM1ao cohort (4), DTI studies of DM2 and more severe DM1co populations have not been reported. This study further characterizes the location and severity of white matter pathology throughout the brain using DTI in DM1ao, DM1co and DM2 populations.

Methods DM1ao, DM1co, and DM2 research subjects were matched by age to control subjects (n=5 for each group). No grossly abnormal findings were observed in structural MRI scans. Axial DTI was performed using the following parameters: The field of view was positioned to cover the entire cerebrum. Acquisition parameters for the dual spin echo, single shot, echo planar, diffusion weighted sequence are: TR=8000msec, TE=83msec, 128x128, 32cm FOV, 2mm skip 0, 64 slices, b value=1000. Diffusion was measured using 12 directions: (Gx,Gy,Gz) = {[1.0,0.0,0.5], [0.0,0.5,1.0], [0.5,1.0,0.0], [1.0,0.5,0.0], [0.0,1.0,0.5], [0.5,0.0,1.0], [1.0, 0.0,-0.5], [0.0,-0.5, 1.0], [-0.5, 1.0, 0.0], [1.0,-0.5, 0.0], [0.0, 1.0,-0.5], [-0.5, 0.0, 1.0]}. Diffusion-weighted images were processed using tools from the FMRIB Software Library (FSL). Structural and DTI images were aligned to the subject's own T1 acquisition using the FSL linear registration tool, and CSF and white and gray matter classes were segmented using the FMRIB Automated Segmentation Tool. Regional brain masks were generated from structural landmarks, leading to the superior frontal (SUP), inferior frontal (INF), superior to corpus callosum (ACC) and occipital (OCC) compartments shown in Figure 1. Average FA was calculated for white matter voxels from each of these compartments.

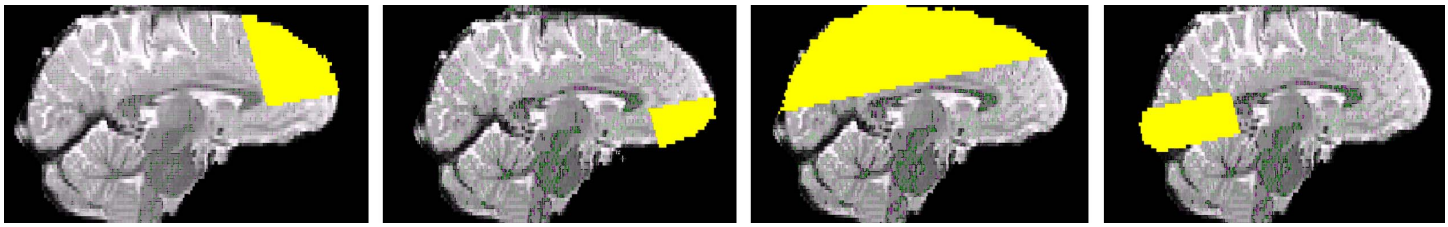

Figure 1: Compartments generated used for regional FA calculation in superior frontal (far left), inferior frontal, superior to corpus callosum and occipital (far right) regions.

Results The results for mean FA are shown in Table 1. Using a one-way ANOVA analysis to probe groupwise differences, a significant reduction in mean FA was found for all compartments in the DM1ao group as compared to the control group. The size of this difference is reflected in the Cohen's effect size and percent reduction in FA. FA differences in the DM1co group relative to controls were of lower magnitude than those seen in DM1ao. The DM2 group showed regional reductions in FA, with significant deficits in the superior and occipital ROIs.

Table 1: FA changes in brain compartments in MD groups

	CTL vs DM1ao	CTL vs DM1co	CTL vs DM2
ACC FA: p-value	.001	.004	.048
ACC FA: effect size	4.75	4.25	1.60
ACC FA: % reduction	16.7	14.9	5.6
SUP FA: p-value	.001	.077	.115
SUP FA: effect size	2.61	1.22	.94
SUP FA: % reduction	23.4	10.9	8.4
INF FA: p-value	.000	.026	.230
INF FA: effect size	4.37	2.48	.74
INF FA: % reduction	27.5	15.6	4.7
OCC FA: p-value	.000	.010	.031
OCC FA: effect size	4.83	3.13	1.22
OCC FA: % reduction	17.6	11.4	4.5

Discussion FA was found to be reduced across multiple brain regions in three myotonic dystrophy populations, with the greatest difference found in the DM1ao group. This compartment-wide FA measure allows for the investigation of diffuse white matter changes. Future studies will need to examine a larger number of subjects to further characterize these observed brain abnormalities.

References

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