Assessing regional gray and white matter changes to understand the CNS related symptoms of Myotonic Distrophy type-1

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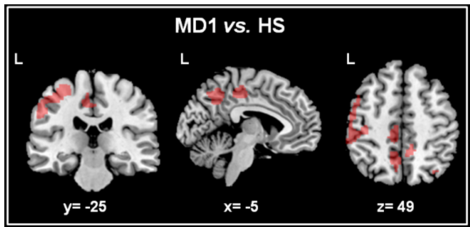
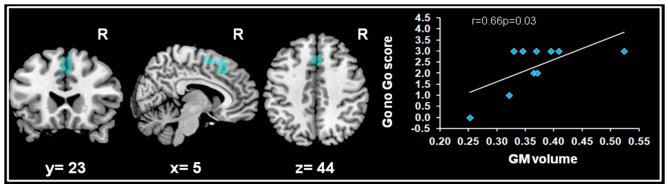
Purpose: Myotonic dystrophy type 1 (MD1) is the most frequent muscle dystrophy, transmitted as an autosomal dominant trait. The clinical picture includes muscle involvement associated with psychiatric disorders and cognitive deficits, which are dominated by executive dysfunctions [1]. Brain tissue involvement has already been demonstrated in patients with MD1 by volumetric and diffusion MRI techniques [1]. However, associations between brain abnormalities and neuropsychological measures have produced conflicting results. Aims of this work were 1) to assess, using Voxel-Based Morphometry (VBM) the presence and extension of gray (GM) and white matter (WM) atrophy in MD1 patients, and its relationship with genetics ; 2) to explore the associations between brain abnormalities and clinical-cognitive features observed in MD1 patients. **Methods:** Participants: 10 patients diagnosed as suffering from MD1 [mean (SD) age 41.1 (9.6) years] were recruited. All patients with MD1 were genetically confirmed as carriers of a mutation on DMPK gene with a CTG triplets' expansion ranging from 54 to 2000 and with the Muscular Impairment Rating Scale (MIRS) score ranging from 1 to 4. Sixteen sex- and age-matched healthy subjects (HS) were also investigated and served as controls. Patients underwent an extensive neuropsychological assessment (including the Frontal Assessment Battery; FAB). Patients and HS underwent a MRI examination at 3T, including the following acquisitions: 1) dual-echo turbo spin echo [TSE] (TR=6190 ms, TE=12/109 ms); 2) fast-FLAIR (TR=8170 ms, TE=96 ms, TI=2100ms); 3) 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix=256x224, n. slices=176, thickness=1 mm); MRI analyses and statistics: a*)VBM on GM and WM maps:*T1-weighted volumes were pre-processed using the VBM protocol [2] implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Statistical analysis was performed on smoothed (12 mm FWHM kernel) GM and WM maps within the framework of the general linear model. We used a two-sample T test design on GM and WM, respectively, to model the groups (MD1 and HS) and test the differences. In VBM analyses the intra-cranial volume (ICV) (obtained by adding up WM volume, GM volume and CSF volume) was entered as a covariate of no interest. P values were considered significant if survived after FWE cluster level correction for multiple comparisons ($p< 0.05$). We have performed multiple regression analyses to test the potential associations between genetic and cognitive profile and regional GM volumes in MD1 patients. **Results:** Neuropsychological assessment: Patients with MD1 showed strict associations between the CTG triplets's expansion and tests exploring the general cognitive efficacy. In particular, we found significant inverse correlations with the MMSE score (r=0.79, p=0.01), with the Total IQ (r=0.81, p=0.01) and, finally, with the Performance IQ (r=0.81, p=0.01). Voxel-Based Morphometry : A) Gray Matter analysis-group comparison: **Figure 1**



A) Patients with MD1 compared to HS showed GM loss in the left posterior cingulate, in the left supramarginal gyrus, in the left pre- and post-central gyrus, and in the precuneus bilaterally (Figure 1)

B) Gray Matter analysis- correlation between frontal functions and GM volumes changes in MD1 patients:

Figure 2



Multiple regression analysis performed in MD1 patients only, revealed a direct association between the Go-No-Go patients' scores (sub-test of FAB) and GM volumes in the anterior paracingulate gyrus bilaterally (with a r=0.66, p=0.03) (see Figure 2)

C) VBM-White Matter analysis: WM loss was found in the MD1 patients' cerebellum (Lobule IX, bilaterally) in the pons and midbrain.

Discussion: this study confirms the presence of widespread GM and WM loss in the brain of patients with DM1. These morphological changes might account for some specific clinical features of DM1. In particular, the association between Go-No-Go patients' scores and GM volume in the paracingulate gyrus might account for the executive deficits, which are likely due to dysinhibition mechanisms.

References:[1]Minnerop et al., 2011. *Brain* 134: 3530-46. [2] Ashburner et al.,2000. *Neuroimage*.11:805-21.