Cerebellar Atrophy in Essential Tremor Using an Automated Segmentation Method

BACKGROUND AND PURPOSE: Essential tremor (ET) is a slowly progressive disorder characterized by postural and kinetic tremors most commonly affecting the forearms and hands. Several lines of evidence from physiologic and neuroimaging studies point toward a major role of the cerebellum in this disease. Recently, voxel-based morphometry (VBM) has been proposed to quantify cerebellar atrophy in ET. However, VBM was not originally designed to study subcortical structures, and the complicated anatomy of the cerebellum may hamper the automatic processing of VBM. The aim of this study was to determine the efficacy and utility of using automated subcortical segmentation to identify atrophy of the cerebellum and other subcortical structures in patients with ET.

MATERIALS AND METHODS: We used a recently developed automated volumetric method (FreeSurfer) to quantify subcortical atrophy in ET by comparing results obtained with this method with those provided by previous evidence. The study included T1-weighted MR images of 46 patients with ET grouped into those having arm ET (n = 27, a-ET) or head ET (n = 19, h-ET) and 28 healthy controls.

RESULTS: Results revealed the expected reduction of cerebellar volume in patients with h-ET with respect to healthy controls after controlling for intracranial volume. No significant difference was detected in any other subcortical area.

CONCLUSIONS: Volumetric data obtained with automated segmentation of subcortical and cerebellar structures approximate data from a previous study based on VBM. The current findings extend the literature by providing initial validation for using fully automated segmentation to derive cerebellar volumetric information from patients with ET.
section thickness, 1.2 mm; scanning time, 12 minutes per volume) were run for all participants. The second scanning was registered to the first scanning by using rigid registration. The first scan and the coregistered second scan were subsequently averaged to create a single high-signal-intensity-to-noise average volume. With the subject supine, cushions were carefully packed around the head to limit motion. The image protocol was identical for all subjects studied.

The image files in DICOM format were transferred to a Linux workstation for morphometric analysis. Subcortical volume analysis was measured automatically by FreeSurfer 4.05 installed on a Red Hat Enterprise Linux v.5. The automated procedures for volumetric measures of these different brain structures have been described previously. This procedure automatically provided segments and labels for $\pm 40$ unique structures and assigned a neuroanatomic label to each voxel in an MR imaging volume on the basis of probabilistic information estimated automatically from a manually labeled training set. Briefly, the segmentation is performed as follows: an optimal linear transform is computed that maximizes the likelihood of the input image, given an atlas constructed from manually labeled images. A nonlinear transform is then initialized with the linear one, and the image is allowed to further deform to better match the atlas. Finally, a Bayesian segmentation procedure is performed, and the maximum a posteriori estimate of the labeling is computed.

The segmentation uses 3 pieces of information to disambiguate labels: 1) the prior probability of a given tissue class occurring at a specific atlas location, 2) the likelihood of the image given that tissue class, and 3) the probability of the local spatial configuration of labels given the tissue class. This latter term represents a large number of constraints on the space of allowable segmentations and prohibits label configurations that never occur in the training set (eg, the hippocampus is never anterior to the amygdala). This technique has been validated against manual tracings in healthy individuals and patients with neurologic disease. The image protocol was identical for all subjects studied.

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Automated labeling of the cerebellum as provided by FreeSurfer. From bottom to top, sections 92, 101, 106, and 110 in the coronal view are shown, respectively. The different structures have unique color codes. After correcting for ICV, MR imaging volumetry using subcortical segmentation reveals cerebellar atrophy in the h-ET group with respect to the controls for absolute gray matter and white matter volumes: mean, respectively: h-ET 86 ± 7.1 and 23.5 ± 3.3 mm³; a-ET 89.6 ± 11.1 and 23.9 ± 3 mm³; healthy controls 91.9 ± 8.2 and 25.7 ± 4.2 mm³.

Table 2: Volumes (mean) measured with an automated volumetric method (FreeSurfer)*

| Volume                  | h-ET (n = 19)        | a-ET (n = 27)        | Controls (n = 28) | P Values |
|-------------------------|----------------------|----------------------|-------------------|----------|
| ICV                     | 1375.8 ± 119.7       | 1434.7 ± 127.5       | 1411.9 ± 122.6    | .22      |
| Cortical gray matter    | 393.8 ± 30.5         | 413.5 ± 49.5         | 404.1 ± 32.6      | .13      |
| Cortical white matter   | 358.9 ± 41.1         | 385.3 ± 57.1         | 384.6 ± 41.9      | .1       |
| Cerebellar gray matter  | 86 ± 7.1             | 89.6 ± 11.1          | 91.9 ± 8.2        | .23      |
| Cerebellar white matter | 23.5 ± 3.3           | 23.9 ± 3             | 25.7 ± 4.2        | .59      |
| Thalamus                | 11.3 ± 1.2           | 12 ± 1.5             | 11.6 ± 1.3        | .11      |
| Putamen                 | 9.1 ± 0.9            | 9.6 ± 1.8            | 8.9 ± 1.1         | .19      |
| Pallidum                | 2.9 ± 0.3            | 3 ± 0.5              | 2.9 ± 0.4         | .54      |
| Caudate                 | 6.6 ± 0.7            | 7.1 ± 1.3            | 6.5 ± 0.8         | .11      |
| Hippocampus             | 6.6 ± 0.7            | 7.1 ± 1.1            | 7 ± 0.8           | .31      |
| Lateral ventricle       | 22.9 ± 14.7          | 25.9 ± 15.9          | 21.5 ± 12.8       | .51      |
| Third ventricle         | 1.5 ± 0.7            | 1.4 ± 0.5            | 1.4 ± 0.6         | .85      |
| Fourth ventricle        | 1.7 ± 0.6            | 1.9 ± 0.6            | 1.7 ± 0.6         | .21      |
| Brain stem              | 18.4 ± 1.9           | 18.8 ± 2.1           | 19.3 ± 2.2        | .54      |

Note: —ICV, indicates intracranial volume.
* For each neuroanatomic volume, ANCOVA statistical test covariate with ICV is performed.
† Significant difference after post hoc analysis between h-ET and control groups, performed with the Duncan t test. Volumes are in cubic millimeters.

Fig 1. Automated labeling of the cerebellum as provided by FreeSurfer. From bottom to top, sections 92, 101, 106, and 110 in the coronal view are shown, respectively. The different structures have unique color codes. After correcting for ICV, MR imaging volumetry using subcortical segmentation reveals cerebellar atrophy in the h-ET group with respect to the controls for absolute gray matter and white matter volumes: mean, respectively: h-ET 86 ± 7.1 and 23.5 ± 3.3 mm³; a-ET 89.6 ± 11.1 and 23.9 ± 3 mm³; healthy controls 91.9 ± 8.2 and 25.7 ± 4.2 mm³.
with VBM and manual tracings. Among all the studied volumes, FreeSurfer showed the presence of atrophy only in the cerebellum and showed this atrophy occurring in a specific subtype of ET (h-ET). This finding confirms evidence provided by our previous VBM study, in which any significant voxel-by-voxel change (increased or decreased) has been found in the whole brain except for a cluster localized in the anterior vermis, which becomes volumetrically (modulation step) reduced only when comparing patients with h-ET with controls.

Although VBM involves spatial deformation to register all the scans into a common space, the current evidence demonstrates that VBM spatial deformation correctly handles the principal distortions in the subcortical gray nuclei and cerebellum. Thus, optimized VBM may represent a sensitive surrogate marker because it provides a reliable objective quantification of atrophy in patients with ET. Damage to the cerebellum has also been confirmed by using a manual volumetric region-of-interest approach (MREG software; available at: www.erg.ion.ucl.ac.uk/MReg.html). However, the manual cerebellar volumetry is time-consuming and dependent on rater experience; thus, automated methods with high reproducibility and accuracy may potentially be more efficient than manual tracings. Although the automated cerebellar volumetry using FreeSurfer has been validated in patients with epilepsy, a direct comparison between automated and manual measurements of the cerebellum in ET could better clarify the exact reliability of our data.

The detected cerebellar volume in patients with h-ET was a few percentage points lower than that of the controls (~7%), reaching a moderate statistical threshold. This decrease may depend on 3 factors: 1) The evidence provided by VBM analysis defines a small cerebellar involvement including only the anterior lobule of vermis. 2) ET is not a uniform disorder characterized by a high heterogeneity in clinical phenotypes, which may affect the magnitude of the detected volumetric change. 3) Our patient sample size was relatively small. As a result, our study may have been underpowered to detect subtle volume loss in some structures.

Another important finding reported by this study is the lack of significant association between clinical findings and the detected cerebellar atrophy. Even if patients with h-ET scored higher on the Fahn–TRS–A and the Brain scales, any significant association was detected with the cerebellar volume loss. Again, the lack of correlation is in agreement with the regression analysis executed in a previous VBM study from our group. All the aforementioned evidence, together with the fact that the detected cerebellar atrophy has been found in familial ET, support the view that a genetic background is implicated in the genesis of cerebellar atrophy.

However, FreeSurfer has limitations. In fact, given the inherent limitations of any fully automated segmentation software, cortical and subcortical labeling may be influenced by several factors, such as section thickness, MR imaging noise level, MR imaging orientation, field strength, and anatomic boundary criteria. However, the exact correspondence between the findings provided by this automated method and those related to manual tracing and voxel-based analysis underscores the utility of this method.

Conclusions
We successfully demonstrated the presence of cerebellar atrophy in patients with h-ET by using an automated segmentation approach. This finding confirms previous voxel-based and manually traced findings, highlights the involvement of the cerebellar region in the pathophysiology of ET, and suggests that a-ET and h-ET may be distinct clinical subtypes of the same disease.

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