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# Relationship between neuropsychological impairment and grey and white matter changes in adult-onset myotonic dystrophy type 1

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ABSTRACT

Myotonic dystrophy type 1 (DM1) has a wide phenotypic spectrum and potentially may affect central nervous system with mild to severe involvement. Our aim was to investigate grey matter (GM) and white matter (WM) structural alterations in a sample of adult-onset DM1 patients and to evaluate relationship with clinical and cognitive variables.

Thirty DM1 patients underwent neuropsychological investigation and 3T-MRI protocol. GM and WM changes were evaluated calculating brain parenchymal fraction (BPF), voxel-based morphometry (VBM), white matter lesion load (LL% and Fazekas scale) and tract based spatial statistical (TBSS).

Patients showed main impairment in tests exploring executive and mnesic domains with visuo-spatial involvement, significantly related to BPF. VBM revealed clusters of widespread GM reduction and TBSS revealed areas of decreased fractional anisotropy (FA) and increased radial diffusivity (RD), mean diffusivity (MD) and axial diffusivity (AD) in patients compared to a group of matched healthy controls. Multiple regression analyses showed areas of significant negative relationship between left temporal atrophy and verbal memory, between RD and mnesic and visuo-spatial cognitive domains, and between AD and verbal memory.

TBSS results indicate that the involvement of normal appearance WM, beyond the signal changes detected with conventional MR imaging (Fazekas scale and LL%), was associated with neuropsychological deficit. These data suggest that disrupted complex neuronal networks can underlie cognitive-behavioural dysfunctions in DM1.



## 1. Introduction

Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy in adults, with a prevalence of about 1 in 8000 people worldwide. It is an autosomal dominant disorder due to an unstable cytosine-thymine-guanine triplet repeat ([CTG]n) expansions on chromosome 19 (Huang and Kuo, 2005), showing no definitive correlation with phenotypic expression (Udd and Krahe, 2012). DM1 can be classified into four clinical forms: congenital, childhood and classical or late-onset (Ekström et al., 2009; Harper, 2001). Classical DM1 form is a multisystem disorder ranging from mild to more severe phenotypes and affecting many organs and tissues, including central nervous system (CNS), this finally responsible of cognitive and behavioural dysfunctions.

Several studies have demonstrated that DM1 patients show a selective impairment in cognitive functioning, particularly in attentional, visuo-spatial, and executive domains (Meola et al., 2003; Winblad et al., 2010); the existence of a "DM1-related-dysexecutive-syndrome" has been already proposed (Meola and Sansone, 2007). Intelligence assessment documented an IQ below average in the DM1 population as compared to healthy subjects, with no clear evidence of a progressive decline (Meola and Sansone, 2007; Jean et al., 2014).

Beside cognitive impairments, in DM1 patients neuropsychiatric comorbidities are frequently reported with variable pathologic behavioural patterns: lack of interest (apathetic behaviour), a decreased emotional participation and an increased irritability are the main clinical features, defined by some authors as "an emotional imbalance" (Meola and Sansone, 2007; Laberge et al., 2013); moreover, a high prevalence of dysfunctional personality has

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been described (Meola et al., 2003; Winblad et al., 2010; Sistiaga et al., 2010).

Previous studies have documented brain abnormalities in DM1 through different imaging techniques and investigated their relationship with cognitive impairment without reaching univocal conclusions. Voxel-based morphometry (VBM) technique showed grey matter (GM) atrophy in several regions of temporal and frontal lobes, hippocampi and thalami (Weber et al., 2010; Minnerop et al., 2011; Schneider-Gold et al., 2015); some studies revealed non-specific pathological findings such as ventricular enlargement and white matter (WM) hyperintensities in different cerebral lobes (Minnerop et al., 2011; Romeo et al., 2010); single photon emission tomography and PET studies demonstrated hypoperfusion and glucose hypometabolism of frontal and temporal lobes (Weber et al., 2010; Meola et al., 1999). Recent studies adopting tractography evaluation (Minnerop et al., 2011; Wozniak et al., 2014) provide data showing microstructural WM damage in interhemispheric, corticospinal and limbic pathways and in frontal, temporal, parietal and occipital lobes. To date, only one study demonstrates that brain atrophy and white matter involvement are progressive over time in DM1 (Conforti et al., 2016).

Although considerable structural CNS involvement on one hand and cognitive deficits on the other hand have been detected in DM1, only few studies investigate their relationship. Some studies have found significant correlations between MR imaging features and neuropsychological profiles (Weber et al., 2010; Wozniak et al., 2014; Caso et al., 2014), while others did not (Minnerop et al., 2011; Romeo et al., 2010).

To this purpose we investigated the structural alterations of GM and WM in a sample of adult-onset DM1 patients and evaluated their relationship with clinical and cognitive variables.

## 2. Material and methods

Thirty patients (24 males, 6 females; mean age 44.6 ± 12.4 years; age range 24–67 years) with clinical and genetic diagnosis of adult form of DM1, according the International Consortium for myotonic dystrophies guidelines (IDMC, 2000), were consecutively recruited at Neurological clinic of University of Pisa. Exclusion criteria were mental retardation (IQ < 70), severe visual impairment, psychiatric illness and a history of substances abuse. None of the patients presented motor or coordination disability sufficient to account for possible delay in any of the neuropsychological tests administered. Patients were grouped on the basis of the number of [CTG]n expansions: 12 patients (40%) were classified as E1 (<150 [CTG]n) and 18 patients (60%) as E2 (150–1000 [CTG]n). The mean disease duration from symptoms onset to the MRI examination was 16.5 ± 11.8 years, while age at onset was 29.0 ± 12.0 years. Patients' mean educational level was 11.3 ± 3.4 years.

Control group was retrospectively selected from our database and included 30 healthy subjects (22 males, 8 females; mean age 44.8 ± 12.6 years; age range 27–68 years) for VBM analyses and 21 subjects (14 males, 7 females; mean age 44.6 ± 12.7 years; age range 27–61 years) for diffusion tensor imaging (DTI) analysis. Age and gender did not significantly differ between patients and controls either for VBM (Mann–Whitney *U* test $p = 0.95$ for age; Fisher's exact test, two tailed $p = 0.54$ for sex), and for DTI (Mann–Whitney *U* test $p = 0.33$ for age; Fisher's exact test, two tailed $p = 0.92$ for sex). All healthy controls beside not to be affected by neurological or psychiatric disorders, had negative neurological examination and no family history for neuropsychiatric illness.

### 2.1. Neuropsychological evaluation

An experienced neuropsychologist, who was unaware of the clinical and MRI data, performed the neuropsychological evaluation. For assessment of immediate memory Immediate and Delayed Recall (IR, DR) of Rey Auditory Verbal Learning Test (RAVLT), Immediate and Delayed Recall (IR, DR) of Rey Osterrieth Complex Figure (ROCF), digit span and Corsi Block-tapping Test (CBT) were administered. Trail Making Tests (TMT-A and TMT-B) were used to assess selective attention and cognitive flexibility and Stroop Test was used to assess automatic response inhibition. Frontal and executive functions were examined by phonemic verbal fluency test (FAS), Frontal Assessment Battery (FAB) and Modified Wisconsin Card Sorting Test (WCST). Rey-Osterrieth Complex Figure was used to assess spatial organization and visuo-constructional skills (ROCF-copy). Patients' raw scores were corrected according to Italian normative values (Spinnler and Tognoni, 1987; Lezak et al., 2012). Percentages of impairment of DM1 patients who showed significant neuropsychological dysfunctions across different cognitive domains were established using Italian normative data for both, score adjustment (sex, age, education) and definition of cut-off thresholds; the latter have been determined as the lower limit of the 95% tolerance interval for a confidence level of 95%.

### 2.2. Data acquisition

MRI imaging was performed with a 3T scanner (Discovery MR750 3.0 T, GE Healthcare, Milwaukee) equipped with an 8-channel head coil with ASSET-technology. The examination protocol included a sagittal CUBE T2 FLAIR sequence (TR 8000 ms; FOV 256 mm; matrix 256 × 256; thickness 1.0 mm; spacing 0 mm; NEX 1.0), a sagittal high resolution 3D T1weighted images with isotropic voxels (TR 8.1 ms; TE 3.2 ms; TI 450 ms; flip angle 12°; FOV 256 mm; matrix 256 × 256; thickness 1.0 mm; spacing 0 mm; NEX 1.0) and DTI performed by using a multiacquisition echoplanar sequence (TR 7000 ms; TE minimum; FOV 240 mm; matrix 128 × 128; thickness 2.9 mm; spacing 0 mm; diffusion gradients applied in 25 directions with b factor = 1000 s/mm$^2$ and 1 b0 volume).

### 2.3. GM evaluation

The evaluation of GM atrophy was performed with a Region of Interest (ROI) based method and using VBM analysis.

In ROI based method FLAIR images, reformatted in axial slices (thickness 4 mm without spacing), were manually segmented using software AW VolumeShare 4 (ADVANTAGE WORKSTATION 4.3, GE Healthcare, Milwaukee) to measure the parenchymal volume and total intracranial volume. Brain parenchymal fraction (BPF) was calculated through the ratio of brain parenchymal to intracranial volume and was considered as an expression of the degree of atrophy, as done in previous studies of volumetric analysis of DM1 patients (Kassubek et al., 2003). Correlations between BPF values and clinical (age, disease duration) and neuropsychological scores were evaluated by using Pearson correlation coefficient, considering p-value statistically significant at $p < 0.05$.

#### 2.3.1. VBM

The automated analysis of T1 structural data was carried out by FSL-VBM (Douaud et al., 2007), an optimised VBM protocol (Good et al., 2001) carried out with FMRIB software library package (FSL) (Smith et al., 2004). As preprocessing step T1 images were corrected for WM lesions using the lesion filling toolbox available in FSL (Battaglini et al., 2012). Structural images were brain-extracted using BET (Brain Extraction Tool) (Smith, 2002), and then they were automatically segmented into GM, WM and cerebrospinal fluid (CSF) tissue-type by FAST4 tool (Zhang et al., 2001). The GM volume images were aligned to the Montreal Neurological Institute (MNI) 152 standard space (Mazziotta et al., 1995) by the affine registration tool FLIRT (Jenkinson et al., 2002), followed by non-linear registration using FNIRT (Andersson et al., 2007). The registered GM images of an equal number of healthy controls and DM1 patients were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. After that all native GM images were non-linearly registered to this study-specific template, modulated and smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.