Graph theory analysis of resting-state functional magnetic resonance imaging in essential tremor

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Introduction

The brain is a complex network in which information is transmitted between functionally linked regions.

Functional connections are organized in a highly efficient small-world manner, characterized by a high level of local neighborhood clustering, along with the existence of connections that guarantee a high level of global communication efficiency within the overall network.

The graph theory approach has been recently applied to data obtained from resting-state functional MRI (rs-fMRI), in order to characterize the functional connectivity within the whole-brain network.

This technology has enabled the characterization of the human brain as a highly efficient large-scale network consisting of nodes or vertices (i.e., brain regions) and pair-wise edges (i.e., functional connectivity) which tend to a highly clustered organization also known as “small-world” network.

Essential tremor (ET) is a neurological disease with both motor and non-motor manifestations, including cognitive dysfunction; however, little is known about its underlying brain basis.

Furthermore, the overall organization of the brain network in ET remains largely unexplored.

Given the relationship between Parkinson’s disease and ET, we hypothesized that in ET patients the topological organization of whole-brain functional networks is disrupted, and that these alterations may be associated with motor and non-motor manifestations (i.e., cognitive dysfunction).

In order to test this hypothesis, rs-fMRI data were acquired from both ET patients and healthy controls.

Graph theory was subsequently used to investigate the differences in the global and regional topological properties between both groups.

Furthermore, we tested correlations between the altered graph theory metrics and clinical variables (e.g., duration and severity of tremor) and neuropsychological tests, and searched for potential topological features that may serve as neuroimaging biomarkers for ET.

Methods

All procedures were approved by the ethical standards committees on human experimentation at the University Hospital “12 de Octubre” (Madrid). Written (signed) informed consent was obtained from all enrollees.

ET patients were consecutively recruited from October 2012 to July 2013 from the outpatient neurology clinic of the University Hospital “12 de Octubre” in Madrid (Spain). A 20 minute, semi-structured, tremor interview was conducted in which demographic information and data on tremor (e.g., duration) were collected.

Two neurologists with expertise in movement disorders (J.B.-L. and J.P.R.), who were blinded to the MRI results, examined the patients and used the Fahn-Tolosa-Marìn tremor rating scale to assign a total tremor score (range = 0 – 144).

Diagnoses of ET were assigned by the two neurologists using the Consensus Statement on Tremor by the Movement Disorder Society.

Healthy controls were recruited either from relatives or friends of the health professionals working at the University Hospital “12 de Octubre” of Madrid (Spain) or among the relatives of patients who came to the neurological clinics for reasons other than ET (e.g., headache, dizziness).

All participants underwent a rs-fMRI and a detailed neuropsychological assessment covering the domains of attention, executive functions, visuospatial and visual functions, verbal memory and language. In order to simplify the neuropsychological assessment for subsequent correlation with the graph theory metrics, we reduced the tests results into a reduced number of composites results.

Graph theory analysis

In order to define the network nodes, the whole brain data of each participant were parceled into 91 cortical areas and 15 subcortical areas from the FMRIB Software Library's Harvard-Oxford atlas and 26 cerebellar areas from the Anatomical Automatic Labeling atlas.

The bivariate correlation of BOLD timeseries between every pair of regions of interest (ROIs) defined by the parcellation was computed for each participant. The scrubbing regressors, provided by CompCor, Artifact Removal Tool and the motion parameters estimated for each participant, were included as covariates.

The resulting correlation matrix for each participant was binarized using only those thresholds that yielded no disconnected nodes in any participant (in our case, ≤ 0.17).

Thus, connectivity matrixes were calculated for every threshold between 0.01 and 0.17, in steps of 0.01, and graphs were built for each subject. In order to understand the functional characteristics of the network, several metrics were explored for each graph. Specifically, Global Efficiency (GE), Local Efficiency (LE), Betweenness Centrality (BC), Cost, Average Path Length (APL), Clustering Coefficient (CC) and Degree were calculated using CONN. Additionally, the small worldness coefficient was calculated using in-house software developed in Matlab (Mathworks Inc.).

Results

No significant differences between both groups in demographic variables were observed (Table 1). As expected, ET patients’ cognitive performance was significantly worse than that of the healthy controls, mainly on attention, executive functions, and language.

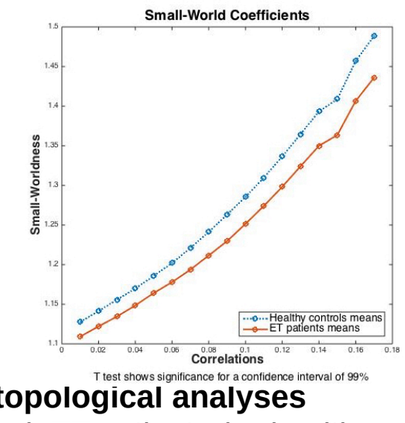
Table 1: Comparison of demographic, clinical and cognitive domains of essential tremor patients vs. healthy controls.

	Essential tremor patients (N = 23)	Healthy controls (N = 23)	*p* value
Age in years	63.3 (68.0) ± 13.4	61.1 (62.0) ± 13.1	0.409[a]
Sex (female)	12 (52.2%)	13 (56.5%)	0.767
Educational level			0.162
Can read and write	8 (34.8%)	4 (17.4%)	
Primary studies	8 (34.8%)	5 (21.7%)	
Secondary studies	5 (21.7%)	7 (30.4%)	
University studies	2 (8.7%)	7 (30.4%)	
Dominant Hand			0.368
Right-handedness	22 (50%)	22 (50%)	
Left-handedness	1 (100%)	0 (0%)	
Mixed-handedness	0 (0%)	1 (100%)	
Tremor duration, years	22.9 (20.0) ± 16.5	-	
Fahn-Tolosa-Marin tremor rating scale score	30.3 (30.5) ± 15.3	-	
Cognitive domains			
Attention			
Direct Digit Span test from the WAIS-III	5.6 (5.0) ± 1.4	5.9 (6.0) ± 1.3	0.428[a]
WAIS-III Digit Symbol--Coding subtest	33.0 (27.0) ± 17.4	53.3 (50.0) ± 19.4	0.010[b]
Executive functions			
Stroop Color–Word Trial	26.4 (27.5) ± 13.3	33.4 (38.0) ± 12.1	0.070[b]
Frontal Assessment Battery	15.4 (16.0) ± 2.9	16.8 (17.0) ± 1.0	0.040[a]
WAIS-III Similarities subtest	16.2 (16.0) ± 6.3	18.2 (18.0) ± 5.6	0.264[b]
Indirect Digit Span test from the WAIS-III	3.8 (4.0) ± 1.2	4.3 (4.0) ± 1.1	0.094[a]
Controlled Oral Word Association Test	26.8 (28.0) ± 13.6	37.0 (39.0) ± 13.1	0.010[b]
Visuospatial and visual functions			
Brief Visuospatial Memory Test-Revised			
Learning total	23.0 (22.0) ± 9.6	27.6 (28.0) ± 6.7	0.080[b]
Delayed free recall trial	8.5 (10.5) ± 3.6	10.1 (11.0) ± 2.4	0.181[a]
Recognition trial	11.4 (12.0) ± 0.9	11.8 (12.0) ± 0.5	0.114[a]
Hooper Visual Organization Test	35.8 (36.0) ± 9.4	40.9 (39.0) ± 8.7	0.060[b]
Verbal memory			
WMS-III Word List			
Learning list	28.3 (28.0) ± 5.6	29.0 (28.0) ± 6.4	0.698[b]
Immediate recall	6.3 (6.0) ± 2.4	6.9 (7.0) ± 2.3	0.386[b]
Delayed recall	5.5 (6.0) ± 2.6	6.8 ± (7.0) 2.3	0.080[b]
Recognition	21.7 (22.0) ± 2.1	22.3 (22.0) ± 1.4	0.395[a]
Language			
Boston Naming Test	44.7 (44.0) ± 11.7	52.6 (53.0) ± 5.2	0.008[b]
Total number of animals as possible in one minute	18.7 (17.0) ± 8.4	21.5 (21.0) ± 6.8	0.090[a]
Depressive symptoms			
17-item Hamilton Depression Rating Scale total score	6.8 (7.0) ± 5.0	5.8 (5.0) ± 5.0	0.541[b]

Mean (median) ± standard deviation and frequency (%) are reported. [a]Mann-Whitney U test or [b]Student's t-test were used for comparisons of continuous data, and X2 test for proportions. WAIS-III = Wechsler Adult Intelligence Scale-Third Edition. WMS-III = Wechsler Memory Scale-Third Edition.

Global graph topological analyses

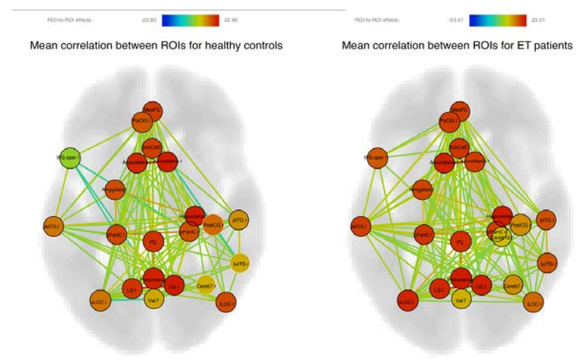
The independent-samples t-test revealed inter-group differences (healthy controls > patients; p < 0.01) in small-worldness (Figure 1).



Regional graph topological analyses

At the regional level, ET patients (vs healthy controls) showed higher values of GE, cost and degree, and a shorter APL in the left inferior frontal gyrus (pars opercularis), right inferior temporal gyrus (posterior division), right inferior temporal gyrus (temporo-occipital part), right inferior lateral occipital cortex, left paracingulate, precuneus bilaterally, left lingual gyrus, right hippocampus, left amygdala, nuclei accumbens bilaterally and left middle temporal gyrus (posterior part).

In other ROIs, ET patients showed higher LE and CC than healthy controls. These regions include the frontal medial cortex bilaterally, subcallosal cortex, posterior cingulate cortex, parahippocampal gyri bilaterally (posterior division), right lingual gyrus, right cerebellar floculus, right postcentral gyrus, right inferior semilunar lobule of cerebellum and culmen of vermis. Finally, the right intracalcarine cortex and the left orbitofrontal cortex showed a shorter APL in ET patients, while the left frontal operculum and the right planum polare showed a higher BC in ET patients.



The above observed changes in connectivity patterns are mostly involved in the pathogenesis of the several non-motor features previously described in ET, such as cognitive dysfunction, depression, singular personality, and impaired visual-motor integration.

Relationships between network characteristics and neuropsychological variables and disease variables in ET patients

Correlation analyses revealed a relationship (p < 0.05) between attention and the graph theory metrics in the left parahippocampal gyrus, left lingual gyrus, right hippocampus, left amygdala and right nucleus accumbens; and between executive functions and graph theory metrics in the right hippocampus, left amygdala and right nucleus accumbens. Additionally, other cognitive domains and clinical variables, such as verbal memory, language, visuospatial functions and depressive symptoms were correlated with the right nucleus accumbens and the posterior cingulate. No relationship between any graph theory metric and tremor severity or duration was observed.

Conclusions

We found differences between ET patients and healthy controls both at the global and the local level, suggesting that ET is characterized by lower small-world values of the network.

At the regional level, we found the existence of multiple connectivity differences in motor and extra-motor related areas.

These data furthermore support the concept that ET is a disorder that disrupts widespread brain regions, including those outside of the brain regions responsible for tremor (i.e., cerebellum, thalamus, motor cortex).