



# Atrophy of cerebellar peduncles in essential tremor: a machine learning–based volumetric analysis

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## Abstract

**Background** Subtle cerebellar signs are frequently observed in essential tremor (ET) and may be associated with cerebellar dysfunction. This study aims to evaluate the macrostructural integrity of the superior, middle, and inferior cerebellar peduncles (SCP, MCP, ICP) and cerebellar gray and white matter (GM, WM) volumes in patients with ET, and compare these volumes between patients with and without cerebellar signs (ETc and ETnc).

**Methods** Forty patients with ET and 37 age- and gender-matched healthy controls were recruited. Atlas-based region-of-interest analysis of the SCP, MCP, and ICP and automated analysis of cerebellar GM and WM volumes were performed. Peduncular volumes were employed in a multi-variate classification framework to attempt discrimination of ET from controls.

**Results** Significant atrophy of bilateral MCP and ICP and bilateral cerebellar GM was observed in ET. Cerebellar signs were present in 20% of subjects with ET. Comparison of peduncular and cerebellar volumes between ETnc and ETc revealed atrophy of right SCP, bilateral MCP and ICP, and left cerebellar WM in ETc. The multi-variate classifier could discriminate between ET and controls with a test accuracy of 86.66%.

**Conclusions** Patients with ET have significant atrophy of cerebellar peduncles, particularly the MCP and ICP. Additional atrophy of the SCP is observed in the ETc group. These abnormalities may contribute to the pathogenesis of cerebellar signs in ET.

## Key Points

- Patients with ET have significant atrophy of bilateral middle and inferior cerebellar peduncles and cerebellar gray matter in comparison with healthy controls.
- Patients of ET with cerebellar signs have significant atrophy of right superior cerebellar peduncle, bilateral middle and inferior cerebellar peduncle, and left cerebellar white matter in comparison with ET without cerebellar signs.
- A multi-variate classifier employing peduncular volumes could discriminate between ET and controls with a test accuracy of 86.66%.

**Keywords** Essential tremor · Middle cerebellar peduncle · Atrophy · Cerebellum · Machine learning

## Abbreviations

AAO	Age at onset	ETnc	Essential tremor without cerebellar signs
DTI	Diffusion tensor imaging	FTMRS	Fahn-Tolosa-Marin tremor rating scale
ET	Essential tremor	GM	Gray matter
ETc	Essential tremor with cerebellar signs	HC	Healthy controls
		ICP	Inferior cerebellar peduncle

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MCP	Middle cerebellar peduncle
MRI	Magnetic resonance imaging
RF	Random forest
ROC	Receiver operating characteristics
ROI	Region of interest
SCP	Superior cerebellar peduncle
SVM	Support vector machine
WM	White matter

## Introduction

Essential tremor (ET) is highly prevalent movement disorder which was classically considered to be a relatively benign disorder with a monosymptomatic course [1, 2]. However, this concept has evolved over time owing to reports of a wide spectrum of motor and non-motor symptoms [3]. Of particular interest is the presence of cerebellar features such as impaired tandem gait and balance, intention tremor, oculomotor abnormalities, and subtle dysarthria [4–8]. These symptoms suggest the possibility of underlying cerebellar or cerebellar pathway dysfunction in ET.

The notion of ET being a neurodegenerative disorder linked with cerebellar dysfunction has been supported by several neuropathological [9, 10] and neuroimaging studies [11–19]. Neuropathological studies in ET have demonstrated degenerative changes in the ET cerebellum involving all Purkinje cell compartments, i.e., dendritic compartment, cell body, and axonal compartment, and changes in basket cell axonal processes and distribution of climbing fiber-Purkinje cell synapses [9]. Neuroimaging studies reveal diffuse structural and functional alterations in several parts of the cerebellum [11, 20]. However, these results are inconsistent across studies and the relationship between these abnormalities and observed cerebellar symptoms persists to be uncertain. This may be attributable to variability in methods of estimation, statistical thresholds, and heterogeneity of subjects with ET.

Previous structural neuroimaging studies using diffusion tensor imaging (DTI) in ET have reported abnormalities in the anisotropy and diffusivity of the cerebellar peduncles, i.e., superior, middle, or inferior cerebellar peduncle [13, 16, 18]. Although these results provide substantial support to the role of the cerebellum in ET pathogenesis, the macrostructural abnormalities of the superior, middle, and inferior cerebellar peduncles in patients with ET have not been examined. Owing to the complex crossing patterns of the cerebellar tracts, diffusion image acquisition protocols utilized in previous studies may not track through such crossings.

This study aims to evaluate the macrostructural volumes of the superior, middle, and inferior cerebellar peduncles and of the cerebellar gray matter (GM) and (WM) in patients with ET, and compare the obtained volumes against healthy controls (HC), and between patients of ET with and without cerebellar signs. The cerebellar peduncles serve as critical conduits for afferent

and efferent connections of the cerebellum, and based on these facts, we hypothesize that abnormalities in these structures, if any, may contribute to the observed cerebellar signs in ET.

## Methodology

### Subject recruitment and clinical evaluation

This study included 40 patients with ET and 37 age- and gender-matched HC (all right-handed). Patients were recruited from the general neurology outpatient clinic and movement disorder services. The diagnosis of ET was based on the consensus statement of the Movement Disorder Society on tremor [21] and confirmed by a trained movement disorder specialist. Demographic details such as gender, age at onset (AAO), age at evaluation, and presence of family history were recorded. Only HC without a family history of ET, parkinsonism, or any other movement disorder were recruited. Tremor of the upper limbs was assessed at rest, with arms outstretched, flexed at the elbow and while performing the finger-nose test. Patients were also evaluated for the presence of head, voice, trunk, and lower limb tremors. Tremor severity was quantified by the Fahn-Tolosa-Marin tremor rating scale (FTMRS) [22]. Cerebellar signs were evaluated by the finger-nose test, knee-heel test, dysdiadochokinesia, and tandem gait. Patients also underwent a detailed neurological examination with special emphasis to rule out parkinsonism and dystonia. We also excluded the presence of thyrotoxicosis, chronic alcohol consumption, and the use of tremorogenic drugs. This study was approved by the institute ethics committee and all subjects provided informed consent prior to recruitment. Some of the subjects included in this study have been part of previous studies from our group [23–26].

### Imaging protocol

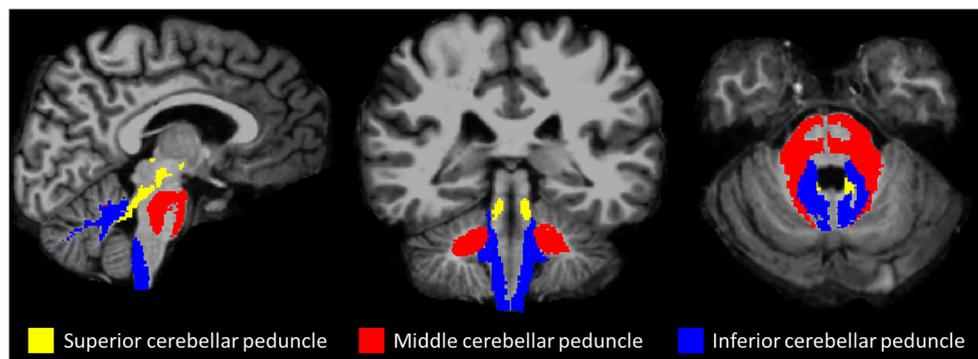
All MRI scans were performed in a 3-T Philips Achieva MRI Scanner. A 16-channel head coil was used to acquire 3D T1-weighted inversion recovery fast gradient echo images. The acquisition parameters were as follows: repetition time, 8.2 ms; echo time, 3.8 ms; flip angle, 8°; slice thickness, 1 mm; number of slices, 165; acquisition matrix, 256 × 256 mm.

Fluid-attenuated inversion recovery images were also acquired and screened by a neuroradiologist for structural abnormalities.

### Image analysis

#### Estimation of cerebellar peduncle volumes and cerebellar gray and white matter volumes

An atlas-based region of interest (ROI) analysis of the infratentorial tracts that involved the superior cerebellar peduncle



**Fig. 1** Representative image demonstrating the superior, middle, and inferior cerebellar peduncles (SCP, MCP, and ICP) as visualized using the infratentorial cerebellar white matter atlas by van Baarsen et al. Tracts were obtained following a deformable registration between the MNI atlas and subject T1 image. The SCP is composed of the dentato-thalamic

pathway which is the predominant cerebellar efferent tract, the MCP is composed of the cortico-ponto-cerebellar pathway which is the main link from the cerebral cortex to the cerebellum, and the ICP is composed of a host of afferent fibers, the olivo-cerebellar pathway, and afferents arising from the spinal cord and vestibular nuclei

(SCP), middle cerebellar peduncle (MCP), and inferior cerebellar peduncle (ICP) was performed (Fig. 1). The ROIs of these tracts have been previously defined in the MNI space [27]. These ROIs were utilized and transferred to the subject space using an elastic registration known as DRAMMS (Deformable Registration via Attribute Matching and Mutual-Saliency Weighting) (<https://www.nitrc.org/projects/dramms/>) [28]. DRAMMS registration uses multi-scale and multi-resolution Gabor attributes (which describe the texture) to find correspondence at each voxel, and uses the idea of mutual saliency weighting, wherein a metric is defined which assigns weights to different voxels quantifying the reliability of the correspondence. We employed DRAMMS between the subject T1 and the MNI template and fine-tuned the registration parameters to achieve the best matching between these images. The deformation smoothness weight was 0.2, and number of iterations = 10. The resulting transformation was used to map the ROIs to the subject space using nearest-neighbor interpolation. For every subject, the registration was checked manually. Pre-processing of T1 images involved skull stripping and bias correction and was performed using FSL5.0.11 (<https://fsl.fmrib.ox.ac.uk/fsl/>). Skull stripping was performed with FSL's brain extraction tool (BET) while the bias correction was performed using FSL's FAST with default parameters. Individual subject's volume of each tract was extracted and these were adjusted for the total intracranial volume.

The pre-processed T1 images were also employed into a Freesurfer 6.0 [29] pipeline for tissue classification and parcellation into multiple regions. The GM and WM ROIs were extracted from these parcellations, following which the GM and WM volumes were obtained. These volumes were normalized to the total intracranial volume for each subject.

### Application of a multi-variate classifier

The normalized volumes of SCP, MCP, and ICP (left and right) were used as features into a multi-variate XGboost classifier framework (<https://xgboost.readthedocs.io/en/latest/>), in

an attempt to discriminate patients from controls [30]. This was implemented in R 3.5.1 (<https://www.r-project.org/>). The parameters used in XGBoost involved a binary logistic classification method with learning rate = 0.01 and maximum depth of trees = 6. The dataset was divided into train and test (80/20), and a 5-fold cross-validation was performed on the training dataset to optimize the classifier parameters. The model was then trained on a complete training dataset and was applied on the test cases. The cross-validation and test accuracies were reported. To validate the classifier sensitivity and specificity, the receiver operating characteristics (ROC) were plotted and the area under the curve was reported. Moreover, we also compared the performance of the XGBoost classifier with other standard machine learning techniques such as random forests (RF) [31] and support vector machines (SVMs) [32].

### Statistical analysis

Based on the presence of cerebellar signs, the ET group was subdivided into ET without cerebellar signs (ETnc) and ET with cerebellar signs (ETc). Statistical analysis of age and gender was performed using a *t* test. Further, comparisons were performed between ET and healthy controls, and between ETnc and ETc using multi-variate analysis of covariance where age and gender were used as nuisance variables. Correction for multiple comparisons was performed using false discovery rates (FDR) [33]. The volumes of right and left cerebellar peduncles were also compared within groups, to ascertain the presence of lateralization of atrophy. The cerebellar ROI volumes of the ET subjects and cerebellar GM and WM volumes were correlated with clinical parameters that included duration of disease, AAO, total FTMRS score, and the motor (part A+B) and activities of daily living (part C) sub-scores of the FTMRS. The residuals obtained after removing the effects of age and gender were employed in the correlation. Level of significance was set at  $p < 0.05$ .

## Results

### Demographics and clinical data

Forty patients with ET and 37 age- and gender-matched healthy controls were included in this study (Table 1). Men outnumbered women in both groups and there were no significant differences between the age at evaluation of patients with ET and healthy controls ( $p = 0.562$ ). Cerebellar signs were observed in 20% ( $n = 8$ ) subjects in the ET group. Upon comparison of the ETnc and ETc subgroups, no significant differences were observed in age ( $p = 0.199$ ), AAO ( $p = 0.261$ ), duration of illness ( $p = 0.612$ ), or FTMRS total score ( $p = 0.413$ ) and subscores (A+B:  $p = 0.883$ ; C:  $p = 0.188$ ; right (A+B):  $p = 0.656$ ; left (A+B):  $p = 0.236$ ). There were no significant differences between the FTMRS right (A+B) and left (A+B) scores in any of the subgroups (ET:  $p = 0.375$ ; ETnc:  $p = 0.374$ ; ETc:  $p = 0.566$ ).

### Volumes of cerebellar peduncles

#### Essential tremor vs healthy controls

There were no significant differences in the total intracranial volume between patients with ET and controls ( $1289.48 \pm 130.60 \text{ cm}^3$  vs  $1296.23 \pm 94.27 \text{ cm}^3$ ,  $p = 0.791$ ). Comparison of volumes of SCP, MCP, and ICP revealed significant atrophy of bilateral MCP and ICP in patients with ET in comparison with controls ( $p = 0.001$ ) (Table 2). Assessment of laterality in healthy controls revealed a significantly lower volume of the right SCP and MCP, whereas in patients with ET, the right MCP and left ICP had significantly lower volumes.

#### Essential tremor without cerebellar signs vs essential tremor with cerebellar signs

There were no significant differences in the total intracranial volume between the ETnc and ETc subgroups ( $1292.40 \pm 142.05 \text{ cm}^3$  vs  $1277.81 \pm 88.89 \text{ cm}^3$ ,  $p = 0.784$ ). Comparison of volumes of SCP, MCP, and ICP revealed significant atrophy of bilateral ICP ( $p = 0.033$ ), with a trend towards significance for the right SCP ( $p = 0.055$ ) and for bilateral MCP ( $p = 0.055$ ) in patients of ETc in comparison with ETnc. Assessment of laterality revealed a significantly lower volume of the left ICP in comparison with the right ICP in both subgroups.

### Correlations

Negative correlations with a trend towards significance were observed between the volume of the right ICP and total FTM score ( $r = -0.302$ ,  $p = 0.058$ ) and between the volume of the right ICP and FTMRS part C score ( $r = -0.304$ ,  $p = 0.055$ ) in patients with ET (Fig. 2). No other correlations with significance or trend towards significance were observed.

### Volumes of cerebellar gray matter and white matter

#### Essential tremor vs healthy controls

Significantly lower volume of bilateral GM was observed in patients with ET in comparison with controls (right:  $p = 0.004$ ; left:  $p = 0.012$ ) (Table 3). No differences were observed when the volume of the cerebellar WM was compared (right:  $p = 0.189$ ; left:  $p = 0.595$ ).

**Table 1** Demographic and clinical features of patients with essential tremor and healthy controls

	HC ( $n = 37$ )	ET ( $n = 40$ )	ETnc ( $n = 32$ )	ETc ( $n = 8$ )	Significance	
					ET vs HC	ETnc vs ETc
Gender (M:F)	27:10	27:13	20:12	7:1	0.627	0.236
Age (years)	46.45 ± 9.93	44.95 ± 12.46	43.68 ± 12.73	50.00 ± 9.84	0.562	0.199
Age at onset (years)	–	34.45 ± 14.24	33.18 ± 14.29	39.50 ± 12.81	–	0.261
Duration of illness (years)	–	9.27 ± 7.65	8.96 ± 7.67	10.50 ± 7.43	–	0.612
Total FTMRS score	–	34.08 ± 13.40	32.51 ± 11.33	37.25 ± 23.89	–	0.413
A+B	–	18.09 ± 7.25	25.53 ± 7.95	26.12 ± 16.50	–	0.883
C	–	16.05 ± 7.32	22.07 ± 10.23	28.68 ± 19.57	–	0.188
Right (A+B)	–	8.62 ± 4.22	9.60 ± 3.77	10.43 ± 7.48	–	0.656
Left (A+B)	–	9.41 ± 3.68	10.43 ± 3.65	8.56 ± 5.01	–	0.236

ET, Essential tremor; ETc, ET with cerebellar signs; ETnc, ET without cerebellar signs; FTMRS, Fahn-Tolosa-Marin tremor rating scale; HC, healthy controls

**Table 2** Volumes ( $\times 10^{-6}$ ) of superior, middle, and inferior cerebellar peduncles, normalized to total brain volume, in patients with essential tremor and healthy controls

	HC ( <i>n</i> = 37)	ET ( <i>n</i> = 40)	ETnc ( <i>n</i> = 32)	ETc ( <i>n</i> = 8)	Significance	
					HC vs ET	ETnc vs ETc
<b>Superior cerebellar peduncle</b>						
Right	0.82 ± 0.08	0.83 ± 0.13	0.85 ± 0.13	0.76 ± 0.10	0.529	0.055
Left	0.88 ± 0.08	0.87 ± 0.10	0.88 ± 0.10	0.82 ± 0.08	0.529	0.063
Significance (R vs L)	0.001	0.127	0.304	0.206		
<b>Middle cerebellar peduncle</b>						
Right	8.29 ± 1.16	6.77 ± 1.05	6.93 ± 1.07	6.12 ± 0.71	0.001	0.055
Left	8.96 ± 1.50	7.44 ± 1.43	7.65 ± 1.47	6.62 ± 0.96	0.001	0.055
Significance (R vs L)	0.035	0.019	0.028	0.256		
<b>Inferior cerebellar peduncle</b>						
Right	3.46 ± 0.41	2.99 ± 0.32	3.05 ± 0.31	2.76 ± 0.24	0.001	0.033
Left	3.27 ± 0.60	2.74 ± 0.39	2.82 ± 0.38	2.42 ± 0.30	0.001	0.033
Significance (R vs L)	0.116	0.002	0.010	0.025		

ET, essential tremor; ETc, ET with cerebellar signs; ETnc, ET without cerebellar signs; HC, healthy controls; L, left; R, right

**Essential tremor without cerebellar signs vs essential tremor with cerebellar signs**

Comparison of the volume of cerebellar WM revealed significantly lower volume of the left cerebellar WM in patients with ETc (right:  $p = 0.262$ ; left:  $p = 0.028$ ) (Table 3). No significant differences in cerebellar GM were observed (right:  $p = 0.180$ ; left:  $p = 0.262$ ).

**Classification using a multi-variate classifier**

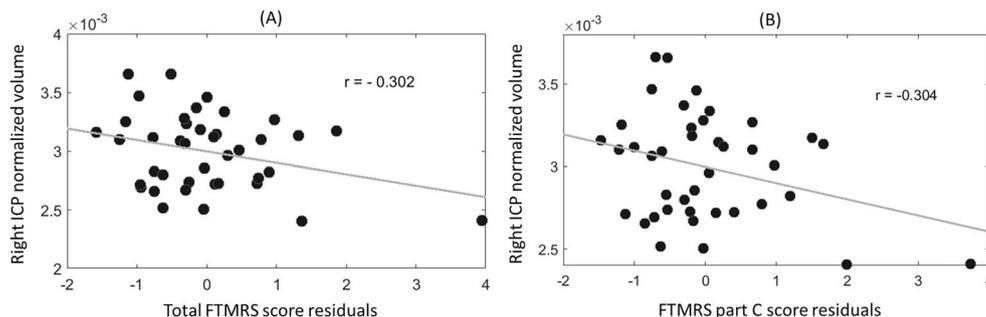
The training dataset contained 62 subjects (ET, 32; HC, 30), while the remaining 15 (ET, 8; HC, 7) subjects were retained for testing the classifier. The XGboost performed with 87.8% cross-validation accuracy and 86.66% testing accuracy. The area under the ROC for cross-validation was 0.88 and area under the ROC for testing was 0.92 (Fig. 3). The other two classifiers (SVMs and RF) used for comparison performed with a cross-validation accuracy of 61.6% and 72.5%

respectively while the test accuracies were 40% and 86.66% respectively.

**Discussion**

In this study, we investigated the volumes of the SCP, MCP, and ICP in patients with ET and compared the obtained volumes between those with and without cerebellar signs. We observed significant atrophy of bilateral MCP and ICP in patients with ET when compared with healthy controls, and comparison of ETnc and ETc revealed significant atrophy of bilateral ICP, with the right SCP and bilateral MCP volumes nearing significance in the ETc subgroup. In addition to this, we also observed significant atrophy of bilateral cerebellar GM in patients with ET, and significant atrophy of the left cerebellar WM in patients with ETc. Our study provides novel findings of macrostructural abnormality of the MCP and ICP in ET, and these observations are highly significant as they

**Fig. 2** Graphs demonstrating the correlations between (a) right inferior cerebellar peduncle and total FTMRS score residuals and (b) right inferior cerebellar peduncle and FTMRS part C score residuals



**Table 3** Volumes ( $\times 10^{-6}$ ) of cerebellar gray and white matter, normalized to total brain volume, in patients with essential tremor and healthy controls

	HC ( $n = 37$ )	ET ( $n = 40$ )	ETnc ( $n = 32$ )	ETc ( $n = 8$ )	Significance	
					HC vs ET	ETnc vs ETc
Gray matter						
Right	35.14 $\pm$ 3.42	31.42 $\pm$ 2.45	31.72 $\pm$ 2.33	30.22 $\pm$ 2.64	0.004	0.180
Left	33.42 $\pm$ 3.78	31.37 $\pm$ 2.82	31.59 $\pm$ 2.83	30.49 $\pm$ 2.59	0.012	0.262
White matter						
Right	9.57 $\pm$ 1.21	10.80 $\pm$ 4.84	11.27 $\pm$ 5.24	8.90 $\pm$ 0.76	0.189	0.262
Left	9.61 $\pm$ 1.26	9.47 $\pm$ 0.91	9.66 $\pm$ 0.83	8.74 $\pm$ 0.86	0.595	0.028

ET, essential tremor; ETc, ET with cerebellar signs; ETnc, ET without cerebellar signs; HC, healthy controls

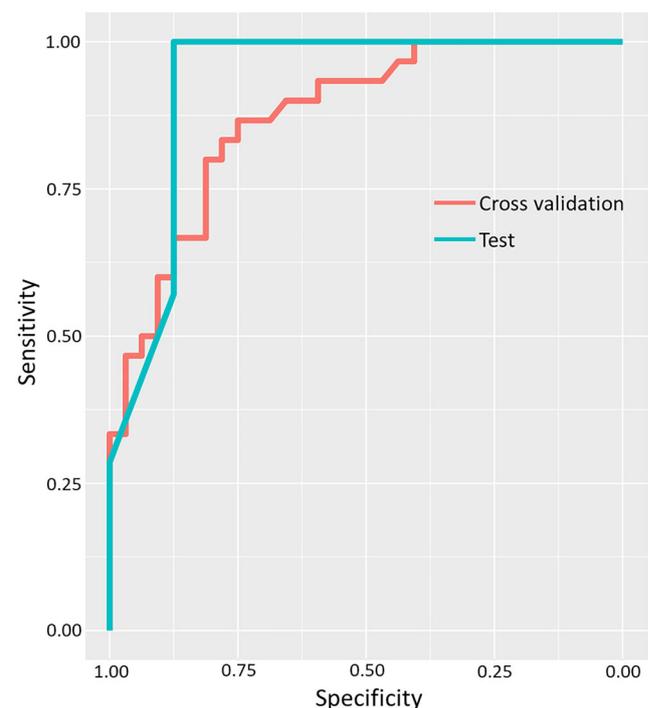
add to the concepts of pathophysiology in ET and provide additional explanations for the presence of cerebellar symptoms in patients with ET. Furthermore, utilization of the cerebellar peduncle volumes in a multi-variate classifier provided a test accuracy of 86.66% for differentiating patients with ET from HC, suggesting the plausible utility of these volumes as diagnostic imaging biomarkers for ET.

Although the exact pathogenesis of ET is uncertain, the popular hypotheses are associated with cerebellar abnormalities, either of the Purkinje cells or alterations in the cerebellar oscillatory networks [9, 14, 34, 35]. Furthermore, the presence of a wide range of subtle cerebellar signs substantiates the possibility of cerebellar involvement in ET. Several structural neuroimaging studies have ascertained morphological metrics in ET, either by volume estimation or via DTI [11, 20]. Although not reported in morphometric studies, the presence of abnormalities of cerebellar peduncles in ET has been previously reported by several DTI-based studies. However, these results are inconsistent and vary from isolated alterations in ICP [18], MCP [36], or SCP [13] to abnormalities in all 3 peduncles [16]. Reduced BOLD activation during a finger tapping task has also been reported in ET [37]. Furthermore, several studies exploring the role of cerebellar repetitive transcranial magnetic stimulation in ET have demonstrated significant improvement in tremor severity, suggesting a role of the cerebellum in the pathophysiology of ET [38, 39]. Additionally, MCP and SCP atrophy has been observed in several other disorders with cerebellar symptoms [40–42].

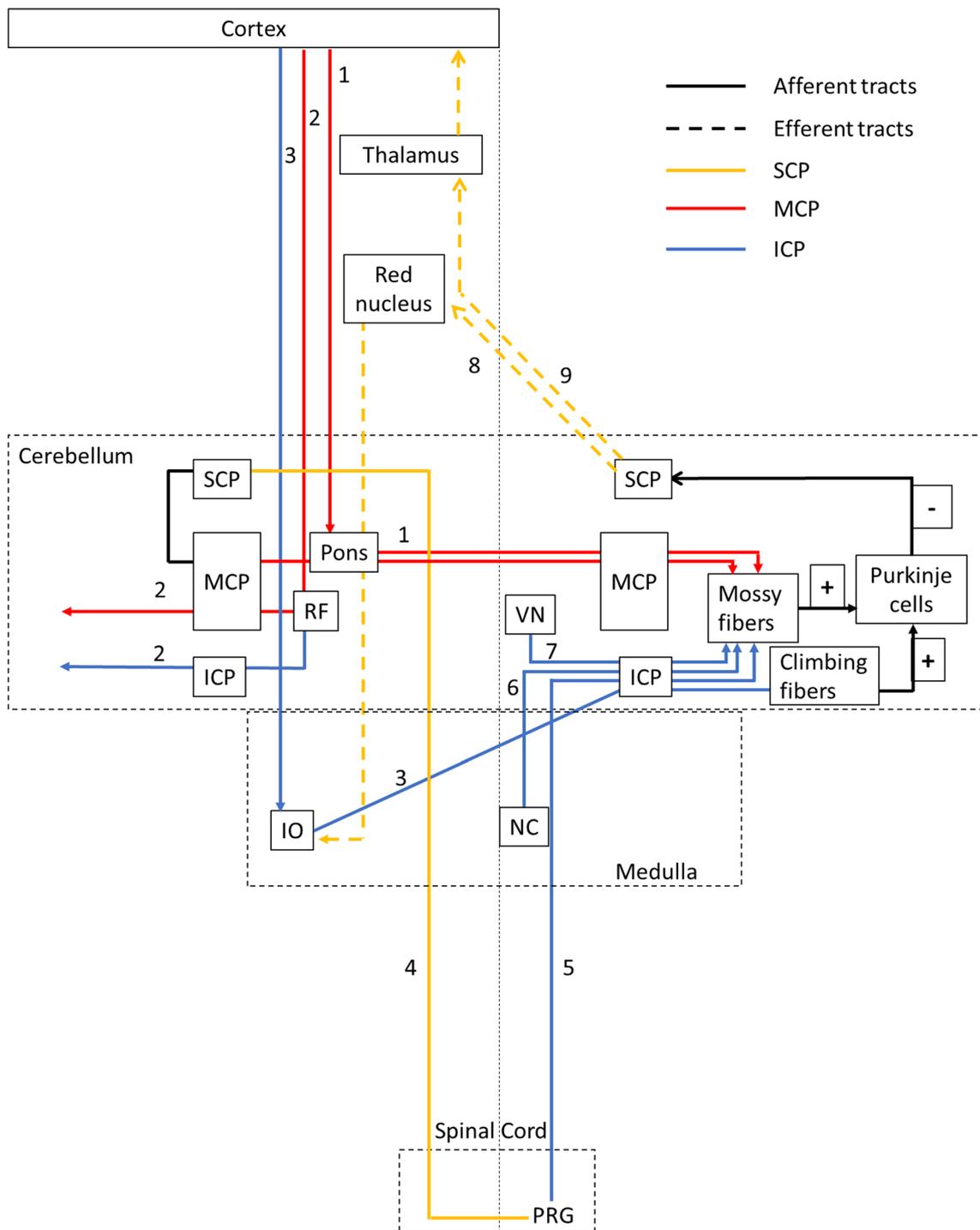
A brief overview of cerebellar afferent and efferent connections is essential to appreciate the implications of the observations of this study. The cerebellum is connected to various parts of the brain via numerous afferent and efferent fibers which are grouped into 3 peduncles—SCP, MCP, and ICP [43, 44]. Most of the afferent fibers enter through the MCP and ICP, and efferent fibers exit through the SCP (Fig. 4). The cortico-ponto-cerebellar pathway is the main link from the cerebral cortex to the cerebellum. It arises from the cortex, descends to the ipsilateral pons, and crosses over to the contralateral cerebellar cortex via the MCP, following which it

ends as excitatory mossy fibers. The ICP serves as a conduit for a host of afferent fibers, the most predominant of which is the olivo-cerebellar pathway which terminates as excitatory climbing fibers. In addition to this pathway, afferents arising from the spinal cord and vestibular nuclei also pass through the ICP. The dentato-thalamic pathway is the predominant efferent which exits through the SCP.

From a functional standpoint, the primary role of the cerebellum is associated with coordination of voluntary movements and control of posture and equilibrium [45]. In order to carry out this function, the cerebellum continually compares the output of the cerebral cortex with the proprioceptive information received from muscles and makes the necessary adjustments. Considering these facts, abnormalities in the



**Fig. 3** Area under the receiver operating characteristics (AUROC) curve for cross-validation training and testing. Cross-validation AUC, 0.88 and testing AUC, 0.92



**Fig. 4** Schematic representation of cerebellar afferent and efferent tracts. Numbers 1 to 7 represent the main afferent tracts and 8 and 9 are the main efferent tracts. (1) Cortico-ponto-cerebellar tract, (2) cortico-reticulo-cerebellar tract, (3) cortico-olivo-cerebellar tract, (4) anterior spinocerebellar tract, (5) posterior spinocerebellar tract, (6) cuneocerebellar tract, (7) vestibulocerebellar tracts, (8) globose-

emboliform-rubral pathway, and (9) dentato-thalamic pathway. ICP, inferior cerebellar peduncle; IO, inferior olive; MCP, middle cerebellar peduncle; NC, nucleus cuneus; PRG, posterior root ganglion; RF, reticular formation; SCP, superior cerebellar peduncle; VN, vestibular nuclei. The efferent fastigial vestibular pathway and fastigial reticular pathway have been excluded from this schematic

MCP and ICP are likely to influence the inputs the cerebellum receives concerning voluntary movement and balance. Hence, it is plausible that abnormalities in cerebellar afferents may

contribute to the subtle cerebellar signs observed in patients with ET. These findings may be extrapolated to a cellular level wherein the reduction in the number of excitatory mossy and

climbing fibers may lead to a reduced excitation of Purkinje cells and subsequent reduction of the inhibitory output. This may compound the pre-existing reduced inhibitory output which occurs due to abnormalities in Purkinje cells and contribute to the pathogenesis of tremor in ET. The peduncular atrophy observed in ET may be secondary to Wallerian degeneration due to loss of Purkinje cells [42].

The observed atrophy of the MCP and ICP in patients with ET is suggestive of abnormalities in the afferent connections to the cerebellum. In addition to the MCP and ICP atrophy, the right SCP was also atrophic in patients with ETc. This observation suggests that irrespective of the presence of cerebellar signs, MCP and ICP atrophy may be observed in patients with ET and the additional SCP atrophy contributes to the development of cerebellar signs. As discussed earlier, the SCP is the only efferent tract from the cerebellum and significantly contributes to normal cerebellar functioning. The role of the SCP in the production of cerebellar signs has been previously reported in cerebellar disorders such as Friedreich's ataxia [41]. Hence, it is plausible that the SCP atrophy observed only in the ETc group may be implicated in the genesis of cerebellar signs in ET.

Structural abnormalities of cerebellar GM and WM have been consistently reported across studies [12, 19, 20, 46], and our observation of cerebellar GM atrophy in patients with ET concurs with these reports. We did not observe significant atrophy of the cerebellar WM despite the observation of atrophy of the MCP and ICP which are integral parts of the cerebellar WM. This may probably be attributable to the comparative normalcy of the remainder of the cerebellar WM in patients with ET. Comparison of cerebellar GM and WM volumes in ETnc and ETc revealed isolated atrophy of the left cerebellar WM in ETc. We did not observe any significant differences of basic demographics or of the FTMRS scores between ETnc and ETc.

Although we observed lateralization of peduncular volumes, we did not observe a significant difference in the right and left FTMRS scores. There were no significant correlations between the disease duration, FTMRS scores, and the volumes of cerebellar peduncles or cerebellar GM and WM. This suggests that the development of additional signs in ET may not simply be secondary to increasing disease severity. From the results of this study and previous studies, it is evident that cerebellar signs in ET may be a by-product of a complex interplay between abnormalities in cerebellar afferent and efferent tracts and intrinsic cerebellar abnormalities.

Finally, based on the significant difference observed in the cerebellar peduncular volumes between patients with ET and HC, we attempted to ascertain if these differences may aid in automated classification of ET and HC. The observed test accuracy of 86.66% in a multi-variate classifier based on these volumes suggests the need for future studies on larger sample sizes to ascertain the plausible utility of this metric in the

diagnosis of ET. Moreover, we illustrated that our choice of classifier was superior as when compared with other learning techniques such as SVMs and RFs. Inherently, XGboost is an optimized implementation of gradient boosting decision trees which builds and combines a large number of individual weak learners to generate a strong learner and therefore can potentially delineate ET from controls more efficiently.

There are several limitations to this study. Although we have observed significant differences between the ETnc and ETc subgroups, the size of the subgroups was small. Future studies with larger groups of ET patients with cerebellar signs are necessary to validate our results. Although not statistically significant, the ETc group was older and had a longer duration of illness in comparison with the ETnc group; this may have influenced the obtained results. We did not quantify the extent of cerebellar abnormalities using scales; hence, we were unable to ascertain the exact influence of cerebellar peduncular atrophy on the presence of cerebellar signs. The exact clinical utility of the classifier has to be established by comparing ET with other tremor disorders such as tremor-dominant Parkinson's disease. Finally, the registration technique for mapping the cerebellar tracts needs to be tested for reproducibility on multiple timepoint scans of the same subject.

## Conclusions

In conclusion, patients with essential tremor have significant atrophy of cerebellar peduncles, particularly the middle and inferior cerebellar peduncles, with additional atrophy of the superior cerebellar peduncle is observed in patients with cerebellar signs. These abnormalities may contribute to the pathology in essential tremor and form an essential component for the pathogenesis of cerebellar signs in essential tremor. These observations provide novel insights into the pathogenesis of cerebellar symptoms in essential tremor and lend support to the notion of essential tremor being a neurodegenerative disorder.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Dr. Pramod Kumar Pal.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** Written informed consent was obtained from all subjects (patients) in this study.

**Ethical approval** Institutional Review Board approval was obtained.

**Study subjects or cohorts overlap** Some study subjects are part of the cohort have been part of previous studies from our group:

Prasad S, Shah A, Bhalsing KS, Kumar KJ, Saini J, Ingalthalikar M, Pal PK. Abnormal hippocampal subfields are associated with cognitive impairment in Essential Tremor. *Journal of Neural Transmission*. 2019 Mar 19:1–0.

Prasad S, Rastogi B, Shah A, Bhalsing KS, Ingalthalikar M, Saini J, Yadav R, Pal PK. DTI in essential tremor with and without rest tremor: Two sides of the same coin? *Movement Disorders*. 2018 September 28.

Bhalsing KS, Kumar KJ, Saini J, Yadav R, Gupta AK, Pal PK. White matter correlates of cognitive impairment in essential tremor. *AJNR Am J Neuroradiol*. 2015;36(3):448–45.

Bhalsing KS, Upadhyay N, Kumar KJ et al (2014) Association between cortical volume loss and cognitive impairments in essential tremor. *Eur J Neurol* 21:874–883.

#### Methodology

- Prospective
- Case-control study
- Performed at one institution

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