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Altered brain network measures in patients with primary writing tremor

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Abstract
Purpose Primary writing tremor (PWT) is a rare task-specific tremor, which occurs only while writing or while adopting the hand in the writing position. The basic pathophysiology of PWT has not been fully understood. The objective of this study is to explore the alterations in the resting state functional brain connectivity, if any, in patients with PWT using graph theory-based analysis.
Methods This prospective case-control study included 10 patients with PWT and 10 age and gender matched healthy controls. All subjects underwent MRI in a 3-Tesla scanner. Several parameters of small-world functional connectivity were compared between patients and healthy controls by using graph theory-based analysis.
Results There were no significant differences in age, handedness (all right handed), gender distribution (all were males), and MMSE scores between the patients and controls. The mean age at presentation of tremor in the patient group was 51.7 ± 8.6 years, and the mean duration of tremor was 3.5 ± 1.9 years. Graph theory-based analysis revealed that patients with PWT had significantly lower clustering coefficient and higher path length compared to healthy controls suggesting alterations in small-world architecture of the brain. The clustering coefficients were lower in PWT patients in left and right medial cerebellum, right dorsolateral prefrontal cortex (DLPFC), and left posterior parietal cortex (PPC).
Conclusion Patients with PWT have significantly altered small-world brain connectivity in bilateral medial cerebellum, right DLPFC, and left PPC. Further studies with larger sample size are required to confirm our results.

Keywords Primary writing tremor · Neuroimaging · fMRI · Functional connectivity · Graph theory

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Introduction

Tremor is an involuntary, rhythmic oscillation of a body part. It is the most common form of movement disorder in adults. The term "task-specific tremor" is used to describe action tremors, which are present only while performing or while attempting to perform specific tasks such as writing, standing, typing, and while playing certain musical instruments [1]. Primary writing tremor (PWT) is a rare task-specific tremor, which occurs only while writing or while adopting the hand in the writing position, in the absence of any apparent causative lesions. PWT is categorized into two phenotypes: (i) type A (appears only during the act of writing) and (ii) type B (appears not only during the act of writing but also when the hand assumes writing posture) [1, 2]. Even after three decades of the introduction of the concept of PWT by Rothwell et al. [3], the neural correlates and natural course of PWT are not fully understood. The basic understanding of the pathogenesis of PWT has remained controversial as it is not clear whether PWT is a variant of essential tremor (ET) [4] or a type of focal dystonia such as writer's cramp (WC) [5] or a distinct

pathological entity [6]. Considering the rarity of the disorder, current literature on PWT is sparse compared to those on ET and WC.

Several studies have explored the neural correlates of PWT using advanced neuroimaging techniques. In a recently published study, which was aimed to explore the microstructural alterations in the gray and white matter in PWT, significant gray matter atrophy was observed in cerebellum and frontal lobe whereas the white matter changes were prominent in the cingulate and several frontal lobe connections [7]. To the best of our knowledge, there are only two published studies on the application of functional magnetic resonance imaging (fMRI) in PWT. Berg et al. [8] in a task-based fMRI study involving three right-handed patients with PWT reported comparatively higher activation in ipsilateral cerebellum, bilateral parietal lobules, contralateral premotor cortex, and several regions in ipsilateral frontal cortex compared to the controls. Sahni et al. in a task-based fMRI study involving six right-handed patients with PWT observed significantly increased activation in contralateral primary and supplementary motor area and decreased activation in cingulate and ipsilateral cerebellum [9]. In the current literature, there are no neuroimaging studies on PWT based on resting state fMRI (rs-fMRI). Unlike the task-based fMRI analyses, which provide insights into the neural activities in isolated regions, rs-fMRI analyses provide integrative analysis of the distributed neural system.

Graph theory-based analyses are one of the advanced mathematical models to analyze the resting state functional brain connectivity [10]. In network analyses based on graph theory, the brain is modeled as a complex network that is represented graphically as a collection of "nodes" representing neural elements (brain regions), which are linked by "edges" representing functional connections among the nodes. Two basic measures that are used to characterize functional brain networks in graph theory are as follows: (i) clustering coefficient, which quantifies the local connectivity as an index of network segregation, and (ii) path length, which quantifies the global connectivity as an index of network integration. A "small world network" is described as a network having high clustering coefficient and low inter-nodal path length. A small-world network is an efficient neural system maintained with remarkably low wiring and energy costs [11]. Graph-based neural network analyses have distinct advantage over other widely used rs-fMRI analyses (amplitude of low-frequency fluctuations, regional homogeneity, independent component analysis, and seed-based connectivity) for two major reasons: (i) visualization of the overall pattern of connectivity among all the brain regions and (ii) quantitative characterization of the global organization in the brain.

This study was aimed to explore the pattern of alterations in the small-world connectivity of brain networks in patients with PWT by comparing the same with a group of healthy controls using graph theory-based network analysis. This may further contribute towards understanding the neurobiology of this rare and complex movement disorder.

Methodology

Subject recruitment and study approval

This prospective case-control study was conducted in a tertiary care neurology institute. Over a period of 5 years, 12 patients with PWT were recruited from the general neurology outpatient clinics and movement disorder services. PWT was diagnosed if the patients had tremor only while writing or holding the pen in the act of writing but not actually writing. Patients with history of any other form of tremor (rest or action or task-specific) or neurological examination revealing rest or action tremor of any other part of the body were excluded. Demographic parameters such as age, age at onset of tremor, duration of illness, gender, and family history of tremor were documented. Writing of the patients with PWT was evaluated by instructing them to write on a plain white paper using a pen. Each patient wrote the following, first with his dominant hand and later with the other hand: (i) alphabets, (ii) numbers, and (iii) sentences first in his mother tongue and then in English. An experienced movement disorder specialist had evaluated all the subjects. Severity of tremor in all patients was assessed by components of the Fahn-Tolosa-Marin (FTM) tremor rating scale corresponding to the act of writing/drawing [12]. Handedness was analyzed by the Edinburg handedness inventory [13]. Mini mental status examination (MMSE) score was used to screen the participants for cognitive impairment.

After confirmation of a clinical diagnosis of PWT, the 12 patients recruited in the current study were scheduled for undergoing MRI. Two patients were eventually excluded from the study, as one of them was unable to complete the MRI protocol whereas the other had white matter hyperintensities suggestive of small vessel disease. Subsequently, ten age, gender, education, and handedness matched healthy controls were recruited from the hospital staffs or spouses of the patients. All the healthy controls were carefully screened for presence of tremor in different parts of the body at rest and while performing tasks such as writing, pouring water from cups, buttoning, and unbuttoning clothes. None of the healthy volunteers had family history of any neuropsychiatric disorders. All the patients and most of the controls were part of our previously published study comparing the microstructural white and gray matter changes in patients with PWT and healthy controls [7].

All the subjects had provided written informed consent for their recruitment in this study and the Institute Ethics Committee had approved this study.

Functional magnetic resonance imaging

Image acquisition

All participants underwent rs-fMRI and structural MR imaging on a 3T-MR scanner (Philips) with a 20-channel head coil. MR images were acquired after temporarily stopping the antitremor medications for at least 72 h. The acquisition parameters for echo-planar images using blood oxygen level-dependent (BOLD) contrast were as follows: volumes: 192; TR: 3000 ms; TE: 30 ms; sections: 34; slice thickness: 4 mm; FOV: 192 × 192 mm^2; matrix = 64 × 64 × 64 mm^3; refocusing pulse: 90°; and voxel size: 3 × 3 × 4 mm^3. After obtaining the fMRI images, T1-weighted, three-dimensional, high-resolution images were acquired for anatomical co-registration and segmentation. T1-MPRAGE was acquired with the following: TR: 8.1 ms; TE: 2.43 ms; FOV = 256 × 256 × 155 mm^3; 1 mm of slice thickness; voxel size: 1 × 1 × 1 mm^3.

Image analysis

Pre-processing The MR image preprocessing was performed using the Statistical Parametric Mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). First five volumes were excluded and the data were realigned for motion correction. The functional images of all the subjects were transformed to the Montreal Neurological Institute standard space by using the deformation field derived in the new segmentation procedure (voxel size: 3 × 3 × 3 mm). In addition, the structural data were segmented for gray matter, white matter, and CSF for nuisance regression of the signals related to white matter and CSF. Head motion correction was done by using the Friston 24-parameters. The maximum head movement was not significant between the two groups for translational (control: 0.70 ± 0.74 mm, PWT: 0.9 ± 0.53 mm; $p = 0.41$) and rotational (control: 0.013 ± 0.012°, PWT: 0.014 ± 0.016°; $p = 0.38$) axis. Finally, the rs-fMRI data were filtered with a 0.01–0.09 Hz band-pass filter.

Brain network construction The nodes of the functional networks were extracted from the rs-fMRI data into 160 spheres (radius = 5 mm) of the Dosenbach atlas [14] using the MarsBaR toolbox® (http://marsbar.sourceforge.net). The time series of a region of interest (ROI) was the average of all the voxels in that ROI. The rs-fMRI time series were correlated region by region for each subject across the length of the time series (L = 187), and a N × N (N is number of ROIs = 160) matrix was constructed by applying a correlation threshold T (Fisher's r-to-z) to the Pearson's correlation coefficients using a sparsity-based method.

Graph theory analysis The network topological properties of the functional brain networks were defined on the basis of a 160 × 160 graph weighted undirected networks, G (N, E), where G is a non-zero subset with nodes (N = ROIs) and edges (E = inter-nodal correlation coefficients, Fisher's Z values) as a measure of functional connectivity between nodes calculated using 2D correlation coefficient. To characterize the functional brain networks, several graph-theory connectivity measures such as clustering coefficient (γ), characteristic path length (λ), and small-worldness (σ) were calculated [15]. To enable comparison of network properties across groups and participants, we used a sparsity threshold in order to ensure the same number of network edges for each participant by retaining only those connections whose edge strengths exceed a given threshold. To avoid biases associated with the use of a single threshold, we determined a sparsity range of $0.06 \le S \le 0.45$, with an increment of $\Delta S = 0.01$. This approach ensures that the thresholded networks were estimable for small worldness and also avoids excess network fragmentation at sparser thresholds [15]. The analysis was done using the brain connectivity toolbox (http://www.brain-connectivity-toolbox.net). Parameters of the small worldness are briefly described below.

(i) *Normalized clustering coefficient (γ)*

γ is defined as the ratio of absolute clustering coefficient of the network (C_i) to random clustering coefficient C_{Rand} ($\gamma = C_i/Crand$). The absolute clustering coefficient (C_i) of a node is the ratio between the number of existing connections (E) and the number of all possible connections in the graph G while C is the average of the absolute clustering coefficient of all nodes. The absolute component of the matrix G was thresholded into a binary connectivity matrix "A." Non-zero entries in E correspond to connections between three anatomical regions. C was calculated using the formula:

$$C = \frac{1}{n}\sum_{i\in N} C_i = \frac{1}{n}\sum_{i\in N}\frac{E_i}{K_i(K_i-1)/3}$$

K_i is the degree (number of connection) of node "i," "N" is the set of all nodes in the network and "n" is the number of nodes. The clustering coefficient "Ci" of that node is defined as "0", if degree of that node (K_i) < 2. C_{Rand} is the averaged clustering coefficient of 1000 matched random networks that keep the same number of nodes, edges, and degree distributions as the real networks of C_i for each sparsity level to obtain a difference in distribution [16]. Using the γ values, the brain region that showed significant differences ($P < 0.05$ FDR corrected) between control and patients were noted and rendered on a brain surface model using the BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

(ii) *Normalized path length (λ)*

λ of a network measures the average connectivity that exists or the overall rounding efficiency of the network. λ is the ratio of absolute characteristic path length L_i to random path length L_{Rand} ($\lambda = L_i/L_{Rand}$). The absolute characteristic path length of a network L was then defined as the mean minimum number of edges that lies between any two nodes in the network.

$$L = \frac{1}{n}\sum_{i\in G} L_i = \frac{1}{n}\sum_{i\in G}\frac{1}{n-1}\sum_{i\neq j\in N}\min\left\{L_{i,j}\right\}$$

Here, min $\{L_{ij}\}$ is the shortest absolute path length between the node i and j. where "N" is the set of all nodes in the network and n is the number of nodes [16].

(iii) *Small worldness (σ)*

It is the ratio between network segregation (γ) and network integration (λ). Mathematically, a real network would be considered as small world if it meets the two conditions: (i) $\gamma > 1$ and (ii) $\lambda \approx 1$. These two conditions can also be summarized into a simple quantitative measurement, $\sigma = \gamma/\lambda > 1$ for networks with a small-world organization [16].

Statistical analysis

Statistical comparisons of the global graph metrics between the two groups were done at both individual sparsity threshold and by using an integrated network summary scalar. The socio-demographic and clinical data were tested for normality using the Shapiro-Wilk test, and appropriate statistics were used. Statistical comparisons of the graph measures (i.e., γ, λ, and σ) between the two groups were done at both individual sparsity threshold (i.e., each sparsity level) and across the examined range of sparsity from S_1 to S_n with an interval of ΔS, where S_1 is 0.6 and S_n is 0.45 and ΔS is 0.01. The AUC for all the graph measures was calculated by using an integrated network summary scalar [17]. The integrated measure provides a summary scalar over the entire sparsity range (i.e., S_1 to S_n) for the topological characterization of brain networks, which is sensitive to topological alterations of brain disorders and are independent of the single threshold selection. In order to evaluate the between-group differences of each measure for individual sparsity and over the range of thresholds, two-sample two-tailed *t* tests were performed. The nodal characteristics of "γ" were calculated over the examined range of 6–45% sparsity thresholds in all nodes ($n = 160$) for each patient, and healthy control and the group difference were calculated using two-sample two-tailed *t* tests. For multiple comparisons, correction was set at 5% of confidence interval of the false discovery rate (FDR). The statistically significant nodes were rendered on a brain surface model using the BrainNet Viewer (http://www.nitrc.org/projects/bnv/). To explore the relationship between altered nodal network measures in "γ" and clinical parameters, we used Pearson's correlation analysis between brain region that showed differential "γ" and FTM score. Age and MMSE scores were taken as covariates for all the correlation analyses.

Descriptive statistics for clinical and demographic variables was performed using SPSS (Version 21). Student's *t* test was used for comparing the continuous variables, and Chi-square test was used for the categorical variables. The statistical level of significance was set at $p < 0.05$.

Results

Demographic and clinical characteristics

There were no significant differences in age, handedness (all right handed), gender distribution (all were males), and MMSE scores between the patients and controls. The mean age at presentation of tremor in the patient group was 51.7 ± 8.6 years, and the mean duration of tremor was 3.5 ± 1.9 years. Of those 10 patients with PWT, three had tremor while holding the pen as well as while writing (type B), whereas the rest had tremor only while writing (type A). Two patients with PWT had a positive family history of tremor. The demographic and clinical details of 10 patients with PWT and 10 controls are provided in Table 1.

Comparison of small-world connectivity parameters

The results of the whole brain small-world connectivity analysis revealed significantly reduced clustering coefficient in patients with PWT compared to controls (Fig. 1a). The path length was significantly higher in PWT group compared to controls (Fig. 1b). Consequently, the PWT group had a comparatively disorganized small-world connectivity compared to the controls (Fig. 1c). The group differences in clustering

Table 1 Demographic and clinical characteristics of the subjects

Parameters	Controls ($n = 10$)	PWT ($n = 10$)	Significance
Gender	All men	All men	NS
Handedness	All right handed	All right handed	NS
MMSE	29.8 ± 0.4	29.8 ± 0.6	NS
Mean age	51.7 ± 8.6 years	50.6 ± 7.8 years	NS
Duration of tremor	–	3.5 ± 1.9 years	–
Mean FTM score	–	10.7 ± 3.0	–

PWT primary writing tremor, *NS* not significant, *MMSE* Mini Mental Status Examination, *FTM* Fahn-Tolosa-Marin tremor rating scale

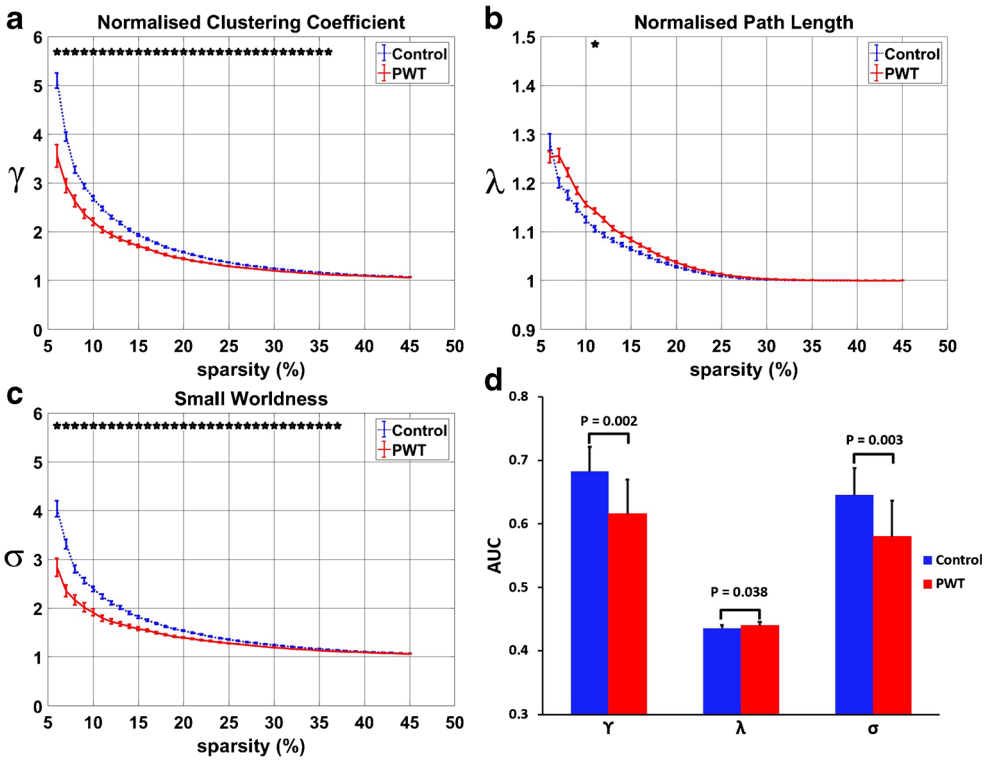

Fig. 1 Graphical representation of the whole-brain small-world network results in patients with PWT and the controls. The graphs (**a**–**c**) show comparison of mean **a** clustering coefficient (γ), **b** characteristic path length (λ), and **c** small worldness (σ) between the PWT (*red line*) and controls (*blue line*) over the network sparsity threshold S ($.06 \leq S \leq .45$, with increment of .01). *Asterisk* indicates the range of sparsity thresholds where the between-group differences were statistically significant ($p < 0.05$, FDR). **d** The bar plots demonstrate the between-group differences in the integrated global parameters. "p" indicates significant reduction in PWT group compared to the controls ($p = 0.002$, $p = 0.038$, and $p = 0.003$ for γ, λ, and σ, respectively)

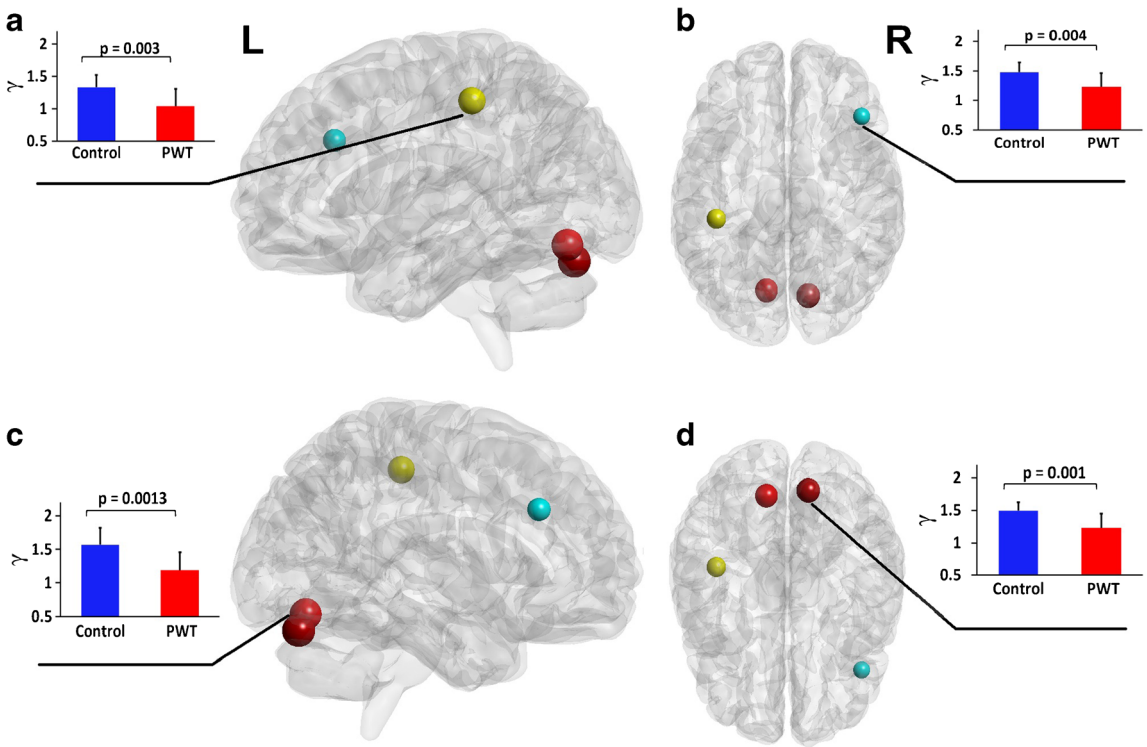

Fig. 2 Brain surface visualization of the brain regions having significant (p value < 0.05, FDR corrected) reductions in the integrated nodal clustering coefficient values (γ) in PWT group compared to controls. Nodal size is proportional to the T-stat value and the color map is indicative of the Cohen's d value. All regions had Cohen's d value > 0.8 indicating large effect sizes. **a** Bar plot showing the difference in the clustering coefficient of left posterior parietal cortex of patients and controls. **b** Bar plot showing the difference in the clustering coefficient of right dorsolateral prefrontal cortex of patients and controls 2. **c** Bar plot showing the difference in the clustering coefficient of left medial cerebellum of patients and controls. **d** Bar plot showing the difference in the clustering coefficient of right medial cerebellum of patients and controls

Table 2 Brain regions having significantly reduced clustering coefficient in patients with PWT compared to controls

Brain regions	Clustering coefficient	*p* value	t-stat value	Cohen's *d*	Effect size	Correlation with FTM score
Left medial cerebellum	Patients: 1.18 ± 0.27 controls: 1.56 ± 0.25	0.0013	3.43	1.46	0.59	$r = -0.87$, $p = 0.001$
Right medial cerebellum	Patients: 1.23 ± 0.21 Controls:1.49 ± 0.12	0.001	3.54	1.48	0.60	$r = -0.74$, $p = 0.01$
Right DLPFC	Patients: 1.23 ± 0.23 Controls: 1.47 ± 0.16	0.004	2.90	1.22	0.52	$r = 0.29$, $p = 0.41$
Left posterior parietal cortex	Patients: 1.03 ± 0.27 Controls: 1.33 ± 0.19	0.003	2.98	1.25	0.53	$r = -0.55$ $p = 0.05$

PWT primary writing tremor, *FTM* Fahn-Tolosa-Marin tremor rating scale, *DLPFC* dorsolateral prefrontal cortex

coefficient, path length, and the overall small worldness are graphically represented in Fig. 1d.

We observed significant difference in the clustering coefficient of four regions of the brain in PWT group compared to the controls. These regions are (i) right medial cerebellum, (ii) left medial cerebellum, (iii) left posterior parietal cortex (PPC), and (iv) right dorsolateral prefrontal cortex (DLPFC) (Fig. 2). When correlation analysis was performed between the clustering coefficients of the aforementioned regions with the FTM scores of the PWT patients, significant negative correlation was observed for the clustering coefficients of right and left medial cerebellum and left posterior parietal cortex (Table 2, Fig. 3).

Discussion

We analyzed the whole-brain functional connectivity using graph theory-based model to compare the small-world brain architecture of patients with PWT with healthy controls. The principal finding of our study is significantly decreased clustering coefficient and increased path length in PWT group compared to controls, suggesting significant disruption of the small-world brain architecture. Bilateral medial cerebellum, right DLPFC, and left PPC are the regions where the PWT group had lower clustering coefficient compared to the controls.

The act of writing is one of the commonly used fine motor skills by humans. Although writing appears to be a simple motor activity, it is regulated by coordinated expression of several neural elements. The complexity of mechanism of writing is underscored by the fact that in addition to motor execution (fine-tuning of finger positions in order to manipulate pen/pencil), it also requires accurate sensory-motor integration for maintaining the limb position, access to the language in which a person is writing, and visual feedbacks [18]. Hence, impairment in any of the aforementioned components may affect the act of writing. Although the existence of a specific "writing center" in the middle frontal gyrus (superior to Broca's area) was described by Sigmund Exner [19], multitude of functional MRI studies have reported several other regions of the brain which are crucial for various aspects of writing. Horovitz et al. have reported significant activation in left dorsal prefrontal cortex, left intraparietal sulcus, and vermis in subjects while writing with the right hand [20]. Similar study by Katanoda et al. revealed higher activation in left superior parietal lobule, posterior part of middle and superior frontal gyrus, and right cerebellum [21].

The regions of the brain having reduced small worldness in our cohort of patients with PWT have been implicated in fMRI and PET studies involving healthy controls as well as PWT while performing writing tasks. The above-mentioned fMRI studies on healthy volunteers have reported cerebellar activation while writing. Patients with PWT in the current study had reduced clustering coefficient in medial part of cerebellum on both sides. The medial cerebellum represents the intermediate zones of cerebellar cortex, present just lateral to the vermis. Bilateral medial cerebellum and vermis constitute the functional subdivision of cerebellum known as spinocerebellum, which receives major inputs

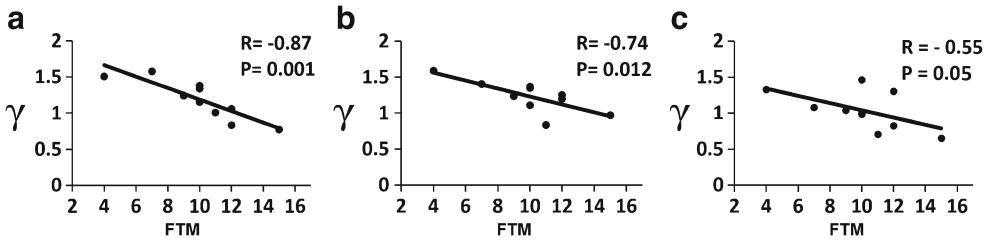

Fig. 3 **a** Correlation of the FTM score with the clustering coefficient of left medial cerebellum. **b** Correlation of the FTM score with the clustering coefficient of right medial cerebellum. **c** Correlation of the FTM score with the clustering coefficient of left posterior parietal cortex

from the spinocerebellar tract and is involved in the integration of sensory input with motor commands to produce adaptive motor coordination as well as proprioception. In addition, studies based on viral tracing technique have suggested existence of projections from the motor cortex to the cerebellar vermis, which are critical for anticipatory postural adjustments of limbs [22]. Although the mechanism remains unclear, it is possible that functional alterations in medial cerebellum impair the sensory-motor integration while adapting the hands in writing position in patients with PWT. The role of cerebellum in sensory-motor integration is well known, and the same has been implicated in several movement disorders [23]. As discussed above, studies on healthy volunteers by Horovitz et al. [20] and Katanoda et al. [21] have also revealed altered activation in vermis and ipsilateral cerebellum, respectively, while performing writing tasks. Our results also get support from a PET-based study by Wills et al. in which patients with PWT had abnormal increase in the activity of bilateral cerebellar hemisphere and vermis [24]. We also observed significant negative correlation of the clustering coefficient in bilateral medial cerebellum with the severity of the tremor, which further consolidates the implications of altered connectivity of medial cerebellum in PWT. As cerebellum is one of the components of an orchestrated activity leading to the act of writing, it is possible that the reduced clustering coefficient and the global increase in path length in PWT are reflections of altered connectivity of the medial cerebellum with other regions of the brain.

In addition to cerebellum, several fMRI studies have also emphasized the role of parietal and frontal lobe structures in writing. Furthermore, lesions in frontal and parietal regions have been reported to be associated with writing tremor [25, 26]. Left PPC and right DLPFC had lower clustering coefficients in our patient group. The PPC is essential for sensory-motor transformations involved in online manual actions [27]. The intraparietal sulcus divides the posterior PPC to form the dorsal superior parietal lobule and the ventral inferior parietal lobule. Result of our study with regards to PPC gets support from several published fMRI studies. Activation of intraparietal sulcus [20, 28] and superior parietal lobule [21] has been reported both during mental writing and while performing writing tasks during fMRI in healthy individuals. Berg et al. [8] observed biparietal activation during a writing task in patients with PWT and speculated that the higher activation in this region reflects the effort to perform the act of writing especially in presence of tremor. There was a significant negative correlation between the FTM score and the clustering coefficient of left PPC in our study, which further reinforces the role of left PPC in the neurobiology of PWT.

Similar to bilateral medial cerebellum and left PPC, the right DLPFC also had reduced clustering coefficient in PWT group compared to controls. However, we did not observe any significant correlation of the FTM scores with the clustering coefficient in right DLPFC. Although not exactly in DLPFC, Berg et al. had also reported increased activation in the right prefrontal cortex (in inferior frontal gyrus) in patients with PWT during writing tasks [8]. Although DLPFC may not be directly related to genesis of tremor, it does have a significant role in kinesthetic, motivational, and spatially related functions [29]. Previous fMRI studies have suggested possible role of right prefrontal cortex in choosing the direction or timing of movements [30, 31]. These observations may indicate involvement of DLPFC in PWT; however, further studies are required to explore the exact role of DLPFC in the neurobiology of PWT. Detailed neuropsychological evaluation was not done in the present study. As DLPFC is associated with executive functions, it is possible that disrupted small-world architecture reflects presence of subtle executive dysfunction in the PWT group in our study. Although we observed alterations in the small worldness in four different regions of the brain in PWT patients, it is unlikely that alterations in these regions are independent pathologies. As the clustering coefficients of bilateral medial cerebellum and left PPC correlated negatively with FTM scores, it is possible that both these regions are part of a complex neural network, alterations in which result in PWT. Interestingly, we did not observe any alterations in the connectivity of the motor cortices or thalamus in the patient group, which have been commonly reported in patients with ET. Hence, studies in future with larger sample size are warranted to confirm the results of our study.

If cerebellar involvement in PWT can be confirmed by further studies, it may have certain therapeutic implications. Repetitive transcranial magnetic stimulatiom (rTMS) has been widely used as a therapeutic measure in several movement disorders [32]. Gironell et al. [33] and Popa et al. [34] have reported significant improvement in tremor in patients with ET after cerebellar rTMS. As we observed alterations in the functional connectivity of bilateral medial cerebellum, they can be targets for therapeutic rTMS in patients with PWT in future clinical trials.

We recognize few limitations in this study and the low sample size is one of them. However, PWT is a rare movement disorder, and the current study is the largest one on PWT from the point of view of sample size. Nevertheless, these findings need to be confirmed by larger studies in future. Only MMSE was done to screen for the cognitive impairment in the subjects, which provides a lower level of diagnostic certainty compared to the extensive neuropsychological evaluations. As we observed changes in the functional connectivity in DLPFC and PPC, which are actively involved in several cognitive functions, comprehensive neuropsychological evaluations could have provided further insights into the actual role of these structures in PWT. Although we report altered measures of functional networks in medial cerebellum, left PPC, and right DLPFC, it is still unclear how exactly these regions

result tremor only while writing especially in the absence of functional alterations in motor cortex and thalamus. This warrants further studies exploring the roles of these areas in the pathogenesis of PWT.

Conclusion

To the best of our knowledge, this is the first rs-fMRI-based study on PWT. Patients with PWT have altered small-world functional brain connectivity compared to controls. The clustering coefficient, which is one of the important parameters of small worldness was significantly lower in right and left medial cerebellum, right DLPFC, and left PPC. In addition to substantiating the role of cerebelleum in PWT, results of this study also indicate possible involvement of PPC and DLPFC in the pathogenesis of PWT. Further fMRI studies involving a larger sample size and integrating neuropsychological evaluation are warranted to confirm the results of this study.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the National Institute of Mental Health and Neurosciences (NIMHANS) Ethics Committee, Bangalore, India, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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