Disrupted Brain Gray Matter Networks in Drug-Naïve Participants with Essential Tremor

Running title: Gray Matter Morphological Networks in Essential Tremor

Abstract

Purpose: To use structural magnetic resonance imaging and graph theory approaches to investigate the topological organization of the brain morphological network based on gray matter in essential tremor, and its potential relation to disease severity.

Methods: In this prospective study conducted from November 2018 to November 2019, 36 participants with essential tremor and 37 matched healthy controls underwent magnetic resonance imaging. Brain networks based on the morphological similarity of gray matter across regions were analyzed using graph theory. Nonparametric permutation testing was used to assess group differences in topological metrics. Support Vector Machine was applied to the gray matter morphological matrices to classify participants with essential tremor vs. healthy controls.

Results: Compared with healthy controls, participants with essential tremor showed increased global efficiency (p<0.01) and decreased path length (p<0.01), abnormal nodal properties in frontal, parietal and cerebellar lobes and dysconnectivity in cerebello-thalamo-cortical network. The abnormal brain nodal centralities (left superior cerebellum gyrus; right caudate nucleus) correlated with clinical measures, both motor (Fahn–Tolosa–Marìn Tremor Rating, p=0.017, r=-0.41) and nonmotor (Hamilton Depression Scale, p=0.040, r=-0.36; Hamilton Anxiety Scale, p=0.008, r=-0.436). Gray matter morphological matrices classified individuals with high accuracy of 80.0%.

Conclusion: Participants with essential tremor showed randomization in global attributes and dysconnectivity in the cerebello-thalamo-cortical network. Participants with essential tremor could be distinguished from healthy controls by gray matter morphological matrices.

Keywords: Essential tremor, graph theory, small world, gray matter, structural MR, machine learning.

1. Introduction

Essential tremor (ET) is one of the commonest neurological movement disorders [1]. The main clinical manifestations are tremor and bilateral abnormalities of upper limb motility and posture, often accompanied by other motor abnormalities and nonmotor features [2]. Brain abnormalities have been detected in ET. The cerebello-thalamo-cortical network defined as the “tremor network” is significantly altered [3]. There are alterations in functional connectivity at the whole-brain level, as well as in specific cortical regions related to clinical symptoms [4]. However, the topological organization of the brain morphological networks in ET is still poorly understood.

MRI studies in ET have mainly focused on structural alterations of local brain regions [5] or functional connectivity [6], neither of which captures the complex connectivity of the gray matter (GM) networks that support both motor and nonmotor processes. The graph theory approach to brain networks has become an important research tool in neurological diseases [4,7]. Most such research has focused on resting state fMRI or diffusion tensor imaging (DTI), and few studies have examined brain GM morphological networks. In this approach, structural MRI is used to characterize the whole brain connection pattern by calculating inter-regional morphological associations [8], based on the structural covariance analysis of GM volume or cortex thickness. Compared with fMRI/DTI, structural MRI has advantages in its practical simplicity, high signal-to-noise ratio, and relative insensitivity to artifacts (e.g. head motion) [9]. Moreover, cortical morphology reflects axon connectivity [10,11], so a structural MRI network approach is a promising addition to the toolkit for characterizing network-level brain organization in health and disease [12,13]. To date, studies have mainly used group-based network analysis, which is of limited value in

investigating individual variability, particularly in identifying structural brain abnormalities in single patients [14]. Recently, a method to describe the morphological networks of individual subjects using T1-weighted MRI scan statistics [9,15] has been applied to individuals at risk of schizophrenia [16] and patients with paroxysmal kinesigenic dyskinesia [17]. Investigation of individual GM structural networks in ET could provide new insights into the basis of the physiological, behavioral, emotional and cognitive abnormalities.

We used a graph-based model to construct an individual morphological network to explore the differences between ET participants and healthy controls (HC), then examined the relationships between individual abnormalities and clinical symptoms. We set out to test three hypotheses. First, given the evidence of abnormal functional network connectivity in ET [4], we hypothesized that, compared with HC, ET participants would show altered topological properties of individual morphological brain networks. Furthermore, given reports of focal abnormalities in the cerebello-thalamo-cortical network [3], we expected significantly altered nodal topological properties in this circuit. Second, based on reported relationships between network characteristics and clinical variables [4,18], we hypothesized that there would be a correlation between individual morphological brain network alterations and clinical severity of ET. Third, given the diagnostic potential of GM morphological network analysis in other brain disorders [19], we hypothesized that structural morphological properties could serve as a neuroimaging biomarker to distinguish ET from HC at the individual level.

2. **Materials and methods**

2.1. Participants

Study participants with ET were consecutively recruited at the movement disorders outpatient clinic of West China Hospital of Sichuan University from November 2018 to November 2019. This prospective study was approved by the local ethics committee of the West China Hospital of Sichuan University, and written informed consent was obtained from all ET participants (or their legal guardians) before enrollment.

Three neurologists experienced in movement disorders (JL, JP and RP, with 5, 4 and 33 years, respectively, clinical neurology experience), blinded to the final MRI results, confirmed the diagnosis of ET using the Consensus Statement on Tremor by the Movement Disorder Society [20]. All drug-naïve ET participants had prominent bilateral upper limb tremor lasting at least 3 years; none were taking anti-tremor treatments (including beta-blockers and GABA derivatives), benzodiazepine, antidepressant or antiepileptic medication; none had other neurological signs such as impaired tandem gait, questionable dystonic posturing, memory impairment, or any other neurological signs of unknown significance. The Fahn–Tolosa–Marìn Tremor Rating Scale (TRS, range 0-144) [21] was used to quantify the severity of ET (including tremor severity, specific writing/drawing tasks, functional disability), the Hamilton Depression (HAMD) and Hamilton Anxiety (HAMA) Scales to quantify depression and anxiety symptoms, respectively, the Mini-Mental State Examination (MMSE) to evaluate mental state, and the Montreal Cognitive Assessment (MoCA) as a rapid screen for cognitive impairment.

Exclusion criteria were: any history of stroke, epilepsy, dementia, psychiatric disease (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria) or

head trauma; tremors from other causes; cognitive impairment, defined according to conventional MMSE and MoCA criteria [22]. Finally, 36 participants with ET (mean age ± standard deviation: 50.0 ± 14.0 years; 16 male/20 female) were included in this study.

Healthy controls (HC) were recruited from the local area by poster advertisements and assessed by neurologists (JL and JP, with 5 and 4 years, respectively, of clinical neurology experience). They were excluded if they had any neurologic illness, or structural brain defects on T2 or T1 weighted images. Finally, 37 right-handed HC participants (age 52.4±6.3 years; 19 male/18 female) were included.

2.2. Data Acquisition and Preprocessing

All subjects underwent scanning in a 3.0 tesla whole-body MRI system (Tim Trio; Siemens Healthineers, Erlangen, Germany) with an 8-channel phased array head coil. A T1-weighted three-dimensional spoiled gradient-recalled sequence was used to obtain a high-resolution 3D-T1 weighted structural image. Participants were instructed to focus their thoughts on nothing in particular and to keep their eyes closed during the acquisition. Head motion was minimized by using foam pads. Two neuroradiologists (JY and XS, with 2 and 6 years, respectively, of neurological MRI experience) verified image quality and evaluated for clinical abnormalities in a double-blinded manner. Scanning parameters were: repetition time (TR) 1900 ms, echo time (TE) 2.26 ms, flip angle 9°, slice thickness 1 mm, single excitation, field of view 256 mm, voxel size 1 mm × 1 mm × 1 mm, 176 layers of sagittal image, matrix 176 × 202 × 200.

The 3D-T1 structural MRI images were processed by SPM12 software in MATLAB R2013b (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), by segmentation [23], manual check, then creation of template and normalization to

Montreal Neurological Institute (MNI) coordinate space using DARTEL. The details are given in Supplementary: MR Data Processing.

2.3. Network construction

An automated data-driven method [9] was used to construct individual structural brain networks based on regional morphological distribution. The network nodes were defined by parcellating the brain into regions of interest based on the Automated Anatomical Labeling 116 template. The Kullback-Leibler divergence-based similarity measure was used to quantify morphological connectivity between pairs of regions [15] and to estimate internodal or interregional network edges, allowing computation of brain networks for individual participants. The details are given in Supplementary: Brain Network Construction.

2.4. Network measures

Individual brain networks can be distinguished by differences in the number of edges [24]. To quantify this difference, a wide range of sparsity thresholds (S) was applied to each correlation matrix defined by the following criteria: the average node degree (the number of all edges connected to a node) of each threshold network over all nodes exceeds $2 \times \log(N)$ (where N is 116, the number of nodes); and the small world scalar σ of the threshold network of all subjects (as defined below) exceeds 1.1 [25].

We used GRETNA (http://www.nitrc.org/projects/gretna/) software to quantify network properties [26]: these are graph theory parameters which can be used to characterize the topological organization of large-scale functional and structural brain networks [7,27]. Both global and nodal network properties were calculated at each sparsity.

The global network properties include two measures: integration and segregation, which represent information processing patterns of the whole brain, ensuring efficient global communication and functional specialization [28]. Specifically, *topological integration* refers to the efficiency of global information communication (i.e. the ability to integrate distributed information in the network), and is measured by three parameters: characteristic path length (L_p), normalized characteristic path length (λ) and global efficiency (E_{glob}). L_p is calculated by averaging the minimum number of connections that link all pairs of network nodes [25]. λ is L_p expressed relative to the mean L_p of 100 matched random networks with the same number of nodes and edges as the real network. E_{glob} measures how efficiently information is exchanged at the global level [29]. *Topological segregation* refers to the ability of densely interconnected groups of brain regions to perform specialized processing procedures, and is measured by three parameters: network clustering coefficient (C_p), normalized clustering coefficient (γ) and local efficiency (E_{loc}). C_p, calculated by averaging over all network nodes, is equivalent to the fraction of each node's neighbors that are also neighbors of each other [25]. γ is the normalized C_p, expressed relative to the mean C_p of 100 matched random networks (as defined above for λ). E_{loc} measures how efficiently information is exchanged at the local level [29]: the level of clustering measured by E_{loc} expresses the local connectedness of a network, with high values interpreted as high levels of local organization [30]. The small-world index (σ) is defined as $\gamma \div \lambda$, which is > 1 when it fulfills the conditions of $\gamma > 1$ and $\lambda \approx 1$ [25].

The local network properties include three node centrality metrics, which are parameters used to determine the importance of a node: nodal degree, nodal efficiency and nodal betweenness [31]. Specifically, *nodal degree* reflects the capacity to communicate information, *nodal efficiency* characterizes the efficiency of parallel

information transfer, and *nodal betweenness centrality* captures the influence of a node over information flow between other nodes in the network. Details of the calculation, application and interpretation of all these metrics can be found in a methodological review [28].

Region pairs with between-group differences of nodal characteristics were identified using the network-based statistics (NBS) toolbox (http://www.nitrc.org/projects/nbs/). We included only nodes that exhibited significant between-group differences (p<0.05, uncorrected) in at least 2 of the 3 nodal centralities, then based on these nodes a connection matrix was created for each participant. All connections were then tested for significance (p<0.05 FWE-corrected network-level) using 5000 permutations, as described elsewhere [32].

2.5. Statistical analysis

The area under the curve was calculated for each network metric over the sparsity range $0.05 < S < 0.40$ with an interval of 0.01 (Supplemental Fig 1). The area under the curve provides a summary scalar of the network topology representation independent of a single threshold selection, and is a sensitive way to detect topological changes in brain networks [31,33].

A nonparametric permutation test (http://www.mathworks.com) was used to assess the significance of differences in the area under the curves of whole brain network metrics [34] and nodal characteristics between ET participants and HC. To address the multiple-comparisons false-positive issue, we adopted the false discovery rate correction method at a significance level of 0.05 [35].

When there were significant inter-group differences in a network metric, SPSS22

software (http://www.spss.com) was used to assess the relationship between these metrics and the symptom severity score and neuropsychological assessment, using multiple linear regression analysis, controlling age, gender and average education years as covariates.

To assess how effectively structural morphological measures can discriminate ET at the individual level, we applied Support Vector Machine to the GM morphological network matrices (116 × 116) to classify ET participants and HC. The model was based on LIBSVM [36] and implemented by the Scikit-Learn library [37], and the steps are described in Supplementary: Support Vector Machine Classification.

3. Results

3.1. *Demographic and clinical comparisons*

As shown in Table 1, there were no significant differences in age, sex and average education years between 36 ET participants and 37 HC. MMSE and HAMD scores of ET participants did show significant differences compared with HC ($p<0.05$).

3.2. *Alterations of global brain network properties*

Each participant had a higher average clustering coefficient ($\gamma>1$) and similar characteristic path length ($\lambda\approx1$) relative to random reference networks, showing that each network had a small world topology ($\gamma/\lambda>1.1$) (Fig 1. A). Participants with ET had significantly increased E_{glob} ($p=0.0002$) and decreased L_p ($p=0.0002$) compared with HC (Fig 1. B). There were no differences between groups in E_{loc} ($p=0.0546$), C_p ($p=0.4173$), γ ($p=0.0589$), λ ($p=0.0548$) or σ ($p=0.1960$).

3.3. Alterations of nodal brain network properties

Brain regions with significant between-group differences were defined by at least 2 abnormal nodal properties in the specific area (false discovery rate corrected, $p< 0.05$). ET participants showed significant changes in some brain regions compared with HC. There were decreased nodal centrality parameters in frontal gyrus (left dorsolateral/medial superior frontal gyrus, right inferior frontal gyrus, triangular/opercular part), right caudate nucleus, lateral hippocampus, left thalamus/angular gyrus and some areas of cerebellar cortex (left superior cerebellum gyrus: left cerebellum_3, left cerebellum_6; right superior cerebellum gyrus: right cerebellum_3; left inferior cerebellum gyrus: left cerebellum_10; right inferior cerebellum gyrus: right cerebellum_9, right cerebellum_10 and vermis_10).

In addition, ET showed increased nodal centrality parameters in right temporal pole (superior temporal gyrus) and left temporal pole (middle temporal gyrus) (Table 2; Fig 2).

3.4. Alterations of subnetwork connectivity

Using the NBS tool to identify network alterations of brain regions showing between-group differences of nodal properties, in the ET group we identified significantly increased connectivity alterations within networks comprising 12 nodes and 11 edges, and decreased connectivity alterations within networks comprising 11 nodes and 10 edges ($p<0.05$, T=3.0, corrected for multiple comparisons using FWE-corrected network-level). This subnetwork involved brain regions mainly in frontal, parietal and cerebellar lobes: details are shown in Fig 2.

3.5. Correlation between network changes and severity of clinical symptoms

The network efficiency of left cerebellum_6 (left superior cerebellum gyrus) was negatively correlated with the TRS score (r=-0.413, p=0.017) and the nodal degree of right caudate nucleus was negatively correlated with HAMD (r=-0.360, p=0.040) and HAMA (r=-0.436, p=0.008) (Fig 3). No correlations were found between any other global or nodal attributes and clinical scales.

3.6. Single-subject classification of ET and HC

It was possible to distinguish ET participants from HC at the single-subject level by using whole brain connection-wide matrices, with a balanced accuracy of 80.0%, sensitivity 78.6%, and specificity 81.5% (p< 0.001).

4. Discussion

Structural MRI can be used to characterize whole-brain connection patterns by using inter-regional morphological associations to define the topological organization of the brain GM morphological network. This powerful quantitative neuroimaging tool has not yet been applied in ET. The present study was designed to investigate alterations in the topological properties of single-subject GM morphological networks in ET participants, their correlations with clinical severity and their potential as diagnostic discriminators. We found alterations in ET in both global properties (increased global efficiency and decreased path length) and nodal properties (mainly in the cerebello-thalamo-cortical network and default mode networks). Some abnormal brain centralities (left cerebellum_6; right caudate nucleus) were correlated with clinical measures. GM morphological matrices classified individuals as ET *vs* HC with high accuracy of 80.0%.

In accordance with our first hypothesis (see Introduction), we found altered topological properties of individual morphological brain networks in ET participants. We briefly discuss the possible implications. To begin with altered *global* topological properties, the ET group showed a shift toward randomized organization, this being defined when there is at least 1 altered measurement of segregation (decreased C_p, γ or E_{loc}) and/or at least 1 altered measurement of integration (increased E_{glob} or decreased L_p or λ); in this group randomization was characterized by increased E_{glob} and decreased L_p. A similar pattern is seen in other neurological and psychiatric disorders, for example Alzheimer's disease (where it has been suggested that single-subject GM graph parameters have potential in monitoring disease progression) [38] and in post-traumatic stress disorder [39]. This pattern reflects a sub-optimal balance between local specialization and global integration: the likely functional consequence of a shift to a more randomized network is impaired modularized information processing and decreased fault tolerance [29]. Furthermore these changes in global network metrics may be causally linked to an increase in long-distance structural axon connections between remote brain areas [34] involving a specific network mainly comprising default mode regions (Fig 2): a decreased path length (Lp) means a decrease in the minimum number of edges between a node and another node, which is equivalent to a number of short distances turning into a long distance). Our findings of loss of small-world characteristics in ET reflect a less optimal topological organization in brain networks, providing further evidence that ET is a disorder with disrupted neuronal network organization.

Turning to *nodal* topologic properties, ET participants showed decreased nodal centralities in frontal gyrus, thalamus and some areas of cerebellar cortex, mainly focused on cerebello-thalamo-(frontal) cortical network (“tremor network”), implying

abnormal intra-connectivity. This is broadly consistent with resting-state evidence of altered functional connectivity in the cerebello-thalamic-cortical circuit in ET, correlated with severity of clinical symptoms [40]. Specifically, the decreased nodal centralities of cerebellar cortex in this circuit may be directly related to ET pathology [41]. About 75% of ET participants show abnormalities in the number and morphology of cerebellar Purkinje cells, the tissue-specific pathology characteristic of ET [42]. Additionally, we found that the efficiency of left cerebellum_6 was negatively correlated with the TRS clinical rating scale, confirming our second hypothesis (see Introduction) and consistent with an earlier finding [43] that abnormal functional connectivity in the cerebellar network correlates with severity score of ET. A range of clinical observations [44,45] link additional motor deficits in ET (such as ataxia, balance and gait disorders, impaired hand-reaching function and intention tremor) to cerebellar dysfunction. These findings all support the notion that the cerebello-thalamo-(frontal) cortical network plays a key role in tremor generation and propagation in ET.

In addition, ET participants showed abnormal nodal centralities in extra-motor areas. One of these is the default mode network (DMN), involving decreased nodal centralities in bilateral hippocampus and left angular gyrus. Furthermore, in analysis of subnetwork connectivity DMN had an increased connection with frontal, partial and cerebellar lobes. A resting-state fMRI study [18] reported increased functional connectivity between DMN and frontal and parietal lobes, suggesting that ET participants have changes in extra-motor functions which rely on the DMN executive and frontoparietal networks. One might speculate that this increased connectivity between DMN, frontal-parietal lobes and cerebellar lobes influences the coordination with whole-brain networks, presumably in response to the pathological disorder of ET.

In addition, right caudate nucleus showed decreased nodal centralities, which were negatively correlated with HAMD and HAMA scores. The caudate nucleus is a part of the basal ganglionic striatum with extensive afferent and efferent connections, and the cortico-striatal-thalamic network has important emotional and motor functions [46]. Abnormalities of the caudate nucleus could impair this, leading to emotional disturbance and depression [46]: this is seen in, for example Parkinson's disease [47] and major depressive disorder [48]. Indeed, ET also seems to be associated with mood disorder [49].

In support of our third hypothesis (see Introduction), structural network analysis using GM morphological matrices was able to distinguish ET from HC individually with a high classification accuracy of 80.0%. Graph-theory analysis provides a powerful framework for characterizing the topological properties of brain networks [50], which have considerable potential as diagnostic biomarkers. Connectome-wide functional connectivity based on resting-state fMRI data permits accurate differentiation of individuals with schizophrenia from HC [51], supporting functional connectivity as a powerful tool for characterizing brain disorders at the individual level [52]. Our results suggest the same may be true of brain structural connectivity, consistent with the identification in ET of abnormalities of whole brain network integration as well as regional atrophy [53,4]. Although machine learning is not yet clinically available, it has potential to meet the need for an objective diagnostic test in the early stages of the disease, improving detection and reducing misdiagnosis. Future studies should investigate how specific our findings are to ET.

Our study has several limitations. First, we calculated interregional similarity (as quantified by the Kullback-Leibler divergence-based similarity) in the distributions of

GM volume to define morphological connectivity. However, the biological basis of this similarity is not clear, and more evidence is needed. Second, we used the Automated Anatomical Labeling 116 Atlas to parcellate the whole brain into 116 regions; however, the choice of template (such as Desikan-Killiany template) for constructing brain networks may affect the network analysis results, and future studies should examine this explicitly. Third, we only evaluated one imaging modality and one classification method; moreover, the high accuracy of classification in this sample does not necessarily imply real-world clinical utility [54]. Future research should aim to define the optimal methodology by using multimodal neuroimaging data and evaluating different classification methods. Fourth, the correlation between the clinical symptom scores and abnormal topological properties did not survive application of controls for multiple comparisons, perhaps because of our relatively small sample size. Fifth, MoCA in the current study was lower than the normal standard [22], perhaps because of effects of education [22,55,56] and age [56] on MoCA scores. Sixth, future studies should study differences between drug-naive and treated ET cohorts to evaluate the effect of the medication on brain network topology.

In summary, our analyses of topological brain morphology networks indicate a shift toward a randomized configuration with possible functional relevance to symptomatology in participants with essential tremor. Furthermore, disrupted nodal centralities in the cerebello-thalamo-(frontal) cortical network and default-mode properties may have a wider impact on brain systems in essential tremor. Finally, the morphology network matrices permitted differentiation of essential tremor from healthy controls with significant accuracy. Our findings provide hope that clinical application of this novel neuroimaging approach could be useful for diagnosis and predicting treatment response in essential tremor.

Conflicts of interest:

The authors declare that they have no conflict of interest.

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Figure legends

Fig 1. Network properties of brain grey matter morphological networks in the ET and HC groups. A, For both groups normalized Cp > ~1 and Lp < ~1 are typical features of small-world topology independent of assumed sparsity (0.05<S<0.40). B, Global topological attribute differences in the ET group relative to HC. Abbreviations: HC, healthy control; ET, essential tremor; AUC, area under the curve; Eglob, global efficiency; Lp, path length; Cp, clustering coefficients.

Fig 2. Differences in nodal topological attributes and network connectivity in brain gray matter morphological networks between the ET and HC groups. Each node denotes a brain region and each line denotes a connection, mapped onto the cortical surfaces using BrainNet software (http://www.nitrc.org/projects/bnv). For nodes, red (blue) color represents areas of increased (decreased) morphological connections; for connections, orange (gray) represents increased (decreased) brain connectivity. Abbreviations: HC, healthy controls; ET, essential tremor; HIP, hippocampus; SPG, superior parietal gyrus; SFGdor, superior frontal gyrus, dorsolateral; IFGoperc, inferior frontal gyrus, opercular part; IFGtriang, inferior frontal gyrus, triangular part; SFGmed, superior frontal gyrus, medial; SPG, superior parietal gyrus; ANG, angular gyrus; CAU, caudate nucleus; THA, thalamus; TPOsup, temporal pole: superior temporal gyrus; TPOmid, temporal pole: middle temporal gyrus; CRBL, cerebellum; _3/_6, superior; _9/_10, Inferior. R, right; L, left.

Fig 3. Brain regions which show abnormal nodal centralities in the brain gray matter morphological networks in ET participants, and their relationships with clinical variables.

A, regions with abnormal nodal centralities in ET which were associated with clinical

symptom severity. B, nodal efficiency of left cerebellum_6 (left superior cerebellum gyrus) was significantly correlated with TRS score. C, nodal degree of right CAU was significantly correlated with HAMD and HAMA scores.

Abbreviations: CAU, caudate nucleus; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; TRS, Fahn–Tolosa–Marìn Tremor Rating Scale.