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REVIEW

The Contribution of Neuroimaging to the Understanding of Essential Tremor Pathophysiology: a Systematic Review

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Abstract

Essential tremor (ET) is one of the most common movement disorders. Over the last 10 years, magnetic resonance imaging (MRI) has shed light on the structural and functional abnormalities possibly involved in ET pathophysiology. In this systematic review, we aimed to identify the cortical and subcortical structures involved and the role that different brain areas play in the pathophysiology of motor and non-motor ET features. We found that structural (grey and white matter) cerebellar damage and connectivity alterations between the cerebellum and various cortical areas play a role in both motor and non-motor symptoms of ET. In particular, many studies found an association between MRI findings and non-motor symptoms.

Keywords Essential tremor · Magnetic resonance imaging · Grey matter · White matter · MRI functional · Systematic review

Introduction

Essential tremor (ET) is a pathological condition mainly characterized by postural and kinetic tremor that predominantly affects the upper limbs [1–3]. Besides tremor, bradykinesia, dystonia, ataxia, and non-motor symptoms, including cognitive impairment and psychiatric disorders, may be present in ET [3–7]. Experimental studies have demonstrated that ET is characterized by the pathophysiological involvement of several brain structures, including the cerebellum, red nucleus, thalamus, and cerebral cortex, with the cerebello-thalamo-cortical pathway (i.e. the so-called tremor network) playing a major role [1, 8]. Magnetic resonance imaging (MRI) has been used to investigate the structural and functional abnormalities of the central nervous system. Although ET is now considered a network disorder, several issues remain unclear, including the specific role that different brain areas play in the pathophysiology of motor and non-motor symptoms. The reliability of these results also needs to be confirmed. In this article, we aimed to systematically review MRI studies investigating brain structural and functional changes in ET in order to identify the cortical and subcortical structures involved and the role that different areas play in the pathophysiology of motor and non-motor symptoms in this condition.

Methods

According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9], two electronic databases, PubMed and Scopus, were used to perform systematic research using the following keywords: "essential tremor" AND "MRI" OR "diffusion tensor imaging" OR "grey matter" OR "fMRI" OR "functional MRI". No restriction was applied to publication dates. The search was concluded on 28 February 2020. First, we identified all corresponding manuscripts in both databases. Abstracts were examined carefully, and the following exclusion criteria were applied: reviews, case reports, articles written in languages other than English, articles on children, articles including patients with tremor syndromes other than ET, and articles including focus ultrasound MRI and deep brain stimulation in ET. We classified articles as structural or functional MRI (fMRI) studies. We further classified the studies according to whether they investigated white matter (WM) or grey matter (GM).

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In accordance with PRISMA guidelines, we prepared a checklist of 10 questions in order to assess the scientific quality of the studies included in our review and any possible source of bias. A point was assigned to each question according to the quality criteria fulfilled (Table 1). We investigated the scientific quality of the various studies on WM, GM, and fMRI and compared the number of positive answers to the 10 quality questions with the Mann–Whitney *U* test. In order to clarify whether the scientific quality of ET research evolved with time, we performed a Spearman correlation test between year of publication and the number of fulfilled criteria for each category. We considered test results, e.g. group differences and correlations, significant with a p value < 0.05.

Results

We obtained 552 articles from PubMed and 337 from Scopus. According to our exclusion criteria, 322 articles were excluded, and 51 original articles were selected. Neuroimaging studies were divided into 30 structural (13 studies assessing GM, 15 studies assessing WM, 2 studies assessing both GM and WM) and 21 fMRI studies (Fig. 1).

Structural MRI

Grey Matter

We identified a total of 15 structural MRI studies assessing cortical or subcortical GM changes in ET (Table 2). Voxel-based morphometry (VBM) was the most common technique used to examine local volume changes in GM, followed by surface-based morphometry (SBM). A significant proportion of studies (6/15, 40%) consistently reported GM changes in the cerebellum of ET patients. The first study using VBM enrolled a heterogeneous sample of patients with arm tremor alone and with both arm and head tremor [10]. When compared with healthy subjects (HS), ET patients with both arm and head tremor showed the most prominent GM volume reduction in the cerebellar vermis [10]. Similar results were found in another study with SBM, which showed that cerebellar atrophy only occurred in ET patients with head tremor [11]. When patients were divided into two groups on the basis of the presence or absence of cerebellar signs, Shin et al. [12] found that patients who had more cerebellar signs had atrophy of several contiguous segments of the cerebellar vermis. Furthermore, in a cerebellar lobule-by-lobule analysis, ET patients with head tremor had reduced GM density in several cerebellar lobules [13]. Results suggesting cerebellar atrophy in ET patients with head tremor were also confirmed by a study comparing ET patients (divided in patients with and without head tremor), HS, and patients with Parkinson's disease [14]. In contrast to the above studies, 2 out of 15 studies (13.3%) based on VBM [15] and SBM analysis [16] did not find any GM alterations in the cerebellum of ET patients.

Using VBM, GM damage was also found in cortical areas [17–19]. Daniels et al. [17] reported that ET patients with both postural and intention tremors had increased GM volume in the temporoparietal junction bilaterally and the right middle occipital cortex. Benito-Leon et al. [18] found reduced GM volume in the bilateral parietal lobes, right frontal lobe, right insula, and cerebellum. Accordingly, Bagepally et al. [19] described widespread atrophy in bilateral frontal and occipital lobes beside the cerebellum in ET patients. Widespread GM reductions in frontal, parietal, and occipital areas were recently confirmed by two studies using tissue probability mapping and SBM [20, 21].

Cortical GM alterations in the parietal [22, 23], occipital, and insular lobes and cerebellum [22] correlated with cognitive impairment in ET patients. However, these findings were not confirmed by other authors who failed to find a relationship between GM cortical alterations using SBM and cognitive deficits in ET patients [16, 24].

White Matter

A total of 17 studies assessed possible WM alterations in ET patients (Table 2). Using whole-brain tract-based spatial statistics (TBSS), several authors found WM damage in various brain areas, including the cerebellum [16, 25–27]. Shin et al. [25] found WM damage in the anterolateral portion of the pons and cerebellum, as well as in the frontal, parietal, and temporal areas. Klein et al. [26] described WM alterations in the parietal lobes and in the inferior cerebellar peduncles in ET patients. Furthermore, Nestrasil et al. [27]

Table 1 Clinical questions used for study selection

Q1:Were a priori hypotheses clearly stated?
Q2:Was the sample size equal or larger than 30 subjects?
Q3:Were clinical information reported?
Q4:Was ET severity measured?
Q5:Was MRI acquisition performed on a 3 T?
Q6:Was neuropsychological profile assessed?
Statistical analysis
Q7:Was correction for multiple comparison used?
Q8:Were covariates of no interest included in the analysis?
Results
Q9:Were correlations between imaging outcomes and clinical scores investigated?
Q10:Were limitations of the study clearly stated?
Yes = 1
No = 0

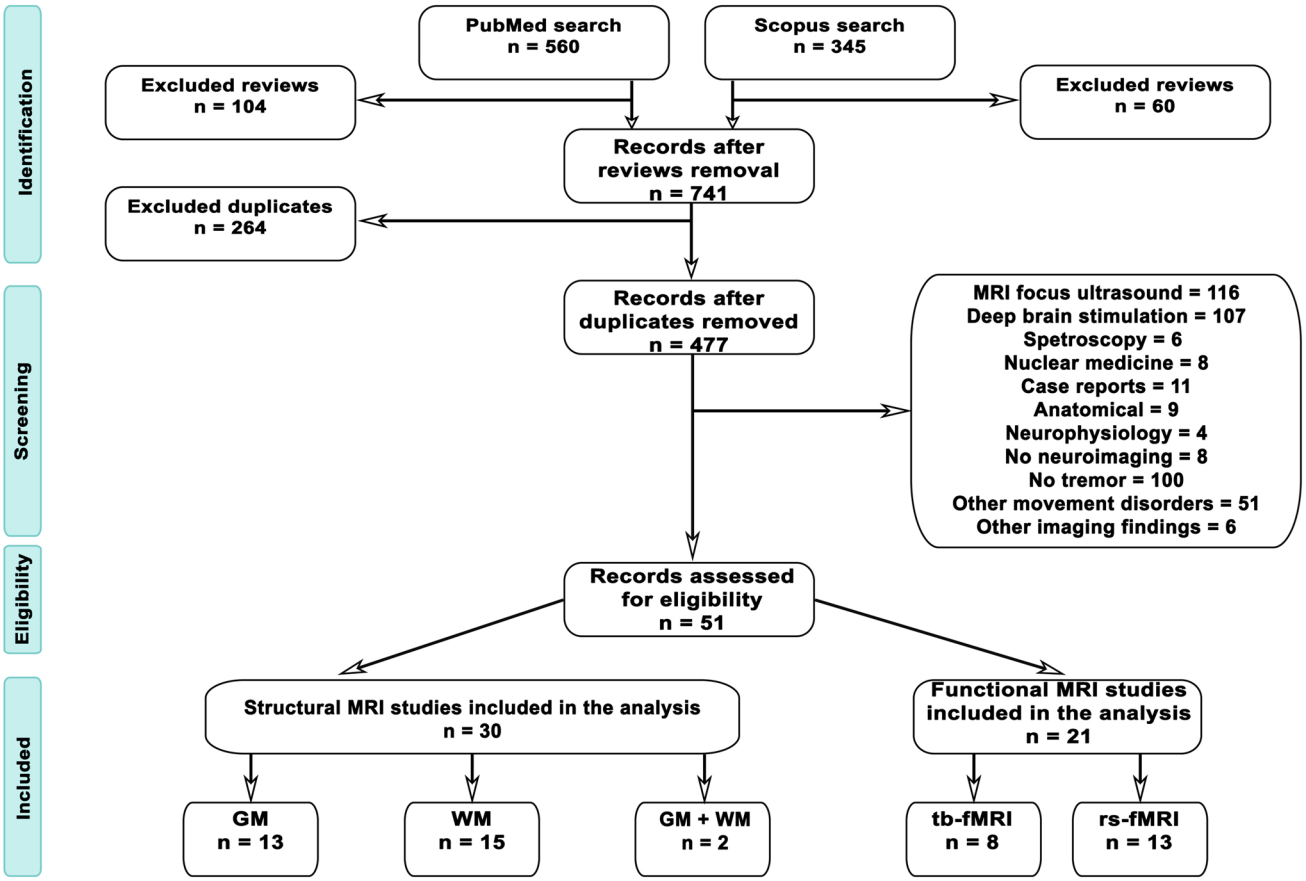

Fig. 1 Flow chart of the procedure used to identify and select studies for the systematic review. GM, grey matter; WM, white matter; fMRI, functional magnetic resonance imaging

described widespread WM abnormalities in both motor and associative tracts involving the bilateral corticospinal tracts, superior longitudinal fasciculi, corpus callosum, fronto-occipital and longitudinal fasciculi, anterior thalamic radiations, and uncinate fasciculi. A correlation between WM changes and clinical motor scores was not present, although the authors did not specifically test possible relationships with non-motor symptoms [27]. More recently, Pietracupa et al. [16] reported similar results, i.e. WM microstructure abnormalities involving the corticospinal tract, cerebellar peduncles, corpus callosum, and several associative WM bundles. Finally, using region of interest (ROI) analysis, Jia et al. [28] measured the apparent diffusion coefficient (ADC) in the basal ganglia, thalamus, red nucleus, and substantia nigra and found ADC abnormalities in the red nucleus alone.

Some authors investigated ET patients who mainly had rest tremor [29, 30]. One study described WM alterations of the cerebellum in ET patients with and without rest tremor and found a lesser degree of damage in those with rest tremor, thus suggesting that cerebellar damage is less evident in ET patients with rest tremor compared to those with postural tremor alone [29]. Conversely, Caligiuri et al. [30] used probabilistic tractography to demonstrate decreased connectivity in the cerebello-thalamo-cortical circuit in postural tremor patients with and without rest tremor. The authors found that only ET patients with rest tremor had decreased connectivity in structures other than the so-called tremor network, such as the globus pallidus, caudate nucleus, and supplementary motor areas [30]. Interestingly, when compared with patients with PD or parkinsonism, ET patients had a greater involvement of the dentate nucleus, cerebellar peduncles, and thalamo-cortical visual pathway [31, 32], but no differences in diffusion tensor imaging (DTI) measures in the substantia nigra [33].

The possible correlation between WM abnormalities and cognitive profile was also investigated [24, 34–36]. Bhalsing et al. [34] found that ET patients with cognitive impairment had significant WM abnormalities in the bilateral frontoparietal regions and in the cingulum, inferior and superior longitudinal and uncinate fasciculi, anterior thalamic radiations, and posterior lobe of the cerebellum. These abnormalities significantly correlated with executive and visuospatial functions and visual-verbal memory abilities.

Table 2 Structural studies

#	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
1	Daniels et al., 2006	27 ET (14 ET patients only postural tremor and 13 patients with additional intentional tremor) 27 HS	ET: 57.9 ± 12.2 HS: 57.5 ± 10.8	1.5 T	GM volume	VBM	↑ GM bilaterally in the region of the temporoparietal junction and the right middle occipital cortex in ET patients with intention tremor	Not performed
2	Quattrone et al., 2008	50 ET (30 h-ET and 20 both a-ET and h-ET) 32 HS	ET: 65.2 ± 4.3 HS: 66.2 ± 8.2	1.5 T	GM volume	VBM ROI analysis of the cerebellum	↓ Vermal GM volume in h-ET patients ROI analysis of the cerebellum: ↓ Total cerebellar volume in h-ET patients ↓ Vermal GM volume in h-ET patients	No correlations
3	Benito-Leon et al., 2009	19 ET 20 HS	ET: 69.8 ± 9.4 HS: 68.9 ± 10.0	1.5 T	GM volume	VBM	↓ GM volume in the bilateral cerebellum and bilateral parietal lobes, right frontal lobe, and right insula WM changes in the right cerebellum, left medulla, right parietal lobe, and right limbic lobe	Between WM in the left medulla and right parietal lobe ($r = -0.60$, $p < 0.01$) and age of tremor onset
4	Cerasa et al., 2009	46 ET (27 both a-ET and h-ET and 19 h-ET) 28 HS	ET: 67.3 ± 11.3 HS: 66.5 ± 7.8	1.5 T	GM volume	VBM	↓ Total cerebellar volume in h-ET patients	No correlations
5	Bagepally et al., 2012	20 ET 17 HS	ET: 38.2 ± 16.5 HS: 40.7 ± 16.5	3 T	GM volume	VBM	↓ GM volume in the cerebellar hemispheres, vermis, bilateral frontal, occipital lobes, left middle temporal gyrus, and right superior parietal lobule ↓ GM volume in bilateral temporal, bilateral frontal, and right parietal lobes in the subgroup comparison between ET patients with and without head tremor	Between GM atrophy in the frontal, temporal, parietal cortices, thalamus, caudate nucleus, and tremor severity

Table 2 (continued)

#	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
6	Bhalsing et al., 2014	25 ET 25 HS	ET: 45.0 ± 10.7 HS: 45.4 ± 10.7	3 T	GM volume	VBM	↓ GM was observed in ET patients with cognitive impairment in and medial frontal gyrus compared to HS ↓ GM in ET patients with cognitive impairment in the medial frontal gyrus, post central gyrus, anterior cingulate, and insula compared to Et patients without cognitive impairment	Between GM of the medial frontal gyrus, superior parietal lobe, middle temporal gyrus, occipital lobe, lentiform nucleus, insular and cingulate cortices, and cerebellum posterior lobe and scores obtained at neuropsychological evaluation
7	Choi et al., 2015	45 ET (19 with h-ET and 26 without) 45 PD 45 HS	ET: 65.9 ± 6.8 PD: 67.5 ± 7.7 HS: 67.6 ± 7.4	1.5 T	GM volume	SBM	↓ Cerebellar volume in h-ET patients vs HS and PD	No correlations
8	Shin et al., 2015	39 ET (20 with cerebellar signs and 19 without) 36 HS	ET: 63.7 ± 13 HS: 65.3 ± 6.8	3 T	GM volume	SBM	↓ GM volume of several contiguous areas of the cerebellar vermis in ET patients vs HS and more evident in ET patients with cerebellar signs vs ET patients without cerebellar signs	Not performed
9	Buijink et al., 2016	Study 1: 36 ET 30 HS Study 2: 8 FCMTE 9 HS Study 3: 45 ET 8 FCMTE 39 HS	Study 1: ET: 54 ± 15 HS: 56 ± 14 Study 2: ET: 50 ± 18 HS: 43 ± 12 FCMTE: 41 ± 13 Study 3: Not given	3 T	GM volume	SUIT DARTEL	FCMTE showed GM atrophy in the cerebellum in hereditary but not ET	Not performed

Table 2 (continued)

#	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
10	Cameron et al., 2017	47 ET 36 HS	Not given	3 T	GM volume	High-resolution tissue probability maps	↓ GM volume in ET and in ET subgroups in the posterior insula, superior temporal gyri, cingulate cortex, inferior frontal gyri, occipital and parietal regions	Not performed
11	Dyke et al., 2017	47 ET 36 HS	ET: 76.0 ± 6.8 HS: 73.2 ± 6.7	3 T	GM volume	SBM	↓ Cerebellar volume in the vermis and several cerebellar lobules	Not performed
12	Pelzer et al., 2017	19 ET 23 HS	ET: 49.47 ± 3.51 HS: 50.93 ± 3.33	3 T	GM volume WM changes	VBM TBSS	↓ GM volume in the right precuneus WM damage in the frontoparietal-regions and the corpus callosum	Between WM alterations in the frontoparietal regions and tremor severity Between WM alterations in the corpus callosum and verbal fluency
13	Serrano et al., 2017	18 ET 18 HS	ET: 63.7 ± 10.5 HS: 63.3 ± 12.0	3 T	GM volume	SBM	↓ cortical thickness in the right inferior parietal and right fusiform areas	No correlations
14	Benito-Leon et al., 2019	13 ET 17 HS	ET: 67.8 ± 7.3 HS: 64.1 ± 11.9	3 T	Cortical thickness	SBM	↓ Cth in the left medial orbitofrontal cortex, left isthmus of the cingulate gyrus, right paracentral lobule, right lingual gyrus, left supramarginal gyrus, right isthmus of the cingulate gyrus, left thalamus, and left amygdala	Between FTM-TRS score and the left medial orbitofrontal cortex roughness Between disease onset and left amygdala volume Between age and the left isthmus of the cingulate gyrus thickness
15	Pietracupa et al., 2019	19 ET 15 HS	ET: 67.0 ± 7.80 HS: 63.0 ± 9.0	3 T	GM volume WM changes	VBM SBM TBSS	↓ Thalamic volume WM abnormalities were detected in most hemisphere bundles	Between ↓ thalamic volume and MoCA scores Between several WM bundles and FTM-TRS, MoCA, and BDI

Table 2 (continued)

16	Shin et al., 2008	10 ET 8 HS	ET: 52.8 ± 11.5 HS: 51.3 ± 11.1	1.5 T	WM changes		↓ FA in the anterolateral portion of the right pons, in the bilateral cerebellum and in the frontal frontal, parietal, and temporal areas	Not performed
17	Jia et al., 2010	15 ET 15 HS	ET: 65.0 ± 11.4 HS: 62.0 ± 7.6	3 T	WM changes	Fibre-tracking method	↑ ADC values in the RN of ET patients	Between ADC value of the red nucleus and tremor severity
18	Nicoletti et al., 2010	25 ET 15 PD 15 HS	ET: 62.96 ± 9.5 PD: 64.60 ± 6.3 HS: 62.47 ± 5.4	1.5 T	WM changes ROI analysis of the DN, RN, SCP, MCP and ventrolateral thalamus	DTIFIT	↓ FA values in the DN of ET patients compared with PD and HS ↓ FA and ↑ MD in patients with ET in the SCP compared with patients with PD and HS	Between ↓ FA values and disease duration in ET patients with longer disease duration
19	Klein et a, 2011	14 ET 20 HS	ET: 61.2 ± 12.0 HS: 60.2 8.1	3 T	WM changes	TBSS ROI analysis of the SCP, MCP e ICP	↑ MD in the frontal and parietal areas of ET patients ↑ MD and ↓ FA in the ICP of ET patients	Between ↑ MD in the frontal and parietal areas and FTM-TRS
20	Prodohel et al., 2014	15 PD 14 MSA 12 PSP 14 ET 17 HS	ET: 61.6 ± 11.0 MSA: 64.3 ± 8.9 PSP: 70.7 ± 5.6 PD: 62.7 ± 7.7 HS: 62.9 ± 9.03 T	3 T	WM changes	ROI analysis of the basal ganglia, DN, RN, SCP, MCP e ICP	DTI measures distinguished PD from ET using DTI measures from the caudate and SN with a sensitivity = 92 and a specificity = 87%	Not performed

Table 2 (continued)

21	Bhalsing et al., 2015	55 ET (35 ET patients with cognitive impairment and 20 without) 55 HS	ET: 45.6 ± 11.7 HS: 46.2 ± 11.4	3 T	WM changes	TBSS	In ET patients with cognitive impairment compared to HS: ↑ MD in the right cingulum and left precuneus ↑ RD in the right medial frontal white matter and left cingulum ↑ AD in the right cingulum and left medial frontal white matter	Between executive function and DTI measures of the frontal white matter, cingulum, inferior superior longitudinal and uncinate fasciculi, anterior thalamic radiations, and posterior lobe of the cerebellum Between visuospatial function and alterations in the right parieto-occipital lobe Between visual-verbal memories and anterior thalamic radiations, inferior longitudinal and uncinate fasciculi, and the posterior lobe of the cerebellum
22	Novellino et al., 2016	67 ET (29 with tremor at rest and 38 without tremor at rest) 39 HS	ET: 65.64 ± 10.4 HS: 64.56 ± 9.4	3 T	Cerebellar WM changes	FDT	↑ MD in the cerebellum of ET patients when compared to HS ↑ MD in the cerebellum of ET patients without tremor at rest subgroup when compared to HS	Between FTM-TRS and MD of cerebellar GM in ET without resting tremor group
23	Caligiuri et al., 2017	49 ET 25 HS	ET: 64.7 ± 10.9 ET (tremor at rest): 63.7 ± 13.5 HS: 65.1 ± 6.7	3 T	WM connectivity	Probabilistic tractography of the cerebello-thalamo-cortical network	↓ Connectivity in the cerebello-thalamo-precentral cortex network bilaterally in ET patients compared to HS ↓ Connectivity in a pathway connecting globus pallidus, caudate, and supplementary motor area, compared to ET and HS	No correlations

Table 2 (continued)

24	Benito-Leon et al., 2017	23 ET 23 HS	ET: 63.3 ± 13.4 HS: 61.1 ± 13.1	3 T	WM changes	TBSS	↑ MD and ↑ AD in the bilateral posterior corona radiata, bilateral superior longitudinal fasciculus, bilateral fornix (cres)/stria terminalis, genu and splenium of the corpus callosum, bilateral anterior and posterior limbs of internal capsule, bilateral retrolenticular region part of internal capsule, and left posterior thalamic radiation	Between DTI measures and language, verbal memory, and visuospatial ability
25	Nestrasil et al., 2018	12 ET 10 HS	45.5 ± 17.5 46.6 ± 14.8	3 T	WM changes	TBSS	↑ MD and ↑ RD in the bilateral corticospinal tracts, the superior longitudinal fascicles, the corpus callosum, the inferior fronto-occipital and longitudinal fascicles, cingulum bundles, anterior thalamic radiations, and uncinate fascicles	No correlations
26	Juttukonda et al., 2019	57 ET 99 PD	ET: 67.5 ± 6.1 PD: 63.4 ± 8.4	3 T	WM changes	FMRIB	↓ FA lateral geniculate body, sagittal stratum, forceps major, pontine crossing tract, and retrolenticular internal capsule in ET patients when compared to PD ↑ RD in the SCP, MCPand ICP of ET patients when compared to HS	

Table 2 (continued)

27	Sengul et al., 2019	62 ET	ET: 46.0 ± 20.4	1.5 T	WM changes	TBSS	Depressed ET patients vs. non-depressed ET patients ↓ FA in left amygdala ↑ RD in left amygdala Anxious patients vs. non-anxious ET patients ↓ FA Left ventrolateral prefrontal cortex and left precuneus	Between BDI scores and FA and RD values in the amygdala Between BAI scores and FA values in the left VLPFC and left precuneus
28	Novellino et al., 2020	60 ET 50 HS	ET: 67.1 ± 7.84 HS: 67.5 ± 6.14	3 T	WM changes	DTI analysis of the hippocampus	↑ MD values in the hippocampus	Between ↑ MD values and memory scores in ET
29	Tantik Pak et al., 2020	40 ET divided in three groups G1: patients with no alexithymia G2: patients with probable alexithymia G3: patients with definite alexithymia	ET: 53.05 ± 19.74	3 T	WM changes	DTI analysis of 32 ROIs	Left orbitofrontal cortex, left anterior cingulate cortex, left amygdala, left insula and right cuneus	DTI alterations correlated with alexithymia severity
30	Sengul et al., 2020	35 ET	ET: 57.5 ± 16.7	3 T	WM changes	DTI analysis of 18 ROIs	Not given	Attention, visuospatial functions, executive function, verbal memory, visual memory, and language correlated with DTI measures

In a subsequent study in ET patients, Benito-Leon et al. [35] described damage to similar regions that significantly correlated with verbal memory and visuospatial ability. In this study, however, patients with ET showed worse performance in various domains, e.g. attention, executive functions, language, and verbal and visual memory, compared to HS, although neuropsychological examination showed that the global scores were within normal range. More recently, Sengul et al. [36] found altered DTI measures in the prefrontal cortical areas, paralimbic and limbic structures, and WM associative bundles, which correlated with various cognitive domains, e.g. attention, visuospatial and executive function, and verbal memory, in non-demented ET patients. In this study, comparison of cognitive scores between patients and HS was not reported, but attention and language were the most affected cognitive functions by duration of tremor and severity of the disease. Correlations between verbal fluency and WM alterations of the corpus callosum were also described by other authors [24]. Interestingly, a recent study demonstrated a correlation between abnormal hippocampus microstructure and cognitive scores in ET patients [37].

WM alterations were also described in ET patients with depression and anxiety. In particular, Sengul et al. [38] described WM alterations in the amygdala related to depressive symptoms and WM abnormalities in the ventro-lateral prefrontal cortex related to anxiety. Pietracupa et al. [16] described a significant association between widespread WM alterations and depression. Finally, a recent study found a relationship between DTI measures and alexithymia [39].

Functional MRI

We selected 21 fMRI studies in ET (Table 3).

A total of 6 studies described several functional alterations during the execution of a motor task in ET patients. Three fMRI studies during a task mimicking postural tremor found functional alterations in cortical areas, the thalamus, and cerebellum in ET patients as compared with HS, suggesting changes in the cerebello-thalamo-cortical circuit [40–42]. Buijink et al. [43] showed a significant correlation between dentate activation during finger tapping and tremor severity, supporting dentate nucleus involvement in ET. Neely et al. [44] described increased brain activity in the motor cortex and supplementary motor area and decreased brain activity in the cerebellum that correlated with force oscillations during a grip force task in ET patients. During a similar task, Archer et al. [45] found functional alterations in the cerebello-thalamo-motor pathway, which also extended to visual and parietal areas and correlated with tremor severity in ET.

Resting-state fMRI (rs-fMRI) studies consistently described functional alterations in the cerebello-thalamo-cortical pathway [46–53], as well as the involvement of default mode, frontoparietal, salience, and visual networks, suggesting a more widespread disruption that also includes non-motor areas [47, 54].

Regarding the cerebello-thalamo-cortical pathway, altered functional connectivity has been described between the cerebellum and cortical frontal areas, including the supplementary motor area, anterior cingulum, and primary motor cortex [50, 55]. Abnormal spontaneous activity in the "tremor network", including the motor-related cortex, basal ganglia, and thalamus, was further confirmed using different methods of rs-fMRI analysis [46, 48, 56].

The role of functional alterations in the tremor circuit was also investigated by using seed-based analysis, which allows functional connectivity of selected brain regions to be investigated. In particular, Fang and colleagues [49] used a seed on the ventral intermediate nucleus (VIM) to demonstrate altered functional connectivity of the thalamic nucleus with the motor cortex and cerebellum. Likewise, Tikoo et al. [52] used a seed on the dentate nucleus to demonstrate functional connectivity alterations between the dentate nucleus and frontal and prefrontal cortices, thalamus, and cerebellar cortex. Accordingly, Nicoletti et al. [57] confirmed altered connectivity of the thalamus and cerebellum with the primary motor cortex, premotor cortex, parietal areas, supplementary motor area, and somatosensory cortex.

When examining the possible correlation between cognitive abilities and fMRI abnormalities, a relationship was suggested by two task-based fMRI studies that explored cognitive function in ET patients [58, 59]. Passamonti et al. [58] found altered functional connectivity between the cerebellum and areas involved in attention and executive functions, such as the dorsolateral prefrontal cortex, inferior parietal lobule, and thalamus, as well as regions related to the default mode network during the performance of a verbal working memory task. Similarly, Cerasa et al. [59] described overactivation of the dorsolateral prefrontal and inferior parietal cortices during the Stroop memory task. Consistent with these results, rs-fMRI studies confirmed the relationship between functional alterations and cognitive performance [47, 54]. In particular, these studies described changes in the default mode, frontoparietal [54], sensorimotor, salience, and cerebellar networks [47] that correlated with Fahn-Tolosa-Marin Tremor Rating Scale motor and cognitive scores. Similarly, a graph theory study on ET patients found widespread functional alterations in several brain areas and the cerebellum, even outside the tremor network, suggesting that overall brain connectivity is disrupted in ET [60]. In particular, the authors described changes in connectivity of the posterior parahippocampal gyri, which was positively correlated with depressive symptoms and negatively with visuospatial functions, and of the right cerebellar flocculus which was negatively correlated with the cognitive domain of attention. The ET patients enrolled in the study did not

Table 3 Functional MRI studies

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
1	Bucher et al., 1997	12 ET 15 HS	ET: 61.1 ± 11.9 HS: 58.2 ± 9.8	1.5 T	Functional activation during a task mimicking postural tremor	WUTSCH	During essential tremor, ET patients showed contralateral activation of the primary motor and primary sensory areas, the globus pallidus, and the thalamus, bilateral activation of the DN, the cerebellar hemispheres, and the RN	No correlations
2	Cerasa et al., 2010	12 ET 12 HS	ET: HS:	1.5 T	Functional activation during a Stroop task	SPM5	↑ Brain response in the dorsolateral prefrontal cortex and in the inferior parietal cortex in ET patients compared to controls	No correlations
3	Passamonti et al., 2011	15 ET 15 HS	ET: 61.6 ± 9.3 HS: 60.4 ± 7.3	3 T	FC during a memory task	ROI analysis of the anterior cingulate cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, insula, superior parietal lobules, inferior parietal lobules, thalamus, caudate, putamen, palladium, and posterior lobes of the cerebellum	↑ Cerebellar response (crus I/lobule VI) compared to HS during attentional-demanding working memory task and altered functional connectivity between crus I/lobule VI and regions dorsolateral prefrontal cortex, inferior parietal lobule, thalamus, precuneus, ventromedial prefrontal cortex, and hippocampus ET patients with low cognitive scores displayed ↓ connectivity between crus I/lobule VI and the dorsolateral prefrontal cortex and ↑ connectivity between crus I/lobule VI and the precuneus	FC between source/seed and precuneus and FAB scores FC between the source/seed and ventrolateral prefrontal cortex and FTM-TRS

Table 3 (continued)

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
4	Fang et al., 2013	20 ET 20 HS	ET: 50.36 ± 14.2 HS: 50.36 ± 14.2	3 T	FC at rest	Regional homogeneity	↓ Regional homogeneity in the anterior and posterior bilateral cerebellar lobes, the bilateral thalamus and the insular lobe of ET patients ↑ Regional homogeneity in the bilateral prefrontal and parietal cortices, the left primary motor cortex, and left supplementary motor area of ET patients	Between the abnormal regional homogeneity values in the bilateral anterior cerebellar lobes and the right posterior cerebellar lobe and tremor severity
5	Broema et al., 2016	21 ET 21 HS	ET: 51.6 ± 17.8 HS: 50.6 ± 16.4	3 T	Functional alterations during a task mimicking tremor		Tremor-related activations bilaterally in the cerebellum in ET patients	Not performed
6	Buijink et al., 2015	40 ET 22 HS	ET: 59.5 HS: 56.5	3 T	Functional alterations during a task mimicking tremor	Effective connectivity: dynamic causal modelling Functional connectivity: seed-based analysis of left M1, left SMA and right cerebellar hemisphere lobules IV, V, VI, and VIII	Effective connectivity analysis: tremor variation during the motor task has an excitatory effect on both the extrinsic connection from cerebellar lobule V to the thalamus, and the intrinsic activity of cerebellar lobule V and thalamus Functional connectivity: ↓ functional connectivity between cortical and cerebellar motor regions	Between functional connectivity between right cerebellar lobules I–IV and the left thalamus and tremor severity Between ↓ functional connectivity and tremor severity
7	Neely et al., 2015	14 ET 14 PD 14 HS	ET: 61.7 ± 11.0 PD: 64.0 ± 8.7 HS: 60.2 9.2	3 T	Functional alterations during a grip force task	AFNI using by a seed-based analysis of cerebellum, M1, and supplementary motor area	↓ Cerebellar cortical functional connectivity in patients with ET compared with HS and PD	Not performed

Table 3 (continued)

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
8	Benito-Leon et al., 2015	23 ET 22 HS	ET: 63.3 ± 13.4 HS: 60.6 ± 13.2	3 T	FC at rest	ICA	↑ Connectivity in the DMN and frontoparietal network) ↓ Connectivity in the cerebellum and visual network	Between connectivity changes in the DMN and frontoparietal network and ET severity and duration Between changes in the DMN and frontoparietal network and attention, executive function, visuospatial ability, verbal memory, visual memory, language and depressive symptoms Between changes in visual network and visual abilities
9	Buijink et al., 2015	31 ET 29 HS	ET: 55.4 ± 15.8 HS: 52.6 ± 16.1	3 T	Functional alterations during a motor task (finger tapping)	Seed-based analysis of the DN	↓ Activation in widespread cerebellar cortical regions, in the inferior olive nucleus, parietal and frontal cortices, compared to HS	Between DN activation and tremor severity
10	Fang et al., 2015	55 ET 40 HS	ET: 46.8 ± 6 1 HS: 44.4 ± 6.7	3 T	FC at rest	ICA	↑ FC in the sensorimotor and salience networks in ET patients ↓ FC in the salience networks and in the cerebellum network in ET patients ↑ FC between anterior and posterior default mode networks in ET patients ↓ FC between the cerebellum network and the sensorimotor and posterior default mode networks in ET patients	FC changes within and between resting-state networks were correlated with the tremor severity and total cognitive scores of ET patient

Table 3 (continued)

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
11	Gallea et al., 2015	20 ET 20 HS	ET: 50.4 ± 15 HS: 50.1 ± 16.4	3 T	FC at rest	ALFF Effective connectivity analysis used dynamic causal modelling (DCM) VBM	↑ Grey matter in the SMA; ↓ Grey matter in lobule VIII ↓ Amplitude of low-frequency fluctuation of BOLD ↓ Effective connectivity between each supplementary motor area and the ipsilateral primary motor hand area ↑ Probability of connection between supplementary motor area fibres and the spinal cord	Between the lower amplitude of low-frequency fluctuation in the SMA and grey matter loss in the cerebellum
12	Yin et al., 2016	24 ET 23HS	ET: 46.4 ± 14.2 HS: 47.2 ± 12.8	3 T	FC at rest	Amplitudes of low frequency fluctuation (ALFF)	↑ ALFF in the bilateral cerebral cortex including the pre- and post-central gyrus, supplementary motor area and paracentral lobule in ET patients ↓ ALFF in the bilateral cerebellum in ET patients	Between ↑ ALFF value in the right precentral gyrus and disease duration Between ↑ ALFF in the bilateral cerebellum and disease duration
13	Fang et al., 2016	35 ET 29 HS	ET: 47.3 ± 11.3 HS: 43.4 ± 14.4	3 T	FC at rest	Seed-based analysis of VIM FC	ET patients displayed VIM-related FC changes, primarily within the VIM motor cortex cerebellum circuit	Between FC changes and tremor severity
14	Mueller et al., 2017	19 ET 23 HS	ET: 55.5 ± 19.2 HS: 50.9 ± 18.0	3 T	FC at rest	General connectivity Selective connectivity of seeds in the VIM and in the pre-motor and sensorimotor cortices	↑ General connectivity in the primary motor cortex and in the anterior cingulate cortex ↓ General connectivity in the cerebellum	Between general connectivity and tremor severity Between selective connectivity between VIM and basal ganglia and tremor severity

Table 3 (continued)

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
15	Archer et al., 2018	19 ET 18 HS	ET: 65.74 ± 11.5 HS: 63.66 ± 7.5	3 T	Functional alterations during a grip force task	Evaluation of BOLD signals Anatomical isolation of the cerebellum by SUIT	BOLD changes within the cerebello-thalamo-motor cortical pathway, extended to other visual and parietal areas in ET patients	Between BOLD changes and tremor severity
16	Wang et al., 2018	17 ET 17 HS	ET: 46.9 ± 18.5 HS: 46.8 ± 18.6	3 T	FC at rest	FOur-dimensional Consistency of local neural Activities (FOCA) Global functional connectivity intensity (gFCI) and density (gFCD)	↑ FOCA values in the bilateral cuneus, the left lingual gyrus, the left paracentral lobule, the right middle temporal gyrus, the bilateral precentral gyrus, the right postcentral gyrus, the pallidum and putamen in ET patients ↓ FOCA in the frontal gyrus, the bilateral anterior cingulate and the medial dorsal nucleus of right thalamus in ET patients	No correlations
17	Wang et al., 2018	ET: 47 HS: 27	ET: 48 .0 ± 13.3 HS: 45.7 ± 14.1	3 T	FC at rest	ALFF	↑ ALFF value in the bilateral posterior lobe of cerebellum cerebellar vermis, bilateral caudate, right middle temporal gyrus and the inferior parietal lobule in the h-ET patients compared to a-ET and HS	Between ALFF abnormality in the cerebellum and tremor severity Between ALFF abnormality in the left precentral gyrus and age at onset and disease duration
18	Li et al., 2020	24 PD 19 ET 25 HS	ET: 48.32 ± 13.1 PD: 53.13 ± 8.49 HS: 49.12 ± 11.8	3 T	FC at rest	ReHo	↓ ReHo in the default mode network, bilateral putamen, and bilateral cerebellum in ET and PD compared with HS,	Between ReHo abnormalities and UPDRS III

Table 3 (continued)

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
19	Tikoo et al., 2019	25 ET 26 HS	ET: 68.4 ± 9.7 HS: 63.2 ± 10.3	3 T	FC at rest White matter changes	Seed-based analysis of the DN ROI analysis of the WM of the SCP, MCP, and ICP	↓ DN FC with cortical, subcortical, and cerebellar areas in ET patients compared to HS ↓ FA and ↑ MD in the SCP, MCP, and ICP	Between the DN FC in the supplementary motor area, pre and post- central gyri, and prefrontal cortex and FTM-TRS score and disease duration Between DN FC changes in the thalamus and caudate and peak tremor frequency Between DN FC in the associative prefrontal and parietal cortices, basal ganglia, and thalamus and MoCA scores

Table 3 (continued)

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
20	Benito-Leon et al., 2019	23 ET 23 HS	ET: 63.3 ± 13.4 HS: 61.1 ± 13.1	3 T	FC at rest	Graph theory	↑ Global efficiency, cost and degree, and ↓ average path length in the left inferior frontal gyrus (pars opercularis), right inferior temporal gyrus (posterior division and temporooccipital part), right inferior lateral occipital cortex, left paracingulate, bilateral precuneus bilaterally, left lingual gyrus, right hippocampus, left amygdala, nucleus accumbens bilaterally, and left middle temporal gyrus ↑ Local efficiency and clustering coefficient values in frontal medial cortex bilaterally, subcallosal cortex, posterior cingulate cortex, parahippocampal gyri bilaterally, right lingual gyrus, right cerebellar flocculus, right postcentral gyrus, right inferior semilunar lobule of cerebellum and culmen of vermis	Between the six cognitive composites and the depressive symptoms with the graph theory metrics in the medial frontal cortex, parahippocampal gyrus bilaterally, left lingual gyrus, right planum temporale, right pallidum, right hippocampus, right nucleus accumbens, and right cerebellum flocculus

Table 3 (continued)

	Authors (year)	Participants (years)	Age Mean (*sd*)	Magnet	Outcome measure	Data analysis method	Imaging findings	Clinical correlation
21	Nicoletti et al., 2020	23 ET 23 HS	ET: 71.6 ± 10.5 HS: 70.3 ± 5.3	3 T	FC at rest	Seed-based analysis	↓ Connectivity between left M1 seed and right premotor cortex, cerebellum and bilateral premotor, parietal areas and SMA ↑ Increased connectivity between left S1 seed, parietal areas, M1, premotor cortex and SMA and ↓ with cerebellum ↑ Connectivity of SMA seed with premotor cortex and ↓ with parietal and precentral areas ↑ Connectivity between left thalamus seed and cerebellum ↓ Connectivity between right cerebellum seeds and other cerebellar areas, precentral and premotor areas	M1 seed: − correlation with disease duration in bilateral premotor areas and right SMA Thalamus seed: + correlation with TRS and disease duration in the bilateral cerebellum and + correlation with TRS in frontoparietal areas SMA seed: − correlation with TRS and disease duration with precentral gyrus Lobule IV–V seed: − correlation with TRS in other cerebellar areas, left M1, bilateral premotor areas, and right SMA and − correlation with disease duration with left M1 and other cerebellar areas Lobule VI and VIII seeds: − correlation with TRS in other cerebellar areas, left M1 and premotor areas, and − correlation with disease duration in other cerebellar areas

show dementia or mild cognitive impairment even though they performed worst on attention, executive functions, and language.

Quality Assessment

Quality assessment results are shown in Supplementary material. Overall, articles investigating fMRI alterations in ET had a higher scientific quality than structural studies, i.e. studies on GM and WM ($z = 2.36$ and $p < 0.02$). Specifically, fMRI studies fulfilled the quality criteria more than studies on GM, $z = 2.26$ and $p < 0.02$, as displayed in Fig. 2. Overall, the year of publication positively correlated with the research quality of structural studies (rho = 0.59, $p < 0.001$). Articles focusing on GM and WM improved with time (rho = 0.60 and $p < 0.02$, rho = 0.52 and $p < 0.02$, respectively). The percentage of adherence to clinical questions is listed in the Supplementary material.

Discussion

In this systematic review, we examined MRI reports of structural and functional brain changes in ET patients. The main finding suggests possible GM damage in the cerebellum [10, 11, 13, 25]. However, some conflicting results have been obtained [15, 16], which may be explained by differences in the clinical features of the ET patients studied. Widespread WM damage and and cerebello-thalamo-cortical functional alterations were consistent findings in many reports [40–46, 48–53, 55]. Overall, both structural and fMRI studies suggested cerebellar and cerebello-thalamo-cortical circuit damage in ET patients [16, 25–27, 29, 30].

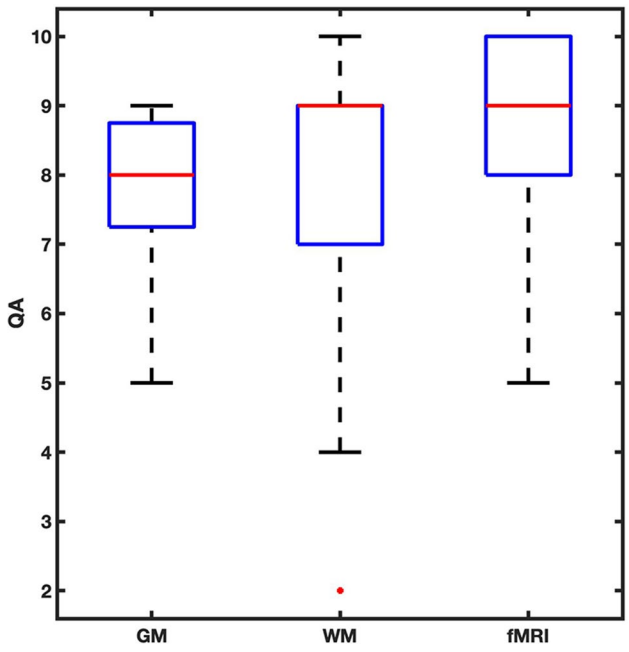

Fig. 2 Box plot showing quality assessment results of the studies included in the review. QA, quality assessment; GM, grey matter; WM, white matter; fMRI, functional magnetic resonance imaging

The Role of Neuroimaging in Understanding the Pathophysiology of Motor Symptoms in ET

The majority of studies found GM damage in the cerebellum in ET. GM alterations have mainly been described in ET patients with head tremor [10, 11, 13] or when cerebellar signs were clinically evident [12]. Reduced GM in the cerebellar vermis and in other contiguous areas [10, 11] may reflect the somatotopic organization of the cerebellum, with head and neck representation located more medially than hand and leg representation. Results supporting the concept that patients with head tremor may represent a distinct ET subtype characterized by prominent cerebellar involvement have been suggested by neurophysiological [6] and post-mortem observations [61]. In keeping with this view, ET patients with head tremor present a lack of propranolol effect, possibly due to the lower affinity of the adrenoreceptor in the cerebellar vermis to beta-blockers [62]. Both GM and WM alterations have also been demonstrated in the cerebellum of ET patients showing arm tremor alone [16, 25, 26, 29, 30]. Accordingly, fMRI studies consistently supported the role of functional abnormalities in the cerebellum and other areas related to the cerebello-thalamo-cortical circuit in ET [40–46, 48–50, 52, 53, 55, 56]. Overall, MRI findings suggest that ET should mainly be considered as a network disorder rather than as an isolated cerebellar dysfunction. This hypothesis is also consistent with neurophysiological observations [63]. For example, it has also been demonstrated that deep brain stimulation of both the ventral intermediate nucleus of the thalamus and the posterior subthalamic area targeting dentato-rubro-thalamic tract fibres is an effective treatment for tremor [64, 65]. In addition, transcranial magnetic stimulation (TMS) studies showed a lack of inhibition and defective plasticity mechanisms at the level of M1 and the cerebellar cortex in ET patients [66]. Thus, neuroimaging and neurophysiological studies underlie the role of functional abnormalities in the cerebello-thalamo-cortical pathway in ET pathophysiology.

Considering the involvement of areas outside the tremor network, several authors described either reduced or increased GM volume in various cortical areas [18–20, 34, 67], providing heterogeneous results. A recent meta-analysis including 10 MRI studies and 241 ET patients [68] concluded that GM volume reduction involves the left precuneus and extends to the left posterior cingulate gyrus. It has been suggested that reduced GM in these structures possibly plays a role in cognitive dysfunction and depression, not in tremor

severity. Conversely, different studies indicate widespread WM damage [16, 25–27], thus suggesting a prominent role of microstructural WM as compared to GM damage in ET pathophysiology. In conclusion, structural alterations in the cerebellum, together with widespread WM microstructural damage, may lead to cerebello-thalamo-cortical pathway dysfunction.

The Role of Neuroimaging in Understanding the Pathophysiology of Non-motor Symptoms in ET

An impairment in several cognitive domains has been described in ET patients [5, 6, 69, 70]. Cognitive impairment in ET patients is heterogeneous and includes deficits in attention, executive functions, verbal fluency, visuospatial functioning, and working memory [5, 6, 69, 70]. Imaging studies indicate a relationship between structural and functional abnormalities and cognitive functions in ET patients [22–24, 34, 35, 47, 54, 58, 60]. Cortical and cerebellar GM loss has been linked to cognitive functions in ET patients with or without global cognitive impairment [22, 23]. Likewise, diffusion MRI studies have confirmed a correlation between widespread WM bundle damage and cognitive abilities in both ET patients with [24] and without cognitive dysfunction [34, 35]. On the other hand, fMRI studies have described a relationship between alterations in several brain networks (default mode, frontoparietal, sensorimotor, and cerebellar networks) and cognitive performance in different domains (executive function, attention, visuospatial ability, verbal memory, visual memory, and language ability), in patients without a global cognitive impairment [47, 54, 58, 60]. Overall, correlations of structural and functional abnormalities with cognitive functions were often described in cognitively unimpaired ET patients who, however, showed a worse performance in selected cognitive domains with respect to healthy subjects [23, 24, 35, 47, 54, 58, 60].

Other studies have suggested abnormal functional connectivity between the cerebellum and cortical areas in patients with unimpaired cognitive performance [52, 59], strengthening the role of cerebello-thalamo-cortical pathway dysfunction in generating motor symptoms and cognitive abnormalities in ET [71]. Indeed, the cerebellum has been found to play a role in regulating cognitive functions [72]. In particular, posterior lobe lesions in the cerebellum result in impairments in executive function, visuospatial processing, linguistic skills, and affect regulation [72]. In keeping with this view, neurophysiological studies suggested that all these neuropsychological changes can be attributed to a relative dysfunction of cortical areas due to a remote effect within the cerebello-thalamo-cortical circuit as a consequence of cerebellar pathology [73].

WM alterations in associative areas [16] and in the amygdala [38] have also been described in ET patients with depressive symptoms. Psychiatric symptoms are thought to reflect the widespread anatomic pathology of ET [74], although the role of tremor disability on mood and personality cannot be excluded. Indeed, Fabbrini et al. [4] found that depression was more frequent in familial cases of ET, suggesting that patients who reported tremor in other family members may be more aware of ET and, consequently, more prone to the development of psychiatric disturbances. Recently, it has also been observed that psychiatric disorders are more common in patients with ET and head tremor, supporting the hypothesis that cerebellar dysfunction could also be an important mechanism underlying psychiatric disorders in ET [6, 75].

Taken together, these findings suggest that functional abnormalities in the connectivity between several cortical areas and the cerebellum, similar to those proposed in motor symptoms, may cause ET-related cognitive and depressive symptoms.

Quality Assessment and Future Directions

Overall, neuroimaging studies investigating brain structural properties of ET patients, especially those investigating GM structure, have shown lower scientific quality with respect to studies using fMRI. We may speculate that the lack of agreement concerning the role of GM damage in ET pathology may arise from the non-rigorous approaches used in the studies included in this survey. However, the quality trend is improving with time even for studies assessing WM and GM. The implementation of combined MRI data/clinical score analysis (i.e. the inclusion of neuropsychological assessment) and improved statistical analysis (i.e. correction for multiple comparisons and inclusion of covariates of no interest) would improve the overall quality of structural MRI studies on ET patients.

Conclusions on ET Pathophysiology

Neuroimaging studies on ET patients have enriched our knowledge of the complex mechanisms underlying ET pathophysiology by showing that structural GM and WM cerebellar damage and connectivity alterations with cortical motor and associative areas play a role in both motor and non-motor symptoms in this condition. The findings strengthen the role of a "network dysfunction" as a pathophysiological substrate of ET.

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and Patrizia Pantano drafted and critically revised the work. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of Interest The authors declare no competing interests.

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