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Tremor and Other Hyperkinetic Movements

Article

# White Matter Hyperintensity Burden on Magnetic Resonance Imaging in Essential Tremor

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## Abstract

**Background:** Whereas structural abnormalities in the cerebellum have been associated with essential tremor (ET), the contribution of vascular disease via white matter hyperintensities (WMHs) and strokes has not been examined. In this study, we have explored these potential associations and hypothesized that ET would be associated with greater overall WMH volume, greater cerebellar WMH volume, and greater infarct presence.

**Methods:** In a cross-sectional magnetic resonance imaging (MRI) study of 540 community-dwelling elderly persons in northern Manhattan, New York, brain measures of total WMH volume and regional WMH volume were derived from $T_2$-weighted fluid attenuated inverse recovery-weighted MR images. The presence of cerebral infarcts on MRI was determined as well.

**Results:** Total WMH volume was greater among 33 ET cases than 507 controls in both univariate (OR=1.41, p=0.038) and fully adjusted analyses (OR=1.44, p=0.03). Cerebellar WMH volume was associated with marginally increased odds of ET in a univariate model (OR=1.52, p=0.11) and significantly increased odds in a fully adjusted multivariate model (OR=1.74, p=0.049). Temporal lobe WMH volume was associated with significantly increased odds of ET in both univariate (OR=3.36, p<0.001) and fully adjusted models (OR=3.73, p<0.001). Large strokes were significantly more common in cases than in controls in unadjusted analyses (OR=3.04, p=0.02) and marginally in adjusted analyses (OR=2.56–2.57, p=0.045–0.056). The distribution of strokes did not differ by diagnosis.

**Discussion:** MRI data in this study indicated that ET was associated with greater total WMH volume, greater cerebellar WMH volume and possibly more strokes. Cerebrovascular disease could play a role in the development of ET.

**Keywords:** Essential tremor, cerebellum, magnetic resonance imaging, white matter hyperintensities, stroke

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## Introduction

Essential tremor (ET) is one of the most widely encountered neurological disorders.[1–5] Structural abnormalities (e.g. Purkinje cell loss and Purkinje cell axonal swellings) have been identified in the cerebellum of ET cases, suggesting that the disorder could be a neurodegenerative condition arising from that brain region.[6,7] Nevertheless, further characterization of the pathogenesis of ET is needed.

ET is a disorder that commonly affects elderly people, demonstrating a clear age-associated rise in incidence and prevalence.[8,9] Moreover, as individuals age, strokes also accumulate[10] and brain white matter hyperintensity (WMH) burden increases, probably reflecting small vessel disease.[11] Cerebrovascular disease has been linked with several late life neurodegenerative diseases, including Parkinson's disease (PD) [12] and Alzheimer's disease (AD),[13] yet its role in ET has yet to be explored.

Previous reports in the stroke literature have documented rare instances of unilateral resolution of tremor in ET cases caused by cerebellar, thalamic, cortical infarcts and hemorrhages.[14,15] These acute lesions, many of which are sizable, grossly disrupt the cerebellar–thalamic–cortical fiber tracts that are implicated in the propagation of action tremor in ET.[14] Whether smaller scattered lesions (e.g., diffuse

white matter changes), particularly of the cerebellum, cumulatively damage underlying tissue and lower the threshold for developing a second pathogenetic process (e.g., ET), is not known. In a similar fashion, the rest tremor of parkinsonism may disappear in the setting of acute stroke,[16] yet vascular disease may also contribute to the pathogenesis of parkinsonism itself (i.e., the disease entity vascular parkinsonism).[17]

The Washington Heights–Inwood Columbia Aging Project (WHICAP) is an ongoing community-based study of aging comprising older participants (≥65 years) of diverse ethnic backgrounds living in northern Manhattan, New York. Using magnetic resonance imaging (MRI), our objective was to examine associations between ET and total WMH volume, regional WMH volume, and stroke presence, hypothesizing that each of these might be greater among ET cases than controls.

## Methods

### Study sample

There were 769 individuals who participated in the WHICAP MRI imaging study, a subset of the 2,776 individuals enrolled in WHICAP II, a prospective study of aging in Medicare-eligible northern Manhattan residents aged >65 years. WHICAP II recruitment and sampling have been described.[18]

The WHICAP MRI sample was recruited at the second follow-up visit of the WHICAP II cohort. Participants were eligible if they had not met criteria for dementia at their prior visit.[11] Of 1,841 eligible participants, 769 were imaged, 407 refused, 283 had imaging contraindications, 166 died, and 216 were lost to follow-up.[11] Refusers were 1 year older, more likely to be female, and less likely to be African-American than participants.[11] Study procedures were approved by the Columbia University Medical Center (CUMC) Institutional Review Board and written informed consent was obtained from all participants.

### In person evaluation

At the WHICAP assessment, trained personnel collected demographic, medical, and medication data. Self-reported comorbidities included diabetes mellitus, heart disease (including arrhythmias, coronary artery disease, and congestive heart failure), and other diseases.

A neuropsychological test battery was performed,[19] including measures of abstract reasoning, learning and memory, language, visuospatial ability, and orientation. As described,[20] dementia diagnoses, later assigned by consensus conference of neurologists and neuropsychologists, were based on the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R).[21]

General physicians also administered a standardized neurologic examination, including a 10-item version of the motor Unified Parkinson's Disease Rating Scale (UPDRS).[20] The general medical doctors assigned a preliminary diagnosis of PD if a participant 1) had ≥two cardinal signs of parkinsonism on neurological examination, 2) was told previously that they had a diagnosis of PD, or 3) had ever used levodopa.[20] PD diagnoses were confirmed by a WHICAP study neurologist based on a second, more detailed, neurologic examination.

### Rating handwriting samples

Each participant generated two handwriting samples and, as in our previous studies,[20,22] ET diagnoses were assigned based on these samples. The first sample, administered as part of the neuropsychological test battery, consisted of a series of five standard shapes (e.g. a triangle, a diamond, a cube) that had to be copied[22] and a trail-making test[23] where the participant was asked to draw a series of lines connecting numbered circles.[22] The second sample, collected during a literacy test, involved the copying of a standardized handwritten sentence, "I have a calendar in my room" onto a sheet of paper. As in prior studies,[20,22] a student (A.P.O.) was trained by a senior movement disorder neurologist (E.D.L.) to rate the severity of tremor in the five shapes and the trail-making test. For each of the six items, the tremor ratings were assigned: 0 (no tremor), 0.5 (possible tremor), 1.0 (clear tremor that was mild), 1.5 (mild to moderate tremor), 2 (moderate or greater tremor). Ratings of 1.0, 1.5, and 2.0 were equivalent to ratings of 2, 3–4, and ≥5, respectively, in Bain et al.[24] The total tremor score for each participant ranged from 0 to 12. Following completion of training, agreement between the student and neurologist was evaluated using 25 handwriting samples, and concordance was substantial (intraclass correlation coefficient [ICC]=0.78). Subsequently, the student reviewed the research record of each participant and rated each of the six items; over the course of the ratings, every 40th (2.5% of sample) handwriting sample was selected for independent co-rating by the neurologist to ensure that agreement remained high. In these selected participants, the ICC=0.76. All ratings were blinded to clinical and MRI data.

### ET diagnosis

The method of diagnosing ET has been documented in detail in several previous publications.[20,22] The main issue in population-based studies is distinguishing ET cases from normal controls with enhanced physiologic tremor. We used previously published guidelines to aid with this distinction.[24] Based on tremor data from ET cases and normal controls, Bain et al.[24] indicated that their tremor rating ≥2 may be used to distinguish an ET case from a normal control with enhanced physiologic tremor because a rating ≥2 was twice that of the 95th percentile seen in healthy controls with enhanced physiologic tremor. Their rating of 2 is equal to our rating of 1.0. A tremor rating of 1.0 on each of our 6 rated items would result in a total tremor score of 6.0. To be more inclusive (accounting for the possibility that 1 of 6 items could have received a rating of 0.5), we considered those with total tremor scores ≥5.5 as having preliminary diagnoses of ET. The neurologist reviewed the records of all participants with preliminary ET diagnoses, and independently re-rated tremor assigning a total tremor score. As an additional test, a handwritten sentence, which was completed by participants, was also rated (E.D.L). A final ET diagnosis was conservatively assigned to participants when the neurologist confirmed a total tremor score ≥5.5 or rated the handwritten sentence

⩾2 (moderate or greater tremor, equivalent to a rating ⩾5 in Bain et al.,[24] and see example in Figure 2[22]).

Participants with final diagnoses of PD (N=4 [0.8%] from final sample of 540 participants) were not assigned final diagnoses of ET nor were participants with tremor related to medications, hyperthyroidism, or another neurologic disorder. Nine of our ET cases later enrolled in another epidemiologic study[22] in which they underwent a detailed 20-minute, neurological and tremor examination (including the following tests for postural and kinetic tremors: arm extension, pouring, drinking, using spoon, finger–nose–finger, and writing with each hand), thereby providing us with an opportunity to validate our diagnostic approach. Tremor during this examination was evaluated and rated by a senior neurologist specializing in movement disorders (E.D.L). Using rigorous research criteria (i.e., presence of moderate or severe kinetic tremor in a minimum of three tasks, and in the absence of PD or dystonia),[25–27] the diagnosis of ET was confirmed in all nine of these cases. A handwritten sentence from one of our ET cases is shown, indicating the presence of typical kinetic tremor (Figure 1).

### MRI acquisition

Image acquisition was performed on an Intera 1.5-T scanner (Philips Intera, Best, the Netherlands) at CUMC. $T_2$-weighted fluid attenuated inverse recovery (FLAIR; TR (repetition time) =11,000 milliseconds, TE (echo time) =144.0 milliseconds, 2,800 inversion time, FOV (field of view) 25 cm, 2 nex (number of excitations), 256 × 192 matrix with 3-mm slice thickness) and $T_1$-weighted (TR=20 milliseconds, TE=2.1 milliseconds, FOV 240 cm, 256 × 160 matrix with 1.3-mm slice thickness) images were acquired in the axial orientation.

### Quantification of WMH volume

WMH volumes were derived in the primary region of interest (ROI; cerebellum, a region likely to be involved in the pathogenesis of ET),[28] secondary ROIs (frontal lobe and basal ganglia, each could be involved in the pathogenesis of ET), and tertiary ROIs (occipital, parietal, temporal lobes, not likely to be involved in ET pathogenesis).

Quantification of WMH volume was performed using in-house developed software, as described.[29] To derive total WMH volume, each FLAIR and $T_1$-weighted image was realigned to a standard anatomical atlas. The $T_1$-weighted images were then segmented into tissue classes, which were used for brain extraction. A Gaussian curve was fit to voxel intensity values on the FLAIR image and the mean and standard deviation (SD) intensity value was derived. WMH seeds were defined as ⩾3.0 SD above the mean for supratentorial regions and ⩾3.5 SD for cerebellum. Each seed was then passed into an iterative mean intensity based region-growing algorithm, with a 10-point connectivity scheme, to search for and label adjacent voxels that fell within 5% of the seed mean. Labeled voxels were added to the image and a new mean was created. The summation of the number of voxels labeled as WMH multiplied by voxel dimensions comprised the total WMH volume. Hyperintense voxels from both gray and white matter were labeled, but for convention we termed all hyperintensities "white matter hyperintensities."

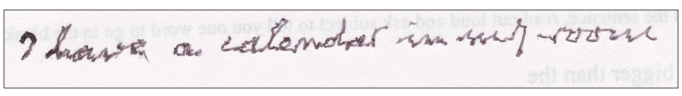

Figure 1. Written sentence from one of our essential tremor cases, an 89-year-old male who was taking no medications and had neither thyroid disease nor Parkinson's disease.

For regional WMH distribution calculation, we used an anatomical atlas created to define WMH in the cerebral lobes, basal ganglia, and cerebellum.[30] The atlas was spatially normalized to each participant's labeled FLAIR image, using the inverse transform matrix generated from the tissue class segmentation of the $T_1$-weighted image. ROIs were defined by a unique identification number for each region. The intersection of the labeled WMH with the unique anatomical label defined the regional WMH volume.

### MRI infarcts

As described,[31] the presence of cerebral infarction on MRI was determined for all participants from the size, location, and imaging characteristics of the lesion and only lesions ⩾3 mm qualified for classification as cerebral infarcts. Infracts were further classified as small (<1 cm) or large (⩾1 cm). Total cranial volume (TCV) was determined manually as previously described.[11] Infarct and cranial volumes were calculated in the Imaging Dementia and Aging Laboratory at UC Davis.

### Final sample

Complete data were available on 540 (70.2%) of 769 participants; 229 participants were excluded because they refused the writing tasks due to poor eyesight or difficulty following instructions. None refused because of tremor. The final sample of 540 participants was similar to the initial sample of 769 in terms of sex (360 [66.7%] vs. 516 [67.1%] women, p=0.87), ethnicity (185 [34.3%] vs. 285 [37.1%] Hispanic, p=0.30) and total WMH volume (7.0 ± 8.2 vs. 7.3 ± 8.5, p=0.52). The final sample of 540 participants was 0.8 years younger than the initial 769 (78.7 ± 5.4 vs. 79.5 ± 5.6 years, p=0.01).

### Statistical analyses

Where distributions of continuous variables were skewed (e.g., total WMH volume), nonparametric tests (Mann–Whitney U test, Kruskal–Wallis test, Spearman's rho) were used. For most analyses, the two-sided level of significance was set at $\alpha$=0.05, but for analyses of regional WMH volume in the five secondary and tertiary regions of interest we applied Bonferroni corrections, thus setting the level of statistical significance at p=0.01 (i.e., 0.05 ÷ 5=0.01). In univariable logistic regression models, diagnosis (ET case vs. control) was the dependent outcome variable, and the various measures of WMH and stroke were the independent predictor variables. Total WMH volume and regional WMH volumes were log-transformed to ensure adequate stabilization of the variance; if zero values were present prior to log-transformation, we anchored the value at one-half of the smallest observed value and then log-transformed the value. We performed two sets of multivariable logistic regression

Table 1. Demographic and clinical characteristics of essential tremor cases vs. controls

| Characteristic | ET | | Control | | p value |
|---|---|---|---|---|---|
| | n=33 | | n=507 | | |
| Age — years | | | | | 0.80[1] |
| Median | 79 | | 78 | | |
| Interquartile range | (74–84) | | (75–82) | | |
| Education — years | | | | | 0.037[1] |
| Median | 8 | | 12 | | |
| Interquartile range | (4–14) | | (8–15) | | |
| Sex — no. (%) | | | | | 0.002 |
| Male | 19 | (57.6) | 161 | (31.8) | |
| Female | 14 | (42.4) | 346 | (68.2) | |
| Race/ethnicity — no. (%) | | | | | 0.55[2] |
| White | 9 | (27.3) | 150 | (29.6) | |
| Black | 9 | (27.3) | 176 | (34.7) | |
| Hispanic | 15 | (45.5) | 170 | (33.5) | |
| Other | 0 | (0.0) | 11 | (2.2) | |
| Total cranial volume — ml | | | | | 0.032 |
| Mean (SD) | 1185.5 | (108.0) | 1137.1 | (124.0) | |
| Range | 1017.3–1442.0 | | 819.8–1586.2 | | |
| Comorbidities — no. (%) | | | | | |
| Diabetes mellitus[3] | 7 | (21.2) | 109 | (21.8) | 0.94[2] |
| Depression[3] | 3 | (9.1) | 41 | (8.1) | 0.74[2] |
| Thyroid disorder[3] | 5 | (15.2) | 62 | (12.5) | 0.59[2] |
| Hypertension[3] | 23 | (69.7) | 336 | (67.2) | 0.77 |
| Heart disease[3] | 11 | (33.3) | 113 | (22.3) | 0.14 |
| Hyperlipidemia[3] | 16 | (48.5) | 236 | (46.5) | 0.83 |
| Peripheral vascular disease[3] | 9 | (27.3) | 96 | (19.2) | 0.26 |
| Dementia[4] | 2 | (6.1) | 20 | (4.0) | 0.64[2] |
| Smoking history — no. (%) | 13 | (39.4) | 179 | (35.7) | 0.67 |

Characteristics are presented as means (SD) and numbers (%); where distributions are skewed, medians and interquartile ranges (IQRs) are reported. Student's *t*-test and $\chi^2$ test results are reported unless otherwise indicated.

[1]Mann–Whitney U test

[2]Fisher's exact test

[3]By self-report.

[4]Diagnosed based on DSM-III-R criteria.

Table 2. Correlates of total white matter hyperintensity (WMH) volume and log total WMH volume

| Characteristic | Total WMH volume | | p | Log total WMH volume | | p |
|---|---|---|---|---|---|---|
| Age — year | 0.21[1] | | <0.0001 | 0.21[1] | | <0.0001 |
| Education — year | −0.08[1] | | 0.06 | −0.08[1] | | 0.21 |
| Sex — mean (SD) | | | 0.54[3] | | | 0.54 |
| Male | 7.09 | (9.03) | | 1.28 | (1.26) | |
| Female | 6.91 | (7.70) | | 1.35 | (1.17) | |
| Race/ethnicity — mean (SD) | | | 0.003[2] | | | <0.0001 |
| White | 4.98 | (5.28) | | 1.04 | (1.17) | |
| Black | 8.86 | (9.94) | | 1.55 | (1.23) | |
| Hispanic | 6.64 | (7.26) | | 1.34 | (1.14) | |
| Other | 8.99 | (14.95) | | 1.30 | (1.37) | |
| Total cranial volume — ml | 0.10[1] | | 0.027 | 0.11 | | 0.016 |
| Comorbidities — mean (SD) | | | | | | |
| Diabetes mellitus[4] | | | 0.024[3] | | | 0.031 |
| Yes | 7.69 | (7.73) | | 1.54 | (1.10) | |
| No | 6.80 | (8.30) | | 1.26 | (1.23) | |
| Depression[4] | | | 0.11[3] | | | 0.15 |
| Yes | 8.82 | (9.33) | | 1.58 | (1.25) | |
| No | 6.80 | (8.02) | | 1.30 | (1.20) | |
| Thyroid disorder[4] | | | 0.78[3] | | | 0.71 |
| Yes | 6.91 | (8.19) | | 1.38 | (1.10) | |
| No | 7.03 | (8.22) | | 1.32 | (1.22) | |
| Hypertension[4] | | | 0.032[3] | | | 0.028 |
| Yes | 7.45 | (8.38) | | 1.41 | (1.19) | |
| No | 6.10 | (7.72) | | 1.16 | (1.23) | |
| Heart disease[4] | | | 0.12[3] | | | 0.043 |
| Yes | 8.59 | (10.61) | | 1.52 | (1.17) | |
| No | 6.46 | (7.14) | | 1.26 | (1.21) | |
| Hyperlipidemia[4] | | | 0.027[3] | | | 0.022 |
| Yes | 6.27 | (7.58) | | 1.19 | (1.22) | |
| No | 7.56 | (8.57) | | 1.44 | (1.18) | |
| Peripheral vascular disease[4] | | | 0.92[3] | | | 0.89 |
| Yes | 6.84 | (7.61) | | 1.34 | (1.17) | |

**Table 2.** Continued

| Characteristic | Total WMH volume | | p | Log total WMH volume | | p |
|---|---|---|---|---|---|---|
| No | 7.04 | (8.33) | | 1.32 | (1.22) | |
| Smoking history — mean (SD) | | | 0.86[3] | | | 0.93 |
| Yes | 7.30 | (8.84) | | 1.33 | (1.25) | |
| No | 6.82 | (7.79) | | 1.32 | (1.18) | |
| Dementia[5] | | | 0.010[3] | | | 0.019 |
| Yes | 11.69 | (11.00) | | 1.93 | (1.27) | |
| No | 6.78 | (7.97) | | 1.30 | (1.20) | |

Correlation coefficients and means (SD) are reported. Pearson's correlation and Student's *t*-test and analysis of variance are reported unless otherwise indicated.
[1]Spearman rank correlation.
[2]Kruskal–Wallis test.
[3]Mann–Whitney U test.
[4]By self-report.
[5]Diagnosed based on DSM-III-R criteria.

analyses; Model 1 included all covariates that were associated in univariable analyses ($p<0.05$) with both ET and the WMH/stroke measure of interest whereas Model 2 was extended to consider all covariates associated with either ET or the particular WMH/stroke measure of interest. Variables considered in adjusted models included age (years), sex, race/ethnicity, education (years), smoking history, self-reported comorbid conditions (diabetes mellitus, depression, thyroid disorder, hypertension, heart disease, hyperlipidemia, and peripheral vascular disease), smoking history, and TCV.

## Results

Thirty-three of 540 participants were diagnosed as ET (prevalence=6.1%, 95% CI [4.1, 8.1]) (see Figure 1). ET cases and controls differed with respect to education, sex and TCV, but were similar in other respects (age, race/ethnicity, comorbidities, dementia diagnoses, Table 1).

Total WMH volume was positively correlated with age (rho=0.21, $p<0.001$) and TCV (rho=0.10, p=0.027) (Table 2) and also differed with respect to race/ethnicity (p=0.003) and several comorbidities (Table 2).

Total WMH volume was greater in ET cases than controls (mean [SD]=9.19 [7.96] vs. 6.82 [8.15], median [interquartile range or IQR]=6.66 [13.13] vs. 3.95 [7.04], Mann–Whitney $z=2.16$, p=0.03).

In univariable analysis (Table 3), log total WMH volume was associated with increased odds of ET (OR 1.41, 95% CI [1.02, 1.94], p=0.038). Although no ET cases were taking valproate, lithium or steroids, two of 33 ET cases were taking other tremor-enhancing medications (both were using asthma inhalers); when these two were excluded, the OR was similar (OR 1.40, 95% CI [1.003, 1.95], p=0.048). In multivariable models, we first included one covariate (TCV) that was associated with both ET and log total WMH (Model 1) and then 10 covariates that were associated with either ET or log total WMH (Model 2); the ORs were similar (OR 1.43 [p=0.035] in Model 1 and OR 1.44 [p=0.030] in Model 2, Table 3).

In the primary ROI (cerebellum), WMH volume was modestly yet not significantly elevated among ET cases than controls (mean [SD]=0.18 [0.20] vs. 0.15 [0.19], median [IQR]=0.11 [0.20] vs. 0.09 [0.20], Mann–Whitney $z=1.38$, p=0.17). In multivariable models (Table 3), cerebellar WMH volume was marginally associated with increased odds of ET in Model 1 (OR 1.58, 95% CI [0.93, 2.67], p=0.09) and significantly associated with ET in Model 2 (OR 1.74, 95% CI [1.01, 3.03], p=0.049). In these models, the odds of ET were similar in both direction and magnitude (range 1.58–1.74).

For secondary and tertiary regions of interest (five comparisons, Table 3), we applied Bonferroni corrections (level of statistical significance, p=0.01), and only the temporal lobe WMH was associated with ET (ORs in Models 1 and 2 in excess of 3.0).

One or more stroke was present on MRI in 168 (33.2%) of 506 participants with complete MRI data; the presence of strokes was associated with sex, TCV, hypertension, and heart disease (Table 4). A marginally higher proportion of ET cases than controls had one or more stroke on MRI (15 [46.9%] vs. 153 [32.3%]; $\chi^2=2.88$, p=0.09, Table 3); in adjusted models, the ORs, which ranged from 1.56 to 1.61, did not reach statistical significance (respective p values=0.25 and 0.20, Table 3). Large strokes were significantly more common in cases than controls (unadjusted OR 3.04, p=0.02) and more common in adjusted analyses (OR 2.57, p=0.045 to OR 2.56, p=0.056) (Table 3). The distribution of strokes did not differ by diagnosis. The three most common areas affected in ET cases were the caudate (12.5% of cases), frontal cortex (9.4%), frontal white matter (9.4%); 3.1% of cases had cerebellar strokes. In controls, the three most common areas were the frontal white matter (7.4%), basal ganglia (5.9%), and cerebellum (4.6%).

**Table 3.** Odds of white matter hyperintensity (WMH) and stroke in essential tremor (ET) cases vs. controls

| | Univariable Analysis | | | Multivariable Analysis[1,2] | |
|---|---|---|---|---|---|
| | | | | Model 1 | Model 2 |
| Measure | ET n=33 | Control n=507 | OR (95% CI) p | OR (95% CI) p | OR (95% CI) p |
| Log Total WMH volume | 1.75 ± 1.10 | 1.30 ± 1.21 | 1.41 (1.02, 1.94) 0.038 | 1.43 (1.03, 1.99) 0.035 | 1.44 (1.03, 2.01) 0.030 |
| *Regional WMH volumes* | | | | | |
| Primary ROI (Cerebellum) | −1.05 ± 0.66 | −1.29 ± 0.81 | 1.52 (0.91, 2.54) 0.11 | 1.58 (0.93, 2.67) 0.09 | 1.74 (1.01, 3.03) 0.049 |
| *Secondary ROIs* | | | | | |
| Frontal lobe | 0.31 ± 0.60 | 0.20 ± 0.58 | 1.39 (0.74, 2.63) 0.31[3] | 1.29 (0.68, 2.45) 0.43[3] | 1.38 (0.70, 2.74) 0.36[3] |
| Basal ganglia | −0.59 ± 0.65 | −0.76 ± 0.62 | 1.67 (0.84, 3.31) 0.14[3] | 1.60 (0.82, 3.12) 0.17[3] | 1.82 (0.89, 3.71) 0.10[3] |
| *Tertiary ROIs* | | | | | |
| Occipital lobe | −0.75 ± 0.86 | −1.11 ± 1.04 | 1.45 (0.98, 2.15) 0.06[3] | 1.44 (0.98, 2.13) 0.07[3] | 1.56 (1.04, 2.33) 0.03[3] |
| Parietal lobe | 0.16 ± 0.79 | −0.04 ± 0.69 | 1.54 (0.88, 2.69) 0.13[3] | 1.44 (0.83, 2.53) 0.19[3] | 1.48 (0.83, 2.64) 0.18[3] |
| Temporal lobe | −0.54 ± 0.51 | −1.05 ± 0.77 | 3.36 (1.74, 6.52) <0.001[3] | 3.38 (1.72, 6.62) <0.001[3] | 3.73 (1.87, 7.43) <0.001[3] |
| *Stroke measures* | | | | | |
| Participant has one or more strokes | 15 (46.9) | 153 (32.3) | 1.85 (0.90, 3.81) 0.09 | 1.61 (0.77, 3.36) 0.20 | 1.56 (0.73, 3.36) 0.25 |
| Number of strokes detected | 0.69 ± 0.93 | 0.55 ±1.15 | 1.09 (0.85, 1.42) 0.50 | 1.03 (0.78, 1.35) 0.84 | 1.07 (0.80, 1.44) 0.65 |
| 1 or more large stroke (⩾1 cm) | 7 (21.9) | 40 (8.4) | 3.04 (1.23, 7.46) 0.02 | 2.57 (1.02, 6.45) 0.045 | 2.56 (0.98, 6.71) 0.056 |
| 1 or more small stroke (>3 mm, <1 cm) | 10 (31.3) | 131 (27.6) | 1.19 (0.55, 2.58) 0.66 | 1.06 (0.48, 2.33) 0.89 | 1.08 (0.47, 2.44) 0.86 |

Means (SD) and numbers (%) are presented.

[1]For analyses of WMH, Model 1 included all variables that in univariable models were associated with both ET and WMH volume (at an $\alpha$ level of <0.05). Hence, Model 1 included the covariate TCV. Model 2 considered all variables that in univariable models were associated with either ET or WMH volume (at an $\alpha$ level of <0.05), and included the following covariates: age, sex, education, race, diabetes mellitus, hypertension, heart disease, hyperlipidemia, dementia, and TCV.

[2]For analyses of stroke, Model 1 included all variables that in univariable models were associated with both ET and stroke presence (at an $\alpha$ level of <0.05). Hence, Model 1 included the covariates sex and TCV. Model 2 considered all variables that in univariable models were associated with either ET or stroke presence (at an $\alpha$ level of <0.05), and included the following covariates: sex, education, hypertension, heart disease, and TCV.

[3]Bonferroni corrections were applied for analyses of regional WMH volume in the five secondary and tertiary regions of interest, thus setting the level of statistical significance at p=0.01.

ROI, region of interest.

Table 4. Demographic and clinical characteristics of participants with vs. without one or more stroke on magnetic resonance imaging (MRI)

| Characteristic | Stroke(s) present (1 or more) | | Absence of strokes | | p value |
|---|---|---|---|---|---|
| | n=168 | | n=338[1] | | |
| Age — year | | | | | 0.71[2] |
| Median | 77 | | 78 | | |
| Interquartile range | (74–82) | | (75–82) | | |
| Education — year | | | | | 0.44[2] |
| Median | 12 | | 12 | | |
| Interquartile range | (8–15) | | (8–15) | | |
| Sex — no. (%) | | | | | 0.012 |
| Male | 68 | (40.5) | 99 | (29.3) | |
| Female | 100 | (59.5) | 239 | (70.7) | |
| Race/ethnicity — no. (%) | | | | | 0.29[3] |
| White | 51 | (30.4) | 96 | (28.4) | |
| Black | 65 | (38.7) | 113 | (33.4) | |
| Hispanic | 51 | (30.4) | 121 | (35.8) | |
| Other | 1 | (0.6) | 8 | (2.4) | |
| Total cranial volume — ml | | | | | 0.034 |
| Mean (±SD) | 1156.7 | (131.5) | 1131.9 | (118.6) | |
| Range | 925.8–1586.2 | | 819.8–1565.5 | | |
| Morbidities — no. (%) | | | | | |
| Diabetes mellitus | 42 | (25.3) | 68 | (20.2) | 0.19 |
| Dementia | 7 | (4.2) | 14 | (4.2) | 0.98 |
| Depression | 16 | (9.5) | 25 | (7.4) | 0.41 |
| Thyroid disorder | 23 | (13.9) | 38 | (11.4) | 0.44 |
| Hypertension | 124 | (75.2) | 213 | (63.2) | 0.007 |
| Heart disease | 53 | (31.5) | 69 | (20.4) | 0.006 |
| Hyperlipidemia | 74 | (44.0) | 159 | (47.0) | 0.53 |
| Peripheral vascular disease | 35 | (21.1) | 64 | (19.0) | 0.59 |
| Smoking history — no. (%) | 59 | (35.5) | 122 | (36.2) | 0.89 |

Characteristics are presented as means (SD) and numbers (%). Where distributions are skewed, medians and IQRs are reported. Student's *t*-test and $\chi^2$ test results are reported unless otherwise indicated.

[1]34 participants had incomplete MRI data.

[2]Mann–Whitney U test.

[3]Fisher's exact test.

## Discussion

This study sought to determine whether WMH and stroke are associated with ET. We found a modest association between total WMH volume and ET diagnosis; even in adjusted analyses, the total WMH volume remained a significant predictor of ET. When exploring regional WMH, we found a marginal association between cerebellar WMH and ET. Subsequent analyses revealed an association for temporal lobe WMH volume but not for other secondary or tertiary ROIs. Separate from the contribution of WMH volume, large strokes ($\geq$1 cm) were associated with increased odds of ET. Taken together, our MRI data suggest that cerebrovascular disease could contribute toward the neuropathogenesis of ET.

In prior MRI studies, subcortical WMH volume has been linked to impaired gait and balance[32] as well as mild Parkinsonian signs in elderly people.[33] Yet no other studies have explored the association between WMH volume and ET. In terms of strokes, several case studies have reported the reversal or improvement of the tremor in ET in the setting of cerebral cortical, cerebellar, and thalamic strokes.[14] By contrast, in one case, a frontal cortical infarction was thought to have produced unilateral hand tremor.[34] Yet the relevance of diffuse white matter changes and the possible role these could play as contributors to the pathogenesis/origins of the disease itself (ET), rather than the role of larger lesions in modifying the propagation of the neurological sign, tremor, in established cases, has not been explored. Hence, the relationship between stroke, tremor in ET, and ET (as a pathogenetic disease entity) is complex and likely is related to the location as well as nature and size of the lesion(s); further studies are needed in order to begin to disentangle these issues.

The association between cerebellar WMH, our primary ROI, and ET was significant in fully adjusted models. Previous positron emission tomography (PET) studies revealed metabolic abnormalities in the ET cerebellum.[35] $^{1}$H-MRS (magnetic resonance spectroscopy) imaging studies reported a reduction of cerebellar N-acetylaspartate/creatine ratio in ET, which may indicate neuronal damage or loss in ET.[36] Structural abnormalities, including Purkinje cell loss, have been reported in the ET cerebellum in post-mortem studies.[37] Whether and how cerebrovascular processes might contribute to the pathophysiology of ET deserves further exploration.

In this sample, participants were >65 years old at the time of MRI acquisition. Although age of onset of ET was unknown, it was likely to have been <65 in many participants (i.e., the sample was likely not restricted to elderly-onset ET).

This study had limitations. The cross-sectional design precluded inferences about the order of events (i.e., whether MRI changes preceded or followed ET) and future studies should address longitudinally collected MRI and clinical data. Secondly, while the prevalence of ET in this study is well within prevalence range reported in this region and elsewhere,[22,38] the study included only 33 ET cases so that sample size may have caused some analyses to be underpowered. Nonetheless, in a number of our analyses, including the comparison of WMH burden in ET cases and controls, the sample size was adequate to detect significant effects. Thirdly, our study was not designed to investigate the associations between asymmetrical ET and regional WMH/infarcts or between familial vs. nonfamilial ET and WMH/infarcts. Fourth, participants with tremor related to medications were not assigned final diagnoses of ET but it is possible that participants on antihypertensive agents (esp. beta-blockers) may have had their tremor masked by these medications. The possible failure to recognize some ET cases and the resultant misclassification would likely have biased our results towards the null. Fifth, while it is possible that strokes may have resulted in weakness, it is not likely that this weakness resulted in oscillations, and we were careful to distinguish clear, regular, oscillations from feeble scrawl and other irregularities that were not strictly oscillatory. Lastly, given the reliance on handwriting samples for establishing ET diagnosis, misclassification is possible; nevertheless, this is likely to have biased our estimates of association toward the null, causing us to underestimate the magnitude of the associations we detected. While it is possible that overall frailty in our participants could have resulted in the appearance of shaky handwriting, and that these were not ET cases, as noted above, we were careful to distinguish clear oscillations from feeble scrawl.

This study had several strengths. This is the first study to address this specific question and to use MRI to evaluate possible cerebrovascular associations with ET. Patients were carefully assessed at an academic medical center with specialists with expertise in aging and tremor evaluation, and raters of ET were blinded from MRI data as were MRI raters from ET diagnoses. Finally, given its population-based rather than medical center-based design, it is unlikely that participants were self-selected to have multiple medical conditions (e.g., ET and cerebrovascular disease).

Subcortical WMH has been linked to various neurological disorders, although the relationship between these hyperintensities and ET had not been studied. In examining associations between WMH, stroke and ET, our MRI data raise the possibility that vascular disease could have a role in the development of ET.

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