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ORIGINAL ARTICLE

No reliable gray matter changes in essential tremor

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Abstract

Background Voxel-based morphometry (VBM) has been used to study human brain gray matter (GM) alterations in essential tremor (ET) for over one decade. However, the literature revealed heterogeneous findings.

Methods We therefore conducted a coordinate-based meta-analysis to synthesize the VBM studies to examine which brain regions show the most reliable GM alterations in patients with ET relative to healthy controls.

Results A total of 16 original VBM studies, comprising 387 patients with ET and 355 healthy controls, were included in this meta-analysis. This quantitative meta-analysis revealed no evidence of robust and reliable alterations in regional brain GM structures in ET. Meta-regression analyses indicate that many moderators (e.g., MR field strength, statistical methodology, age, onset age, gender, illness severity, illness duration, and family history) account for some of the heterogeneity in GM across studies.

Conclusions High heterogeneity in GM alterations across studies may reflect true heterogeneity in ET regarding the clinic, etiology, and pathology, as well as possibly the VBM methodological variations. Currently, this heterogeneity limits the use of VBM as a reliable tool to distinguish ET from healthy controls. In order to improve reproducibility of VBM results in ET, future research may benefit from increasing the sample size, comprehensively subtyping ET phenotypes, and using well-designed and standardized imaging acquisition and analytical protocols. Furthermore, data sharing should be considered as a high priority.

Keywords Essential tremor · Voxel-based morphometry · Gray matter · Coordinate-based meta-analysis

Abbreviations

AES-SDM	Anisotropic effect-size signed differential mapping
ET	Essential tremor
FTM-TRS	Fahn-Tolosa-Marin Tremor Rating Scale
GM	Gray matter
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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SDM Seed-based *d* Mapping
VBM Voxel-based morphometry

Introduction

Essential tremor (ET) is the most common form of pathological tremor, with a worldwide prevalence estimated at 0.9%, which increases markedly with age [1]. ET is characterized by bilateral upper limb postural or kinetic tremor with a frequency between 4 and 12 Hz [2]. ET disrupts daily activities and increases the risk of mortality [3]. Genetic and environmental factors have been suggested to be implicated in the pathogenesis of ET [4]. ET is now recognized as a syndrome with clinical, pathological, and etiological heterogeneity [5]. Reliable biomarkers are absent in ET and its misdiagnosis rate is high [6–8]. Despite its extraordinarily high prevalence, the exact pathophysiology of ET remains unclear. Although remained debated, possible underlying mechanisms, including abnormal neuronal oscillations within in the cortico-thalamo-olivo-cerebellar network (tremor network), GABAergic dysfunction, and cerebellar degeneration, have been proposed, all of which underscore the critical role of the cerebellum [4].

During the past two decades, the rapid development of neuroimaging techniques has contributed significantly to a better understanding of the underlying pathophysiology of ET [9, 10]. However, progress in the identification of biomarkers for ET is still underway. Voxel-based morphometry (VBM) is a non-invasive brain magnetic resonance imaging (MRI) technique that allows exploring structural differences between groups at a whole-brain level without a priori hypothesis [11]. Since VBM is a quick and relatively easy morphometric technique, it has been widely used for detecting gray matter (GM) abnormalities in neurological disorders, such as Alzheimer's disease [12] and Parkinson's disease [9, 13]. Functional imaging studies in ET have shown the most consistent finding involving the cerebellar system [9, 10]. However, VBM studies yielded substantially variable and inconclusive results regarding the directions (increase or decrease) or locations of brain GM changes in ET. Some studies only detected GM decrease in ET [14–20]. In contrast, three studies observed both GM increase and decrease [21–23]. Other studies, however, reported no significant GM differences between patients with ET and healthy controls [24–31]. Among the published VBM studies, seven detected GM abnormalities but with variable distribution in the cerebellum [14, 18–23]. These reported discrepancies related to the GM changes may potentially be attributed to differences in sample sizes, demographic and clinical characteristics of the patients (age, onset age, gender, illness duration, symptom severity, and clinical subtypes), and imaging protocols (imaging acquisition, image-processing methodology, and statistics) utilized across studies.

We faced challenges when interpreting these heterogeneous results. A clear picture of ET-related GM changes have not yet emerged. Meta-analysis offers promise to combine studies and provide more robust results by obtaining larger sample sizes with greater statistical power. The aim of this study was therefore to conduct a coordinate-based meta-analysis to quantitatively synthesize the VBM studies to examine which brain regions show the most consistent and robust GM alterations in patients with ET relative to healthy controls. More specifically, exploratory analyses of potential confounders, including demographic, clinical, and imaging factors, on GM changes were performed.

Methods

Literature search

Using the following terms: (essential tremor) AND ((voxel-based morphometry) or vbm or (gray matter) or (gray matter) or voxel*), we systematically searched the online electronic databases of PubMed, Web of Science, and Embase. A supplemental manual search was conducted within the reference lists of the included papers and relevant reviews to obtain additional eligible studies. The literature search was initially performed on June 10, 2018, and updated on August 21, 2018, with no imposed date or language restrictions of publication. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the present study [32].

Study eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: (1) original articles were published in peer-reviewed journals in English; (2) patients had been diagnosed with ET according to the recognized criteria [33–37]; (3) a VBM analysis using the same threshold throughout the whole brain was employed to compare GM volume or density differences between patients with ET and healthy controls; (4) three-dimensional coordinates in the Montreal Neurological Institute (MNI) or Talairach stereotactic space were available. Studies were excluded if (1) peak coordinates could not be retrieved from the published articles or after contacting the authors, (2) a sample size was less than 10 subjects in each group, (3) only region-of-interest analysis was performed, (4) longitudinal or interventional studies did not report GM comparisons between patients with ET and healthy controls at baseline, and (5) the sample of a study was overlapped with others with a larger sample size.

Data extraction and quality assessment

For each included study, the following information are as follows: the first author's family name, publication year, sample size, age, gender, total Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) score, illness duration, percent of patients with head tremor, percent of patients with a positive family history, diagnostic criteria, MR field strength, MR sequence, voxel size, imaging processing software package, template, processing methods, modulation, smooth kernel, covariate, statistical threshold and coordinates, their corresponding *t* statistics, and their stereotactic reference space were extracted.

Quality assessment of the collected articles was done using a 10-point checklist based on previous neuroimaging coordinate-based meta-analyses [38, 39]. This checklist integrated sample characteristics and imaging-specific methodology used in the studies (details in Supplementary Table 1).

Two authors independently performed the literature search and screen, data extraction, and quality assessment for each study included in the meta-analysis. Any disagreements were resolved by consensus with a third author.

Data analyses

Sociodemographic data

Sociodemographic data of ET and control groups (e.g., age and gender distribution) were compared using the STATA software package with random-effects models (version 12.0, Stata Corporation, College Station, TX, USA).

Meta-analysis of all included VBM studies

To conduct a coordinate-based meta-analysis of VBM studies that compared regional GM differences between patients with ET and healthy controls, the Seed-based *d* Mapping (SDM), also called anisotropic effect size, signed differential mapping (AES-SDM) software package (latest version 5.15) was used (https://www.sdmproject.com/). SDM has been proven to be an invaluable tool for integrating the findings of voxel-based neuroimaging studies in neuropsychiatric disorders [40–44]. Analyses were conducted in accordance with the standard processes described in the SDM tutorial (https://www.sdmproject.com/software/tutorial.pdf). First, SDM recreated an effect size map and an effect size variance map of GM differences patients with ET and healthy controls for each VBM study based on peak coordinates and their corresponding *t* statistics using a default anisotropic non-normalized Gaussian kernel. Afterwards, SDM voxel-wisely calculated the mean of the study maps that produced a mean map using random-effects general linear models, weighted by the sample size, and intra-study variance, and between-study heterogeneity. Finally, significant results were obtained using a default combination of thresholds: $p < 0.005$, peak height $Z > 1$, and cluster size > 10 voxels that have been shown to optimally balance the sensitivity and specificity [45, 46].

The main analyses were complemented with the analyses of heterogeneity, jackknife sensitivity, and publication bias to ensure that only the most replicable and robust of the results were retained [47]. Heterogeneity analyses were conducted to know which brain regions are more heterogeneous between studies using a random effects model with Q statistics [45, 46]. Jackknife sensitivity analyses were similar to the main meta-analysis, iteratively repeating the meta-analyses of all the studies but one each time to test the contribution of each study to the reported results [45, 46]. A result from the main meta-analysis was considered not robust if it did not reached significance in two or more iterations in the jackknife sensitivity analyses [47]. For analyses of heterogeneity and jackknife sensitivity, a default combination of thresholds were set at $p < 0.005$, peak height $Z > 1$, and cluster size > 10 voxels [45, 46]. Publication bias of each cluster reported in the main meta-analysis was examined using the Egger's test ($p < 0.05$) [48].

Subgroup meta-analyses

Subgroup meta-analyses would be conducted additionally, such as meta-analyses of VBM studies that applied 3.0T MRI scanners or VBM studies that used modulated methods or corrected thresholds.

Meta-regression analyses

To further explore the sources of GM heterogeneity across studies, meta-regression analyses were carried out to examine the potential effects of moderators, including mean age, age at onset, gender, total FTM-TRS score, illness duration, percent of patients with head tremor, and percent of patients with a positive family history if they were reported in ten or more studies. A more conservative threshold of $p < 0.0005$ with peak height $Z > 1$, and cluster size > 10 voxels was adopted [45, 46].

Results

Included studies

The search produced 192 references. After assessment of eligibility according to the inclusion and exclusion criteria, 16 original VBM studies [14, 15, 18–31] were finally included in the qualitative coordinate-based meta-analysis. Flow diagram of identification, screening, and inclusion of studies is presented in Fig. 1. This meta-analysis included 387 patients with ET (mean age from 38.2 to 76 years, 223 males and 164 females, illness duration from 4.7 to 35 years) and 355 healthy controls (mean age

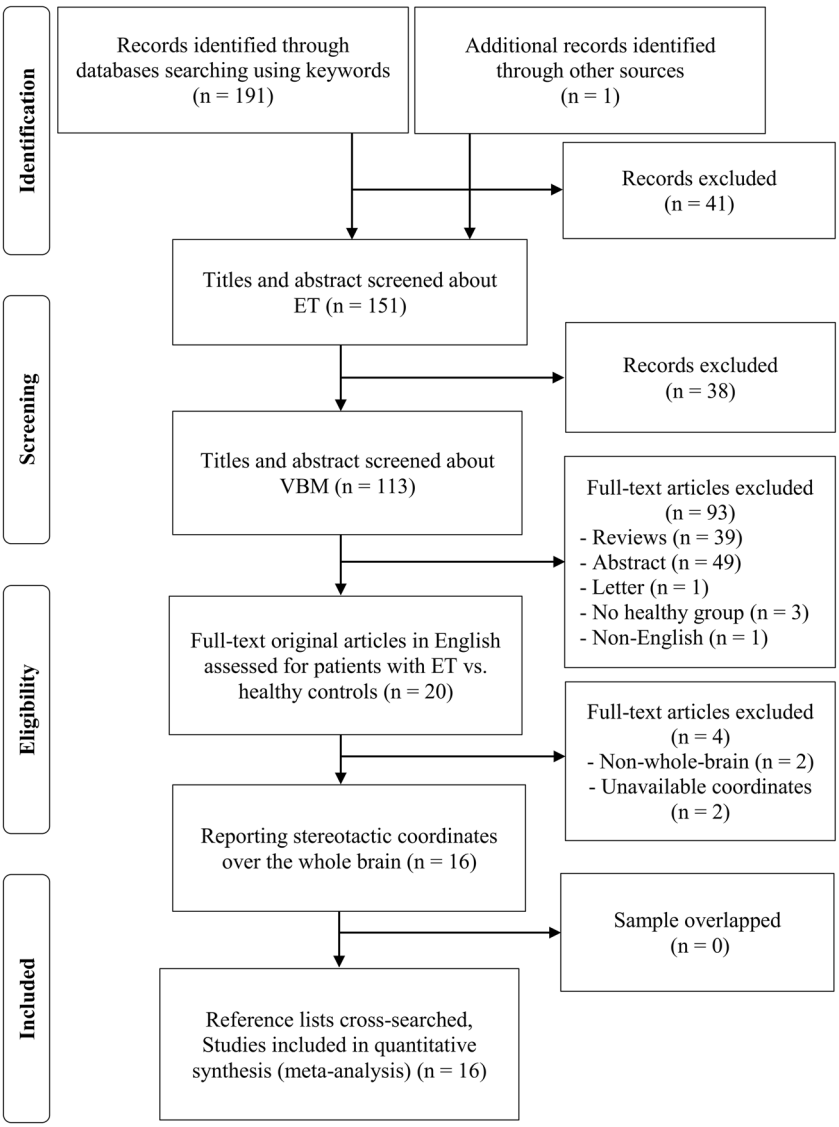

Fig. 1 Flowchart of the inclusion and exclusion criteria for the meta-analysis. ET, essential tremor; VBM, voxel-based morphometry

from 40.7 to 73.3 years). Gender distribution in the healthy control group was not available from one study [25]. The coordinates of one study were obtained by contacting the authors [15]. Of the 16 studies, 14 applied 3.0T MRI scanners, 11 used corrected thresholds in the imaging statistical analyses, 11 reported the total FTM-TRS score, 10 reported the percent of patients with a positive family history of ET, and only six reported the percent of ET patients with head tremor. Demographic and clinical variables, imaging-specific data, and quality assessment scores are described in Tables 1 and 2.

Data analysis

Sociodemographic data

There were no significant differences between patients with ET and healthy controls with respect to mean age (available from all studies, standardized mean difference = 0.077; 95% confidence interval (CI) = − 0.069 to 0.22, $Z = 1.03$, $p = 0.30$) or gender distribution (available from 15 studies, relative risk = 0.95, 95% CI = 0.80 to 1.12, $Z = 63$, $p = 0.53$).

Meta-analysis of all included VBM studies

The main meta-analysis of all studies identified that patients with ET relative to healthy controls showed GM decrease in the right putamen extending to the Rolandic operculum, insula, superior temporal gyrus and Heschl gyrus (cluster 1), right cerebellum (hemispheric lobules IV/V and III and vermic lobule III, cluster 2), and right cerebellum (hemispheric lobule VIII, cluster 3) (Fig. 2 and Table 3). The heterogeneity analysis showed significant statistical heterogeneity between studies in above three reported clusters with GM abnormalities (Table 4). The jackknife sensitivity

Table 1 Demographic and clinical characteristics of VBM studies included in the meta-analysis

Study	Sample (male)	Age (SD)	Age at onset (SD)	Duration (SD)	Total FTM-TRS score (SD)	Family history	Head tremor	Diagnostic criteria	Quality[#]
Daniels et al. (2006) [24]	ET 27 (18) HC 27 (18)	57.9 (12.2) 57.6 (13.5)	31.8 (21.8)	26 (17.5)	33.9 (13.7)	NA	NA	Deuschl et al. 1998	9.0
Quattrone et al. (2008) [31]	ET 50 (24) HC 32 (16)	65.2 (14.3) 66.2 (8.1)	45.8 (18.4)	19.3 (14.9)	NA	100%	40%	Deuschl et al. 1998	10
Benito-Leon et al. (2009) [14]	ET 19 (10) HC 20 (10)	69.8 (9.4) 68.9 (10)	58.8 (11.4)	11.0 (6.8)	NA	NA	58%	Louis et al. 2001	9.5
Klein et al. (2011) [25]	ET 14 (9) HC 20 (NA)	61.2 (12) 60.2 (8.1)	48.0 (NA)	13.2 (12.1)	17 (7.6)	64%	0%	Deuschl et al. 1998	9.0
Bagepally et al. (2012) [18]	ET 20 (15) HC 17 (14)	38.2 (16.5) 40.7 (16.5)	33.5 (NA)	4.7 (4.5)	29.7 (14.9)	55%	50%	Deuschl et al. 1998	9.5
Fang et al. (2013) [26]	ET 20 (12) HC 20 (12)	50.3 (14.2) 50.3 (14.2)	35.3 (9.9)	14.6 (7.7)	28 (NA)	55%	25%	Louis et al. 1998	9.5
Lin et al. (2013) [22]	ET 10 (5) HC 13 (9)	63.4 (8.7) 65.3 (11.1)	48.2 (NA)	15.2 (7.91)	NA	NA	NA	NA	8.0
Bhalsing et al. (2014) [20]	ET 17 (12) HC 25 (19)	45 (10.7) 45.4 (10.7)	35.16 (NA)	9.84 (6.63)	36.65 (15.19)	59%	NA	Chouinard et al. 1997	9.5
Cerasa et al. (2014) [19]	ET 14 (8) HC 23 (13)	64.4 (9.1) 64.4 (7.1)	53.2 (15.3)	12.8 (11.9)	10.1 (4.6)	64%	NA	Deuschl et al. 1998	9.5
Gallea et al. (2015) [21]	ET 19 (12) HC 19 (12)	50.4 (15) 50.1 (16.4)	29.1 (NA)	21.3 (13.7)	38.9 (20.8)	NA	NA	Deuschl et al. 1998	9.5
Nicoletti et al. (2015) [27]	ET 32 (17) HC 12 (4)	69.7 (9.7) 67.4 (4.8)	56.3 (5.5)	13.4 (12.9)	25.6 (9.5)	53%	NA	Deuschl et al. 1998	9.5
Buijink et al. (2016) [28]	ET 36 (23) HC 30 (19)	56 (14) 54 (15)	29 (NA)	27 (16)	NA	100%	50%	Bain et al. 2000	9.5
Fang et al. (2016) [26]	ET 26 (19) HC 26 (19)	47.3 (11.3) 43.4 (14.4)	34.3 (13)	12.9 (7.2)	20.4 (8.6)	42%	NA	Deuschl et al. 1998	9.5
Archer et al. (2018) [30]	ET 19 (7) HC 18 (8)	65.74 (11.56) 63.66 (7.58)	42.09 (NA)	23.65 (19.87)	39.21 (20.33)	NA	NA	Deuschl et al. 1998	9.0
Cameron et al. (2018) [15]	ET 47 (24) HC 36 (10)	76 (6.8) 73.3 (6.5)	41.0 (20.5)	35 (NA)	20.4 (6.1)	NA	57%	Louis et al. 1998	9.0
Cao et al. (2018) [23]	ET 17 (8) HC 17 (7)	39.65 (8.12) 42.24 (9.47)	27.53 (13.00)	12.71 (7.55)	NA	57%	NA	Deuschl et al. 1998	9.0

VBM, voxel-based morphometry; *SD*, standard deviation; *FTM-TRS*, Fahn-Tolosa-Marin Tremor Rating Scale; *FWHM*, full width half maximum; *ET*, essential tremor; *HC*, healthy controls; *NA*, not available; *SPM*, statistical parametric mapping; *DPARSFA*, Data Processing Assistant for Resting-State fMRI Advanced edition; *FSL*, Functional MRI of the brain Software Libraries package; [#] a maximum score of 10 for each study

Table 2 Imaging characteristics of VBM studies included in the meta-analysis

Study	MR scanner	MR sequence	Voxel size (mm^3)	Software	Template	Methods	Modulation	FWHM	Covariate	Threshold
Daniels et al. (2006) [24]	Philips Gyroscan Intera	TFE	1.2 × 1.2 × 1.2	SPM2	NA	Optimized VBM	No	NA	NA	$p < 0.05$ corrected
Quattrone et al. (2008) [31]	GE Signa NV/I, 1.5 T	SPGR	1.2 × 0.94 × 0.94	SPM2	Custom	Optimized VBM	Yes	10 mm	TIV, total GM volume, age, gender	$p < 0.001$ corrected
Benito-Leon et al. (2009) [14]	GE Signa, 3.0 T	IR-FGE	1.0 × 1.0 × 1.0	SPM5	MNI	VBM5	Yes	6 mm	TIV, age, gender	$p < 0.001$ uncorrected
Klein et al. (2011) [25]	Siemens Trio, 3.0 T	FLASH	1.0 × 1.0 × 1.0	SPM5	MNI 152	VBM5	No	8 mm	Age	$p < 0.05$ FWE corrected
Bagepally et al. (2012) [18]	Phillips Achieva, 3.0 T	MPRAGE	1.0 × 1.0 × 1.0	SPM5	MNI 152	VBM5	Yes	8 mm	TIV, age, gender, age at onset	$p < 0.001$ uncorrected
Fang et al. (2013) [26]	GE Signa Hdxt, 3.0 T	NA	NA	DPARSFA	MNI	VBM	No	4 mm	NA	$p < 0.05$ FDR corrected
Lin et al. (2013) [22]	GE Signa HDx, 3.0 T	Gradient-echo pulse	NA	SPM8	MNI 305	DARTEL VBM8[a]	Yes	8 mm	NA	$p < 0.000001$ uncorrected
Bhalsing et al. (2014) [20]	Philips Achieva, 3.0 T	IR-FGE	NA	SPM8	MNI	VBM8	Yes	8 mm	TIV, age, gender	$p < 0.05$ FWE corrected
Cerasa et al. (2014) [19]	GE Discovery MR-750, 3.0 T	SPGR	1.0 × 1.0 × 1.0	SPM8	MNI	DARTEL VBM8	Yes	8 mm	TIV, age	$p < 0.001$ uncorrected
Gallea et al. (2015) [21]	Siemens MAGNETOM Trio, 3.0 T	MPRAGE	1.0 × 1.0 × 1.0	SPM8	MNI	DARTEL VBM8	Yes	10 mm	Age, gender	$p < 0.05$ FWE corrected
Nicoletti et al. (2015) [27]	GE Discovery MR-750, 3.0 T	SPGR	NA	FSL	Custom	Optimized VBM	Yes	3 mm	Age, gender	$p < 0.05$ FWE corrected
Buijink et al. (2016) [28]	Philips Intera, 3.0 T	TFE	1.0 × 1.0 × 1.0	SPM8	MNI, SUIT	DARTEL VBM8	Yes	8 mm and 4 mm[b]	TIV, age	$p < 0.05$ FWE corrected
Fang et al. (2016) [29]	GE Signa Hdxt, 3.0 T	NA	NA	DPARSFA	MNI	VBM	Yes[c]	4 mm	NA	$p < 0.05$ FDR corrected
Archer et al. (2018) [30]	Philips Achieva, 3.0 T	NA	1.0 × 1.0 × 1.0	SPM8	MNI, SUIT	DARTEL VBM8	No	8 mm and 4 mm[c]	NA	$p < 0.05$ FWER corrected
Cameron et al. (2018) [15]	Siemens Tim Trio, 3.0 T	MPRAGE	1.0 × 1.0 × 1.2	SPM12	ICBM 2009a atlas	TPMs	Yes	4 mm	TIV, age, gender, MoCA score	$p < 0.05$ FWE corrected
Cao et al. (2018) [23]	GE Signa HDxt, 3.0 T	Fast SPGR	1.0 × 1.0 × 1.0	FSL	Custom	VBM	Yes	NA	NA	$p < 0.005$ uncorrected

VBM, voxel-based morphometry; *MR*, magnetic resonance; *FWHM*, full width half maximum; *TFE*, turbo field echo; *SPM*, statistical parametric mapping; *NA*, not available; *SPGR*, spoiled gradient-recalled; *TIV*, total intracranial volume; *GM*, gray matter; *IR-FGE*, inversion-recovery fast gradient echo; *FLASH*, fast low angle shot; *MPRAGE*, magnetization prepared rapid gradient echo; *DPARSFA*, data processing assistant for resting-state fMRI advanced edition; *FSL*, functional MRI of the brain software libraries package; *DARTEL*, diffeomorphic anatomical registration through an exponentiated lie algebra; *SUIT*, spatially unbiased infratentorial template; *ICBM*, international consortium for brain mapping; *TPMs*, tissue probability maps; *MoCA*, Montreal Cognitive Assessment; *FWER*, family-wise error rate; *FWE*, family-wise error; *FDR*, false discovery rate. [a] Lin et al. (2013) reported both traditional VBM and DARTEL VBM results, the latter were included; [b] 8 mm for the cortex and 4 mm for the cerebellum; [c] Fang et al. (2016) reported both modulated and un-modulated VBM results, the former were included

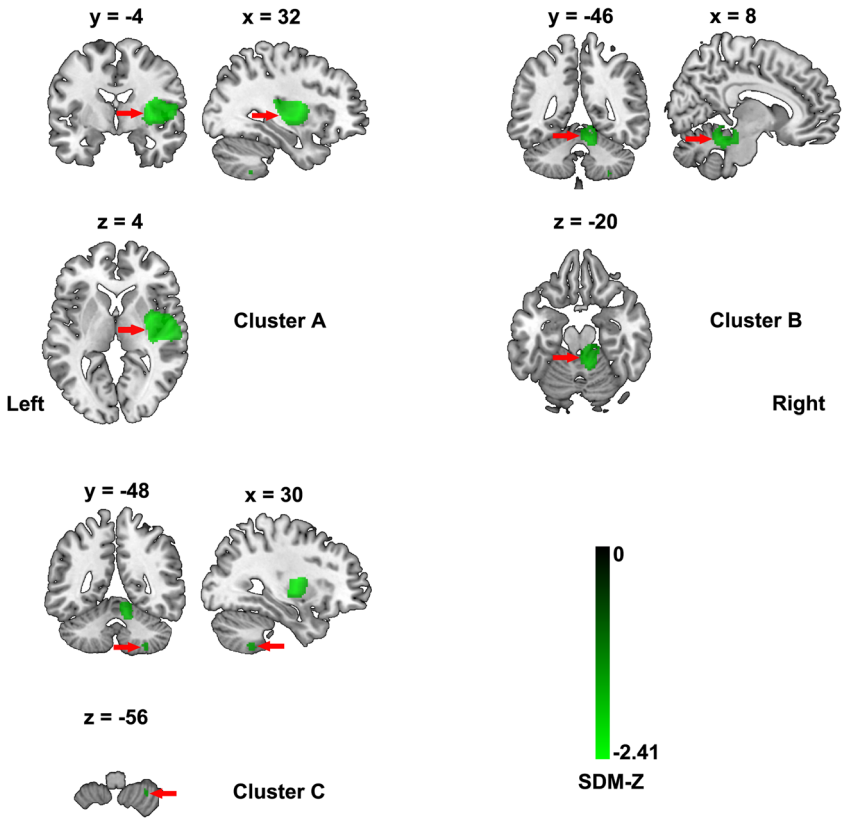

Fig. 2 Regions showing reduced gray matter in patients with ET compared with healthy controls in the pooled meta-analysis of VBM studies. SDM, Seed-based *d* Mapping; ET, essential tremor; VBM, voxel-based morphometry. Cluster A: Right putamen/Rolandic operculum/insula/superior temporal gyrus/Heschl gyrus (BAs 48 and 22); Cluster B: Right cerebellum, hemispheric lobules III and IV/V /vermic lobule III; Cluster C: Right cerebellum, hemispheric lobule VIII

analyses revealed that the three clusters survived 15, 14, and 13 out of 16 iterations, respectively (Table 3). Non-significant Egger's tests ($p > 0.05$) indicated no presence of publication biases in the three clusters reported in the main meta-analysis (Table 2).

Subgroup meta-analysis

When the meta-analysis was restricted to studies that applied 3.0T MRI scanners (14 studies), the results showed GM increase in the left inferior frontal gyrus and decrease in the right putamen extending to the Rolandic operculum, insula, Heschl gyrus and superior temporal gyrus, right cerebellum (hemispheric lobule VIII), and bilateral medial superior frontal gyri in patients with ET relative to healthy controls. The heterogeneity analysis showed significant statistical heterogeneity between studies in all above-reported clusters and the bilateral medial superior frontal gyri with GM abnormalities (Table 2). The jackknife sensitivity analyses revealed that the four clusters survived 12, 12, 11, and 12 out of 14 iterations, respectively (Table 2). Egger's tests revealed a publication bias in the left inferior frontal gyrus with GM increase ($p < 0.05$). The other three clusters with GM abnormalities did not show publication biases revealed by the non-significant Egger's tests ($p > 0.05$) (Table 2).

When the meta-analysis was restricted to studies that used a modulation step in the VBM analysis, patients with ET relative to healthy controls showed GM increase in the left inferior frontal gyrus and decrease in the right putamen extending to the Rolandic operculum, insula, superior temporal gyrus and Heschl gyrus, right cerebellum (hemispheric lobules IV/V and III and vermic lobules IV/V and III), and right medial superior frontal gyrus. All above-reported clusters but the right medial superior frontal gyrus with GM abnormalities demonstrated significant statistical heterogeneity between studies (Table 2). The jackknife sensitivity analyses revealed that the four clusters survived 10, 12, 11, and 10 out of 12 iterations, respectively (Table 2). Egger's tests revealed a publication bias in the left inferior frontal gyrus with GM increase ($p < 0.05$). The other three clusters with GM abnormalities did not show publication biases (Table 3).

When the meta-analysis was restricted to studies that used corrected thresholds in the VBM statistics (11 studies), the results showed GM decrease in the right superior temporal gyrus extending to the Rolandic operculum, insula, Heschl gyrus, bilateral medial superior frontal gyri, and left cerebellum (hemispheric lobules VIII and IX) patients with ET relative to healthy controls (Table 3). The heterogeneity analysis showed significant statistical heterogeneity between studies in all above-reported clusters with GM abnormalities (Table 3). The jackknife sensitivity analyses revealed that the three clusters survived 10, 10, and 9 out of 11 iterations, respectively (Table 3). Egger's tests ($p > 0.05$) revealed no publication biases in the three clusters reported (Table 3).

Table 3 Clusters of regional gray matter reduction in patients with essential tremor relative to healthy controls

Anatomical regions	Peak MNI coordinate	Voxels	SDM-Z	*p* (SDM)	Heterogeneity	Sensitivity analysis	*p* (Egger's test)
Meta-analysis of all included studies (*N* = 16)							
Right putamen/Rolandic operculum/insula/superior temporal gyrus/Heschl gyrus (BAs 48 and 22)	32, − 4, 4	2797	− 2.41	0.000012	Yes	15 out of 16	0.35
Right cerebellum, hemispheric lobules III and IV/V/vermic lobule III	8, − 46, − 20	548	− 1.98	0.00034	Yes	14 out of 16	0.58
Right cerebellum, hemispheric lobule VIII	30, − 48, − 56	41	− 1.54	0.0038	Yes	13 out of 16	0.098
Subgroup meta-analysis of studies using 3.0T MRI scanners (*N* = 14)							
Left inferior frontal gyrus (BAs 45 and 48)	− 44, 20, 18	1115	1.10	0.000013	Yes	12 out of 14	0.0020
Right putamen/Rolandic operculum/insula/Heschl gyrus/ superior temporal gyrus (BAs 48 and 22)	32, − 12, 6	1768	− 1.79	0.00056	Yes	12 out of 14	0.97
Right cerebellum, hemispheric lobule VIII	30, − 48, − 56	311	− 1.63	0.0016	Yes	11 out of 14	0.15
Right/left medial superior frontal gyri (BA 10)	6, 60, 16	102	− 1.64	0.0019	No	12 out of 14	0.14
Subgroup meta-analysis of studies using modulated VBM methods (*N* = 12)							
Left inferior frontal gyrus (BAs 45 and 48)	− 44, 20, 18	1145	1.19	0.0000054	Yes	10 out of 12	0.005
Right putamen/Rolandic operculum/insula/superior temporal gyrus/Heschl gyrus (BAs 48 and 22)	32, − 4, 0	1768	− 2.54	0.0000091	Yes	12 out of 12	0.64
Right cerebellum, hemispheric lobules IV/V and III/vermic lobules IV/V and III	8, − 42, − 24	566	− 2.22	0.00010	Yes	11 out of 12	0.90
Right medial superior frontal gyri (BA 10)	8, 62, 16	12	− 1.64	0.0030	No	10 out of 12	0.58
Subgroup meta-analysis of studies using corrected thresholds (*N* = 11)							
Right superior temporal gyrus/Rolandic operculum/insula/ Heschl gyrus (BAs 48 and 22)	60, − 26, 16	310	− 1.23	0.0024	Yes	10 out of 11	0.32
Right/left medial superior frontal gyri (BA 10)	2, 40, 34	188	− 1.23	0.0024	Yes	10 out of 11	0.32
Left cerebellum, hemispheric lobules VIII and IX	− 20, − 42, − 50	66	− 1.30	0.0018	Yes	9 out of 11	0.17

MNI, Montreal Neurological Institute; *SDM*, Seed-based *d* Mapping; *n*, number of studies; *BA*, Brodmann area; *MRI*, magnetic resonance imaging; *VBM*, voxel-based morphometry

Meta-regression analyses

Meta-regression analyses suggested that the ET sample with an older mean age had more prominent GM increase in the right cerebellum (hemispheric lobule VIII) and GM decrease in the right Rolandic operculum extending to the insula, superior temporal gyrus, Heschl gyrus, and putamen than the sample with a younger mean age. The patient sample with an older

Table 4 Regions with heterogeneity of gray matter changes among all included studies

Anatomical regions	Peak MNI coordinate	Voxels	*Z*	*p*
Right insula/Rolandic operculum/Heschl gyrus/superior temporal gyrus/putamen (BAs 48 and 22)	40, − 16, 14	1004	3.59	0.0000026
Left cerebellum, hemispheric lobule VIII	− 10, − 56, − 38	385	1.80	0.00078
Right cerebellum, hemispheric lobules IV/V and III/vermic lobule III	10, − 38, − 14	140	2.04	0.00041
Right cerebellum, hemispheric lobule VIII	26, − 50, − 48	105	1.55	0.0015
Left inferior frontal gyrus, triangular part (BA 48)	− 44, 20, 18	69	1.72	0.00099
Right hippocampus (BAs 27 and 37)	24, − 34, 2	57	2.03	0.00043
Right inferior frontal gyrus, triangular part (BA 48)	38, 16, 22	20	1.38	0.0021
Cerebellum, vermic lobule IX	8, − 56, − 34	17	1.40	0.0020
Right supplementary motor area (BA 6)	10, 2, 52	13	1.45	0.0018

MNI, Montreal Neurological Institute; *SDM*, Seed-based *d* Mapping; *BA*, Brodmann area

mean onset age tended to exhibited more GM atrophy in the right insula extending to the Rolandic operculum, putamen, Heschl gyrus and superior temporal gyrus, and right supplementary motor area than the patient sample with a younger mean onset age. More percent of male patients in the ET sample tended to show more GM decrease in the right cerebellum (hemispheric lobule VIII). A longer illness duration in the ET sample was associated with more GM increase in right cerebellum (hemispheric lobule VIII), and more GM decrease in the right Rolandic operculum extending to the superior temporal gyrus. A higher mean total FTM-TRS score in the ET sample showed more GM increase in the bilateral supplementary motor areas and more GM decrease in the left cerebellum (hemispheric lobules VIII and IX). Meta-regression analysis also revealed that more percent of patients with a positive family history in the ET sample showed more pronounced GM decrease in the right insula, extending to the putamen, Rolandic operculum, and Heschl gyrus and right cerebellum (hemispheric lobules IV/V and III/vermic lobule III). The results of these meta-regression analyses are summarized in Table 5. There were too few studies (less than 10 studies reported) to explore the potential effect of head tremor on GM changes in the ET sample.

Discussion

In this study, we conducted a quantitative coordinate-based meta-analysis of 16 VBM studies, comprehensively complemented by jackknife sensitivity, heterogeneity, publication bias, subgroup, and meta-regression analyses in order to identify the most reproducible and robust GM changes in ET. Although the main meta-analysis identified GM decrease in the right putamen extending to the Rolandic operculum, insula, superior temporal gyrus and Heschl gyrus, and right cerebellum (hemispheric lobules IV/V and III, vermic lobule III, and hemispheric lobule VIII) in patients with ET relative to healthy controls, the following complementary analyses suggested that such findings were not sufficiently robust and reliable.

The lack of reliable brain GM alterations in ET may reflect the current evidence that ET is a condition with significant clinical, etiological, and pathological heterogeneity. Clinically, ET was classically viewed a movement disorder characterized by bilateral upper limb postural or kinetic tremor; however, it is emergingly recognized that it is not a single disease but a more complex and heterogeneous clinical entity. The presence of other motor features (intentional tremor, resting tremor, gait ataxia, postural instability, and eye-motion

Table 5 Meta-regression analyses

Confounder	Anatomical regions	Peak MNI coordinate	Voxels	SDM-Z	*p*
Age	Gray matter changes in older patient samples compared with younger patient samples ($N = 16$)				
	Right cerebellum (hemispheric lobule VIII)	32, − 52, − 56	242	2.13	0.000042
	Right Rolandic operculum/insula/superior temporal gyrus/Heschl gyrus/-putamen (BAs 48 and 22)	56, − 20, 14	1670	− 3.03	0.00000054
Age at onset	Gray matter changes in patient samples with older mean age at onset compared to patient samples with younger mean age at onset ($N = 16$)				
	Right insula/Rolandic operculum/putamen/Heschl gyrus/superior temporal gyrus (BAs 48 and 22)	32, − 4, 14	1085	− 2.01	0.000028
	Right supplementary motor area (BA 6)	10, 2, 52	39	− 1.94	0.000048
Gender	Gray matter changes in studies with more male patients ($N = 16$)				
	Right cerebellum (hemispheric lobule VIII)	32, − 52, − 56	202	− 2.40	0.000061
Illness duration	Gray matter changes in studies with longer disease durations ($N = 16$)				
	Right cerebellum (hemispheric lobule VIII)	32, − 50, − 56	136	1.06	0.000057
	Right Rolandic operculum/superior temporal gyrus (BAs 48 and 22)	60, − 20, 14	37	− 3.04	0.000054
Total FTM-TRS score	Gray matter changes in studies with higher total FTM-TRS scores ($N = 11$)				
	Right supplementary motor area (BA 6)	10, 2, 54	70	1.35	0.000014
	Left supplementary motor area (BA 6)	− 10, − 2, 60	46	1.24	0.00012
	Left cerebellum (hemispheric lobules VIII and IX)	− 20, − 42, − 50	214	− 2.41	0.000053
Family history	Gray matter changes in studies with more patients with a positive family history ($N = 10$)				
	Right insula/Rolandic operculum/Heschl gyrus (BA 48)	44, − 24, 12	42	− 2.89	0.000028
	Right cerebellum (hemispheric lobules IV/V and III/vermic lobule III)	8, − 42, − 22	35	− 2.94	~0
	Right putamen/insula/Rolandic operculum/Heschl gyrus (BA 48)	32, − 10, 8	25	− 2.89	0.000018

MNI, Montreal Neurological Institute; *SDM*, Seed-based *d* Mapping; *N*, number of comparison experiments; *N*, number of studies reported; *BA*, Brodmann area; *FTM-TRS*, Fahn-Tolosa-Marin Tremor Rating Scale

abnormalities) [49] and non-motor symptoms (cognitive, psychiatric, sensory and autonomic dysfunction, and sleep disturbance) is increasingly evident in ET [50–53]. As ET remains a clinical diagnosis, this heterogeneity can pose diagnostic difficulties. In addition, many limitations of the old diagnostic criteria for ET [33–37], which were utilized in the VBM studies, have been recognized [2]. Variations in the diagnostic criteria may be a potential main confounding factor for the heterogeneity of results. Etiologically, ET was traditionally viewed as a genetic disorder; however, current thinking is that multiple genes in combination with environmental factors likely contribute to its etiology [4, 54]. Heterogeneous pathology in ET has also been revealed by several postmortem studies [55–62]. There is still debate as to whether ET is caused by neurodegeneration or abnormal neuronal oscillation in the cerebello-thalamo-cortical circuit.

Unfortunately, aforementioned heterogeneity has not been deeply explored in the original VBM studies [10]. Some VBM studies demonstrated that the tremor phenomenology [18, 24, 31] and cognitive function [20] were confounding factors on GM alterations in ET. Our meta-regression analyses further indicate that many other moderators, such as age, onset age, gender, illness duration, total FTM-TRS score, family history in the ET samples, significantly contribute to the heterogeneity of GM alterations across the VBM studies. Difference in sample sizes that range from 10 to 50 with a mean of 24.2 ET patients in the current meta-analysis may be another heterogeneity source of GM alterations. Small sample size undermines the reliability of neuroimaging results [63, 64]. Multicenter data sharing to increase sample size and to improve reproducibility is encouraged [65, 66]. Although above analyses of patient characteristics help to explain the heterogeneity observed across studies, they are far from sufficient. Other potential confounding factors, such as neuropsychological characteristics and administered medications, might also contribute to the heterogeneity. Unfortunately, insufficient information reported in the original studies prevents us from systemically examining these moderating effects. Thus, the high heterogeneity in GM alterations across studies might be related to heterogonous ET populations. These discrepancies highlight the need to increase the sample size, address inconsistencies in sample characteristics and comprehensively subtype ET phenotypes in future research.

The heterogeneity in imaging acquisition, preprocessing, postprocessing, and statistical methods used in VBM studies might be another of the potential reasons of inconsistent findings. The studies included in the meta-analysis exhibited many variations in image acquisition conditions, such as MR scanner, filed strength, sequence, and voxel resolution. Our subgroup meta-analysis of studies that applied a 3.0 MRI scanner indicates that MRI-filed strength is a confounding factor of GM heterogeneity. VBM enables the exploration of local GM volume or concentration difference between diagnostic categories [11] but the methods to do this reliably are currently in evolution. The newer the algorithm and more recent the software used (e.g., statistical parametric mapping) is, the more robust the result is [67]. Preprocessing of imaging data is crucial for a VBM analysis, which includes three basic steps: registration, segmentation, and spatial smoothing. We noted variability across studies in the reference template for registration, methods for segmentation, Gaussian kernel for spatial smoothing, and software used in the VBM analyses. In addition, modulation is a necessary step for VBM [67]. Four of the 16 studies performed the VBM analyses without modulation [24–26, 30]. We conducted a subgroup meta-analysis of the studies that used the modulation approach and found that it was a moderator of GM heterogeneity across studies. The choice of covariates is also important for VBM [67]. Of the covariates included in the VBM studies, age and gender are the two most common. Total intracranial volume (TIV) is another important covariate that should be included in the VBM analysis [67]. However, only seven of the 16 VBM studies used TIV as a covariate [14, 15, 18–20, 28, 31]. Some studies did not provide any information about the covariates used [22, 24, 26, 29, 30]. Furthermore, statistical methodology varied among the different studies. Eleven of the 16 studies applied corrected thresholds. In contrast, the remaining five applied uncorrected thresholds. Some studies reported inconsistent results when applying both corrected and uncorrected thresholds [15, 31]. The results of our subgroup meta-analysis of studies that used a corrected threshold were a little different from the results from pooling all the studies. In order to obtain valid results, a correction for multiple comparisons ($p < 0.05$, family-wise error) at the voxel or cluster level with an uncorrected minimum $p < 0.001$ for the voxel threshold has been recommended [67]. Cameron et al. recently utilized improved methodologies to assess brain GM changes in ET with high-resolution atlas and tissue probability maps for segmentation and normalization in the VBM analysis [15]. They demonstrated widespread GM volume loss in ET, beyond the cerebellum. Their study highlighted the need to use an updated and improved atlas in VBM [15]. Thus, different imaging acquisition and VBM analytical protocols may lead to different results. Such protocols should be well-designed and standardized in future studies [67–69].

The results of our meta-analysis are not consistent with those of a recent meta-analysis by Han et al. [70]. Han et al. included a total of 10 VBM studies in their meta-analysis and demonstrated the consistent GM changes in the left precuneus extending to the left posterior cingulate gyrus. Our meta-analysis included 16 VBM studies with more samples, thus increasing the statistical power. The results of a coordinate-based meta-analysis are susceptible to the number of datasets included [71], which contributes to understanding the disparities between the two meta-analyses.

For neuroimaging research, lack of replication of findings across studies was still a major problem. Coordinate-based meta-analysis is helpful to summarize the whole-brain VBM results and offer insights that are not apparent from the

individual studies [72]. However, we should note that our coordinate-based meta-analysis is based on the peak coordinates and their corresponding *t* statistics rather than on raw images or statistical brain maps, which may bias the results. The current meta-analysis did not detect reliable and robust GM changes in ET, but by no means, do we imply that this conclusion is definitive. A more optimal way to obtain valid GM changes in ET is to pool the raw images and clinical data from different studies and re-analyze them with a standardized approach, which should be considered as a high priority. To achieve this goal, it requires scientists to share their original data. The importance of data sharing in the field of neuroimaging research is growingly recognized [66, 73, 74]. Some researchers have developed the open-source database platforms for archiving, analyzing, and sharing of neuroimaging data [73, 75]. Through these database platforms, confirmatory analyses and data aggregation may accelerate progress in understanding the brain structures underpinning ET.

Conclusions

This comprehensive meta-analysis of whole-brain MRI-VBM studies did not identify a robust and reliable pattern of brain GM changes in patients with ET relative to healthy controls. Heterogeneity in GM alterations across studies may reflect the true heterogeneity underlying the clinic, etiology, and pathology of ET or the VBM methodological variations. These inconsistent results hindered the translational value of VBM in capturing ET-related GM structural changes. The establishment of a MRI biomarker of GM structures for ET remains an open challenge [10]. In order to improve reproducibility of VBM results in ET, future research should increase the sample size, address inconsistencies in sample characteristics, comprehensively subtype ET phenotypes, use well-designed and standardized imaging acquisition and analytical protocols, and further consider data sharing as a key priority.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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