Cognitive Decline and White Matter Integrity Degradation in Myotonic Dystrophy Type I

Maria Margarita Lopez-Titla pt, Amanda Chirino, Sara Vanessa Cruz Solis, Carlos R. Hernandez-Castillo pt, Rosalinda Diaz, Luz del Carmen Márquez-Quiroz, Jonathan J Magaña pt, Luis Beltrán-Parrazal pt, and Juan Fernandez-Ruiz pt

From the Instituto de Neuroetología, Universidad Veracruzana, Xalapa, 91190, México(MMLT); Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de México, 04510, México(AC, SVCS, RD, JFR); CONACYT-Instituto de Neuroetología, Universidad Veracruzana, Xalapa, 91190, México(CRHC); Laboratorio de Medicina Genómica, Departamento de Genética (CENIAQ), Instituto Nacional de Rehabilitación-Luis Guillermo Ibarra Ibarra (INR-LGII), Ciudad de México, 14389, México(LDCMQ, JJM); Escuela de Ingeniería, Departamento de Biotecnología, Instituto Tecnológico y de Estudios Superiores de Monterrey-Campus, Ciudad de México, 14380, México(JJM); Centro de Investigaciones Cerebrales, Universidad Veracruzana, Xalapa, 91190, México(LBP); and Facultad de Psicología, Universidad Veracruzana, Xalapa, 91700, México(JFR).

ABSTRACT

BACKGROUND AND PURPOSE: **Myotonic Dystrophy Type I (DM1) is a neurodegenerative, genetic, and multisystemic disorder with a large variety of symptoms due to a CTG trinucleotide expansion located on Dystrophia Myotonica Protein Kinase (DMPK) gene. Previous reports have shown cognitive deterioration in these patients. Given that white matter (WM) degradation has also been reported in DM1 patients, here we explored if alterations in the cognitive profile of DM1 patients could be related to the deterioration of WM.**

METHODS: **A total of 22 classic DM1 patients with age range (18-56 years) and 22 matched healthy control subjects were neuropsychological evaluated by the Cambridge Neuropsychological Test Automated (CANTAB). Patients were evaluated with the Muscular Impairment Rating Scale (MIRS). We then evaluated the cerebral WM integrity using the Fractional Anisotropy (FA) index obtained from the Diffusion Tensor Imaging (DTI) data acquired with a 3T MR scanner.**

RESULTS: **DM1 patients showed generalized reduction of WM integrity across the brain. Similarly, patients' neuropsychological evaluation showed significant deficits in memory and problem-solving tasks. Correlation analyses showed a significant correlation between FA deterioration at frontal, temporomedial, and parietal lobes and delayed matched to sample deficits.**

CONCLUSIONS: **Our results suggest that despite the pervasive WM integrity loss in DM1 disorder, specific memory impairments can be associated to discreet areas of WM deterioration in these patients.**

Keywords: DTI, MRI, DM1, CANTAB, memory.

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Correspondence: Address correspondence to Juan Fernandez-Ruiz, Departamento de Fisiología, Facultad de Medicina, Edificio A, 4°piso. Universidad Nacional Autónoma de México, Ciudad de México, C.P. 04510, México. E-mail: jfr@unam.mx.

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Introduction

Myotonic Dystrophy Type I (DM1), also called Steinert's disease, is the most common neuromuscular dystrophy, affecting 1/7400 individuals among the Caucasian population. DM1 is caused by a genetic mutation consisting of a CTG trinucleotide expansion located in the 3′-untranslated region of Dystrophia Myotonica Protein Kinase (DMPK) gene on human chromosome 19q 13.3 that codes for DMPK. DM1 is a multisystemic disorder characterized by distal muscle weakness, myotonia, muscle facial weakness, fatigue, cardiac conduction abnormalities, and numerous debilitating neurological and neuropsychiatric manifestations.[1] The symptoms progression reduces the patient life expectancy and affects their quality of life.[2]

Phenotypically, patients with DM1 have been classified into four categories: congenital, classic adult, classic mild, and premutation. The categorization is based on age at onset and clinical features. The size of the CTG repeats has been correlated with the severity of the symptoms and age of onset, accounting for the anticipation phenomenon observed from generation to generation.[2]

The main clinical manifestations of DM1 are sleep disturbances, personality alterations, mood swings, and detriment in cognitive performance.[3] Classic DM1 patients are characterized on average by a low IQ often accompanied by attention deficits, memory, executive and visuospatial functions, hypersomnia, and behavioral problems.[4] Previous neuropsychological characterization studies of DM1 suggest a detriment in all cognitive domains.[5] The DM1 patient can present a combination of cognitive deficits in different domains such as social cognition, memory, language, executive functions, and visuospatial functioning.[5]

White matter (WM) lesions in DM1 are related with widespread changes in WM cerebral integrity.[6] WM lesions located within anterior temporal lobes represent a characteristic

Table 1. Demographic and Clinical Results for DM1

Variable	DM1 (22 patients)
Gender	16 males, 6 females
Age (years)	34.6 ± 9.6 (18-56)
Education level (years)	11.8 ± 2.8 (9-16)
CTG repeats	539.14 ± 241.72 (127-1,093)
DM1 age onset	20.59 ± 10.77 (1-50)
Montreal Cognitive Assessment	
26-30 Normal	19
≤25 Detriment	3
Mini Mental State Examination	
30-27 Normal	15
26-24 Suspicious	6
23-13 Detriment	1
12-9 Dementia	0

DM1, Myotonic Dystrophy Type 1. Data are presented in mean ± standard deviation (range).

feature in myotonic dystrophy type 1.[7] However, a clear pattern of degeneration of WM and its possible relation with specific cognitive alterations in DM1, it is still not clear.[8] For example, changes in the IQ index and visuoconstructive and executive functional scales are found to correlate with brain atrophy distributed at the parietal and subcortical levels.[9] However, there is still a dearth of information related to the neural basis of the cognitive detriment of DM1 patients, for example, the few reports on the cognitive changes in these patients are diverse and even contradictory in certain cases.[5]

The main objective of this investigation was to further study the relationship between the neuropsychological profile and the integrity of the cerebral WM in classic DM1 patients. For this purpose, we assessed the cognitive profile of DM1 patients with the Cambridge Neuropsychological Test Automated Battery (CANTAB),[10] and the deterioration of cerebral WM with the value of the FA index obtained from Diffusion Tensor Imaging (DTI) with MRI.[11]

Methods

Subjects

Twenty-eight DM1 patients categorized as classic DM1 phenotype based on the age of onset of the first referred symptom (>18 years) volunteered to participate in this study. However, only 22 patients completed the cognitive testing and, thus, were matched to 22 control volunteers matched by age, gender, and education level. The DM1 patients were identified through molecular diagnosis by Polymerase Chain Reaction (PCR) and CTG triplet repeat-PCR (TP-PCR) analyzed by capillary electrophoresis and small-pool-PCR tests at Instituto Nacional de Rehabilitación (INR) Luis Guillermo Ibarra Ibarra as previously reported.[12] Table 1 refers to the demographic and clinical characteristics of DM1 patients. All participants signed an informed consent to participate in this research as stated in the declaration of Helsinki.[13]

Clinical Evaluation

The muscular detriment of DM1 patients was evaluated using the Muscular Impairment Rate Scale (MIRS). MIRS scale is an ordinal five-point rating scale, established in accordance with the clinically recognized distal to proximal progression of the muscular involvement in DM1, based partly on a manual muscle testing (MMT) of 11 muscle groups.[14] All DM1 patients showed myotonic discharges according to muscle needle examination (Nicolet Viasys Voking Select, Madison, Wisconsin).[12]

The participants were clinically evaluated with a miniclinical interview conducted by a neurologist, the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA) were applied. MMSE is a 30-point questionnaire that evaluates cognitive impairment, any score of 27 or more indicates a normal cognition; below this, scores can indicate dementia (9-12), detriment (13-23), or suspicious (24-26) cognitive impairment.[15] MOCA scores range between 0 and 30, a score of 26 or over is considered to be normal.[16]

CANTAB Cognitive Assessment

Additionally, patients were evaluated with 19 CANTAB tests that assess cognitive domains of attention, global memory, visual memory, and executive functions.[10]

The analysis of the CANTAB cognitive data between control and classic DM1 patient group was performed in SPSS version 24. We used a *t*-student or a Mann–Whitney U test, where applicable. We corrected by False Discovery Rate (FDR) for multiple comparisons with $q = .05$, and we calculated the effect size with a Cohn's d or a statistics *r*, where applicable.[17]

CANTAB tests with different difficulty levels were analyzed using a mixed Analysis of Variance model for independent variables. The cognitive results of control and patient group were taken as the between subject factor and the levels of each stage were considered as the intrasubject factor.[17]

MRI Acquisition

The MRI acquisition was carried out at Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz" with a 3T Philips Ingenia scanner (32-channel head sense coil). The MRI protocol included T1-weighted, T2-weighted and DTI. The T1 parameters were TR/TE = 7.0/3.5 milliseconds, gap = 0, 180 sagittal slices with spatial resolution of 1 mm^3, time of acquisition 3 minutes 20 seconds. The DTI image parameters were: 32 diffusion directions, $b = 800$ seconds/mm^2, and a volume without diffusion weight $b = 0$ seconds/mm^2, TE = 60 milliseconds, TR = 7103 milliseconds, Flip Angle = 8, gap = 0 and 70 axial slices per volume with spatial resolution of 2 mm^3, time of acquisition 5 minutes. The total scan time duration was approximately 40 minutes per participant. Five additional control subjects also matched for age and gender had to be retrospectively selected from our dataset for the DTI to compensate for controls that did not fulfill the MRI safety criteria (disclosing medical conditions just before entering the MRI facilities), or that declined to further participate in the MRI acquisition.

Image Analysis

The structural images were evaluated by a neuroradiologist as a part of the clinical evaluation for each patient. These qualitative evaluations revealed typical lesions previously described in DM1 patients, however, quantitative analyses of those lesions were not performed. DTI images were analyzed with FMRIB software FSL version 5.0.9.[18] The images were masked to exclude nonbrain tissue such as skull, meninges, and neck tissue and corrected by motion artifacts and eddy currents to obtain the FA, Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity (RD) maps by DTIFIT.[19] Then Tract

Based Spatial Statistics (TBSS) algorithm was used to obtain the WM skeleton that is the common center of the WM for all the participants in our sample. This methodology allows to make voxel-based comparisons and it helps to solve the coregistration and smoothing problems between the different FA, MD, AD, and RD maps. We applied nonlinear co-registration (FNIRT) and used the standard space FMRIB58_FA.[19]

Image Statistical Analysis

Voxel-wise General Linear Models (GLM) were applied for the statistical analyses. We used *t*-tests for the comparison between groups, and *F* tests for regression analyses between FA maps and CANTAB scores, age, and CTG repetitions from DM1 patients. *F* test uses the Snedcor's *F*-distribution to compare multiple regression models simultaneously.[20] The regressors were standardized and controlled by the number of CTG repetitions and by the age of onset of the disease of the patients.[9]

We corrected by multiple comparisons to control the Family wise error (FWE) with a nonparametric permutation inference and applied Threshold Free Cluster Enhancement (TFCE) (randomise with 500 permutations).[21]

We obtainded the Montreal Neurological Instituto (MNI) coordinates of the voxel with the highest statistical significance in each cluster of the F map, using the JHU ICBM-DTI-81 WM Labels and JHU White-Matter Tractography atlases.[22] For each patient, we calculated the average FA value of an sphere (2 mm radius) centered in the local maxima voxel then we correlated those values with CANTAB tests values. We performed linear fitting to the data with Origin version 9, and obtained the Pearson's correlation coefficient. We used the standard error of the mean (SEM) to calculate the error bars for the correlation scatter plots.

Results

Clinical Evaluation

The patients show typical DM1 manifestations, including myotonia, muscle weakness, weakness of facial and levator palpebrae muscles and cataracts. Fifteen DM1 patients´ scores were within the normal cognitive performance range as evaluated with the MMSE. However, six patients scored within the suspicios cognitive impairment range (Table 1). From these, 3 male patients had 551, 748, and 1018 CTG repetitions, while 3 female patients had 598, 814, and 456 CTG repetitions. Four of those patients had the lower value of years of education that the DM1 patients reported in our sample (9 years). Finally, just one DM1 patient score was within the cognitive impairment range in the MMSE (male patient, 50 years old with, 9 years of education, and 462 CTG repetitions). The cognitive performance of the patients evaluated by MOCA test was normal for 19 patients. Three patients with a score below the norm were 2 male and 1 female patients. The only male patient with cognitive impairment according to MMSE also resulted with cognitive impairment according to MOCA. No relation was found between these scores and the neuroimaging results.

Muscular Evaluation

Patients were evaluated with the MIRS scale to measure muscle impairment (1 being the lowest value and 5 being the highest value for the muscle impairment progression evaluation).[14] From our sample, 3 patients scored 4, 18 patients scored 3, and 1 patient scored 1 (18-year-old male patient, 11 years of level of education, and 295 CTG repetitions, the cognitive performance determined by the MOCA and MMSE scales for this patient was normal). No relation was found between this score and the neuroimaging results.

Neuropsychological Evaluations with CANTAB

DM1 patients showed cognitive deficits as measured with CANTAB. Only the variables showing significant differences with the control are reported in Tables 2 and 3.

WM Evaluation

FA maps comparison analysis between groups showed significant differences ($P \leq .05$) in the cerebral WM skeleton in a generalized and bilateral way as it is showed in Figure 1. The area with the largest WM deterioration is located in the right corticospinal tract at the brain stem level (MNI coordinates $x = 8$, $y = -34$, $z = -43$). The MD, RD, and AD comparison analyses between groups showed significant differences ($P \leq .05$) as it is showed in Figure 2. The FA decreases in the same areas where the MD, RD, and AD increases which confirms the deterioration of the WM involved in DM1.

Correlation between FA and Age, CTG Repetitions and Cognitive Scores

The correlation analyses between the FA and age values and CTG repetitions for DM1 patients respectively did not show significant results. Then, we performed the correlation analyses between FA values and neuropsychological data from the 8 CANTAB tests that showed significant impairments listed in Tables 2 and 3. These analyses showed significant correlations only between Delayed Matched to Sample (DMS) deficits and WM deterioration.

Probability of Error Given Error

The DMS probability of error given error was found related to the WM skeleton areas shown in Figure 3. The areas found were cerebral anterior areas among which are forceps minor of the corpus callosum, the uncinate fascicle, and the anterior cingulum. The correlation map has 4 significant clusters. Local maxima of each cluster are listed in Table 4. The relationship between FA and the DMS probability given error for the clusters listed in Table 4 are shown in Figure 4.

The correlation between FA and DMS probability error given error in DM1 patients is negative, this is an indication that a better preservation of the integrity of the WM is associated to a smaller chance of making a mistake after a previous erroneous response. The brain WM areas related to DMS were gyrus rectus bilaterally, left anterior inferior fronto-occipital fasciculus, forceps minor of the corpus callosum bilaterally, anterior cingulate fasciculus, and uncinate fasciculus bilaterally.[23]

Mean Total Correct for all Delays

The variable DMS mean total correct for all delays correlates with areas of the WM skeleton shown in Figure 5. The areas correlated to this variable were localized in the temporal lobes (more marked on the right side) and bilaterally in the frontal lobes.

The correlation map had 3 significant clusters, the local maxima for each cluster is listed in Table 4. The scatter plots showing

Table 2. Neuropsychological Results

Test	Variable	Controls	Patients	*t*	*U*	*P* corrected	Cohen's *d*
Delayed Matched to Sample	Probability error given error	.036 ± .07, (0-.22)	.16 ± .19, (.00-.56)	–	125	.025	$r = .370$
Reaction Time	Simple choice accuracy score	8.95 ± .22, (8-9)	8.2 ± 2.02, (0-9)	–	139	.038	$r = -.370$
Match to Sample	Total correct	46.55 ± 2.33, (40-48)	45 ± 2.79, (38-48)	–	114.50	.025	$r = .375$
Motor Screening	Mean error	8.25 ± 1.83, (5.3-12.9)	10.23 ± 3.10, (5.21-16.66)	2.46	–	.025	$d = .777$
Spatial Span	Span length	6.7 ± 1.34, (5-9)	5.55 ± 1.50, (3-8)	–	116.5	.025	$r = -.367$

The results are presented in mean ± standard deviation (range) unless otherwise indicated.

Table 3. Neuropsychological Results for the Mixed Analysis of Variance

Test	Variable	Control	Patients	*F*	*P* corrected	Eta-square
Delayed Matched to Sample	Total correct (0 s, 4 s, 12 s)	8.65 ± .78, (6.33-9.33)	7.92 ± 1.37, (4.67-9.67)	5.250	.0375	.121
Stocking of Cambridge	Problems solved minimum movements	2.2 ± .45, (1.5-2.75)	1.71 ± .66, (.00-2.75)	6.955	.0250	.155
One Touch Stocking of Cambridge	Problems solved on first choice	2.83 ± .86 (.00-3.67)	2.54 ± .65 (.83-3.33)	5.424	.0500	.128
Rapid Visual Information	Total correct rejections (stage 5, 6, 7)	81.47 ± 4.83, (75-90)	77-80 ± 4.78, (66-85)	2.95	.0125	.075

The results are presented in mean ± standard deviation (range) unless otherwise indicated. s, seconds.

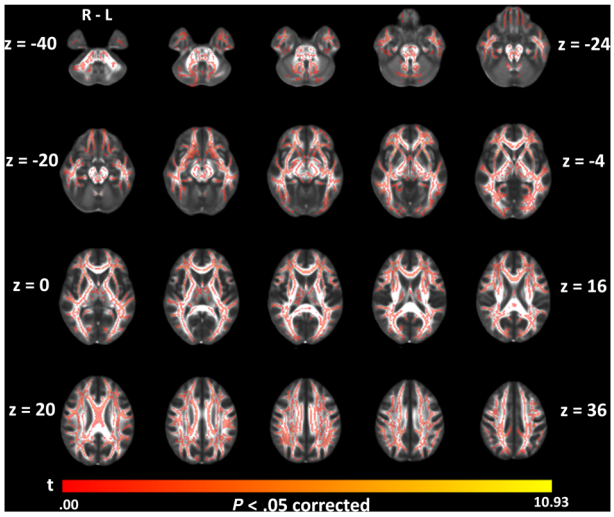

Fig 1. Axial slices of Fractional Anisotropy *t*-map ($P < .05$ corrected) for the comparison between groups, shown in radiological convention, right left (R-L). The map has a single significant cluster (1,07,355 voxels).

the relationship between FA and DMS mean total correct for all delays for each one of the clusters are shown in Figure 6.

The areas of cerebral WM associated with the DMS mean total correct for all delays belong to the optical radiation (bilateral), right anterior thalamic radiation fasciculus, the anterior part of the right uncinate fasciculus, the anterior part of lower fronto-occipital fasciculus (bilateral), the anterior part of the right inferior-longitudinal fasciculus, fornix (bilateral), left anterior limb of the internal capsule, external capsule (bilateral), right retrolenticular part of the internal capsule, corticopontine fasciculus (bilateral), corticospinal tract (bilateral), cerebral peduncle (bilateral), stria terminalis (bilateral), genu of the corpus callosum (bilateral), the anterior part of the right superior-longitudinal fasciculus, the anterior part of the right superior fronto-occipital fasciculus, and the anterior part of the right side of the superior corona radiata.[11]

The correlation between FA and DMS mean total correct for all delays is positive, which indicates that patients with more correct answers are those who showed a better preservation WM integrity, which hints that a good cognitive performance of DM1 patients in the processes of short-term visual memory and new learning may be highly related to the integrity of the WM located in the temporal, frontal, and parietal lobes.[24]

Discussion

CANTAB Cognitive Results

Our results obtained with the CANTAB battery assessment identified specific cognitive impairments in sensorimotor, attention, memory, and executive functions domains in patients with DM1.

Our findings support previous studies, suggesting that the cognitive impairment in DM1 patients is heterogeneous and involves different domains.[5] For example, a previous study showed that DM1 patients have poor performance in neuropsychological tasks that evaluate visuoconstructive and visuospatial perception, as well as social cognition.[25] Another study using CANTAB to evaluate the cognitive profile for DM1 found a detriment in the quality of life of patients that was related to a poor performance in DMS and Spatial Recognition Memory (SRM).[26] Given this variability, it has been suggested that a standardization of the neuropsychological tests battery applied and the systematic evaluation of the clinical, cognitive, and neurological characteristics for DM1 patients is necessary to obtain consistent results among different samples populations of DM1 patients belonging to the same phenotype.[5]

WM Evaluation

The evaluation of the integrity of cerebral WM in DM1 included FA, MD, RD, and AD comparison analyses between

Table 4. Voxels with Higher Significance Characteristics

Variable	Cluster	MNI Coordinate (*x*, *y*, *z*)	*P* corrected	Pearson Correlation Coefficient	Region
Probability error given error	1	(11, 20, 21)	.03	−.64	Right Forceps Minor
	2	(12, 30, −5)	.05	−.49	Right Forceps Minor
	3	(14, 45, −14)	.05	−.49	Right Forceps Minor
	4	(−16, 31, 35)	.05	−.60	Left Uncinate Fasciculus
Total correct all delays	1	(8, 17, 20)	.02	.62	Right Anterior Cingulum
	2	(−18, −45, 29)	.05	.47	Left Splenium of Corpus Callosum
	3	(−21, −55, 23)	.05	.60	Left Precuneus Cortex

MNI = Montreal Neurological Institute (MNI) coordinates.

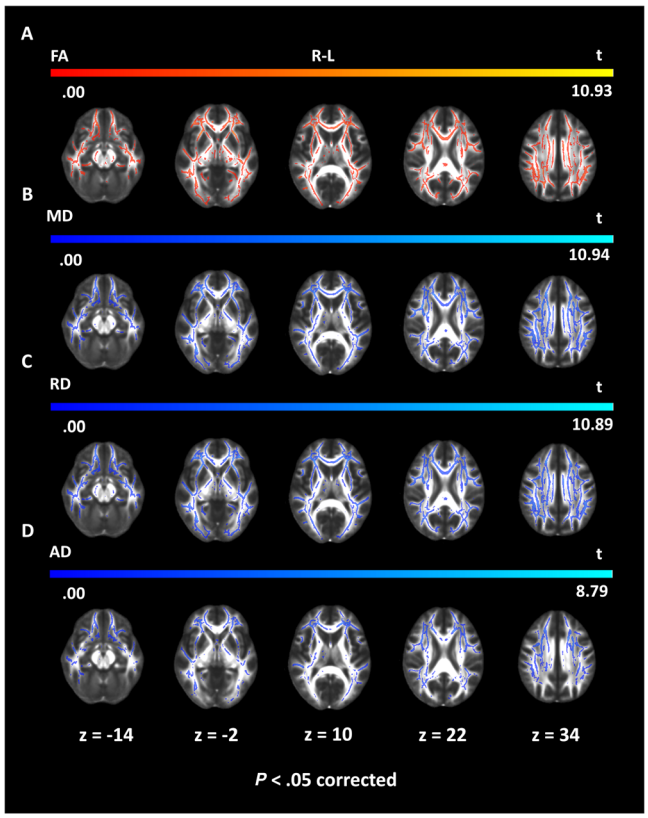

Fig 2. Axial slices of Fractional (FA), Mean Diffusivity (MD), Radial Diffusivity (RD), and Axial Diffusivity (AD) *t*-maps ($P < .05$ corrected), shown in radiologic convention right left (R-L). Yellow-red scale indicates that FA decreased, and blue-blue light scale indicates that MD, RD, and AD increased in patients compared to healthy subjects. (A) FA, (B) MD, (C) RD, (D) AD.

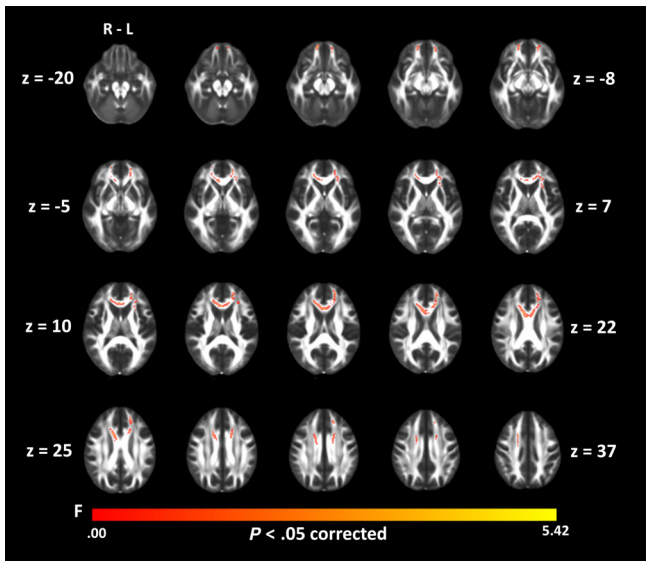

Fig 3. Axial slices of the correlation analysis of Fractional Anisotropy and Probability Error Given Error, shown in radiological convention, right left (R-L).

control and patient groups. These analyses showed widespread and bilateral degeneration of the cerebral WM.[27] FA decreased while MD, RD, and AD increased, confirming the WM deterioration result. This WM deterioration would probably affect both sensorimotor and cognitive domains. We observed that the most deteriorated WM region was the cortical-spinal tract in the brainstem region, which is related to sensory-motor functions altered in DM1 patients.[23] Regarding the cognitive domains, it has been hypothesized that this widespread WM degeneration may be associated with the cognitive impairment in different processes for DM1 patients,[3,9,28] as describe in the next section.

The use of WM skeleton allows the study of the whole brain instead of just focusing in a particular tract; to attain good quality data for tractography would require an increment in the number of diffusion directions,[29] with the consequent increase in acquisition time, increasing the probability of having larger movement artifacts due to the characteristic motor disorder in DM1 patients.

Correlation Analysis between FA, Age, and Cognitive Scores

According to previous studies, DM1 patients have more severe and more diverse symptoms and earlier age onset with larger CTG repetitions,[9] and a correlation between the damage to the integrity of the cerebral WM with the expansion of the number of mutated alleles;[27] however, it has also been shown that the count of the number of repetitions varies from different tissues and over time with respect to the symptomatology of the DM1 (0 to 3000 repetitions), which has put in doubt the reliability in the count of the repetitions obtained of blood samples from the peripheral circulation of patients.[30] This can lead to confusing and contradictory results on the correlation between the different variables evaluated, such as the deterioration of the integrity of the WM, muscle strength data, and neuropsychological data with the number of CTG repetitions. In this work, we did not find a correlation between the damage to the integrity of WM and the length of the expansion of CTG repetitions, neither with the age of classic DM1 patients.

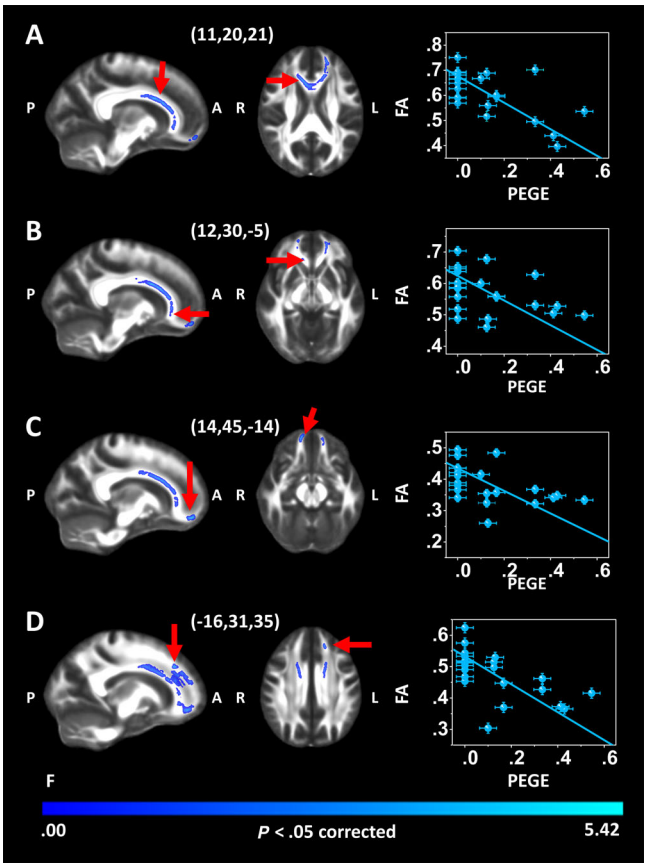

Fig 4. Correlation of Fractional Anisotropy (FA) with Probability Error of Given Error (PEGE): sagittal view (left column), axial view (middle column), and scatter plots (right column) of clusters local maxima (red arrows). (A) Cluster 1 local maxima in right Forceps Minor (FM). (B) Cluster 2 local maxima in right FM. (C) Cluster 3 local maxima in right FM. (D) Cluster 4 local maxima in left Uncinate Fasciculus. Cerebral views are shown in radiological convention: posterior (P), anterior (A), right (R), and left (L), respectively and in (*x,y,z*) Montreal Neurological Institute coordinates.

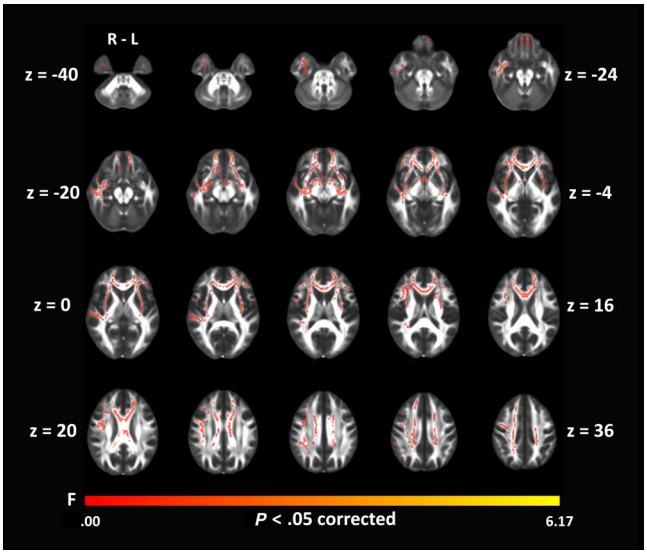

Fig 5. Axial slices of the correlation analysis of Fractional Anisotropy and Mean Total Correct for all Delays, shown in radiological convention, right left (R-L).

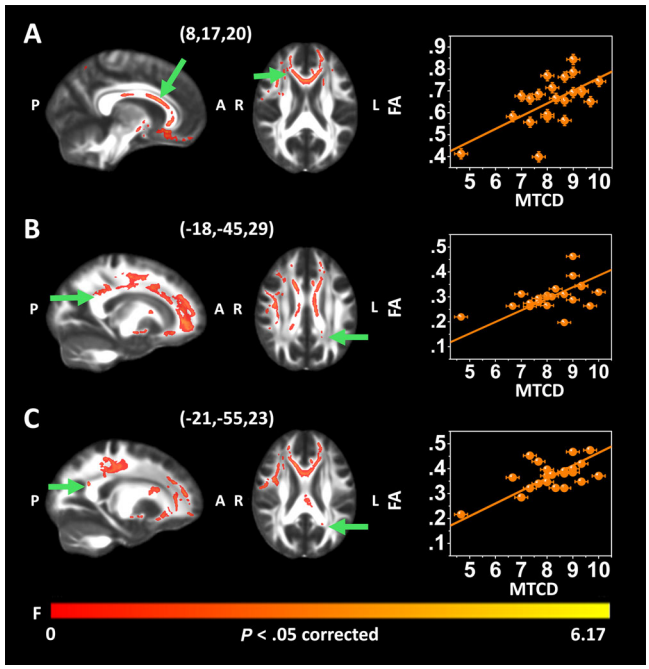

Fig 6. Correlation of Fractional Anisotropy (FA) with Mean Total Correct for all Delays (MTCD): sagittal view (left column), axial view (middle column), and scatter plots (right column) of clusters local maxima (green arrows). (A) Cluster 1 local maxima in right Anterior Cingulum. (B) Cluster 2 local maxima in left splenium of Corpus Callosum. (C) Cluster 3 local maxima in left Precuneus Cortex. Cerebral views are shown in radiological convention: posterior (P), anterior (A), right (R), and left (L), respectively and in (*x,y,z*) Montreal Neurological Institute coordinates.

Correlation Analysis between FA and Cognitive CANTAB Values

There is a scarcity of studies available that have directly investigated the relationship between cognitive changes in DM1 patients with neuroimaging data.[5,6,7,9,31] Here, we found that errors in visual memory are related to loss of integrity in WM connecting the frontal lobes, specifically in the forceps minor and the uncinate fasciculus. The forceps minor connects the lateral and medial surfaces of the frontal lobes, and has been involved in executive functions,[32] while the uncinate fasciculus is a major fiber tract connecting the inferior frontal, anterior, and mesial temporal lobes, and changes in diffusivity have been related to reduced verbal and visual memory performance.[33]

Our results also show a significant correlation between visual memory and WM integrity in the anterior cingulum, the splenium of the corpus callosum, and the precuneus. These results are supported by previous findings showing the wide involvement of these areas not only in memory but in wider aspects of cognition[34–36] including visuospatial processes[37] and selective attention.[38]

In conclusion, here we have found cognitive deficits as measured with a computerized cognitive battery in DM1 patients. Furthermore, we also found a significant loss of WM integrity across the brain. However, DM1 patients only showed a small number of significant correlations between deficits in the memory cognitive domains, and deterioration in particular WM tracks in these patients.

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