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Neuroanatomical correlates of dystonic tremor: A cross-sectional study

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ABSTRACT

Purpose: This study is aimed at investigating the neuroanatomical patterns characterizing dystonic tremor in comparison with essential tremor.
Methods: Voxel-based morphometry and cortical thickness data of 12 patients with dystonic tremor, 14 patients with essential tremor and 23 age- and sex-matched healthy control subjects were analyzed.
Results: Patients with dystonic tremor showed a thickening and increased gray matter volume (surviving whole-brain correction for multiple comparisons) of the left sensorimotor cortex when compared to other groups. Otherwise, patients with essential tremor were characterized by a subtle atrophy of the anterior cerebellar cortex.
Discussion: Our multimodal structural neuroimaging study demonstrated that patients with dystonic tremor and essential tremor are characterized by different neuroanatomical abnormalities. The involvement of the sensorimotor cortex in patients with dystonic tremor suggests that this disorder may share some pathophysiological mechanisms with focal dystonia.

1. Introduction

Dystonic tremor (DT) is defined as a postural/kinetic tremor with irregular amplitude and variable frequency occurring in an extremity or body part affected by dystonia [1]. Diagnosing this disorder may be challenging because tremor observed in patients suspected of having DT resembles essential tremor (ET), and dystonia may be subtle and difficult to recognize only on clinical grounds.

In the last few years, advances have been reached in the definition of the pathophysiological mechanisms underlying ET and DT. Evidences support the hypothesis that ET is a progressive disease sustained by neurodegenerative processes [2–5]. Neuroimaging [3,4] and post-mortem [5] studies in patients with ET demonstrated the presence of pathological changes mainly involving the cerebellum [6]. Otherwise, very recent studies demonstrated abnormality of sensorimotor integration circuits [7] or increased blink recovery cycle [8] in patients with DT, suggesting that this disorder might be associated with brain dysfunctions different from those detected in ET.

The current study is aimed at investigating the presence of neuroanatomical changes in patients with DT with respect to patients with ET and healthy controls by combining two complementary morphologic MR measurements: voxel-based morphometry (VBM) [9] and cortical thickness (FreeSurfer) [10] in a multi-method unbiased approach. We used both methods in order to receive any complementary piece of information. Indeed, whereas VBM provides a general measure of gray matter (GM) volume, which conflates the contributions of thickness and surface, cortical thickness analysis captures the columnar architecture of the cortex.

2. Methods

2.1. Subjects

From April 2010 to November 2013, we prospectively identified 12 consecutive patients with a diagnosis of DT (six with neck dystonia associated with head tremor without limbs tremor and six with unilateral dystonic limb tremor without dystonia elsewhere; no patient had facial dystonia) and 14 patients with ET. DT and ET were diagnosed according to the consensus criteria of the Movement Disorders Society on tremor [1]. Tremor and dystonia were assessed by Fahn–Tolosa–Marin rating scale [11] and Unified

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Dystonia Rating Scale (URDS), respectively. All enrolled patients underwent an accurate clinical history and videotaped neurological examination to better define clinical characteristics of DT. Exclusion criteria were the presence of brain lesions (evidence of structural abnormalities as revealed by radiological examination) or depression symptoms (as assessed by the Structured Clinical Interview for DSM-IV Axis I disorders). Moreover, every patient underwent DAT-SPECT. No patients with DT or ET received botulinum toxin injections.

Twenty-three volunteers with no previous history of neurological or psychiatric diseases and with normal MRI of the brain were matched for demographical variables with patients. All participants gave written informed consent, which was approved by the Ethical Committee of the University 'Magna Graecia' of Catanzaro, according to the Helsinki Declaration.

2.2. MRI data acquisition

Brain MRI was performed according to our routine protocol [12] by a 3 T scanner with an 8-channel head coil (Discovery MR-750, GE, Milwaukee, WI, USA). Structural MRI data were acquired using a 3D T1-weighted spoiled gradient echo (SPGR) sequence. Subjects were positioned to lie comfortably in the scanner with a forehead-restraining strap and various foam pads to ensure head fixation.

2.3. VBM data processing and analysis

Data were processed and examined using the SPM8 software where we applied VBM implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters incorporating the DARTEL toolbox that was used to obtain a high-dimensional normalization protocol. Images were bias-corrected, tissue classified and registered using linear and non-linear transformations, within a unified model [9]. Subsequently, the warped GM segments were affine transformed into Montreal Neurological Institute (MNI) space and were scaled by the Jacobian determinants of the deformations (modulated GM volumes). Finally, the modulated volumes were smoothed with a Gaussian kernel of 8 mm.

2.4. Cortical thickness data processing and analysis

To corroborate voxel-based findings we further performed cortical thickness analysis of the cortical mantle by using FreeSurfer v5.1 [10] with a well-established methodology [13]. In particular, we were interested in confirming findings provided by VBM analysis. Briefly, images were first corrected for intensity nonuniformity and registered via affine transformation (12 parameters) to Montreal Neurological Institute (MNI) space. Then, images underwent a further intensity normalization using a different automated algorithm and were automatically skull stripped. Next, the entire cortex was visually inspected prior to analysis by a neuroradiologist with a high level of neuroanatomical expertise, who was blinded from the MRI results. For each subject, thickness measurements across the cortex were computed by finding the point on the gray–white boundary surface that was closest to a given point on the estimated pial surface and averaging between these two values. Finally, cortical maps were smoothed with a 10-mm full-width at half maximum Gaussian kernel.

2.5. Statistical analysis

Statistical analyses were performed with Statistical Version 6.0 (www.statsoft.com). One-way ANOVA, unpaired *t*-test and χ^2 were used to assess potential differences between groups for all demographic and clinical variables. All statistical analyses had a two-tailed alpha level of <0.05 for defining significance.

2.6. VBM statistics

The GM volume maps were statistically analyzed using the general linear model based on Gaussian random field theory. Statistical analysis consisted of an analysis of covariance (AnCOVA) used for investigating the main effect of group (*F*-test). Age and total intracranial volume (ICV) were included in the model as covariates of no-interest. Two approaches to statistical threshold maps were applied. First, we applied a conservative approach with a whole-brain statistical threshold correction ($P < 0.05$, family-wise error (FWE)). Second, since that in vivo evidence of GM abnormalities in DT has never been reported, for exploratory purpose the data were also presented by using a less-stringent, uncorrected threshold ($P < 0.001$, cluster (k) threshold $= 10$ voxels) to detect subtle morphological changes.

2.7. Cortical thickness statistics

Surface-based group analyses were performed using general linear model. Statistical significance of between-group cortical thickness was evaluated using a clusterwise correction for multiple comparisons from Monte Carlo *z*-field simulation [14]. To correct for multiple comparisons, spatial clusters of thickness differences were defined as continuous patches of vertices with *P*-values less than 0.05 (two-tailed). The *P*-values for these clusters were determined by Monte Carlo simulation (10,000 iterations). Only clusters that survived this correction with *P*-values less than 0.05 (two-tailed) were deemed significant.

3. Results

3.1. Clinical data

Demographic and clinical features of all subjects are listed in Table 1. No significant differences were detected in demographical and clinical data between groups.

3.2. VBM data

VBM analysis, investigating the neuroanatomical changes occurring when the three groups were analyzed together (AnCOVA,

Table 1
Demographic, clinical and DAT-SPECT imaging characteristics.

Variables	DT	ET	Controls	*P*-Values
N[c]	12	14	23	
Men, *n*. (%)	6 (50%)	8 (57%)	13 (56%)	0.91[b]
Age (years)	62.9 ± 15	66.3 ± 9.1	64.4 ± 7.1	0.27[d]
Age at onset (years)	50.2 ± 15.9	53.2 ± 15.3	–	0.41[c]
Disease duration (years)	10.9 ± 8.9	12.8 ± 11.9	–	0.32[c]
Familiarity[a], *n* (%)	6 (50%)	9 (64%)	–	0.73[b]
MMSE	27.4 ± 1.6	26.2 ± 3.7	27.2 ± 3.7	0.58[d]
UDRS	5 ± 0.9	–	–	-
Fahn–Tolosa	11.3 ± 9.1	10.1 ± 4.6	–	0.44[c]
DAT-SPECT				
Left putamen	2.16 ± 0.3	2.15 ± 0.29	2.20 ± 0.29	0.85[d]
Right putamen	2.13 ± 0.51	2.21 ± 0.27	2.21 ± 0.28	0.72[d]

DT: dystonic tremor; ET: essential tremor. MMSE: mini mental state examination. UDRS: Unified Dystonia Rating Scale.
[a] Positive family history regarding tremor.
[b] χ^2 test.
[c] Unpaired *t* test.
[d] One-way ANOVA.