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Diffusion tensor imaging reveals widespread white matter abnormalities in children and adolescents with myotonic dystrophy type 1

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Abstract

Diffusion Tensor Imaging was used to evaluate cerebral white matter in 16 patients (ages 9–18) with myotonic dystrophy type 1 compared to 15 matched controls. Patients with myotonic dystrophy showed abnormalities in mean diffusivity compared to controls in frontal, temporal, parietal, and occipital white matter and in all individual tracts examined. Whole cerebrum mean diffusivity was 8.6% higher overall in patients with myotonic dystrophy compared to controls. Whole cerebrum fractional anisotropy was also abnormal (10.8% low overall) in all regions and tracts except corticospinal tracts. Follow-up analysis of parallel and perpendicular diffusivity suggests possible relative preservation of myelin in corticospinal tracts. Correlations between Wechsler working memory performance and mean diffusivity were strong for all regions. Frontal and temporal fractional anisotropy were correlated with working memory as well. Results are consistent with earlier studies demonstrating that significant white matter disturbances are characteristic in young patients with myotonic dystrophy and that these abnormalities are associated with the degree of working memory impairment seen in this disease.

Keywords

Diffusion Tensor Imaging; DTI; Myotonic Dystrophy; Child; MRI

1. Introduction

Myotonic dystrophy type 1 (DM1) is an inherited neuromuscular condition and represents one of the most common form of muscular dystrophy. The disease is associated with mutations on Chromosome 19q13.3 in the form of trinucleotide repeat expansion in the 3'-untranslated region of the dystrophin myotonia protein kinase gene (*DMPK*). Myotonic Dystrophy is multi-systemic, frequently involving ocular, gonadal, cardiac, endocrine, muscular and central nervous system (CNS) abnormalities (Jozefowicz and Griggs 1988; Anastasopoulos, Kimmig et al. 1996; Schara and Schoser 2006; Meola and Sansone 2007; Sovari, Bodine et al. 2007). The focus on CNS involvement in adult-onset DM1 has increased in recent years, and a number of studies have clearly demonstrated cognitive

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involvement as well as underlying brain anomalies (Glantz, Wright et al. 1988; Censori, Danni et al. 1990; Censori, Provinciali et al. 1994; D'Angelo and Bresolin 2006; Meola and Sansone 2007).

Previous magnetic resonance imaging (MRI) studies of adult-onset DM1 have revealed evidence of atrophy (cortical, brainstem, and callosal) and white matter lesions (Censori, Provinciali et al. 1994; Hashimoto, Tayama et al. 1995; Bachmann, Damian et al. 1996; Martinello, Piazza et al. 1999; Antonini, Mainero et al. 2004; Minnerop, Luders et al. 2008; Romeo, Pegoraro et al. 2010). Volumetric changes, including ventriculomegaly and callosal hypoplasia, have also been observed in the childhood-onset form (Glantz, Wright et al. 1988; Hashimoto, Tayama et al. 1995; Martinello, Piazza et al. 1999). The non-specific white matter lesions are most frequently seen in subcortical regions in adult-onset DM1 (Bachmann, Damian et al. 1996) and in periventricular regions in both childhood-onset and adult-onset DM1 (Glantz, Wright et al. 1988; Kuo, Hsiao et al. 2005). White matter lesions have also been observed in temporal white matter in studies examining adult-onset disease (Kornblum, Reul et al. 2004) and studies examining both forms (Huber, Kissel et al. 1989; Di Costanzo, Di Salle et al. 2002; Kornblum, Reul et al. 2004). Abnormally low levels of cerebral metabolites, including N-acetylaspartate (NAA), creatine and choline, have been observed with magnetic resonance spectroscopy (MRS), especially in the frontal white matter of patients with adult-onset DM1 (Vielhaber, Jakubiczka et al. 2006). There is some evidence from earlier studies that the white matter abnormalities visualized with MRI are associated with underlying neuropathological changes at autopsy including "severe loss and disordered arrangement of myelin sheaths and axons" (Ogata, Terae et al. 1998). In general, though, more recent studies using newer imaging methods have revealed rather widespread white matter disturbances with unknown neuropathological correlates. As a result of these studies, it has been suggested that neuropathological studies may not yet be fully able to characterize the true extent of white matter disruption in myotonic dystrophy (Di Costanzo, Di Salle et al. 2002) and that even 'normal-appearing white matter' is likely disturbed at a microstructural (and, perhaps functional) level.

The presence of white matter microstructural abnormalities in DM1 has been highlighted by studies that have utilized advanced MRI techniques including magnetization transfer imaging (MTI), T-2 Relaxometry, and DTI. Naka et al. (2002) reported disturbances in the magnetization transfer ratio in both white matter lesions (identified by hyperintensities) and in so-called "normal-appearing white matter", suggesting subtle disturbances at a microstructural level in patients with adult-onset DM1. Using T2-relaxometry, DiCostanzo et al. (2001) provided further evidence for white matter disruption throughout the brain in adult-onset DM1. In a study utilizing DTI, Fukuda et al. (2005) reported lower fractional anisotropy (FA) in all regions of interest that were examined in their patients with adult-onset DM1. Another study (Ota, Sato et al. 2006) that employed DTI found significantly lower FA throughout the corpus callosum in patients with adult-onset DM1 compared to control subjects. Most recently, Minnerop et al. (Minnerop, Weber et al. 2011) applied DTI and tract-based spatial statistics (TBSS) to patients with adult-onset DM1 and found evidence for widespread white matter microstructural abnormalities. Fractional anisotropy (FA) was reduced in all association fiber tracts, in the corpus callosum, and in projection fibers including the corticospinal tracts. Increases in mean diffusivity (MD) and radial (perpendicular) diffusivity were also seen in the same brain regions as the FA decrements. Our own previous studies, both using Diffusion Tensor Imaging (DTI), have demonstrated specific white matter abnormalities in both childhood-onset (Wozniak, Mueller et al. 2011) and adult-onset (Franc, Muetzel et al. 2012) forms of the disease. One striking aspect of the published DTI studies is the consistent finding that white matter microstructural abnormalities are not confined to specific regions, but are rather widespread throughout the brain.

In a previous DTI study of children with DM1, we demonstrated highly significant white matter abnormalities in inferior frontal, superior frontal, supra-callosal, and occipital white matter (Wozniak, Mueller et al. 2011). The overall degree of white matter disturbance, as evidenced by whole-cerebrum DTI metrics, was correlated with full-scale IQ. An examination of Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV) subtest scores revealed a particularly strong relationship between perceptual reasoning and overall white matter integrity. Trend-level associations between whole-cerebrum FA and working memory and processing speed were also seen in that study. The goal of the current study was to replicate our earlier study with a new sample and to apply more advanced methods, including detailed white matter tractography, to the question of microstructural white matter disturbance in children with DM1.

2. Materials and Methods

2.1. Consent

Patients and their parents underwent a comprehensive informed consent process which included a discussion of the risks and benefits of the study, a consent form signed by the parent, and an assent form signed by the patient. All procedures were reviewed and approved by the University of Minnesota's institutional review board (IRB).

2.2. Subjects

The participants included 16 children and adolescents with myotonic dystrophy type 1 (8 male; 8 female) and 15 control subjects (6 male; 9 female). None of these participants were from our previous study (Wozniak, Mueller et al. 2011). Participating patients were recruited from a University-based neuromuscular clinic. Diagnoses were established by polymerase chain reaction (PCR) and southern blot. The mean age of the patients was 13.9 with a range of 9–18. Patients with myotonic dystrophy were age and gender-matched with healthy control participants (mean age=13.5), who were recruited from the community. Control participants were excluded for neurologic disorder or other medical condition with effects on the brain, psychiatric disorder, learning disability, concussion, or low IQ (more than 1 standard deviation below normal). Table 1 contains details about each of the participants with myotonic dystrophy.

2.3. Neuropsychological Assessment

Participants completed the following neuropsychological measures: the Wechsler Intelligence Scale for Children 4th edition (Wechsler 2003) or the Wechsler Adult Intelligence Scale (3rd ed. or 4th ed.) (Wechsler 1997; Wechsler 2008), the Wisconsin Card Sorting Test (WCST) (Heaton, Chelune et al. 1993), and the California Verbal Learning Test (CVLT-II or CVLT-C) (Delis, Kramer et al. 1994; Delis, Kramer et al. 2000). Participants who were age 16 or younger were administered the Wechsler Intelligence Scale for Children while 17 yearolds were administered the Wechsler Adult Intelligence Scale. In addition, the Behavior Rating Inventory of Executive Functioning (BRIEF) (Gioia, Isquith et al. 2000) was administered to the patients' primary caregivers to assess for behavioral expressions of executive function deficits. All neuropsychological instruments were administered by a licensed pediatric neuropsychologist (J.R.W.) or a trained research assistant under his supervision.

2.4. MRI acquisition procedures

Subjects were scanned using a Siemens 3T TIM Trio MRI scanner with a 12-channel parallel array head coil. The imaging sequence and parameters for each scan are listed in Table 2. The magnet was the same one used in our previous study (Wozniak et al., 2011) but the system had undergone the TIM upgrade prior to this study, which included all new

hardware, software, and a change from an 8-channel coil to a 12-channel head coil. The upgraded system showed a slight improvement in signal to noise ratio (SNR) but not enough to significantly affect the ability to detect abnormalities of the type seen in the current study. Most participants had the MRI scan and the neurocognitive testing on the same day (median days between = 0); For one participant, the MRI and testing were separated by 6.2 months and, for a few others, the two were separated by one day or a few days (mean days between = 6.1, SD = 29.9). Participants were not sedated for the MRI scan nor were their usual medications modified for purposes of the MRI scan.

2.5. MRI processing

FreeSurfer (Dale, Fischl et al. 1999) was used to define white matter regions of interest (ROIs) and several tools from the FMRIB's Software Library (FSL) version 4 were used in the post-processing (Smith, Jenkinson et al. 2004; Woolrich, Jbabdi et al. 2009).

2.5.1. T1 processing—Cortical reconstruction and segmentation were applied to the 1mm isotropic volume. Processing included removal of non-brain tissue, automated Talairach transformation, segmentation, intensity normalization, tessellation of the grey matter/white matter boundary, topology correction, surface deformation, and automated parcellation. In healthy adult, FreeSurfer morphometric procedures have been demonstrated to have high test-retest reliability (Han, Jovicich et al. 2006). The DTI FA map was aligned to the FreeSurfer skull-stripped brain image using a linear registration. This created a registration matrix from the FA map to the FreeSurfer brain (FLIRT: FMRIB's Linear Image Registration Tool) (Jenkinson and Smith 2001). The inverse registration matrix was created and FreeSurfer white matter ROIs were aligned to the FA map in each subject's native DTI space.

2.5.2. DTI processing—Eddy current distortion was corrected using the eddy current correction routine from FDT (FMRIB's Diffusion Toolbox (Behrens, Woolrich et al. 2003)). Geometric distortions caused by susceptibility-induced field inhomogeneities were corrected using the DTI field map data using FUGUE (FMRIB's Utility for Geometrically Unwarping EPIs) (Smith, Jenkinson et al. 2004). The diffusion tensor was computed with FDT; Mean Diffusivity (MD) (mean of the three eigenvalues), Fractional Anisotropy (FA) (the magnitude of the tensor that is due to anisotropic diffusion), parallel diffusivity (1st eigenvalue), and perpendicular diffusivity (mean of the 2nd and 3rd eigenvalue) were derived (Basser and Pierpaoli 1995).

2.5.3. Region of interest definition—Freesurfer cortical parcellation resulted in 32 gray matter regions of interest (ROIs) in each hemisphere. Freesurfer also defined white matter ROIs associated with each of these gray matter ROIs by utilizing the boundaries of the cortical parcellation and incorporating the white matter voxels within those boundaries and within 5 mm of the cortical gray matter. Four lobar ROIs (frontal, temporal, parietal, and occipital) were created by combining averaging appropriate bilateral Freesurfer ROIs (See Table 3 & Figure 1). In addition, Freesurfer identified right and left corpus callosum ROIs which were averaged together for purposes of analysis.

2.5.4. DTI tractography method—Crossing fibers were estimated from the diffusion data, resulting in voxel-wise probability distributions of fiber directionality (FMRIB's Bedpostx) (Behrens, Berg et al. 2007). Probabilistic tractography utilized these distributions to generate eight white matter tracts (four per hemisphere) using a priori seed and target ROIs (Probtrackx, FMRIB's tractography tool) (Behrens, Berg et al. 2007). Seed and target regions were chosen based on known brain anatomy, in some cases by merging white matter ROIs together (see Table 4). For example, the right corticospinal tract was generated using a

right brainstem seed and a target in the right pre-central cortex. The four pairs of tract ROIs generated were left and right: corticospinal tracts, inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus. Figure 2 illustrates these individual tracts within a single hemisphere in a single subject. Mean FA, MD, parallel diffusivity, and perpendicular diffusivity were derived from each of the tract ROIs.

3. Results

The groups did not differ in age, $t(1,29) = .469$, $p = .643$ nor gender, $\chi^2 = .313$, $p = .722$. Group comparisons on a battery of cognitive functioning revealed significant differences across the range of domains (Table 5). Participants with myotonic dystrophy performed significantly below controls on standardized IQ measures (WISC-IV or WAIS-III/WAIS-IV). Full-scale IQ and all of the index scores were significantly lower for patients with DM1. Group differences were also significant for measures of verbal learning (CVLT-C or CVLT-2) and executive functioning (WCST). A parent-report instrument, the BRIEF Parent-Report (Gioia, Isquith et al. 2000), indicated significant “real-world” executive functioning deficits in participants with DM1 compared to controls.

An independent samples t-test revealed a highly significant group difference in fractional anisotropy (FA) averaged across the whole cerebrum white matter, $t(1,29) = 6.00$, $p < .00001$ (Cohen's d effect size = 2.2). Participants with DM1 had FA that was 10.8% lower than those in the control group. A similarly large difference was seen for whole cerebrum mean diffusivity (MD), $t(1,29) = 8.20$, $p < .00001$ (effect size = 3.0). Those with DM1 had MD that was 8.6% higher than those in the control group. Both of these differences suggest widespread white matter microstructural abnormalities in DM1.

To test for regional differences in white matter abnormalities, four lobar ROIs were examined: Frontal, Temporal, Parietal, and Occipital, as well as the corpus callosum. Because there were no significant differences in the effects in right or left hemisphere, the right and left ROIs were averaged together for these analyses. Table 6 contains these results. Large, highly statistically significant group differences were seen across all four lobes, with the largest effect sizes seen in frontal lobe and temporal lobe white matter. In the callosum, FA was not significantly lower in DM1, but MD was significantly elevated in DM1 compared to controls.

An additional analysis of white matter integrity was conducted at the level of individual subject-specific white matter tracts. Because there were no significant right-left differences, the right and left tracts were averaged together for these analyses. Table 7 contains these results. Again, large and highly significant group differences were observed. In the corticospinal tracts, there was no significant difference in FA, but there was in MD. To evaluate this finding further, the mean parallel diffusivity ($\lambda_{||}$) and perpendicular diffusivity ($\lambda_{\perp}$) of the tracts were examined. In the corticospinal tracts, those with DM1 showed higher $\lambda_{||}$ compared to controls (4.1%) to a similar degree seen in the other tracts; similarly, mean $\lambda_{||}$ was 4.7% higher in the ILF, 4.8% higher in the SLF, and 4.5% higher in the uncinate ROIs. In contrast, $\lambda_{\perp}$ was only slightly higher in the corticospinal tracts of those with DM1 compared to controls (4.3%) whereas it was increased significantly in the ILF (13.1%), SLF (14.0%), and uncinate (13%). In other words, although all tracts examined showed significant abnormalities in children and adolescents with DM1, the mean perpendicular diffusivity in the corticospinal tracts was somewhat less impacted than the other tracts.

The relationship between measures of white matter integrity and cognitive functioning were examined. Pearson correlations were computed between the four lobar measures (FA and MD) and the four cognitive indices from the Wechsler intelligence tests. Because there were significant group differences (DM1 vs. controls) in both cognitive functioning and in mean

diffusivity, these correlations were computed only for those participants with DM1. Table 8 contains the correlations. A clear pattern emerged, suggesting that working memory was the only cognitive domain that was significantly associated with white matter status in these children and adolescents with DM1. Verbal comprehension, perceptual reasoning, and processing speed were not correlated with white matter integrity.

4. Discussion

These results are highly consistent with our earlier report of widespread white matter abnormalities in both children and adults with DM1 (Wozniak, Mueller et al. 2011; Franc, Muetzel et al. 2012). Replication of the previous study was important given the small sample size of the initial study. Furthermore, because our MRI scanner underwent a substantial hardware upgrade and head coil change between the two studies, the consistency in findings suggests that they are generalizable and supports the conclusion that there are, indeed, microstructural white matter abnormalities in DM1. The current study built on the prior study by examining individual tracts in DM1 and by uncovering an intriguing pattern in the corticospinal tracts specifically.

In one set of analyses, we observed significant white matter disturbances, relative to control participants, in four lobar regions of interest: frontal, temporal, parietal, and occipital. These effects were very large as indicated by the range of Cohen's d effect sizes (1.7 to 3.6). In a separate set of analyses using tractography, we observed similar levels of disturbance in all of the white matter tracts examined. The effect sizes in individual tracts varied considerably, but were generally very high – with many greater than 2.0. In examining the relationship between white matter integrity and cognitive functioning, we found that all four of the lobar MD measures were significantly correlated with the working memory index score from the Wechsler scales. Greater white matter abnormality, as indicated by higher MD, was correlated with lower working memory index scores. Pearson correlations ranged from $-.62$ to $-.67$. We also observed correlations between working memory and FA in the $.44$ to $.57$ range, with significant correlations in the frontal and temporal regions and trend-level correlations in the parietal and occipital regions. These findings were consistent with the $.64$ correlation (trend-level) observed in our earlier study between whole cerebrum FA and working memory in children with DM1 (Wozniak, Mueller et al. 2011). In the prior study, perceptual organization, working memory, and processing speed were correlated at trend levels with whole-cerebrum FA, perhaps reflecting a more global association in a small number of participants ($n=8$) across a wide range of DM1 severity. The current study, with twice as many participants, seems to reveal a more specific association between white matter integrity and working memory skill.

These results in children and adolescents are also relatively consistent with the white matter abnormalities seen in adults with DM1. Several DTI studies of adults with DM1 have now shown similar widespread abnormalities in the white matter that are not regionally specific. Takaba et al. (2003) first showed white matter diffusion abnormalities in adults with DM1. In a later study, the same research group reported lower FA and higher mean diffusivity (MD) throughout the brain in so-called “normal-appearing white matter” in adults with DM1 (Fukuda, Horiguchi et al. 2005). Ota et al. (2006) found lower FA and higher MD in multiple regions of corpus callosum in adults with DM1. Franc et al. (Franc, Muetzel et al. 2012) reported lower FA and higher MD in adults with DM1 compared to control participants and showed an association between white matter abnormality and facial muscle atrophy. Minerop et al. (Minnerop, Weber et al. 2011) reported lower FA and higher MD in almost all white matter tracts that were included in their study of adults with DM1. Thus, all of the available DTI studies of patients with DM1 provide consistent evidence of white matter microstructural abnormalities throughout the brain.

It is important to note that the nature of the underlying white matter pathology reflected in these DTI abnormalities is not yet fully understood. Clearly, these DTI-based white matter measures are not specific to DM1 or any other particular illness. In fact, DTI is sensitive to multiple types of disturbances in the white matter including physical damage such as shearing (Huisman, Schwamm et al. 2004), demyelination (Fox, Cronin et al. 2010), and Wallerian degeneration of white matter. In addition, it is known that DTI metrics, including FA, are sensitive to normal developmental changes (Ben Bashat, Ben Sira et al. 2005; Bonekamp, Nagae et al. 2007). DTI may be sensitive to differences in myelin water content, axonal packing density, axonal size, or other physical attributes of white matter tissue (Beaulieu 2002). Thus, a number of possible changes to white matter microstructure in DM1 could lead to the diffusion abnormalities seen in the current study and in previous DTI studies of DM1. It has been proposed that the underlying white matter pathology in DM1 has been generally underestimated (2002) and that, in fact, there may be significant myelin abnormalities. DiCostanzo et al. (Di Costanzo, Di Salle et al. 2001) have shown increased T2 relaxation times in DM1 and have suggested that this may be the result of alterations in myelin and changes in interaxonal water content. Further evidence for the possibility of myelin involvement in DM1 comes from studies showing broad magnetization transfer imaging (MTI) abnormalities (low magnetization ratio) in normal-appearing white matter (Naka, Imon et al. 2002; Giorgio, Dotti et al. 2006). Some of these potential alterations in myelin may be difficult to detect as pathological changes at autopsy, but it is possible that these abnormalities may have significant functional consequences nonetheless.

An unexpected finding in the current study was comparable FA in DM1 and controls but significantly higher MD in patients with DM1 compared to controls in the corticospinal tracts. Further examination revealed that abnormalities in parallel diffusivity were similar across all tracts examined in DM1, but that perpendicular diffusivity was only moderately abnormal in the corticospinal tracts among those with DM1 whereas it was significantly abnormal in the other tracts. In a global sense, parallel diffusivity is thought to reflect aspects of axonal integrity while perpendicular diffusivity reflects integrity of the cell membrane and myelin sheath (Song, Sun et al. 2002; Song, Sun et al. 2003; Song, Yoshino et al. 2005). The current finding could indicate a relative preservation of myelin in the corticospinal tracts at this age in DM1 compared to other tracts. Certainly, further examination of individual tract integrity in those with DM1 is warranted, perhaps especially so during childhood and adolescence when important changes in axonal structure and myelination may be interacting with pathological processes in a more regional pattern than is currently understood.

In the current study, we observed a moderate but non-significant relationship between global cognitive functioning (full-scale IQ) and white matter integrity. However, in our previous study, we did observe a stronger relationship between the two: there was a Pearson correlation of .74 between full-scale IQ and whole-cerebrum FA in that study. Clearly, a substantial proportion of children with DM1 do indeed have global cognitive impairments and there is a relationship between CTG repeat length and overall IQ, suggesting that IQ may be somewhat of a proxy for disease severity (Steyaert, Umans et al. 1997; Steyaert, de Die-Smulders et al. 2000; Angeard, Gargiulo et al. 2007; Ekstrom, Hakenas-Plate et al. 2009). In addition to frequently having low IQ, children with DM1 have very high rates of autism-spectrum conditions (Ekstrom, Hakenas-Plate et al. 2008), especially when CTG repeat length is high. Again, this suggests a relationship between the genetic determinants of the disease, the resulting brain pathology, cognition, and overall functioning. It is unclear, as of yet, how much of a role the underlying white matter pathology may play in this relationship. The current results suggest that, in childhood DM1, the significant white matter disturbance reported here plays only a partial role in the overall neurocognitive status of the child.

We did observe a significant relationship between white matter integrity and working memory from the Wechsler scales. This finding suggests that further investigation of white matter abnormalities in childhood DM1 is warranted, especially given the very high incidence of attention problems and diagnosable ADHD in these children (Goossens, Steyaert et al. 2000). In adults with DM1, Winblad et al. (Winblad, Lindberg et al. 2006) have reported that executive functioning deficits, including working memory problems, are particularly characteristic of the neurocognitive profile. A number of others have also characterized the executive functioning abnormalities in adult DM1 (Meola, Sansone et al. 2003; Modoni, Silvestri et al. 2004; Meola and Sansone 2007; Romeo, Pegoraro et al. 2010), yet we know very little about the relationship between white matter status and executive functioning in adults as of yet.

5. Conclusion

In conclusion, there is now convincing evidence from DTI studies that white matter abnormalities are common and widespread in both the childhood-onset and adult-onset forms of DM1. Further investigation is needed to understand the course of these white matter disturbances and how they relate to other important aspects of the disease including age of onset, muscular status, and a range of cognitive functions.

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Fig. 1. Illustration of four lobar regions of interest (blue = frontal; yellow = parietal; red = temporal; green = occipital) created by averaging individual Freesurfer parcellations.

Fig. 2.
Illustration of white matter tract regions of interest in one hemisphere including the inferior longitudinal fasciculus (green), superior longitudinal fasciculus (yellow), corticospinal tract (blue), and uncinate fasciculus (red)

Table 1

Subject characteristics for 16 participants with Myotonic Dystrophy Type 1.

Subject	Age	Sex	Transmission	CTG Repeats	VCI	PRI	WMI	P I	FSIQ
1	14	Female	Paternal	600	98	77	74	70	76
2	10	Male	Maternal		63	53	62	62	51
3	9	Female	Maternal		87	88	71	91	81
4	17	Male	Paternal	530	107	93	90	86	99
5	14	Female	Paternal	515	108	100	94	80	97
6	11	Female	Paternal	253	112	100	94	88	101
7	14	Male	Paternal		61	59	83	59	56
8	17	Female	Paternal	400	82	69	69	84	67
9	14	Female	Paternal	617	61	53	50	53	45
10	13	Female	Paternal		87	73	104	91	84
11	15	Female	Maternal		59	82	52	59	56
12	9	Male	Maternal		71	63	62	56	56
13	13	Male	Maternal		91	79	86	73	78
14	18	Male	Maternal		110	86	94	93	95
15	18	Male	Maternal		88	86	71	69	78
16	17	Male	Paternal		110	94	102	86	99

Note: Exact CTG repeat counts were not available for some subjects because of the inexact nature of southern blot analysis.

Note: VCI = Wechsler Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index; FSIQ = Full Scale Intelligence Quotient.

Table 2

MRI sequence and parameters.

Sequence	Imaging Parameters	Purpose	Time
Scout	3 plane localizer	Positioning	1 min
T1-weighted MPRAGE	TR=2530ms, TE=3.65ms, TI=1100ms, 224 slices, voxel size=1×1×1mm, FOV=256mm, flip angle=7 degrees, GRAPPA 2.	Segmentation & cortical parcellation	5 min
Diffusion weighted (DTI)	TR=8500ms, TE=90ms, 64 slices, voxel size=2×2×2mm, FOV=256mm, GRAPPA 2, 30 volumes with b=1000 s/mm ² & 6 with b=0 s/mm ² .	Computation of the diffusion tensor	6 min
DTI Field-map	Positioned to match DTI, 64 slices, voxel size=2×2×2mm, FOV=256mm TR=700ms, TE=4.62ms/7.08ms, flip angle=90 deg.	Correction of geometric distortions for DTI	3 min

Table 3

FreeSurfer parcellations included in lobar regions of interest (ROIs).

White Matter ROI	FreeSurfer parcellations assigned to each ROI
Frontal	Superiorfrontal, rostralmiddlefrontal, caudalmiddlefrontal, pars opercularis, pars triangularis, pars orbitalis, lateralorbitofrontal, medialorbitofrontal, precentral, paracentral, frontal pole
Parietal	Superiorparietal, inferiorparietal, supramarginal, postcentral, precuneus
Temporal	Superiortemporal, middletemporal, inferiortemporal, fusiform, transversetemporal, entorhinal, temporal pole, parahippocampal
Occipital	Lateraloccipital, lingual, cuneus, pericalcarine

Table 4

Seed and target regions used to generate tracts using probabilistic tractography

White Matter Tract	Seed Regions	Target Regions
Inferior Longitudinal Fasciculus	Entorhinal and temporal pole	Lateraloccipital and inferiorparietal
Superior Longitudinal Fasciculus	Caudalmiddlefrontal, and parsopercularis	Superiortemporal and inferiorparietal
Corticospinal	Brainstem	Precentral
Uncinate Fasciculus	Parsorbitalis, medialorbitofrontal and lateralorbitofrontal,	Entorhinal and temporal pole

Table 5

Neuropsychological results by group.

Measure	Control	Myotonic Dystrophy	Significance (p)
	Mean (SD)	Mean (SD)	
Wechsler Verbal Comprehension	114 (13)	87 (19)	.0001
Wechsler Perceptual Organization	115 (16)	78 (16)	<.0001
Wechsler Working Memory	110 (11)	79 (17)	<.0001
Wechsler Processing Speed	99 (13)	75 (14)	<.0001
Full-Scale IQ	114 (14)	76 (19)	<.0001
California Verbal Learning Test (total)	58 (9)	44 (16)	.008
Wisconsin Card Sorting Test (total errors)	108 (16)	91 (16)	.009
BRIEF General Executive Composite	45 (8)	63 (10)	<.0001

Note: SD = Standard Deviation. All tests were administered to all subjects; Higher BRIEF scores indicate greater executive dysfunction; Lower Wisconsin Card Sorting Test error scores indicates greater executive dysfunction.

Table 6

Comparison of myotonic dystrophy to controls on measures of fractional anisotropy (FA) and mean diffusion (MD) in whole cerebrum and five regions of interest.

Control (n = 15)		Myotonic Dystrophy (n =16)		Statistical tests			
	Mean	SD	Mean	SD	t	p	Effect size (Cohen's d)
Fractional Anisotropy (FA)							
Whole cerebrum	.372	.013	.334	.021	6.00	<.00001 *	2.2
Frontal lobe	.336	.012	.297	.019	7.01	<.00001 *	2.5
Temporal lobe	.322	.016	.286	.023	4.92	=.00003 *	1.8
Parietal lobe	.359	.016	.318	.027	5.02	=.00002 *	1.8
Occipital lobe	.298	.019	.261	.024	4.72	=.00006 *	1.7
Corpus callosum	.606	.032	.586	.046	1.42	=.16626	0.5
Mean Diffusivity (MD)							
Whole cerebrum	.800	.017	.872	.030	8.20	<.00001 *	3.0
Frontal lobe	.782	.018	.856	.030	8.25	<.00001 *	3.0
Temporal lobe	.846	.017	.927	.027	9.95	<.00001 *	3.6
Parietal lobe	.785	.017	.856	.030	8.00	<.00001 *	2.9
Occipital lobe	.769	.015	.835	.038	6.25	<.00001 *	2.3
Corpus callosum	1.04	.068	1.12	.104	2.45	=.01989 *	0.9

NOTES: Mean Diffusivity values are $\times 10^{-6}$ mm²/second.

* = significant at p<.05 level

Table 7

Comparisons of myotonic dystrophy to controls on measures of fractional anisotropy (FA) and mean diffusion (MD) in individual white matter tracts.

	Control (n = 15)		Myotonic Dystrophy (n =16)		Statistical tests	
	Mean	SD	Mean	SD	t	p
<i>Fractional Anisotropy (FA)</i>						
Corticospinal tract	.578	.024	.577	.025	0.08	.94084
Inferior Longitudinal Fasciculus (ILF)	.476	.021	.433	.022	5.50	<.00001
Superior Longitudinal Fasciculus (SLF)	.474	.018	.426	.028	5.61	<.00001
Uncinate Fasciculus	.394	.026	.346	.017	5.99	<.00001
<i>Mean Diffusivity (MD)</i>						
Corticospinal tract	.770	.014	.802	.025	4.50	.00010
Inferior Longitudinal Fasciculus (ILF)	.841	.020	.919	.048	5.87	<.00001
Superior Longitudinal Fasciculus (SLF)	.767	.019	.843	.042	6.39	<.00001
Uncinate Fasciculus	.848	.021	.927	.026	9.44	<.00001

Note: Mean Diffusivity values are $\times 10^{-6} \text{ mm}^2/\text{second}$; Mean values represent the average of the right and left tracts.

Table 8

Pearson correlations between cognitive functioning and DTI measures of white matter integrity for patients with DM1 only (controls excluded).

	FSIQ		VCI		PRI/POI		WMI		PSI	
	r	p	r	p	r	p	r	p	r	p
<i>Fractional Anisotropy</i>										
Frontal lobe	.26	.33	.21	.24	-.03	.24	.55*	.03	.33	.21
Temporal lobe	.24	.36	.32	.23	-.09	.73	.57*	.02	.27	.31
Parietal lobe	.11	.68	.18	.50	-.16	.56	.44	.09	.08	.78
Occipital lobe	.19	.48	.24	.38	-.01	.98	.45	.08	.21	.43
<i>Mean Diffusivity</i>										
Frontal lobe	-.40	.12	-.44	.09	-.18	.49	-.62*	.01	-.34	.20
Temporal lobe	-.40	.13	-.41	.12	-.15	.58	-.67**	<.01	-.32	.22
Parietal lobe	-.42	.11	-.45	.08	-.18	.52	-.65**	<.01	-.42	.12
Occipital lobe	-.47	.07	-.48	.06	-.34	.20	-.62*	.01	-.41	.11

NOTE: FSIQ = Full-Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index; POI = Perceptual-Organizational Index; WMI = Working Memory Index; PSI = Processing Speed Index