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

(Short title: Functional connectivity and graph theory in essential tremor)

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ABSTRACT. Essential tremor (ET) is a neurological disease with both motor and non-motor manifestations; however, little is known about its underlying brain basis. Furthermore, the overall organization of the brain network in ET remains largely unexplored. We investigated the topological properties of brain functional network, derived from resting-state functional MRI data, in 23 ET patients vs. 23 healthy controls. Graph theory analysis was used to assess the functional network organization. At the global level, the functional network of ET patients was characterized by lower small-world values than healthy controls - less clustered functionality of the brain. At the regional level, compared with the healthy controls, ET patients showed significantly higher values of global efficiency, cost and degree, and a shorter average path length in the left inferior frontal gyrus (pars opercularis), right inferior temporal gyrus (posterior division and temporo-occipital part), right inferior lateral occipital cortex, left paracingulate, bilateral precuneus bilaterally, left lingual gyrus, right hippocampus, left amygdala, nucleus accumbens bilaterally, and left middle temporal gyrus. In addition, ET patients showed significant higher local efficiency and clustering coefficient values in the frontal medial cortex bilaterally, subcallosal cortex, posterior cingulate, parahippocampal gyri bilaterally (posterior division), right lingual gyrus, right cerebellar flocculus, right postcentral gyrus, right inferior semilunar lobule of cerebellum and culmen of vermis. In conclusion, the efficiency of the overall brain functional network in ET is disrupted. Further, our results support the concept that ET is a disorder that disrupts widespread brain regions, including those outside of the brain regions responsible for tremor.

INTRODUCTION

The current view of essential tremor (ET), one of the most common adult neurological disorders (Benito-León, 2009; Louis and Ferreira, 2010), is that it may be a family of diseases, unified by the presence of kinetic tremor, and characterized by etiological, clinical and pathological heterogeneity (Benito-León, 2014; Benito-León and Louis, 2006; Benito-León and Louis, 2007; Benito-León and Louis, 2011a; Benito-León and Louis, 2011b). Aside from classic motor manifestations, ET is now considered a heterogeneous entity associated with a number of non-motor manifestations,(Sengul, et al., 2015a; Sengul, et al., 2015b) including cognitive disorders (Benito-León, et al., 2006a; Benito-León, et al., 2006b; Benito-León, et al., 2011; Bermejo-Pareja, et al., 2007; Cersonsky, et al., 2018; Collins, et al., 2017), depressive symptoms (Louis, et al., 2007), personality changes (Thenganatt and Louis, 2012), changes in sleep patterns (Benito-León, et al., 2013; Gerbin, et al., 2012), changes in visual reaction time (Jiménez-Jiménez, et al., 2010), and hearing impairment (Benito-León, et al., 2007; Ondo, et al., 2003).

Clinical and neuroimaging data suggest that ET motor symptoms could arise from cerebello-thalamo-cortical network abnormalities (Benito-León, 2014; Benito-León and Louis, 2006; Benito-León and Louis, 2007; Benito-León and Louis, 2011a; Benito-León and Louis, 2011b). Several studies have also demonstrated the presence of tremor-related activity in cerebral cortical structures (Ibanez, et al., 2014;

Raethjen, et al., 2007). In line with this, changes in the integrity of frontal and parietal areas involved in movement sequencing might be associated with tremorgenic activity in ET (Benito-León, et al., 2019), similar to that suggested for Parkinson's disease (Benito-León, et al., 2018). Notwithstanding, very little is known about the underlying causes and alterations in brain networks, mainly those involved in non-motor manifestations in ET, and, hence, further study is needed.

There are fewer neuroimaging studies that have examined functional alterations in ET patients (Louis, et al., 2014), especially those which acquired data during resting state conditions (i.e., with participants awake, but relaxed and not involved in any task). Resting-state functional MRI (rs-fMRI), is a suitable neuroimaging modality for the evaluation of many neurological and psychiatric diseases (Barkhof, et al., 2014; Benito-León, et al., 2016; Hacker, et al., 2012). To date, only a few studies have explored connectivity alterations in ET, and those that did were mainly focused on the cerebello-thalamo-cortical network, which is mainly related to motor symptoms (Buijink, et al., 2015; Caligiuri, et al., 2017; Mueller, et al., 2017), or on the study of surgical therapeutic applications (Akram, et al., 2018; Tuleasca, et al., 2018). In a recent study, ET patients showed increased connectivity in resting-state networks involved in cognitive processes and decreased connectivity in the cerebellum and visual networks (Benito-León, et al., 2015). Changes in network integrity were associated not only with ET severity and ET duration, but also with cognitive ability. (Benito-León, et al., 2015) Further, in at least three networks (default mode network and frontoparietal networks), increased connectivity was associated with worse performance on different cognitive domains and depressive symptoms.(Benito-León, et al., 2015)

Neither seed-based functional connectivity nor the independent component analysis approach, which are the most widely used rs-fMRI analysis techniques, can completely characterize the brain functional network (Calhoun and de Lacy, 2017; Joel, et al., 2011), which is in turn dynamic, as it provides support for several cognitive and emotional processes (Carhart-Harris and Friston, 2010; Deco, et al., 2011) that might be altered in ET. For that reason, the graph theory approach has been recently applied to data obtained from rs-fMRI, to characterize the functional connectivity within the whole-brain network (Medaglia, 2017; Wang, et al., 2010a) with a moderate to high reliability (Braun, et al., 2012). 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 (Medaglia, 2017; Wang, et al., 2010a). Lower small-worldness values are related with worse performance in neuropsychological tasks(Langer, et al., 2013))(Douw, et al., 2011) and are commonly found in a wide variety of diseases, such as schizophrenia or epilepsy, when comparing with healthy control groups (Lynall, et al., 2010; Vlooswijk, et al., 2011). Graph theory analysis also provides regional metrics to define the connectivity properties of particular brain regions, such as their connections with the rest of the brain, the length of these connections or the relationship with their nearest regions (Wang, et al., 2010b). Unlike previous techniques, graph theory approach permits one to not only visualize the overall connectivity pattern among all the brain regions, but also to quantitatively characterize the global organization (Medaglia, 2017; Wang, et al., 2010a) providing a novel insight into the biological mechanisms of many neurological diseases, such as mild cognitive impairment and Alzheimer's disease (Khazaee, et al., 2016), epilepsy (Chiang, et al., 2014), Huntington's disease, and Parkinson's disease (Gargouri, et al., 2016; Gottlich, et al., 2013; Sreenivasan, et al., 2019; Zhang, et al., 2015), among others. Only one previous study applied graph theory analysis to longitudinal rs-fMRI data in eight ET patients before and after a focal lesion in the ventralis intermedius nucleus of the thalamus, using MRI-guided high-intensity focused ultrasound(Jang, et al., 2016). Thalamotomy led to changes in both the global brain network and motor circuit (Jang, et al., 2016). However, the fact that the sample size was small (N=8) as well as selection factors (e.g., as surgical patients, the ET patients included in the study had a more severe form of the disease) does not permit one to draw reliable conclusions. Hence, the topological organization of whole-brain functional networks in ET patients remains largely unknown. The identification of specific abnormalities of the efficiency of the brain functional network at the global and regional levels in ET could provide novel insights into the understanding of underlying pathological mechanisms of this entity.

Given the relationship between Parkinson's disease and ET (Benito-León, et al., 2009; LaRoia and Louis, 2011; Louis and Ottman, 2013; Tarakad and Jankovic, 2018), 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). 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.

Participants

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).(Jankovic and Tolosa, 1988)

Diagnoses of ET were assigned by the two neurologists using the Consensus Statement on Tremor by the Movement Disorder Society.(Deuschl, et al., 1998)

ET patients with a history of stroke, epilepsy, or head trauma were excluded from the study. Furthermore, based on a detailed clinical mental status examination, we excluded ET patients with dementia, using the Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV criteria.(American Psychiatric, 1994) or mild cognitive impairment, using Peterson/Winblad criteria (Petersen and Morris, 2005; Winblad, et al., 2004) (impairment on one neuropsychological score defined as at least 1.5 standard deviation [SD] below normative expectations).

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). Enrolment at clinics was consecutive, beginning in October 2012. Controls were age-frequency-matched to the ET patients. None of the controls had a history of a neurological disorder (e.g., ET, Parkinson's disease, dementia) and none had received a neurological diagnosis from a physician. None reported having a first-degree or second-degree relative with ET or Parkinson's disease. Each control was examined by two neurologists (J.B.-L. and J.P.R.), who were blinded to the MRI results, to further rule out any neurological conditions, including dementia, using DSM–IV criteria,(American Psychiatric, 1994), mild cognitive impairment, using Peterson/Winblad criteria (Petersen and Morris, 2005; Winblad, et al., 2004), Parkinson's disease or any other movement disorders.

Neuropsychological Assessment

All participants underwent a detailed neuropsychological assessment covering the domains of attention (Direct digit span and Digit Symbol--Coding both from WAIS-III), executive functions (Stroop Color–Word Trial, Frontal Assessment Battery, WAIS-III Similarities subtest, Indirect Digit Span test from the WAIS-III, and the Controlled Oral Word Association Test), visuospatial and visual functions (Brief Visuospatial Memory Test-Revised, Benton Judgment of Line Orientation Test, and the Hooper Visual Organization Test), verbal memory (WMS-III Word List), and language (Boston Naming Test and total number of animals as possible in one minute).(Benito-León, et al., 2015; Puertas-Martin, et al., 2016) In addition, severity of depressive symptoms was measured by the original 17-item version of the Hamilton Depression Rating Scale.(Hamilton, 1960). For the current study, we applied the Bech criteria to classify depressive symptoms as minor depression or dysthymia (score ranging from 8 to 14), and moderate or severe depression (≥15).(Bech, 1993)

Testing was performed by a trained neuropsychologist using standardized procedures. The entire neuropsychological battery took approximately 1.5 h to administer. The tests, which have been described elsewhere, (Bermejo-Pareja and Puertas-Martin, 2012), were selected in part to avoid the effects of any hand tremor because they made, in general, minimal demands on motor processes. Raw scores were transformed into z scores based on the mean and SD values from healthy controls. Higher z scores indicate better performance.

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.(Ackerman and Cianciolo, 2000) All tests results were z-standardized. Then, a factorial analysis (principal components analysis) of these z-scores, excluding the 17-item version of the Hamilton Depression Rating Scale score that constituted a factor by itself, revealed four factors grouping these tests. The cognitive domain of tests was also considered, and then the first factor was divided into three, obtaining the six following composites (Table 1): attention (Direct digit span and digit-symbol coding both from WAIS-III), executive functions (Stroop Color–Word Trial, Frontal Assessment Battery, WAIS-III Similarities subtest and Indirect Digit Span test from the WAIS-III), visuospatial and visual functions (learning list and delayed recall from the Brief Visuospatial Memory Test-Revised, and the Hooper Visual Organization Test), recognition (WMS-III recognition, recognition from the Brief Visuospatial Memory Test-Revised), verbal memory (learning list, immediate recall and delayed recall from the WMS-III) and language (Boston Naming Test, total number of animals as possible in one minute, and Controlled Oral Word Association Test). The 17-item version of the Hamilton Depression Rating Scale score was used individually. The Benton Judgment of Line Orientation Test was excluded because it did not correlate with any factor. The composite score was then used as a continuous variable in partial correlation analyses with the network metrics, controlling the effect of sex and age.

MRI procedure

Patients and healthy controls were positioned in the scanner and immobilized with a custom-fit blue bag vacuum mold (Medical Intelligence, Inc.) to prevent image artifacts. Earplugs and noise-reduction headphones were used to attenuate scanner noise. A strict criterion for head movement assessment was adopted (maximal absolute head movement less than 1.0 mm and 1.0° in the x, y, and z directions). Neither ET patients nor healthy controls were excluded from the analysis due to this criterion.

Images were acquired on a General Electric Signa 3T MR Scanner (General Electric Healthcare, Fairfield, CT) using a whole-body radiofrequency (RF) coil for signal excitation and quadrature 8-channel coil for reception. For the structural image, a high-resolution, three-dimensional T1-weighted gradient Echo-SPGR was acquired (TR = 9.2ms, TE = 4.128ms, TI = 500ms, field of view = 240mm, acquisition matrix = 240x240, slice thickness = 1 mm, full brain coverage, resolution = 1x1x1mm, flip angle = 120º, and 166 sagittal slices).

Resting-state fMRI data consisted of 120 volumes of a repeated gradient-echo echo planar imaging T2*-weighted sequence (repetition time (TR) = 3s, echo time (TE) = 28ms, voxel dimensions = 2.7x2.7x2.8 mm, 39 oblique ACPC-oriented slices, flip angle=90º, and 6 dummy scans). During the functional acquisition (total run = 6 minutes), participants were instructed to relax with their eyes closed and not to engage in cognitive or motor activities.

All volumes were visually reviewed and manually reoriented. Preprocessing was performed using CONN (available at https://www.nitrc.org/projects/conn) and SPM12 (available at: http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The preprocessing pipeline included: fieldmap correction, realign and unwarp, slice-timing correction, denoising (CompCor and Artifact Removal Tool), normalization to MNI space, and smoothing (FWHM 8mm).

Graph theory analysis

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 (available at http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and 26 cerebellar areas from the Anatomical Automatic Labeling atlas.(Tzourio-Mazoyer, et al., 2002) The bivariate Pearson 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. Due to the large amount of comparisons between groups that the graph theory analysis implies, and the fact that all the metrics in a node are highly interrelated, the correction for multiple comparisons in analysis requires a special treatment. An option is to apply a correction over the graph prior to network analysis, thresholding the connectivity matrixes. The thresholding method has proved capable of reducing the false positives resulting of the comparison of low correlated nodes between groups.(Drakesmith, et al., 2015). For this reason, the correlation previously obtained for all participants were binarized, thresholding them over increasing correlation values in steps of 0.1, starting from 0.1. The maximum threshold selected was the value for which every node remained connected with at least one other node (in our case ≤ 0.17). Thus, within the maximum threshold, every node has at least one correlation of 0.17 or higher with another node and no node becomes isolated. To simplify the interpretation of the results, the thresholds are always positive, and therefore the resulting binarized matrixes represent only positive correlations between nodes. The resulting 17 binarized connectivity matrices for each subject constituted the graphs in the subsequent analyses.

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.). This metric is the result of dividing the γ clustering coefficient by the λ average path length coefficient, where $\gamma = Cp/Cp{-}rand$ and $\lambda = Lp/Lp{-}rand$ (Cp and Lp are the average of the clustering coefficients and APL coefficients over all nodes respectively, and Cp-rand and $Lp{-}rand$ are the same averages, but calculated from a matched random network). This random network was created using the Brain Connectivity Toolbox (available at https://www.nitrc.org/projects/bct/), always preserving the degree of the original network and randomly rewiring each pair of nodes when possible. The definitive γ and λ were the result of averaging 50 repetitions of each parameter with different random networks each time. After that amount of repetitions, the coefficient values remain stable.

Sample Size and Statistical Analyses

In several recent publications on suitable sample sizes for functional neuroimaging studies using graph theory analysis, it has been found that a group size of approximately 20 is sufficient.(Gargouri, et al., 2016; Sreenivasan, et al., 2019)

Statistical analyses were conducted using R (available at https://www.r-project.org/). Mean scores (age and neuropsychological variables) were compared using Student's t-tests for continuous and normally distributed data, and Mann–Whitney U test for non-normally distributed data, where appropriate, while a chi-squared test was used to compare the sex and educational level distribution between the two groups.

The differences between groups for each graph theory metric (GE, LE, BC, cost, APL, CC and degree) were analyzed through univariate analyses of covariance, including age, sex, dominant handedness, and educational level as covariates. The educational level was coded from 1 to 4 (1 – under primary education; 2 – primary education; 3 – secondary education; and 4 –university studies). Levene's test was used to explore the homoscedasticity of the factors to meet the analysis of variance assumptions. Marginal means estimation informed about the direction of the differences. Bonferroni correction for multiple comparisons was applied for the seven metrics contrasts of each ROI and threshold (correction over seven tests) to diminish the Type I error of simple effects. Every ROI and the whole network were analyzed through the 17 correlation thresholds previously determined (0.01 to 0.17). An independent samples t-test was used to compare the small-worldness between groups.

Finally, the partial correlation coefficient was used to analyze the correlations between the ROIs that showed inter-group differences and both the cognitive domains (neuropsychological assessment composites) and the clinical variables (duration and severity of disease) in ET patients, controlling the effect of age and sex.

DATA AVAILABILITY

The original database from the study can be obtained by contacting the first author (J.B.-L.).

RESULTS

Clinical and neuropsychological testing results

Of the 26 ET patients who were initially eligible, two had ET with dystonic features after reviewing their videotapes by a senior expert in movement disorders (E.D.L) and were therefore excluded. One was excluded from the final analyses because he developed incident Parkinson's disease during follow-up. None of the patients and healthy controls were excluded because of neurological comorbidities, including dementia or mild cognitive impairment, or structural abnormalities on conventional MRI images. According to Fazekas visual rating scale, all participants had Fazekas score ≤1 (i.e., normal in the elderly).(Fazekas, et al., 1987)

The final sample included 23 ET patients (12 women and 11 men) and 23 healthy controls (13 women and 10 men). No significant differences between both groups in demographic variables (age, sex, handedness and educational level) were observed (Table 1).

The mean tremor duration was 22.9 ± 16.5 and the mean total tremor score was 29.3 ± 15.7 (median 30). (Table 1). In addition to arm tremor, rest tremor was also present on tremor examination in six (26.1%) ET patients. Further, head tremor was also present in seven (30.4%) ET patients. In these seven patients, the head tremor was intermittent, and it took place in the "yes-yes" direction". All the ET patients had a normal [(123) I]FP-CIT single photon emission computed tomography scan. Fifteen (65.2%) were taking one or more anti-tremor medications (six propranolol, one primidone, one clonazepam, one clonazepam and propranolol, one gabapentin and primidone, one primidone and propranolol, one zonisamide and primidone, one zonisamide and propranolol, one zonisamide, primidone, and alprazolam, and one zonisamide, primidone, and propranolol).

The results of neuropsychological performance are listed in Table 1. As expected, ET patients' cognitive performance was significantly worse than that of the healthy controls, mainly on attention, executive functions and language. No participant met criteria for mild cognitive impairment. Of the 23 ET patients, 15 had no depression (65.2%), six (26.1%) had dysthymia or moderate depression and two (8.7%) had severe depression vs. 16 without depression (69.6%), seven (30.4%) with dysthymia or moderate depression and none (0.0%) with severe depression in the healthy control group ($p = 0.348$, Fisher exact test).

Global graph topological analyses

Analyses of covariance showed inter-group significant differences in the first three levels of correlation (0.01-0.03). Pairwise comparisons of the marginal means showed differences in BC and APL (healthy controls > ET patients; $p < 0.05$ Bonferroni corrected), and GE, cost, and degree (ET patients > healthy controls; $p < 0.05$ Bonferroni corrected) (Table 2). Sex was the only covariate that showed a significant effect over most dependent variables. No other significant effects or interactions were found.

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

Regional graph topological analyses

Table 3 shows the significant differences between both groups in each ROI at a 0.17 correlation threshold. Figure 2 shows the mean binary adjacency matrixes for the 0.17 correlation by groups. Some metrics were consistently significant at a lower correlation, such as 0.15, and were included as interesting ROIs (highlighted with “a” in Table 3).

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. Figure 3 shows all the significant ROIs obtained and their interconnections.

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 (see Table 4).

Relationships between network characteristics and neuropsychological variables and disease variables (severity and duration of disease) in ET patients.

To understand the relationship between the inter-group differences observed in the network topology (see Table 3) and the neuropsychological variables, a correlation analysis was performed in ET patients. These analyses revealed a relationship ($p < 0.05$) between the six cognitive composites and the depressive symptoms with the graph theory metrics in the medial frontal cortex, parahippocampal gyrus bilaterally, left lingual gyrus, right planum polare, right pallidum, right hippocampus, right nucleus accumbens and right cerebellum flocculus (Table 5). No relationship between any graph theory metric and tremor severity or duration was observed.

DISCUSSION

Our results show that topological organization of whole-brain functional networks is disrupted in ET. Specifically, ET patients are characterized by lower small-world values of the network - less clustered functionality of the brain - together with altered connectivity patterns in specific systems. The results in the metrics of the global network are only significant in very low thresholds and therefore were discarded. At the regional level, we found the existence of multiple connectivity differences between ET patients and healthy controls in motor and extra-motor related areas. Interpreting these data is challenging; nonetheless, each of the observed changes in connectivity patterns can be linked to one of the several non-motor features previously described in ET, such as cognitive dysfunction, depression, personality style, and impaired visual-motor integration. The data also 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). Interestingly, analogous results regarding widespread disruptions have been reported in Parkinson's disease as well (Gottlich, et al., 2013; Zhang, et al., 2015).

The pathogenesis of ET remains unclear, although clinical and neuroimaging data suggest, as in other tremor disorders, such as orthostatic tremor,(Benito-León and Domingo-Santos, 2016) that it may be related to the existence of alterations in the cerebello-thalamo-cortical network (the so called "tremor network").(Benito-León and Louis, 2011a; Benito-León and Louis, 2006). The studies that have provided evidence of involvement of the "tremor network" have however used a different methodology; specifically, they focused on the areas involved in motor symptoms, and measured the tremorgenic activity using surface electromyography (Ibanez, et al., 2014; Raethjen, et al., 2007) The current study did not focus only in the motor-related symptoms and therefore we did not acquire specific measures in this sense, besides the Fahn-Tolosa-Marin scores of severity and duration. Notwithstanding, intergroup differences in some of the areas typically related with motor symptoms in ET, such as cerebellar regions, pallidum and sensorimotor regions, were found in the regional graph topological analysis. Our results show changes in ET that are widespread and not restricted to the tremor network. Table 4 summarizes the most important findings in this study at the regional level and discusses the potential relationship between each finding and the pathogenesis of ET.

The significant correlations of graph theory metrics with neuropsychological scores provided us some useful information to interpret the functional connectivity differences between healthy controls and ET patients. Of special interest were the changes in connectivity of the posterior parahippocampal gyri (higher LE and CC), a region associated with visuospatial processing and episodic memory, which were positively correlated with depressive symptoms and negatively with visuospatial functions. The involvement of the parahippocampal gyri in the pathogenesis of depressive symptoms in ET is unclear. However, increased connectivity of the posterior cingulate cortex with the parahippocampal gyri has been associated with future depressive symptoms in remitted depressed patients.(Zamoscik, et al., 2014). The same pattern appears on the right cerebellum floculus (higher LE and CC) with an inverse correlation between these metrics and the cognitive domain of attention. In other regions the results were not so clear but were not in conflict with the previous patterns. Overall, it is still too soon to fully understand the neuropsychological implications of the changes in connectivity of these regions, which are altered in ET patients. Maybe some of the alterations are related with neuropsychological compensatory mechanisms, not only with a lower cognitive performance.

The lack of correlation between any graph theory metric and tremor duration or severity merits an explanation. Overall, tremor duration is not a reliable variable since differences in reported age of onset in ET patients may vary widely, and in up to one fifth of patients may be substantial.(Louis, 2013) With respect to severity, one should in mind that the Fahn-Tolosa-Marìn tremor rating scale is a motor scale (Jankovic and Tolosa, 1988) and most the observed inter-group differences in connectivity were found in extra-motor areas.

The study was not without limitations. First, the diagnosis of ET was based on clinical criteria and further supported by normal [(123) I]FP-CIT single photon emission computed tomography scan results. None of the ET patients had post-mortem assessments, so that it was not possible to determine whether they had the types of changes that have been reported in ET (Louis, 2016). Second, the study was designed to distinguish ET cases from healthy controls, and we did not include any diseased control groups (e.g., patients with Parkinson’s disease or dystonia). Inclusion of such comparison groups in subsequent studies will allow us to determine whether the findings of this study are unique to ET or whether they extend in part or fully to patients with other movement disorders. Nonetheless, the current findings are internally valid, and they provide an initial step towards identifying and delineating an ET signature. Third, there is some evidence that there is clinical heterogeneity in ET and that some subgroups of patients seem to differ from others in selected imaging studies.(Caligiuri, et al., 2017; Wang, et al., 2018) Two such subgroups are the patients with rest or head tremor. While it would have been interesting to have stratified our study group, based on rest and head tremor, the sample size was too small to do so. Fourth, an objective measure of the motor symptoms via surface electromyography would be more able to detect the relationship between motor symptoms and the functional connectivity of the brain than the clinical diagnosis employed. Finally, fifteen (65.2%) of the ET patients were assessed while taking stable doses of anti-tremor medications. As some medications used to treat ET (i.e. propranolol or benzodiazepines) might cause changes in brain networks (Brown, et al., 2015; Narayanan, et al., 2010), studying patients off medication seems preferable to assess the unmasked effects of the disease. However, in unmedicated ET patients, tremor can cause movement artifacts that may confound neuroimaging findings. Moreover, despite receiving anti-tremor medications the patients in our sample still showed significant motor impairments (as assessed with the the Fahn-Tolosa-Marìn tremor rating scale), which indicates that these medications did not reverse the pathogenesis of the disease.

In conclusion, graph theory analysis is a novel and promising approach for the study of ET, as it may provide new insights into the pathophysiology of this entity, mainly in non-motor symptoms (esp., cognitive symptoms). 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 - less clustered functionality of the brain. At the regional level, we found the existence of multiple connectivity differences between ET patients and healthy controls in motor and extra-motor related areas. Most importantly, 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). Finally, our results constitute a first step to further explore the neural basis of the non-motor manifestations in ET.

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Competing interests

The authors declare no competing financial interests.

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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	0.425[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]
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]
Hooper Visual Organization Test	35.8 (36.0) ± 9.4	40.9 (39.0) ± 8.7	0.060[b]
Recognition			
Recognition trial (BVMT-R)	11.4 (12.0) ± 0.9	11.8 (12.0) ± 0.5	0.114[a]
Recognition (WMS-III)	21.7 (22.0) ± 2.1	22.3 (22.0) ± 1.4	0.395[a]
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]
Language			
Boston Naming Test	44.7 (44.0) ± 11.7	52.6 (53.0) ± 5.2	0.006[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]
Controlled Oral Word Association Test	26.8 (28.0) ± 13.6	37.0 (39.0) ± 13.1	0.010[b]
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 chi-square test for proportions. WAIS-III = Wechsler Adult Intelligence Scale-Third Edition. WMS-III = Wechsler Memory Scale-Third Edition.

Table 2: Results for the Global Network.

Correlation threshold	Metric	Healthy controls	Essential tremor patients	*p* value
0.01	Global Efficiency	0.786 ± 0.020	0.796 ± 0.022	**0.043**[1]
	Local Efficiency	0.837 ± 0.018	0.845 ± 0.019	0.063
	Betweenness Centrality	0.003 ± 0.000	0.003 ± 0.000	**0.043**[2]
	Cost	0.571 ± 0.041	0.592 ± 0.044	**0.043**[1]
	Average Path Length	1.429 ± 0.041	1.408 ± 0.044	**0.043**[2]
	Clustering Coefficient	0.675 ± 0.036	0.690 ± 0.039	0.063
	Degree	93.111 ± 6.655	96.461 ± 7.216	**0.043**[1]
0.03	Global Efficiency	0.769 ± 0.021	0.779 ± 0.022	**0.048**[1]
	Local Efficiency	0.828 ± 0.018	0.835 ± 0.020	0.074
	Betweenness Centrality	0.003 ± 0.000	0.003 ± 0.000	**0.048**[2]
	Cost	0.538 ± 0.042	0.558 ± 0.045	**0.048**[1]
	Average Path Length	1.462 ± 0.042	1.442 ± 0.045	**0.048**[2]
	Clustering Coefficient	0.655 ± 0.037	0.671 ± 0.040	0.074
	Degree	87.661 ± 6.810	91.009 ± 7.318	**0.048**[1]
0.05	Global Efficiency	0.752 ± 0.021	0.762 ± 0.023	0.059
	Local Efficiency	0.819 ± 0.018	0.826 ± 0.020	0.092
	Betweenness Centrality	0.003 ± 0.000	0.003 ± 0.000	0.059
	Cost	0.505 ± 0.042	0.524 ± 0.046	0.060
	Average Path Length	1.496 ± 0.042	1.476 ± 0.046	0.059
	Clustering Coefficient	0.637 ± 0.037	0.652 ± 0.041	0.092
	Degree	82.242 ± 6.840	85.452 ± 7.496	0.060
0.07	Global Efficiency	0.736 ± 0.021	0.745 ± 0.024	0.070
	Local Efficiency	0.810 ± 0.019	0.817 ± 0.021	0.107
	Betweenness Centrality	0.003 ± 0.000	0.003 ± 0.000	0.071
	Cost	0.471 ± 0.042	0.490 ± 0.047	0.070
	Average Path Length	1.529 ± 0.042	1.510 ± 0.047	0.071
	Clustering Coefficient	0.620 ± 0.038	0.634 ± 0.042	0.108
	Degree	76.827 ± 6.894	79.933 ± 7.664	0.070
0.09	Global Efficiency	0.719 ± 0.021	0.728 ± 0.024	0.075
	Local Efficiency	0.802 ± 0.020	0.808 ± 0.021	0.120
	Betweenness Centrality	0.003 ± 0.000	0.003 ± 0.000	0.075
	Cost	0.438 ± 0.042	0.457 ± 0.047	0.075
	Average Path Length	1.562 ± 0.043	1.544 ± 0.047	0.075
	Clustering Coefficient	0.603 ± 0.039	0.616 ± 0.043	0.121
	Degree	71.466 ± 6.897	74.518 ± 7.685	0.075
0.11	Global Efficiency	0.703 ± 0.021	0.711 ± 0.023	0.100
	Local Efficiency	0.794 ± 0.020	0.800 ± 0.022	0.133
	Betweenness Centrality	0.004 ± 0.000	0.004 ± 0.000	0.103
	Cost	0.407 ± 0.043	0.424 ± 0.047	0.099
	Average Path Length	1.595 ± 0.043	1.578 ± 0.047	0.103
	Clustering Coefficient	0.588 ± 0.040	0.601 ± 0.044	0.135
	Degree	66.283 ± 6.977	69.049 ± 7.636	0.099
0.13	Global Efficiency	0.687 ± 0.022	0.695 ± 0.024	0.110
	Local Efficiency	0.786 ± 0.021	0.792 ± 0.023	0.150
	Betweenness Centrality	0.004 ± 0.000	0.004 ± 0.000	0.109
	Cost	0.375 ± 0.043	0.392 ± 0.047	0.110
	Average Path Length	1.630 ± 0.045	1.613 ± 0.048	0.109
	Clustering Coefficient	0.574 ± 0.041	0.586 ± 0.045	0.152
	Degree	61.172 ± 7.042	63.837 ± 7.667	0.110

0.15	Global Efficiency	0.671 ± 0.022	0.679 ± 0.024	0.118
	Local Efficiency	0.779 ± 0.021	0.785 ± 0.023	0.152
	Betweenness Centrality	0.004 ± 0.000	0.004 ± 0.000	0.116
	Cost	0.345 ± 0.042	0.361 ± 0.047	0.120
	Average Path Length	1.667 ± 0.046	1.649 ± 0.050	0.116
	Clustering Coefficient	0.560 ± 0.041	0.573 ± 0.046	0.156
	Degree	56.242 ± 6.849	58.827 ± 7.684	0.120
0.17	Global Efficiency	0.654 ± 0.022	0.662 ± 0.024	0.127
	Local Efficiency	0.772 ± 0.021	0.778 ± 0.024	0.161
	Betweenness Centrality	0.004 ± 0.000	0.004 ± 0.000	0.119
	Cost	0.316 ± 0.041	0.331 ± 0.046	0.134
	Average Path Length	1.708 ± 0.049	1.690 ± 0.052	0.119
	Clustering Coefficient	0.548 ± 0.041	0.560 ± 0.046	0.168
	Degree	51.548 ± 6.761	53.977 ± 7.555	0.134

Values are expressed in means ± standard deviation from the analysis of covariance. [1] Essential tremor patients > Healthy controls; [2] Healthy controls > essential tremor patients. Every threshold follows the same contrast direction pattern. Significant values are in bold font.

Table 3: Regional graph topological analyses.

Region of interest	Global Efficiency		Local Efficiency		Betweenness centrality		Cost		Average Path Length		Clustering Coefficient		Degree	
	L	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**
Inferior frontal gyrus, pars opercularis	**E>H**						**E>H**		**H>E**				**E>H**	
Middle temporal gyrus, posterior part	**E>H[a]**						**E>H[a]**		**H>E[a]**				**E>H[a]**	
Inferior temporal gyrus, posterior division		**E>H**						**E>H**		**H>E**				**E>H**
Inferior temporal gyrus, temporo-occipital part		**E>H**						**E>H**						**E>H**
Postcentral gyrus				**E>H[a]**								**E>H[a]**		
Superior lateral occipital cortex			**E>H**							**H>E[b]**	**E>H**			
Inferior lateral occipital cortex		**E>H**						**E>H**		**H>E**				**E>H**
Intracalcarine cortex										**H>E**				
Frontal medial cortex			**E>H**								**E>H**			
Subcallosal cortex			**E>H**								**E>H**			
Paracingulate gyrus	**E>H**						**E>H**		**H>E**				**E>H**	
Posterior cingulate			**E>H**								**E>H**			
Precuneus	**E>H**						**E>H**		**H>E**				**E>H**	
Frontal orbital cortex									**H>E**					
Parahippocampal gyrus, posterior division			**E>H**	**E>H**							**E>H**	**E>H**		
Lingual gyrus	**E>H**			**E>H**			**E>H**		**H>E**			**E>H**	**E>H**	
Frontal operculum					**E>H**									
Planum polare						**H>E**								
Pallidum										**H>E[b]**				
Hippocampus		**E>H**										**E>H**		
Amygdala	**E>H**						**E>H**		**H>E**				**E>H**	
Nucleus accumbens			**E>H**	**E>H**							**E>H**	**E>H**		
Inferior semilunar lobule, caudal part				**E>H[a]**		**H>E[a]**						**E>H [a]**		
Biventral lobule, rostral part						**H>E[b]**								
Cerebellar tonsil						**H>E[b]**								
Flocculus				**E>H**								**E>H**		
Culmen of vermis			**E>H[a]**								**E>H[a]**			
Tuber of vermis					**H>E**									

[a] Consistent significance at a threshold of 0.15 and lower; [b] Not significant at lower thresholds. E: Essential tremor patients. H: Healthy controls

Table 4: Regional graph topological differences and its relationship with the pathogenesis of essential tremor.

Regional graph topological differences	**Function**	**Possible meaning in essential tremor**
Precuneus/posterior cingulate cortex	Disruption of this network may play an important role in developing Alzheimer's disease (Yokoi, et al., 2018).	Older-onset essential tremor is associated not only with a higher odds of prevalent Alzheimer's disease(Benito-León, et al., 2006a), but also with an increased risk of Alzheimer's disease (Bermejo-Pareja, et al., 2007).
Frontal operculum	This is a key node in a network for exerting control over cognitive processes (Higo, et al., 2011).	Cognitive deficits have been described in essential tremor (Benito-León, et al., 2006b).
Right hippocampus and the parahippocampal gyri	Involved in episodic memory (Ekstrom and Bookheimer, 2007).	Memory deficits have been described in essential tremor (Benito-León, et al., 2006b).
Left inferior frontal gyrus (pars opercularis)	The posterior part of the inferior frontal gyrus, traditionally referred to as Broca's area, is thought to play a critical role in processing both the phonological aspects and meanings of words, and hence is crucial for language production and comprehension (Gabrieli, et al., 1998).	In population-based studies and clinical series (Benito-León, et al., 2006b; Puertas-Martin, et al., 2016), verbal fluency has been found to be impaired in ET patients.
Nucleus accumbens bilaterally	The nucleus accumbens is related with the impulsivity associated with drug addictions (Dalley, et al., 2007) and with depression.(Francis and Lobo, 2017)	Personality characteristics have been observed in essential tremor; patients are more prone to a personality characterized by greater higher harm avoidance (Thenganatt and Louis, 2012). Essential tremor patients also have an increased odds and risk of depression (Louis, et al., 2007).
Left amygdala	This is a key brain structure regulating different aspects of emotional processing, including recognition of emotional expression	An inverse relation has been described between facial emotion recognition and tremor severity in ET patients.(Auzou, et al.,

	in faces, as well as in mediating emotional interference during tasks requiring cognitive resources (Adolphs and Spezio, 2006).	2014). In addition, ET patients did not perform as well in joy and fear recognition, and they had subtle abnormalities in risk detection (Auzou, et al., 2014).
Left amygdala and several cerebellar regions.	Startle hyporeactivity might be mediated by aberrant cerebellar input to the amygdala, which is involved in priming the startle response in emotional contexts (Lafo, et al., 2017).	ET patients respond abnormally in terms of startle reactivity to emotional pictures (Lafo, et al., 2017).
Parahippocampal gyrus, posterior cingulate, and lingual gyrus bilaterally	These brain regions are involved in visual tasks (Yang, et al., 2015).	Impaired visual-motor integration in ET has been described.(Bares, et al., 2010) Changes in the connectivity of the lingual gyrus, which may be related to internally directed attention (Benedek, et al., 2016), correlated negatively with attention domain.
Right inferior lateral occipital cortex	The extrastriate body, which is well-known to respond to visual processing of static and moving human bodies (Astafiev, et al., 2004; Lingnau and Downing, 2015), is located in the lateral occipital cortex. Further, the extrastriate body responds during the perception of other people's body parts or during goal-directed movements of the observer's body parts (Astafiev, et al., 2004; Lingnau and Downing, 2015). Finally, the lateral occipitotemporal cortex represents varied aspects of action, ranging from perception of tools and bodies and the way they typically move (Lingnau and Downing, 2015).	Given the involvement of the lateral occipital cortex in the control of movement, its deterioration could plausibly be involved in the genesis of tremor (Serrano, et al., 2017).

Table 5: Matrix of partial correlations among the cognitive domains and the ROIs that showed differences between essential tremor patients versus healthy controls.

Region of interest	Attention		Executive function		Verbal memory		Recognition		Visuospatial/ visual functions		Language		Depressive symptoms	
	r	***p* value**	**r**	***p* value**	**r**	***p* value**	**r**	***p* value**	**r**	***p* value**	**r**	***p* value**	**r**	***p* value**
Medial Frontal Cortex														
Betweenness centrality					-0.476	0.022	-0.494	0.017						
Right parahippocampal gyrus, posterior division														
Local efficiency													0.563	0.005
Clustering Coefficient									-0.431	0.045			0.577	0.004
Left parahippocampal gyrus, posterior division														
Local Efficiency									-0.473	0.023			0.441	0.035
Betweenness Centrality									0.483	0.019				
Clustering Coefficient									-0.475	0.022			0.428	0.042
Left lingual gyrus														
Local Efficiency											-0.435	0.038		
Betweenness Centrality			0.443	0.034					0.454	0.03				
Clustering Coefficient											-0.435	0.038		

Right planum polare														
Global Efficiency			0.436	0.044			0.461	0.027						
Local Efficiency			0.451	0.031										
Cost			0.428	0.041			0.459	0.028						
Average Path Length							-0.445	0.033						
Degree			0.428	0.041			0.459	0.028						
Clustering Coefficient			0.422	0.045										
Right pallidum														
Betweenness Centrality	0.475	0.022												
Right hippocampus														
Betweenness Centrality					-0.504	0.014								
Right nucleus accumbens														
Betweenness Centrality	0.581	0.003	0.497	0.016					0.563	0.005	0.585	0.003		
Right cerebellum flocculus														
Local efficiency	-0.481	0.02												
Clustering Coefficient	-0.456	0.029												

Figure 1: Small-world results, with the means for healthy controls and essential tremor patients, and the Student's t-test results of the mean comparison below the plots.

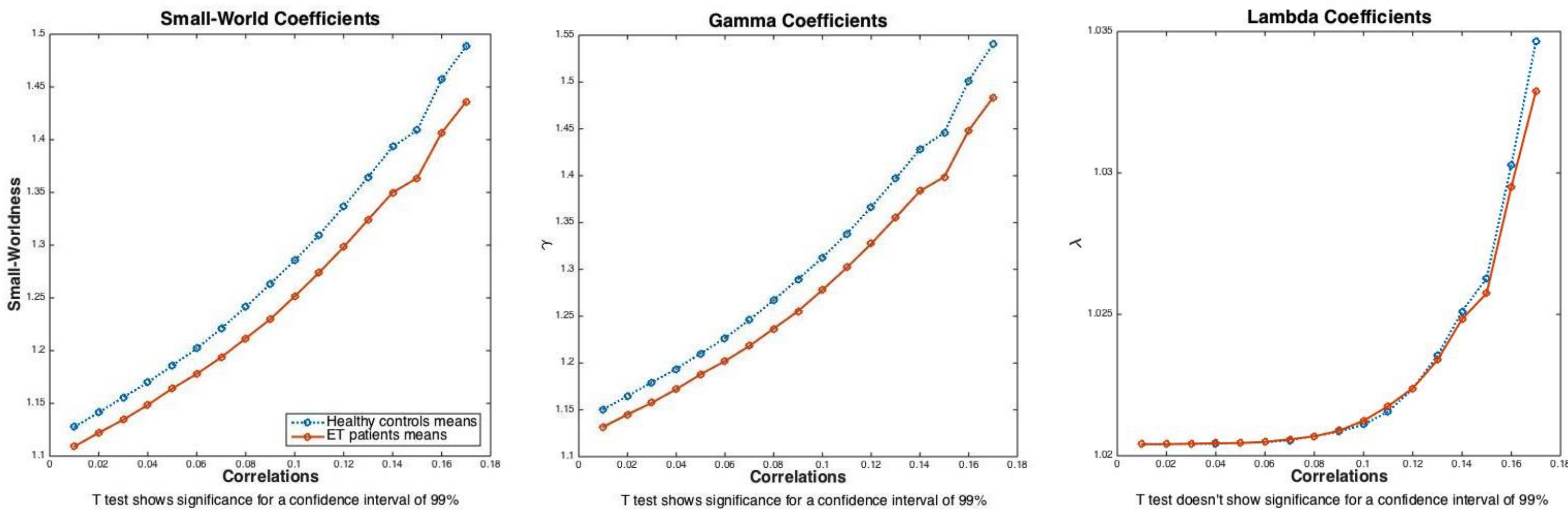

Figure 2: Mean binary adjacency matrixes by group, at a correlation threshold of 0.17. The mean values are those present in at least half of the subjects.

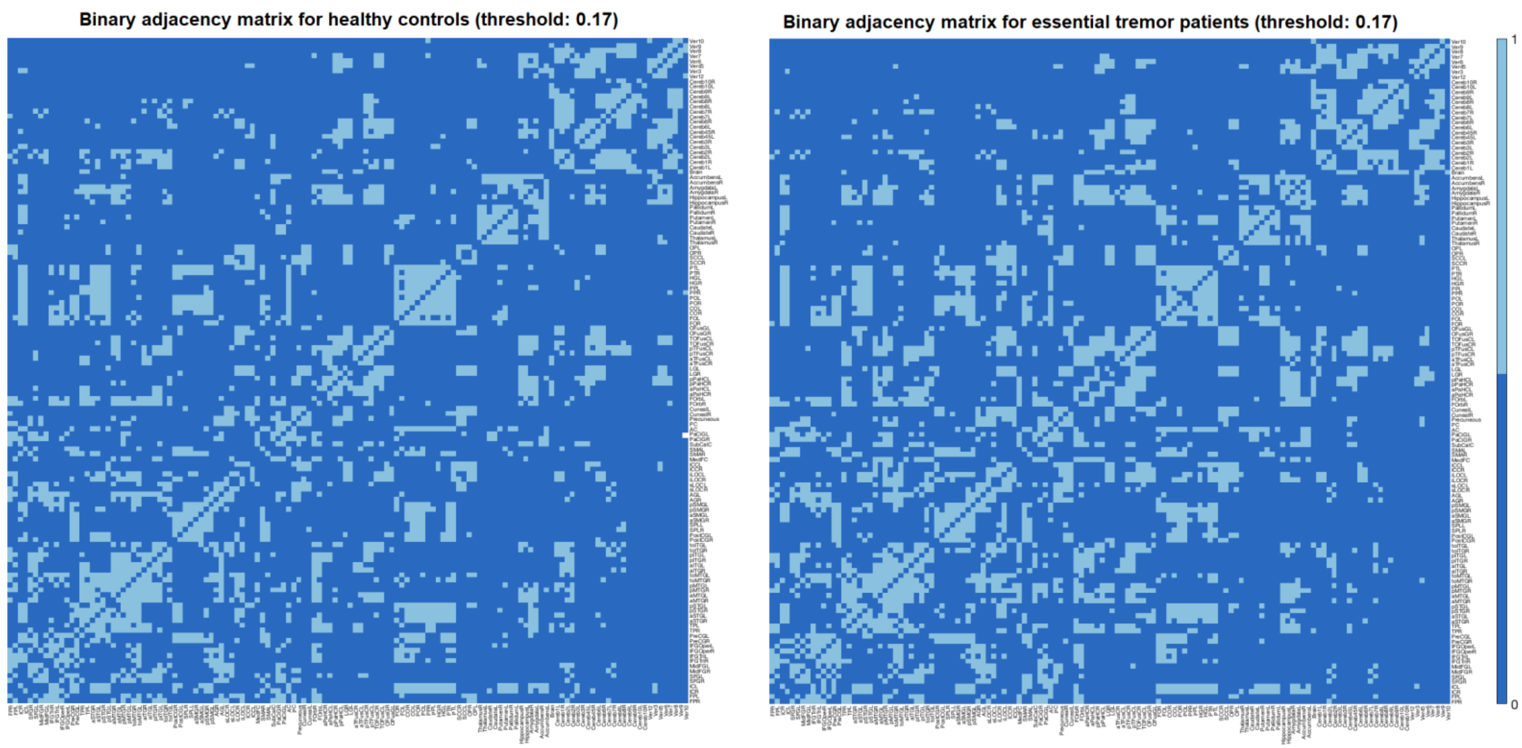

Figure 3: Axial view of the significant ROIs and their correlations by groups. Node intensity values represent the F statistic over the null hypothesis that all ROIs correlations are equal to 0. Edges intensity values represent the T statistic over the null hypothesis that its correlation is equal to 0. False discovery rate correction for multiple comparisons was applied to the significance level for the correlation contrasts between the significant ROIs.