Voxel-based morphometry shows no decreases in cerebellar gray matter volume in essential tremor

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Abstract—*Objective:* To investigate cerebellar gray matter volume in patients with essential tremor (ET). *Methods:* We used voxel-based morphometry (VBM) based on high-resolution T1-weighted MRI to compare gray and white matter density between 27 patients with ET and 27 age- and sex-matched healthy control subjects. Fourteen patients had only postural tremor, whereas 13 patients showed additional intention tremor. *Results:* VBM failed to demonstrate regional decreases in gray and white matter volume in patients with ET. There was, however, an expansion in gray matter depending on the type of tremor. Compared with age-matched control groups, patients with intention tremor showed a relative expansion of gray matter bilaterally in the region of the temporoparietal junction and the right middle occipital cortex. *Conclusions:* The lack of a consistent decrease in gray and white matter density argues against a progressive neurodegenerative process in essential tremor that leads to a substantial decrease in cerebellar gray matter volume. Patients with predominant intention tremor show a relative expansion of gray matter areas involved in higher order visuospatial processing, which might represent a long-term result of adaptive reorganization compensating the higher demands on the visuospatial control of skilled movements in case of trembling.

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Lesioning as well as functional neuroimaging studies have provided converging evidence that a disturbance of the corticocerebellothalamocortical loop is the pathophysiologic mechanism of essential tremor (ET).[1-13] Supporting a major role of the cerebellum in the pathophysiology of ET, recent studies have shown that tremor is accompanied by cerebellar motor dysfunction in patients with ET.[14-19] Though these studies have revealed new insights into the pathophysiology of ET, the nature of this condition remains to be clarified.

An ongoing discussion is centered around the question of whether ET is a neurodegenerative disease[20] or a pure "receptor disease."[21,22] The first hypothesis is supported by two independent proton MR spectroscopy (MRS) studies that reported a reduced *N*-acetylaspartate/creatine ratio in patients with ET vs control subjects.[23,24] The latter hypothesis is supported by two lines of evidence. First, the ingestion of alcohol can improve tremor and the cerebellar gait abnormality in patients with ET.[25] Second, a knockout model, mice lacking the gene for the $\alpha 1$ subunit of the γ-aminobutyrate receptors show generalized alcohol-sensitive trembling, like ET.[21,22] Histopathologic data are inconclusive. Qualitative postmortem examinations have revealed no consistent histopathologic abnormalities in small groups of patients with ET,[26,27] yet a quantitative histologic assessment of the cerebellum is still lacking.

Here we used voxel-based morphometry (VBM) of high-resolution T1-weighted MRI to investigate whether ET is associated with subtle morphologic abnormalities in the cerebellum. As patients with an intentional component of the kinetic tremor (referred to as ET_{IT}) have a higher tremor intensity and a longer tremor duration and display other cerebellar signs,[14] we predicted that morphometric abnormalities in the cerebellum would be more pronounced in patients with ET_{IT}.

Methods. *Subjects.* Twenty-seven patients (18 men, 9 women) with ET and a mean age of 57.9 years (SD 12.2 years) were included in the study. All patients fulfilled the criteria for the diagnosis of definite ET as defined by the Consensus Statement of the Movement Disorder Society on Tremor.[28] Fourteen patients had only postural tremor (ET_{PT} group), whereas 13 patients had additional intention tremor (ET_{IT} group) as defined by at least two 2 uni- or bilaterally on the Clinical Rating Scale for Intention Tremor.[14] The mean ages of the ET_{PT} group and ET_{IT} group are given in table 1. Patients were recruited from a database of the Movement Disorders Clinic of the Department of Neurology (University Hospital Schleswig–Holstein, Kiel Campus). Only patients with a postal code starting with a "2" (which means Schleswig–Holstein and the north of Niedersachsen) were contacted. Control subjects were spouses of the participating patients or were recruited from announcements on notice boards of the department. Subjects with a history of other neuropsychiatric or systemic dis-

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Table 1 *Summary of group characteristics*

	Controls		Patients with ET	
	Control group 1	Control group 2	ET_{PT} group	ET_{IT} group
Age, y	51.0 ± 14.6	64.7 ± 7.0	54.1 ± 13.1	61.8 ± 10.3
Sex, F/M	4:10	5:8	5:9	4:9
Age at onset, y			35.5 ± 20.2	27.9 ± 22.7
Duration of ET, y			18.7 ± 14.5	33.9 ± 20.3
Fahn scale			23.9 ± 11.0	44.6 ± 16.0
Bain scale			33.6 ± 8.6	39.2 ± 16.5
Ataxia Rating Scale			8.6 ± 1.9	16.2 ± 5.9

Data are given as means ± SD. The total score is given for each rating scale.

ET_{PT} = essential tremor with postural tremor; ET_{IT} = essential tremor with intention tremor.

eases or substance abuse were excluded. Eleven patients were not receiving medication at the time of the study. The others were treated with β-receptor antagonist (7 patients), primidone (3), gabapentin (1), clonazepam (1), or a combination therapy with β-receptor antagonist + primidone + gabapentin (2), β-receptor antagonist + gabapentin (1), or primidone + gabapentin (1). Twenty-seven healthy individuals matched for age, gender, and handedness were examined as the control group. As patients with ET_{IT} were significantly older than patients with ET_{PT}, we studied two healthy control groups that were age and sex matched to the ET_{IT} or ET_{PT} group (table 1). The study was approved by the Ethics Committee of the Medical Faculty at the Christian Albrechts University Kiel. All individuals gave written informed consent before participation in the study.

Clinical assessment. Patients were interviewed concerning their medical history, including the duration of illness, lateralization of symptoms, sensitivity to ethanol exposure, family history, and actual medication. ET was clinically assessed by the Fahn Tremor Rating Scale.[29] Patients rated subjective impairment using the Bain scale.[30] To evaluate ataxia of the upper limb, we scored the hand and arm items of the Ataxia Rating Scale.[31] Intention tremor was separately rated during the finger-to-nose test using the Clinical Rating Scale.[14] Data are given as means ± SD. *T* tests were used to compare demographic variables and clinical scores.

VBM. All subjects were scanned on a 1.5 T Philips Gyroscan Intera scanner (Philips Medical Systems) using a standard head coil. A three-dimensional T1-weighted turbo field echo (TFE) sequence generating 110 contiguous axial slices covering the whole brain (slice thickness: 1.2 mm; matrix size: 256 × 256; voxel size: 1.2 mm^3). TFE imaging used an echo time (TE) of 3.5 milliseconds, repetition time (TR) of 7.5 milliseconds, and a flip angle of 8° degrees. Images were preprocessed and analyzed using statistical parametric mapping software (SPM2; Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) in MATLAB 6.5 (MathWorks, MA). Preprocessing was performed according to an optimized VBM protocol.[32] Categorical comparisons of gray and white matter images were performed on a voxel-by-voxel basis using analysis of variance (ANOVA). As patients with ET_{PT} were on average approximately 8 years younger than patients with ET_{IT}, statistical analysis included two groups of healthy controls, which were age matched according to the ET_{PT} and ET_{IT} group. Therefore, the ANOVA model consisted of four groups: patients with ET_{PT}, patients with ET_{IT}, and two healthy control groups that were age and sex matched to the ET_{IT} or ET_{PT} group. For each group, we defined linear contrasts to test for differences in gray and white matter density among groups. This model allowed us to perform an overall comparison between both groups but also to assess the specific impact of tremor type on changes in brain structure.

Significance threshold was set at $p < 0.05$ after correction for multiple independent comparisons. Based on previous MRS results,[11,23,24] we predicted that ET would be associated with morphometric abnormalities in the cerebellum. Given our a priori hypothesis, we applied a small volume correction (SVC) for each cerebellar hemisphere using a sphere with a 2.5-cm radius. Outside the cerebellum, correction for multiple comparisons was performed for the entire brain volume.

Power calculation (http://www.stat.uiowa.edu/rlenth/Power/) revealed that the sample size (2 × 27 individuals) was sufficient to reach a statistical power of 80% (20% risk of type II errors) at a significance level of $\alpha = 0.05$ for a difference of the means that equals or exceeds 80% of the SD.

Results. *Clinical findings.* Table 1 summarizes the main clinical features. Whereas the age was well matched between each ET group and the corresponding group of healthy control subjects ($p > 0.4$), patients with ET_{PT} were younger than patients with ET_{IT} ($p = 0.05$). The same applied for the corresponding control groups ($p < 0.003$). Patients with ET_{IT} also showed a longer duration of tremor ($p = 0.03$). All patients with ET_{PT} at least had a slight kinetic tremor without intentional component. Both patient groups differed in tremor severity ($t = 3.9$, $p = 0.001$). The ET_{IT} group scored higher in the Fahn Tremor Rating Scale (ET_{IT}: 44.6 ± 16.0 vs ET_{PT}: 23.8 ± 11.0). Patients with ET_{IT} also had higher ataxia scores (ET_{IT}: 16.2 ± 5.9; ET_{PT}: 8.6 ± 1.9; $t = 4.5$, $p = 0.001$). In contrast, the total score of the Bain scale did not differ in both patient groups, indicating that the subjective impression of tremor-associated impairment was matched between groups (ET_{IT}: 39.1 ± 16.5; ET_{PT}: 33.6 ± 8.7; $t = 1.1$, $p = 0.28$).

Structural MRI. Between-group comparisons revealed no decreases in gray matter density in patients with ET compared with healthy control subjects. This was the case for the overall comparison between patients and controls as well as for separate comparisons between patients with ET_{IT} or ET_{PT} and the corresponding control groups. No cluster in the cerebellar gray matter showed a decrease in gray matter in patients at a very liberal statistical threshold ($p < 0.05$, uncorrected). Even if the statistical threshold was decreased further to a level that is statistically not acceptable ($p < 0.1$, uncorrected), only two small cerebellar clusters were identified showing a subtle nonsignificant decrease in gray matter density (maximal $T = 1.78$).

When we tested for specific morphometric changes in the brain depending on the tremor type, we found a tremor type (ET_{PT} vs ET_{IT}) by group (patients vs controls) interaction in superior temporal cortex, posterior insular cortex and supramarginal gyrus, right hemispheric hippocampus

Table 2 *Between-group interaction (i.e., interaction between the type of tremor [ET_{IT} vs ET_{PT}] and group [patients vs controls])*

Area	Side	Cluster extent, no. of voxels	*Z* score	*x,y,z* coordinates
Superior temporal gyrus	L	11,175	4.39	−63, −40, 17
Middle temporal gyrus			3.73	−58, −58, 20
Superior temporal gyrus			3.41	−46, 36, 20
Superior temporal gyrus	R	15,341	4.08	62, −39, 20
Superior temporal gyrus			3.88	61, −36, 12
Supramarginal gyrus			3.88	43, −28, 27
Parahippocampal gyrus	R	8,038	4.17	20, −25, −17
Hippocampus			3.95	21, −33, 2
Retrosplenial cortex	R	8,800	3.70	14, −54, 28
Retrosplenial cortex			3.69	12, −61, 20
Middle occipital gyrus			3.58	29, −76, 23

(ET_{IT} > age-matched controls) > (ET_{PT} > age-matched controls). The contrast that directly compared the ET_{IT} and ET_{PT} group revealed no significant differences. Cortical areas in which gray matter density was relatively increased in patients with ET_{IT} but not in patients with ET_{PT} relative to the corresponding age-matched control groups. All reported clusters are significant at $p < 0.05$ corrected for multiple nonindependent comparisons across the entire brain.

ET_{IT} = essential tremor with intentional component; ET_{PT} = postural tremor.

formation, retrosplenial cortex, middle occipital gyrus, and left middle occipital cortex (table 2; figure). In the older control group (matched to the age of patients with ET_{IT}), these areas showed a decrease in gray matter density relative to the younger control group (matched to the age of patients with ET_{PT}), presumably reflecting normal atrophy in these regions caused by aging (figure). These age-dependent decreases in gray matter were absent in patients. On the contrary, patients with ET_{IT} who were on average 8 years older than patients with ET_{PT} showed a tendency toward an increase in gray matter compared with patients with ET_{PT} patients (figure). Patients with ET_{IT} showed a bilateral expansion in gray matter density in the posterior part of the superior temporal gyrus. The left hemispheric temporal cluster extended into adjacent posterior insular cortex and the temporo-occipital junction, while the right hemispheric cluster also covered posterior insular cortex and supramarginal gyrus. In the right hemisphere, there were two additional clusters showing an increase in gray matter in patients with ET_{IT} but not ET_{PT}. The first cluster was located in the right hippocampal and parahippocampal cortex. The left parahippocampal cortex also showed a relative increase in gray matter (figure), but this cluster did not reach significance. The second cluster covered the right retrosplenial cingulate cortex and extended into the middle occipital gyrus. Despite a more liberal threshold (SVC), no morphometric changes that were specific to the type of tremor were found in the cerebellum.

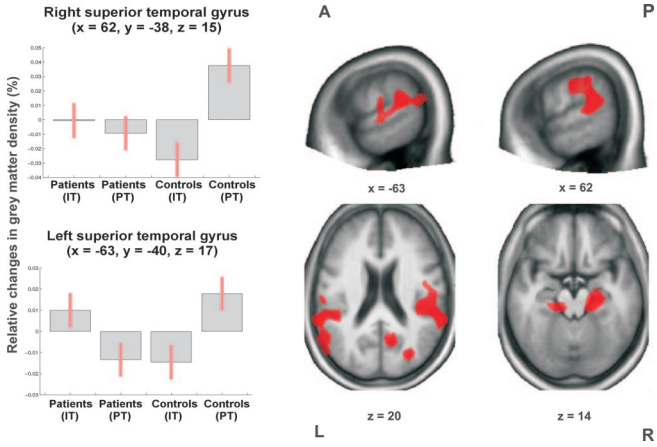

Figure. The red areas represent statistical parametric maps of brain regions showing a higher gray matter density selectively in the essential tremor with intentional component (ET_{IT}) but not in the postural tremor (ET_{PT}) group relative to the corresponding age-matched control groups (height threshold: $p < 0{,}01$ uncorrected; cluster threshold = 1,000 voxels). The maps are superimposed on the T1-weighted averaged image of all participants. x, y, z denote the stereotactic coordinate corresponding to each slice. A = anterior; P = posterior. The bar graphs give the mean gray matter densities of voxels showing peak differences in the right and left superior temporal gyrus. The error bars represent the CIs of the mean. The older control group (matched in age to the ET_{IT} group) showed a decrease in gray matter density relative to the younger control group (matched in age to the ET_{PT} group). On the contrary, patients with ET_{IT} exhibited a tendency toward an increase in gray matter density despite the fact that patients with ET_{IT} were significantly older than patients with ET_{PT}.

Discussion. We used VBM of high-resolution structural MR images to pinpoint regional changes in macroscopic brain structure in a group of clinically well-characterized patients with ET. With respect to a carefully matched control group, ET was not associated with a major regional atrophy of brain

structures. We cannot exclude subtle changes in cerebellar gray matter density to have escaped detection but these atrophic changes must range below the age-related changes seen in healthy subjects and patients with ET. Advanced ET and specifically intention tremor in ET have been strongly linked to cerebellar dysfunction.[14,20,33,34] Accordingly, ataxia scores were significantly higher in our patients with ET_{IT} than in those with ET_{PT}. However, a subgroup analysis, which separately compared both subgroups, patients with ET_{IT} and ET_{PT}, with healthy age-matched controls, failed to find a specific structural abnormality in the cerebellum that was specifically associated with ET_{IT}. As VBM has previously been shown to be highly sensitive to detect regional atrophy in neurodegenerative diseases causing movement disorders,[35-39] these findings argue against a diffuse neuronal loss in ET in the cerebellum that translates into a decrease in gray matter volume. Hence, signs of cerebellar dysfunction in some patients with ET cannot be attributed to gross structural abnormalities in the cerebellum. The lack of macroscopic MRI abnormalities in vivo is therefore in accordance with qualitative postmortem findings that found no consistent loss of cerebellar neurons in small groups of patients with ET.[26,27]

Although there were no regional decreases in gray matter density in patients with ET, distinct brain regions showed relative increases in gray matter volume in patients with ET_{IT} but not in patients with ET_{PT} relative to the corresponding control groups. This relative increase in gray matter density in patients with ET_{IT} was mainly caused by an attenuation of age-dependent reduction in gray matter found in healthy control subjects.

The superior temporal gyrus showed a bilateral increase in gray matter density in patients with ET and predominant intention tremor. Recent functional neuroimaging studies on the temporal and ordinal control of learned movement sequences have shown that the superior temporal gyrus is heavily implicated in the temporal control of movement sequences, goal-directed preparatory activity, control of polyrhythmic movements, and sensorimotor coordination.[40-44] In case of ET_{IT}, visuomotor areas are challenged to compensate for ataxia and intention tremor. We therefore propose that the increase in gray matter density in patients with ET_{IT} reflects a structural long-term consequence of enhanced neuronal activity in these areas, which counteracts normal age-dependent atrophy.

The same line of reasoning may apply for the relative expansion in gray matter of right mesial temporal and retrosplenial cortices in patients with ET and intention tremor. The hippocampus,[45-47] parahippocampal cortex,[48,49] and retrosplenial cortex[50,51] subserve egocentric representations of spatial knowledge. The retrosplenial cortex is thought to transform egocentric and allocentric reference frames.[52] As intention tremor perturbs the feedback information about self-motion, it is conceivable that the presence of intention tremor (and the concurrent increase in tremor severity in patients with ET_{IT} relative to patients with ET_{PT}) hampers efficient integration of allocentric and egocentric spatial information. The tremor-related perturbation imposes increased processing demands on the mesiotemporal and retrosplenial network, causing a chronic increase in neuronal activity and a secondary expansion of gray matter in these regions. A comparable task-induced expansion of gray matter density has been reported in a recent longitudinal VBM study in young adults when they acquired juggling skills. In this study the lateral occipital cortex showed a bilateral expansion in gray matter over a period of 3 months in the group that had learned to juggle but not in nonjugglers. The expansion in gray matter shrunk after 3 months when jugglers no longer practiced the task.[53] However, in contrast to the VBM study in young healthy jugglers, the gray matter increases in patients with ET_{IT} do not reflect an active expansion of the gray matter but an attenuation of normal aging-related atrophy.

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