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MAGNETIC RESONANCE

White matter rather than gray matter damage characterizes essential tremor

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Abstract

Objectives We investigated changes in gray matter (GM) and white matter (WM) in the whole brain, including both cortical and subcortical structures, and their relationship with tremor severity, psychiatric symptoms, and cognitive impairment in patients affected by essential tremor (ET).

Methods We studied 19 ET patients and 15 healthy subjects (HS). All the subjects underwent a 3-T MRI study based on 3D-T1 and diffusion tensor images. For the GM analysis, cortical thickness was assessed by using the Computational Anatomy Tool, basal ganglia and thalamus volumes by using the FMRIB software library, and cerebellum lobular volumes by using the spatial unbiased atlas template. For the WM assessment, we performed a voxel-wise analysis by means of tract-based spatial statistics. Patients' tremor severity and psychiatric and cognitive disorders were evaluated by means of standard clinical scales. Neuroimaging data were correlated with clinical scores.

Results We found significantly smaller right and left thalamic volumes in ET patients than in HS, which correlated with cognitive scores. We did not observe any significant differences either in cortical thickness or in cerebellar lobular volumes between patients and HS. WM abnormalities were detected in most hemisphere bundles, particularly in the corticospinal tract, cerebellar peduncles, and corpus callosum. The WM abnormalities significantly correlated with tremor severity, cognitive profile, and depression.

Conclusion Our study indicates that ET is characterized by several GM and WM changes of both infra- and supratentorial brain structures. The results may help to better understand mechanisms underlying tremor severity and psychiatric and cognitive impairment in ET.

Key Points

- *We performed a comprehensive evaluation of gray and white matter in the same sample of patients with essential tremor using recently developed data analysis methods.*
- *Essential tremor is characterized by widespread gray and white matter changes in both infra- and supratentorial brain structures. The results may help to better understand motor and non-motor symptoms in patients with essential tremor.*

Keywords Essential tremor · Magnetic resonance imaging · Gray matter · White matter

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Abbreviations

3D-T1	Three dimensional T1-weighted
AD	Axial diffusivity
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CAT12	Computational Anatomy Tool
CSF	Cerebrospinal fluid
DTI	Diffusion tensor imaging
ET	Essential tremor
FA	Fractional anisotropy
FAB	Frontal Assessment Battery

FIRST	FMRIB's Integrated Registration and Segmentation Tool
FSL	FMRIB software library
FTM-TRS	Fahn-Tolosa-Marin Tremor Rating Scale
FWE	Family-wise error
GM	Gray matter
HS	Healthy subjects
MD	Mean diffusivity
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
RD	Radial diffusivity
SPM12	Statistic parametric mapping version 12
SUIT	Spatially unbiased infratentorial toolbox
TBSS	Tract-based spatial statistics
TE	Time echo
TIV	Total intracranial volume
TR	Repetition time
VBM	Voxel-based morphometry
WM	White matter

Introduction

Essential tremor (ET) is a common movement disorder clinically characterized by postural and kinetic tremor mainly affecting the upper limbs [1, 2]. Recent evidence suggests that ET is a heterogenous condition that affects not only the upper limbs but also the head, voice, and lower limbs [2, 3]. Tremor may be isolated or combined with other clinical features such as dystonia, parkinsonism, and ataxia (ET plus) [2]. In addition, ET patients may also exhibit a number of non-motor disturbances, including depression [4, 5] and impaired cognition [6].

In ET, magnetic resonance imaging (MRI) examinations have revealed gray matter (GM) abnormalities in frontal, temporal, and occipital cortex [7–11], insula, precuneus [8, 9], and cerebellum [9, 12–16]. A recent metanalysis, however, highlighted a reduction in GM volume only in the left precuneus and posterior cingulate gyrus, which might be related to cognitive and mood disorders rather than to tremor severity [17]. In the majority of MRI studies, GM changes have been assessed by means of voxel-based morphometry (VBM). No study has assessed cortical GM by means of surface-based methods [18], which provide better measures of neuronal and glial cell density at a sub-voxel precision level and adopt the spatially unbiased infratentorial toolbox (SUIT), allowing cerebellar lobular volumetry to be assessed accurately [19]. MRI studies have also demonstrated that ET patients may have widespread white matter (WM) changes in forebrain areas and the cerebellum [20–23]. In the previous MRI studies, GM and WM changes' studies have rarely been assessed in the same samples of patients, which makes it difficult to draw firm conclusions on the possible cooccurrence of these structural abnormalities in ET patients. In addition, previous MRI studies have failed to demonstrate a clear association between brain damage and tremor severity [7, 9, 12, 13, 15, 21–23], and only reported a relationship between GM and WM damage and cognitive abnormalities [24, 25].

The aim of the present study was to investigate possible GM and WM changes and their relationship with motor and non-motor symptoms in ET. For this purpose, we performed a systematic whole-brain investigation of GM and WM in cortical and subcortical structures and a correlation analysis between GM and WM changes and tremor severity and psychiatric and cognitive disorders in patients with ET.

Materials and methods

This study included 19 ET patients (mean age ± SD, 67.00 ± 17.80; 10 males) and 15 healthy subjects (HS) (mean age ± SD, 63.00 ± 9.00; 7 males). Subjects were recruited at the Neurology Unit at IRCCS Neuromed, Pozzilli (Isernia, Italy). The diagnosis of ET was made according to clinical criteria [2]. The demographic and clinical information collected included current age, age at ET onset, family history, tremor distribution, exposure to drugs, and comorbidities. Two neurologists with expertise in movement disorders assessed the patients' clinical state by using the Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) [26]. The patients' cognitive profile was assessed by using the Montreal Cognitive Assessment (MoCA) [27] and the Frontal Assessment Battery (FAB) [28]. Depression and anxiety were evaluated respectively by means of the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) [29].

All the subjects underwent a 3-T MRI scan within a week of the clinical evaluation.

The study was conducted with the approval of the institutional ethics committee and in accordance with the Declaration of Helsinki. Specific national laws have been observed, too. Written informed consent was obtained from each participant.

MRI acquisition

All the participants underwent a standardized MRI protocol on a GE 3.0T Signa HD (General Electric Medical Group, GE Healthcare), including the following sequences: (1) high-resolution three-dimensional T1-weighted (T1-3D) magnetization-prepared rapid acquisition with gradient echo sequence (repetition time [TR] = 1900 ms, echo time [TE] = 2.93 ms, flip angle = 9, field of view [FOV] = 260 mm, matrix = 256 × 256, 176 contiguous sagittal 1-mm-thick slices); (2) diffusion tensor imaging (DTI) single-shot echo-planar spin-echo sequence with one $b = 0$ and 30 gradient directions, $b = 1000$ s/mm (TR = 12,200 ms, TE = 94 ms, FOV = 192 mm, matrix = 96 × 96, and on 72 contiguous axial 2-mm-thick slices); (3) dual turbo

spin-echo proton density and T2-weighted images (TR = 3320 ms, TE = 10/103 ms, FOV = 220 mm, matrix = 384 × 384, 25 axial 4-mm-thick slices, 30% gap).

MRI data analysis

In all patients and HS, the segmentation of all the GM and WM measures was performed in the native space. No major movement artifacts were detected at the visual quality control.

Gray matter measures

Cortical thickness

We used CAT12 (Computational Anatomy Tool), a tool running under SPM12 (Statistical Parametric Mapping version 12 - Ashburner 2005) that contains a processing pipeline for surface-based morphometry, to obtain cortical thickness measures [18]. T1-3D underwent spatial registration to standard template (in MNI space) and tissue segmentation into GM, WM, and cerebrospinal fluid (CSF). Segmented GM volumes were modulated by applying the scaling factor, calculated by means of registration parameters, to account for total intracranial volume (TIV) variations. After CAT12 plotting of the segmentation distribution, all the subjects were included within 3 SD (no outliers).

Deep nucleus volumes

Absolute tissue volumes for subcortical structures were estimated through FMRIB's Integrated Registration and Segmentation Tool (FIRST) [30]. FIRST searches through linear combinations of shape modes of variation for the most probable shape instance according to the intensities observed on T1-weighted images. Subcortical structures, i.e., the caudate nucleus, putamen, globus pallidus, and thalamus, were segmented from the T1-3D images. Normalized volumes of subcortical structures were then obtained by multiplying the estimated subcortical volumes based on FIRST by the volumetric scaling factor of each individual based on SIENAX, which uses the brain and skull images to estimate the scaling between the subject's image and standard space [31].

Cerebellar volumes

Cerebellar volumes were calculated by using SUIT version 3.2 implemented in SPM12 [32]. The cerebellum of ET patients and HS was isolated on T1-3D images by using "suit_isolate_seg." The isolated cerebellum was then normalized using the "suit normalize dartel" to align the isolated cerebellum from the native subject space to the SUIT atlas template space using the affine transformation matrix and non-linear flow field. The cerebellum in the SUIT atlas space was resliced further using "suit_reslice_dartel" to preserve the volume of different cerebellar lobules into the SUIT atlas. Lastly, the resulting SUIT atlas was realigned back to the native subject space using "suit_reslice_inv." The lobular volumes of the cerebellum were calculated through "Lobuli-ROI analysis with atlas" and were computed as the sum of the hemispheres and vermis after being normalized for TIV. Finally, the global volume of the cerebellum was calculated as the sum of all the lobules, whereas the anterior and posterior cerebellar volumes were calculated as the sum of lobules I–V and VI–X, respectively. Lobular volumes of ET patients and HS were compared by using the two-sample *t* test in SPSS (SPSS Inc.).

The results were reported at a significance level of $p < 0.05$ after correction for multiple comparisons.

White matter measures

In the preprocessing phase, all the diffusion tensor imaging (DTI) images were motion-corrected and eddy current–corrected to avoid distortions due to the gradient directions applied. Mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) maps were generated using DTI Fit, included in FMRIB's Diffusion Toolbox, which is part of the FMRIB software library (FSL) version 4.1.9. This program fits a diffusion tensor model at each voxel. A voxel-wise statistical analysis of FA, MD, AD, and RD data was performed by using tract-based spatial statistics (TBSS) [33]. All diffusion and FA maps of both the patients and HS were first aligned into a common space using a non-linear registration tool. All the images were then transformed into Montreal Neurological standard space. The mean FA image was generated and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the subjects. Each subject's aligned FA data was then projected onto this skeleton, and the resulting data fed into voxel-wise general linear modeling cross-subject statistics. We used a threshold of 0.2 for the creation of the mean FA skeleton so as to include the main WM tracts but exclude peripheral tracts, which may cause significant inter-subject variability and/or partial volume effects with GM and CSF. All the data were anatomically localized using the JHU ICBM-DTI-81 White-Matter Labels and the JHU White-Matter Tractography atlases included in the FSL distribution [34].

Statistical analysis

The Shapiro-Wilk normality test was performed to check for the normal distribution of the demographic and clinical data. Parametric or non-parametric tests were used for normally distributed and non-normally distributed data. Differences in gender were tested by means of the chi-square test and differences in age by means of the Mann-Whitney test. Volume comparisons of subcortical structures and cerebellar lobules were assessed by means of the *t* test using SPSS. In ET, correlations between brain

volumes (altered in comparison with HS) and clinical measures were assessed by means of Pearson's correlation. Group comparison of cortical thickness between HS and ET patients was performed by using CAT12 and a general linear model, with age and TIV as nuisance covariates. Results were thresholded at $p < 0.05$ corrected for family-wise error (FWE). The group comparison of DTI parameters was performed in TBSS by means of a voxel-by-voxel permutation non-parametric test (5000 permutations) using threshold-free cluster enhancement, which obviates the need for an arbitrary threshold for the initial cluster formation. Age and gender were entered into the model as covariates of no interest. Correlations between voxel-wise DTI parameters and clinical measures were also assessed by using threshold-free cluster enhancement. The results were reported at a significance level of $p < 0.05$ after FWE correction for multiple comparisons.

Results

There were no significant differences in age ($p = 0.07$) or gender ($p = 0.13$) between ET patients and HS. In patients with ET, the mean FTM-TRS was 25.52 ± 12.51, the mean MoCA score was 25.5 ± 12.51, and the mean FAB value was 13.67 ± 2.79 (Table 1). The mean BDI and BAI scores were 8.21 ± 7.29 and 7.00 ± 6.84, respectively. Tremor in all the patients was limited to the upper limbs; only 4 of the 19 patients (21%) also had head tremor.

Table 1 Clinical demographic data

	Gender	Age	Family history	Disease duration	TRS	MoCA	FAB	BDI	BAI
1	F	74	Yes	6	42	23.00	14.8	20	9
2	F	70	Yes	10	32	22.4	11.80	0	14
3	M	73	Yes	8	45	24.40	9.50	5	3
4	F	54	Yes	15	43	28.00	16.70	16	26
5	F	62	Yes	3	22	22.78	13.80	11	3
6	M	66	Yes	22	23	22.98	16.70	1	12
7	M	76	No	3	14	23.72	13.70	7	4
8	F	68	No	3	8	17.98	10.90	15	14
9	M	69	Yes	15	31	21.11	13.70	24	3
10	M	59	Yes	30	17	16.50	17.52	0	0
11	F	65	Yes	7	24	19.11	10.40	6	3
12	F	76	Yes	24	33	22.72	8.90	10	2
13	F	74	Yes	11	28	18.72	10.90	20	20
14	M	36	Yes	3	10	22.85	13.19	0	2
15	F	67	Yes	18	20	29.78	14	3	4
16	M	63	Yes	29	51	21.11	17.40	2	5
17	M	73	Yes	14	14	22.58	14.20	7	3
18	M	80	No	4	18	25.66	17.20	5	3
19	M	68	Yes	9	10	22.98	17.90	4	3

GM measures

The FIRST analysis yielded significantly smaller right and left thalamic volumes in ET patients than in HS ($p = 0.012$ and $p = 0.013$, respectively). We did not observe any significant volume differences between ET patients and HS in the caudate, putamen, or pallidum (Table 2).

Surface-based analysis did not reveal any significant differences in cortical thickness between ET patients and HS ($p > 0.05$). Similarly, the SUIT analysis yielded similar cerebellar lobular volume values in ET patients and HS (Supplementary Materials).

White matter measures

Significant DTI differences were observed between ET patients and HS. ET patients exhibited changes in all four DTI measures (FA, MD, AD, RD) (Fig. 1). Decreased FA and increased MD, RD, and AD values were detected in both hemispheres in most WM bundles, including the corticospinal tract, anterior thalamic radiation, superior and inferior longitudinal fasciculi, inferior fronto-occipital fasciculus, and superior and middle cerebellar peduncles, bilaterally, as well as the corpus callosum. Major differences between ET patients and HS were detected in MD values (Fig. 1).

Correlation analysis

Both the right and left thalamic volumes significantly correlated with MoCA scores (p value < 0.01). Thalamic volumes did not correlate with any other clinical or neuropsychological scores (all $ps > 0.05$). Moreover, FA and MD abnormalities significantly correlated with the clinical scores of FTM-TRS, MoCA, FAB, and BDI (Fig. 2). WM measures did not correlate with the BAI scores ($p > 0.05$). In addition, when we investigated correlations between the 180 cortical regions (segmented in CAT12) and the FA or MD values in clusters

Table 2 Values of the mean volume of subcortical nuclei, expressed in mm^3, of ET patients and HS and the p values yielded by the 2-tailed t test when the two groups were compared

	Mean volume HS	Mean volume ET	p value
Left thalamus	1.03×10^3	0.98×10^3	$p = 0.01$
Right thalamus	1.01×10^3	0.95×10^3	$p = 0.01$
Left caudate	5.50×10^3	5.70×10^3	$p = 0.50$
Right caudate	1.03×10^3	1.08×10^3	$p = 0.17$
Left pallidum	1.56×10^3	1.60×10^3	$p = 0.21$
Right pallidum	5.52×10^3	5.58×10^3	$p = 0.41$
Left putamen	5.52×10^3	5.68×10^3	$p = 0.42$
Right putamen	5.67×10^3	5.58×10^3	$p = 0.21$

Significant p-values are $p < 0.05$

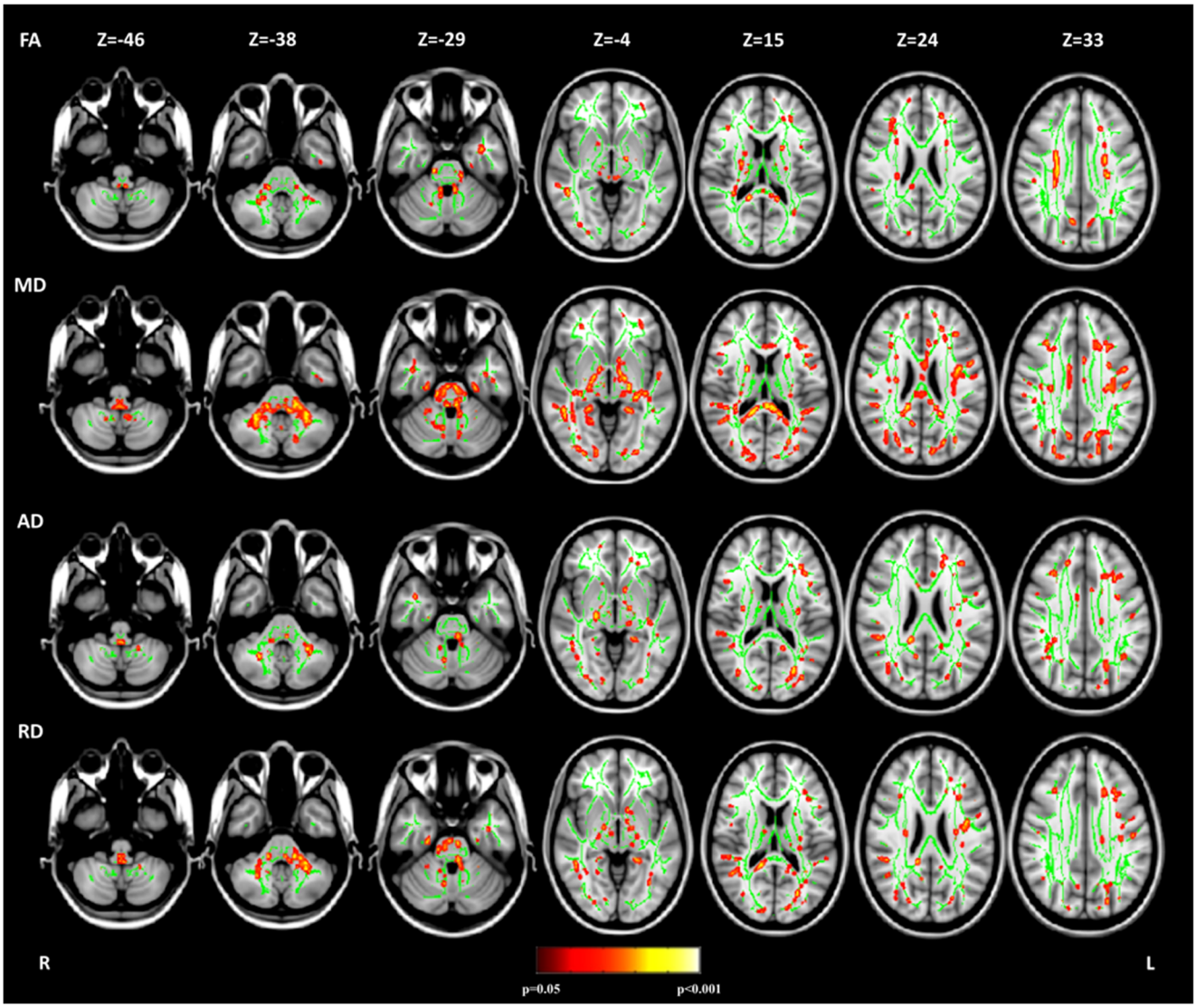

Fig. 1 Statistical map shows voxels that reveal differences in DTI parameters between ET patients and HS (red or yellow indicates lower or higher significance, respectively). The background images are the standard MNI T1 template and the FA skeleton (green). FA is significantly lower, and MD, AD, and RD are higher in the patient group than in controls. Differences are widespread and evident in the corticospinal tract, anterior thalamic radiation, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps major and minor of the corpus callosum, superior and middle cerebellar peduncles, and left cingulum. All WM tracts are overlaid on MNI152 1-mm standard image (TBSS analysis, two-sample, $p < 0.05$, FWE corrected). ET, essential tremor; HS, healthy subjects; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity

in which significant differences were detected between patients and HS, we did not observe any significant correlations.

Discussion

In this study, we performed a systematic evaluation of GM and WM abnormalities by using recently developed data analysis methods in patients with ET and we investigated the possible relationships between brain structural abnormalities and motor and non-motor symptoms. We found GM loss in the thalamus alone. No GM changes were present in cortical areas or in the basal ganglia and cerebellum. Widespread ultrastructural damage affected most of the WM bundles. Thalamic volume loss correlated with MoCA scores while WM changes were significantly associated with the clinical scores of tremor severity, depression, and cognitive impairment.

Gray matter changes

This study demonstrated thalamic atrophy in ET. This finding is in keeping with the hypothesis of a cerebello-thalamo-cortical circuit dysfunction in the pathophysiology of ET [35, 36]. No previous studies have reported any differences

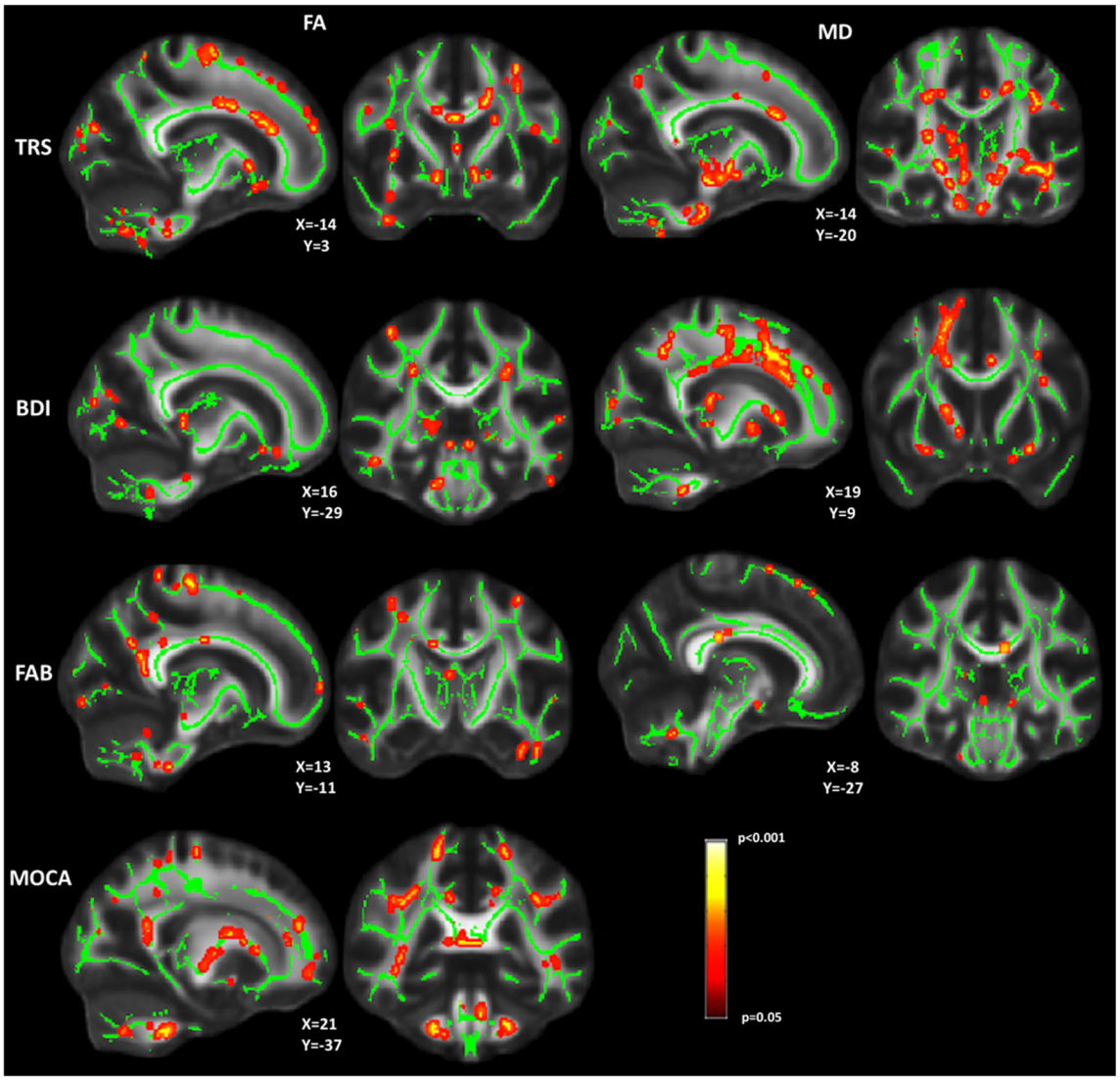

Fig. 2 Statistical map showing correlations with clinical scores in red voxels. The background images are the standard MNI T1 template and the FA skeleton (green). FA negatively correlates with FTM-TRS and BDI and positively correlates with FAB and MoCA scores whereas MD positively correlates with FTM-TRS and BDI and negatively correlates with FAB scores (TBSS analysis, one-sample, $p < 0.05$, *tfce* corrected). FA, fractional anisotropy; MD, mean diffusivity; FTM-TRS, Fahn-Tolosa-Marin Tremor Rating Scale; BDI, Beck Depression Inventory, FAB, Frontal Assessment Battery; MoCA, Montreal Cognitive Assessment

in thalamic volume between ET patients and HS [8–10], probably owing to differences in the methodological approach, i.e., voxel-wise versus segmentation/registration methods. The segmentation/registration method, which allows volume-wise estimation of subcortical structures, may be more sensitive to volume changes than conventional whole-brain voxel-based morphometry methods [37]. Differences between our results and those reported in previous studies might also be due to clinical differences between the patients studied, particularly in the occurrence of cognitive changes, which was not addressed in previous studies [8–10]. In the present study in ET patients, the thalamic volume directly correlated with the MoCA scores, indicating that the lower the thalamic volume, the lower the cognitive functions. The thalamus is considered to play an important role in cognitive features [38, 39] such as working memory, attention, and executive functions [40, 41]. In keeping with our results, thalamic atrophy has been reported to be associated with cognitive impairment in a variety of neurological disorders, including Alzheimer's disease and multiple sclerosis [42, 43]. We did not detect any correlation between reduced thalamic volume and the severity of tremor in the ET patients we studied. One possible explanation is that tremor severity depends to a greater extent on functional abnormalities in the cerebello-thalamo-cortical circuit than on neurodegenerative changes [33, 34].

In this study, we did not observe any changes in cortical thickness as assessed by surface-based methods. Previous VBM studies detected GM alterations in various cortical areas

[7–11], with a marked variability in the location of cortical abnormalities. A recent meta-analysis of 10 VBM MRI studies, however, showed that no major changes in cortical areas, with the exception of a reduction in GM volume in the left precuneus and posterior cingulate gyrus, were observed in a cohort of 241 ET patients [17]. The aforementioned reduction in GM, which was the main conclusion of the meta-analysis, was interpreted as being related to the role these structures play in cognitive dysfunction and depression rather than to tremor severity. Differences in cortical GM results in ET patients may depend on the data analysis performed. Although both VBM and surface methods quantify the global amount of GM variation across subjects, VBM only assess the amount of GM in a voxel whereas surface methods provide a more comprehensive measure of cortical GM, including the two orthogonal components of cortical volume, i.e., cortical thickness and surface area [37]. Indeed, surface methods better reflect the highly folded geometry of the cerebral cortex.

Another result that deserves a comment is the lack of GM abnormalities observed in the cerebellum. Some controlled post-mortem studies on ET patients have revealed degenerative changes in the cerebellum, i.e., signs of compromised Purkinje cells, including both axonal and dendritic changes [44, 45], whereas others have not [46]. Moreover, previous MRI studies on GM changes in ET have yielded discrepant findings. On the one hand, [16] reported increased cerebellar volume in ET patients, a finding that the authors interpreted as a possible compensatory mechanism. On the other hand, MRI studies on ET have revealed a reduction in cerebellar volumes, particularly in the vermis, in patients with head tremor [12, 13, 15] and in those with cerebellar signs, e.g., intention tremor and altered tandem gait [14]. These findings suggest that cerebellar atrophy is a feature of specific ET subtypes. In order to minimize the clinical heterogeneity of the ET patients in our study, we excluded cases with isolated head tremor, and only a limited number of the patients included had head tremor in addition to upper limb tremor. According to the recent diagnostic criteria, cases with cerebellar signs are now categorized as ET "plus" [2]. The lack of GM cerebellar abnormalities in our study may be explained by the fact that cortical cerebellar abnormalities in ET are diffuse and not so severe as to determine MRI-detectable cerebellar atrophy.

White matter changes

ET patients exhibited abnormalities in several WM bundles, including the bilateral corticospinal tracts, cerebellar peduncles, and corpus callosum, as well as in associative fasciculi, including the inferior fronto-occipital, superior, and inferior longitudinal and uncinate fasciculi, cingulum bundles, and anterior thalamic radiations. These findings point to a widespread ultrastructural involvement of WM bundles in ET and are in keeping with the findings of a recent DTI study, in which similar WM alterations were reported [47]. The altered DTI measures in the superior cerebellar peduncles support the hypothesis of a pathophysiological involvement of the cerebellar connections in ET [21]. The superior cerebellar peduncle prevalently consists of efferent fibers and its outputs are part of the cerebello-thalamic-cortical pathway, which is known to be involved in the genesis of ET [36]. Damage to efferent fibers, which are concentrated in the superior cerebellar peduncle, may in turn result in a structural disconnection and lead to clinical symptoms.

With regard to the clinical correlates of WM changes, we found a significant correlation between measures of WM abnormalities and the clinical scores of tremor severity, as assessed by FTM-TRS.

Our results are in contrast to those of other authors, who did not find any correlations between measures of WM abnormalities and the clinical scores of tremor severity, as assessed by FTM-TRS [47]. WM abnormalities in our study also correlated with non-motor symptoms, i.e., depression and cognitive functions. By contrast, the significant correlations we observed between diffusion WM changes and cognitive abnormalities are in keeping with those of other studies [25]. Although cognitive dysfunction has previously been reported in ET [48], to our knowledge, it correlated with brain damage in only two studies [24, 25].

Conclusions

Our study demonstrates that while GM damage in ET is limited to the thalamus, WM damage is widespread, involving the majority of WM bundles. The severity of tremor is significantly associated with ultrastructural WM abnormalities in the corpus callosum, corticospinal tracts, superior longitudinal fasciculi, and cerebellar peduncles. In addition, the significant correlations between thalamic volume and MoCA as well as between WM abnormalities in many WM bundles and the MoCA, FAB, and BDI scores point to an extensive involvement of brain structures underlying non-motor functions in ET. Taken together, our findings suggest that ET should be considered a network disorder characterized by the widespread involvement of both infra- and supratentorial brain structures rather than the result of focal cerebellar structural abnormalities.

Since the number of the patients we studied was relatively small, further investigations based on larger samples of patients are needed to shed more light on the concomitant presence of GM and WM alterations as well as on their relationship with motor and non-motor symptoms in ET.

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Compliance with ethical standards

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Case-control study
- Performed at one institution

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