Cerebellar involvement in Myotonic dystrophy type-1: a pioneering study

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy observed in adults[1]. It is caused by a CTG triplet repeat expansion within the myotonic dystrophy protein kinase (DMPK) gene located on chromosome 19q13.3, whose inheritance is autosomal dominant[2]. DM1 is a multi-systemic disorder dominated by muscular impairment, but involving also other organs including the brain[1]. It is becoming increasingly clearer that most of the impairment observed in patients with DM1 is driven by higher-level dysfunctions[3-6]. DM1 brains have been demonstrated to be structurally damaged in both tissue, the grey (GM) and white matter (WM)[3-6], with a specific anatomical distribution of abnormalities. This structural damage has been consistently reported across independent studies[3-6], and it was more recently associated with CGT triplet expansions in the DMPK gene and measures of clinical severity[7]. Several studies, involving both structural and functional brain imaging , indicated the cerebellar damage plays a critical role in DM1 pathophysiology[7]. However no previous studies investigated directly the cerebellum in DM1 patients. Aim of the present study was to perform a deteiled structural investigation of the cerebellum in patients with DM1 using an approach based on voxel-based morphometry (VBM).

MATERIAL AND METHODS

42 DM1 patients

30 Healthy subjects (HS)

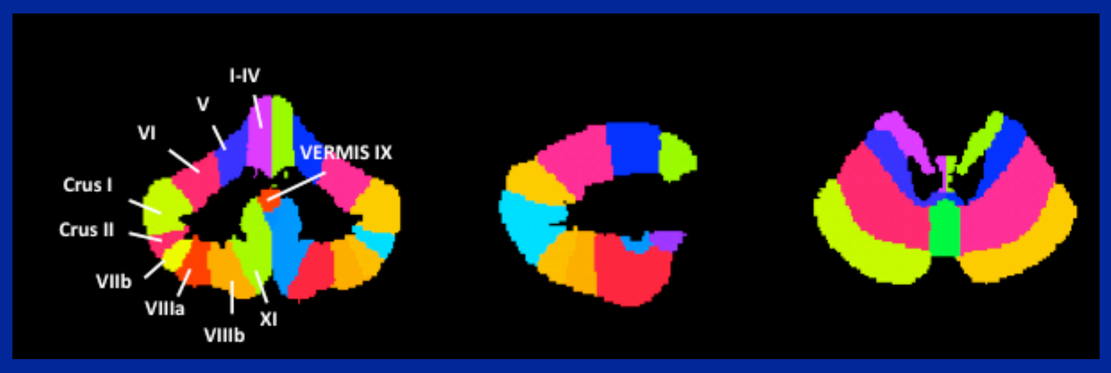
→ T1-weighted images at 3T MRI

→ PENN emotional recognition test

VBM of cerebellum

The cerebellum were pre-processed individually in SPM-8 using SUIT tool[7]. Cerebellar grey (GM) and white (WM) matter were extracted. The images were smoothed using a 8-mm FWHM Gaussian kernel. Statistical analyses were performed on smoothed GM maps within the framework of the general linear model. A two-sample t-test was used for assessing between group differences in regional GM cerebellar volumes. Results were considered significant at p values <0.05 after FWE cluster-level correction.

Spatially Unbiased Atlas Template of the Cerebellum (SUIT)[7]



PENN emotional recognition test

→

Correlations were tested between cerebellar GM volumes and PENN scores in DM1 patients

RESULTS

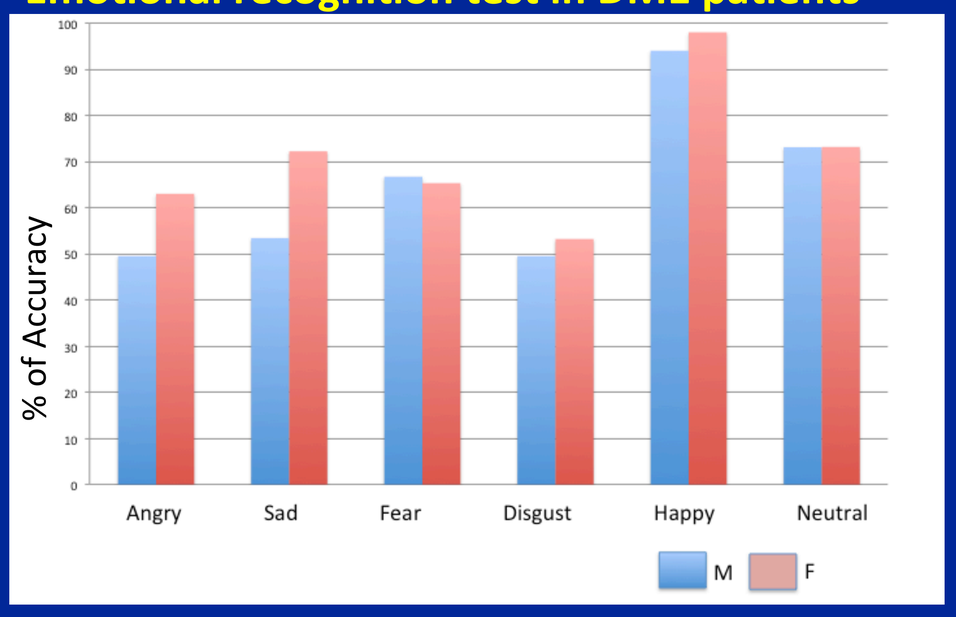
Demographic features of participants

	DM1 patients N=42	HS N=30
Mean (SD) age [years]	41.5 (12.6)	39.6 (13.8)
Gender (F/M)	24/21	21/13
Mean (SD) years of formal education	12.4 (2.2)	14.0 (3.3)

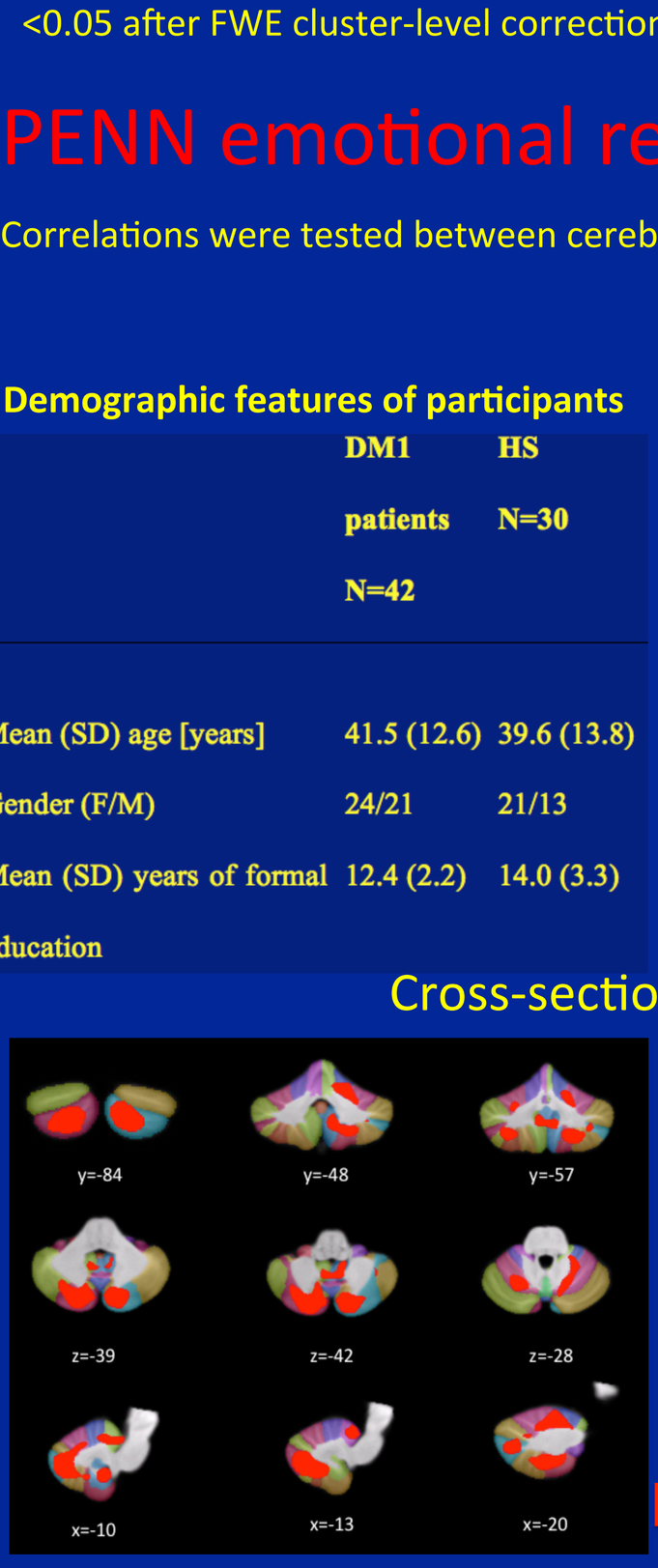
Clinical features of DM1 patients

	DM1 patients
Age at onset:	
Childhood-onset (age range: 6-16 years)	38.7%
Adulthood-onset (age range:18-60 years)	61.2%
Size of CTG triplets' expansion on DMPK gene:	
Mean (SD) [range]	527.9 (383.0) [54- 2000]
IDMC nomenclature:	
E1 (CTG range: 50-150) (N and %)	3 (7.0%)
E2 (CTG range: 151-500) (N and %)	22 (52.3%)
E3 (CTG range: 501-1000) (N and %)	14 (33.3%)
E4 (CTG range >1000) (N and %)	3 (7.0%)

Emotional recognition test in DM1 patients



Cross-sectional comparison



DM1<HS

Patients with DM1 compared to HS revealed a pattern of regional GM atrophy (in red) in the cerebellar cortex. Specifically DM1 showed reduced GM volumes in the anterior (lobules I-IV bilaterally), the posterior (lobules VI-VIII Crus-II bilaterally, right lobule IX and Crus-I) and vermian (Vermis IX) structures.

Correlations

We found in DM1 patients significant direct correlations between accuracy in the PENN recognition test and GM volumes in the cerebellum. Specifically, GM atrophy in the Crus-II, Crus-I and Vermis IX, were significantly associated with the Disgust ($p<0.05$).

DISCUSSION

GM reduction in DM1 patients affected cerebellar areas that are known to sub-serve both, motor and cognitive/affective functions. This is consistent with previous data showing that abnormal functional connectivity within cerebral and cerebellar networks of DM1 brains may account for peculiar deficits in patients' social cognition[6]. Specifically, this study clarifies the potential critical role of structural cerebellar abnormalities in altering DM1 patients' functional connectivity and behaviour. Further, this cerebellar pattern of GM atrophy we found in DM1 patients is likely to contribute accounting for patients' deficit in motor planning and coordination.

References

1) Meola and Cardani, Biochimca et Biophysica Acta, vol. 1852, pp. 594-606, 2015; 2) Brook, et al. Cell, vol. 68, 799-808, 1992; 3) Serra et al. JAMA Neurology, vol. 71, pp. 603-611, 2014; 4) Serra et al.. Functional Neurology, vol. 25, pp. 1-11, 201; 5) Serra et al., Neural Plast. 2016, 2696085 ; 6) Serra et al. PLoS One. 2016 Jun 3;11(6):e0156901; 7) Diedrichsen et al. Neuroimage. 2009 May 15;46(1):39-46.