ORIGINAL ARTICLE

Reduced small world brain connectivity in probands with a family history of epilepsy

R. D. Bharath[a], G. Chaitanya[b,c], R. Panda[a], K. Raghavendra[c], S. Sinha[c], A. Sahoo[d], S. Gohel[d], B. B. Biswal[d] and P. Satishchandra[c]

[a]*Department of Neuroimaging and Interventional Radiology (NIIR), National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore;* [b]*Department of Clinical Neurosciences, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore;* [c]*Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India; and* [d]*Department of Biomedical Engineering, New Jersey Institute of Technology (NJIT), Newark, NJ, USA*

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Background and purpose: The role of inheritance in ascertaining susceptibility to epilepsy is well established, although the pathogenetic mechanisms are still not very clear. Interviewing for a positive family history is a popular epidemiological tool in the understanding of this susceptibility. Our aim was to visualize and localize network abnormalities that could be associated with a positive family history in a group of patients with hot water epilepsy (HWE) using resting-state functional magnetic resonance imaging (rsfMRI).

Methods: Graph theory analysis of rsfMRI (clustering coefficient γ; path length λ; small worldness σ) in probands with a positive family history of epilepsy (FHE+, 25) were compared with probands without FHE (FHE−, 33). Whether a closer biological relationship was associated with a higher likelihood of network abnormalities was also ascertained.

Results: A positive family history of epilepsy had decreased γ, increased λ and decreased σ in bilateral temporofrontal regions compared to FHE− (false discovery rate corrected $P \leq 0.0062$). These changes were more pronounced in probands having first degree relatives and siblings with epilepsy. Probands with multiple types of epilepsy in the family showed decreased σ in comparison to only HWE in the family.

Conclusion: Graph theory analysis of the rsfMRI can be used to understand the neurobiology of diseases like genetic susceptibility in HWE. Reduced small worldness, proportional to the degree of relationship, is consistent with the current understanding that disease severity is higher in closer biological relations.

Introduction

Inheritable epilepsies are seen in a considerable number of patients who present to epilepsy clinics. Several studies have reinforced the hypothesis of a genetic propensity for seizures, which makes some more susceptible to seizures and some refractory to treatment [1–3]. Analysis of the Epilepsy Family Study of the Columbia University [4] data suggests that information about the family history of epilepsy (FHE) in parents and siblings is fairly accurate with a sensitivity of around 85% in identifying idiopathic epilepsy in the family [5]. Familial aggregation studies in subjects up to 40 years of age show the cumulative incidence of epilepsy to be 3.6% in siblings and 10.6% in offspring compared to 1.7% in the general population [6]. Both genetic and environmental factors are thought to influence the susceptibility to epilepsy and it is not clear how these factors interact to influence the actual risk.

Epilepsy research has immensely benefited from graph theory analysis of electroencephalography (EEG)/intracranial electroencephalography, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging data by improving localization, lateralization [7], seizure

Correspondence: P. Satishchandra, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029, India (tel.: +9180-26995454/5150; fax: +9180-26566811; e-mail: drpsatishchandra@yahoo.com).

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prediction [8] and seizure propagation pathways [9]. Graphs are mathematical descriptions of complex networks consisting of n nodes which are connected by l edges [10]. Although progressive reduction in the small worldness of default mode network (DMN) with the duration of disease has been reported [11–14], studies that have exclusively looked into disease neurobiology like frequency of seizures, age at onset of seizure, association with childhood febrile convulsions or psychiatric diseases are few. A recent study found connectivity diversity to correlate with duration of disease in patients with mesial temporal sclerosis (MTS) [15]. Connectivity diversity is a graph measure which measures variability in interregional connections. One study has found carbamazepine reducing betweenness centrality in disease matched temporal lobe epilepsy (TLE) patients [15]. Another study found increased temporal and decreased DMN connectivity in patients with higher frequency of seizures using seed-to-voxel connectivity analysis [16].

In this study, our aim was to visualize and quantify network abnormalities in probands with an FHE using graph theory analysis of resting state fMRI (rsfMRI). Probands with hot water epilepsy (HWE) were chosen as this type of reflex epilepsy has a higher prevalence (10%–23%) of a positive FHE (FHE+) [17,18] and most patients do not require continuous antiepileptic drugs and usually are not associated with cognitive dysfunction [19,20].

Materials and methods

Participants

This prospective study was conducted in a tertiary care neurological institute between 2012 and 2014. FHE+ was identified as the presence of epilepsy in relatives up to the third degree, based on patient and relative interviews. In patients with no FHE (FHE−), the possibility of a recent common ancestor was excluded. A family history of febrile seizures was not considered as FHE+. Amongst 100 consecutive patients (right handed) a definite account of FHE could only be ascertained in 58 patients. Amongst these, 25 patients were FHE+ and 33 patients were FHE−. In the FHE+ group, all probands except three had only one affected relative. Two had two affected maternal relatives and one had four affected paternal relatives. Both groups were comparable across several clinico-demographic factors (Table 1). Those patients who did not have any history of prior trauma or psychiatric illnesses and had no contraindications for MRI were enrolled in the study. Structural MRI (RDB) and scalp EEG (PSC/SS) were normal in all the subjects.

Within the 25 probands with FHE+, 14 had affected first degree relatives (FDRs) and 11 had second degree or higher affected relatives (>FDR); eight (Mat) had affected maternal relatives, 10 (Pat) had affected paternal relatives and seven (Sibs) had affected siblings; 13 had FHE of only HWE and 12 had FHE other than HWE. These subgroups were also statistically comparable across all the clinico-demographic variables (Table 2).

Imaging data of 30 age and gender matched (M: F = 21:9; age 29.1 ± 9 years) healthy subjects were selected from the existing imaging databank at the institute. The study was approved by the institutional ethics committee and written informed consent was obtained from all participants.

Image acquisition

All patients in the interictal state underwent rsfMRI (185 dynamics; TR/TE/FA 3000 ms, 30 ms, 90°; 34 slices; 64 × 64 matrix, 3 × 3 × 4 mm voxel size; eyes closed and awake state) and T1-MPRAGE (TR/TE/

Table 1 Clinico-demographic details of the patients with hot water epilepsy (HWE)

	Family history of epilepsy (N = 58)		
	Present (n = 25)	Absent (n = 33)	P value
Gender (M:F)	21:4	24:9	0.38
Age (years)	29.1 ± 13.1	28.2 ± 10.31	0.77
Age at onset (years)	18.14 ± 11.5	23.72 ± 10.3	0.056
Duration of epilepsy (years)	10.96 ± 8.8	4.48 ± 4.4	0.01
Total number of seizures	28.92 ± 27.8	17.61 ± 20.3	0.079
Duration between last seizure and MRI scan (median; interquartile range)	13; 14.5–30	14; 3.5–168	0.7
Type of seizure in probands (HWE only:both HWE and unprovoked seizures)	19:14	10:15	0.23
Type of seizure in probands (CPS only:CPS with sec gen)	19:6	18:15	0.14
Frequency of seizures (≤1/month:>1/month)	15:10	21:12	0.77
Treatment history (drug naive:on AEDs)	10:15	16:17	0.52

AEDs, antiepileptic drugs; CPS, complex partial seizure; HWE, hot water epilepsy; MRI, magnetic resonance imaging; sec gen, secondary generalization.

Table 2 Clinico-demographic features of FHE+ group

	Degree of relationship to probands		
	FDRs (n = 14)	>FDR (n = 11)	P value
Gender (M:F)	12:2	9:2	0.6
Age (years)	30.6 ± 14.4	19.1 ± 7.9	0.25
Age at onset (years)	19.7 ± 14.1	15.8 ± 6.5	0.74
Duration of epilepsy (years)	10.8 ± 9.2	3.4 ± 3.2	0.087
Total number of seizures	26.1 ± 27.4	24.3 ± 5.9	0.66
Duration between last seizure and MRI scan (median; interquartile range)	13.5; 3–153	13.0; 3.75–228.5	0.22
Type of seizure in probands (CPS only:CPS with sec gen)	10:04	09:02	0.45
Type of seizure in probands (HWE only:both HWE and unprovoked seizures)	06:08	04:07	0.53
Frequency of seizures (<1/month:>1/month)	09:05	06:05	0.47
Treatment history (drug naive:on AEDs)	09:05	06:05	0.47
	Probands with maternal or paternal or siblings affected		
	Mat (n = 8)	Pat (n = 10)	Sibs (n = 7)	P value
Gender (M:F)	06:02	09:01	06:01	0.68
Age (years)	28.2 ± 17.5	25.2 ± 9.2	35.8 ± 10.9	0.25
Age at onset (years)	18.4 ± 11.4	15.4 ± 4.9	21.8 ± 17.7	0.54
Duration of epilepsy (years)	9.8 ± 8.5	9.8 ± 8.3	14.0 ± 10.4	0.57
Total number of seizures	24.6 ± 32.1	32.2 ± 31.0	29.1 ± 20.3	0.85
Duration between last seizure and MRI scan (median; interquartile range)	7; 3.5–319.5	29; 3.5–160.75	5; 3–92	0.61
Type of seizure in probands (CPS only:CPS with sec gen)	07:01	07:03	05:02	0.65
Type of seizure in probands (HWE only:both HWE and unprovoked seizures)	04:04	03:07	03:04	0.67
Frequency of seizures (<1/month:>1/month)	05:03	07:03	03:04	0.52
Treatment history (drug naive:on AEDs)	05:03	06:04	04:03	0.98
	Type of epilepsy in family		
	FHE of HWE (n = 13)	FHE other than HWE (n = 12)	P value
Gender (M:F)	13:00	08:04	–
Age (years)	24.9 ± 10.16	33.67 ± 14.8	0.09
Age at onset (years)	14.5 ± 9.46	22.08 ± 12.5	0.09
Duration of epilepsy (years)	10.4 ± 8.2	11.58 ± 9.74	0.74
Total number of seizures	29.9 ± 30.8	27.8 ± 26.1	0.85
Duration between last seizure and MRI scan (median; interquartile range)	7; 2.5–137.5	16.5; 4.25–319.5	0.46
Type of seizure in probands (CPS only:CPS with sec gen)	09:04	10:02	0.36
Type of seizure in probands (HWE only:both HWE and unprovoked seizures)	09:04	06:06	0.28
Frequency of seizures (<1/month:>1/month)	07:06	08:04	0.51
Treatment history (drug naive:on AEDs)	07:06	08:04	0.40

AEDs, antiepileptic drugs; CPS, complex partial seizure; FDR, first degree relative; FHE, family history of epilepsy; HWE, hot water epilepsy; Mat, probands with affected maternal relatives; MRI, magnetic resonance imaging; Pat, probands with affected paternal relatives; sec gen, secondary generalization; Sibs, probands with affected siblings.

FA 1900 ms, 2.43 ms, 90°; FOV 256 × 256 and ST 1 mm) in a 3 T Skyra MRI (Siemens, Erlangen, Germany) with a 20-channel head coil.

Data preprocessing

The functional and structural MRI preprocessing was performed using SPM8 toolbox [21]. Preprocessing steps included realignment, segmentation of the structural data for regressing out white matter and cerebrospinal fluid effects, normalization to MNI152 standard space of 3 × 3 × 3 mm^3 and motion correction using Friston's 24-motion parameter temporal band pass filtering with 0.01–0.09 Hz. The head movement was not significant between the groups (FHE+ 1.1 ± 0.44 mm, FHE− 1.1 ± 0.44 mm, control 1.05 ± 0.4 mm; P = 0.9). The nodes of functional networks were extracted from rsfMRI data into 200

anatomical regions of interest (ROIs) of Craddock's template [22] using MarsBaR toolbox® (http://marsbar.sourceforge.net). The time series of an ROI was the average of all the voxels in that ROI. The rsfMRI time series were correlated region by region using Pearson's correlation ('corr' function in MATLAB 2013®) for each subject across the length of the time series (L = 180 time) and a 200 × 200 matrix was constructed by applying a correlation threshold T (Fisher's r-to-z) to the correlation matrix.

Network topology analysis

The topological properties of the brain functional networks were defined on the basis of a 200 × 200 graph $G(V, E)$, where G is a non-zero subset with vertices V = ROIs and edges E = internodal correlation coefficients (Fisher's Z values), as a measure of functional connectivity between nodes. The normalized clustering coefficient (γ), the normalized characteristic short path length (λ) and the small worldness (σ) over network sparsity thresholds of 6%–40% with an increment of 1% were analyzed [23]. Using the γ values, the brain regions showing significant differences [24] in the two groups (over the range of 6%–40% sparsity thresholds) were noted. The statistically significant nodes were rendered on a brain surface model using the BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

Statistical data analysis

Clinical data were tested for normality using the Shapiro Wilk's test and the appropriate statistics were used to look for intergroup variability. For network indices, intergroup comparisons were performed using the two-tailed 'ttest2' function in MATLAB 2013®. A false discovery rate corrected P value of <0.0062 was taken as significant for network measures (http://www-personal.umich.edu/~nichols/FDR/).

Results

Analysis of 25 FHE+ and 33 FHE− with 30 clinically matched healthy controls revealed that several areas in the temporofrontal lobes showed alterations in small world parameters in FHE+ patients (Fig. 1). All these changes involved bilateral cerebral hemispheres and were proportional to the degree of biological relationship. There was no significant correlation of network indices with the measured head motion (γ, $r = -0.03$, $P = 0.73$; λ, $r = 0.11$, $P = 0.67$; σ, $r = 0.17$, $P = 0.42$).

Small world connectivity differences between FHE+ and FHE−

A positive FHE had lower γ compared to the FHE− group (sparsity 6%–35%) (Fig. 2a). FHE+ had significantly longer λ (sparsity 14%–24%) compared to controls and reduced σ (sparsity 6%–32%) compared to the FHE− group. The regions which showed significant decreases in γ are provided in Table 3, part (a). Although the duration of epilepsy was significantly different between the groups, it did not correlate with any of the small world indices (γ, $r = -0.21$, $P = 0.092$; λ, $r = -0.16$, $P = 0.53$; σ, $r = -0.09$, $P = 0.64$).

Small world connectivity differences with degree of relation in FHE+

The FDR group had a lower γ (sparsity 6%–24%), longer λ (sparsity 16%–24%) and reduced σ (sparsity 6%–24%) compared to the >FDR group (Fig. 2b). The regions which showed significant decreases in γ are provided in Table 3, part (b).

Small world connectivity differences associated with type of relation in FHE+

Patients with affected siblings had lower γ compared to both the Mat (sparsity 7%–20%) and Pat (sparsity 6%–23%) groups (Fig. 2c) (Table 3, part (c)). Sibs also had longer λ compared to the Mat (sparsity 10%–17%) and Pat groups (sparsity 8%–18%). Sibs had lower σ compared to the Mat (sparsity 8%–20%) and Pat groups (sparsity 6%–24%).

Small world connectivity differences associated with multiple types of epilepsy in the family

An FHE other than HWE had several areas (Table 3, part (d)) with lower γ compared to an FHE of HWE (sparsity 6%–29%). An FHE other than HWE had significantly decreased σ (sparsity 6%–29%).

Discussion

In this study, it has been demonstrated that probands with FHE show significantly reduced small worldness in temporofrontal regions compared to those with no affected relative in the family. Probands having an affected FDR had decreased σ compared to those with >FDR. These changes were more severe in probands with affected siblings. Probands with affected maternal relatives had reduced σ compared to those with affected paternal relatives. Those with FHE of

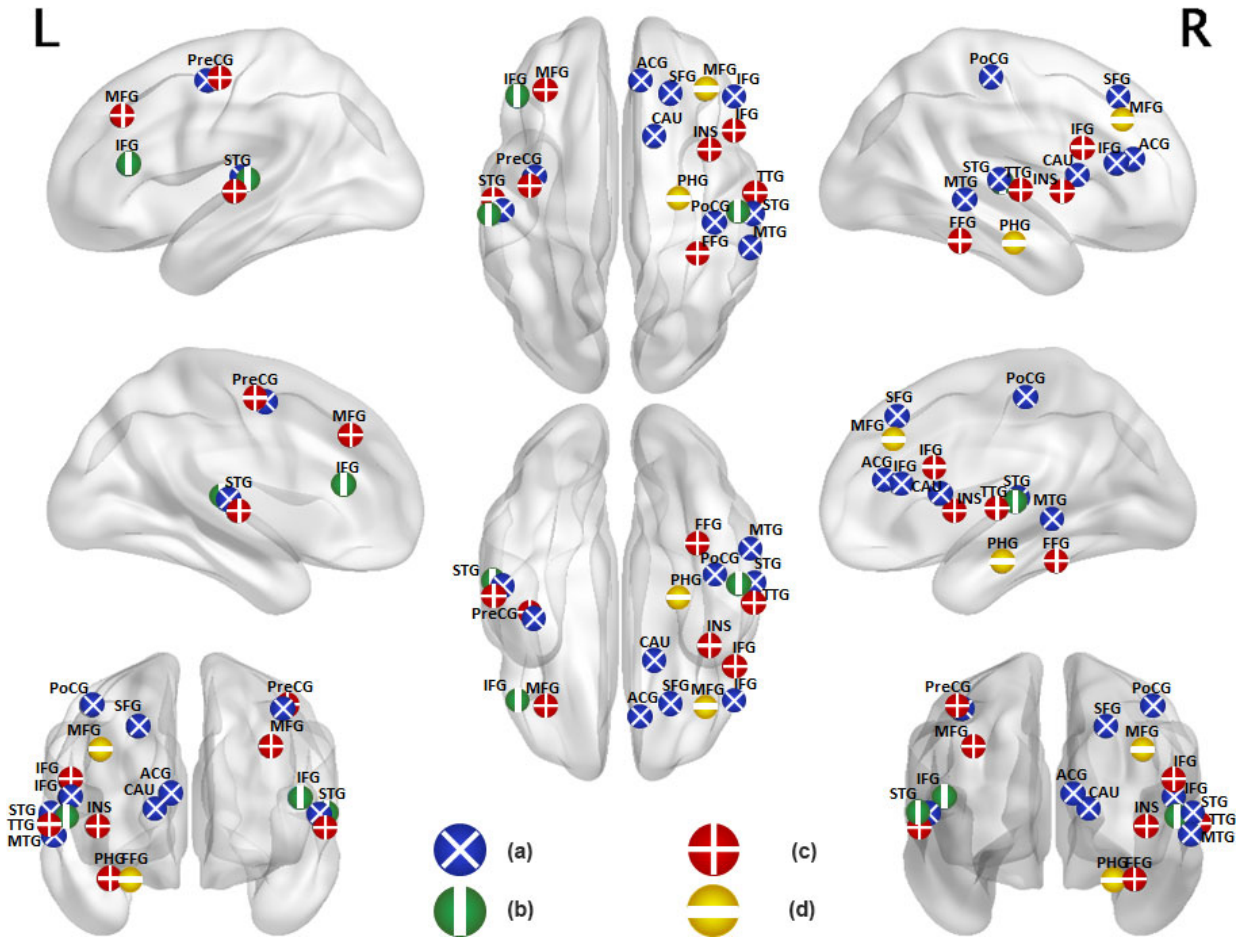

Figure 1 The brain regions derived from the normalized clustering coefficient. The brain regions that showed significant differences ($P < 0.0062$ false discovery rate) between the patient groups (sparsity 6%–40%) were rendered onto a surface model of the brain: (a) represents the difference between FHE+ and FHE−, (b) between FDRs and >FDR, (c) between Sibs with Mat and Pat groups and (d) between FHE of HWE and FHE other than HWE. [Colour figure can be viewed at wileyonlinelibrary.com].

multiple types of seizures had reduced small worldness compared to only HWE. Our findings report network alterations to be associated with a genetic susceptibility to epilepsy in patients with HWE. The evidence of abnormal connectivity as a correlate for inheritance susceptibility is consistent with evidence from twin studies demonstrating the effect of genes on the global efficiency of brain networks. It was also found that genetic effects could be regional, involving bilateral posterior cingulate, medial prefrontal cortex, dorsolateral prefrontal cortex, superior parietal, lateral temporal lobes and medial occipital cortex [25,26]. In line with this, it was interesting to note that the network abnormalities in our study were also regional and involved the temporal lobe (bilateral superior temporal, right middle temporal gyri), frontal lobe (right superior and inferior frontal gyri, left precentral gyrus), right postcentral gyrus, caudate and right anterior cingulate network abnormalities in probands with a FHE. A reduction in the small world properties, i.e. reduction of absolute clustering coefficients [11,27] and absolute path length [12], is noted in various types of epilepsy. Unlike the current findings there are also reports of increased clustering in patients with TLE making the reports using graph theory analysis variable [9,28,29]. One of the main reasons for this variability could be because almost all these studies report changes in comparison to healthy controls, reflecting the combined alterations due to epilepsy, cognitive and sensory deficits. Epilepsy related network abnormalities are in turn dependent on several disease related factors like the duration of disease, type of seizure, frequency of seizures, effect of drugs etc. Within-group studies in carefully matched patient groups like the current study are one way to reduce this variability. Neuronal graph theory models have demonstrated that the clustering coefficient increases during the major part of the disease in MTS and

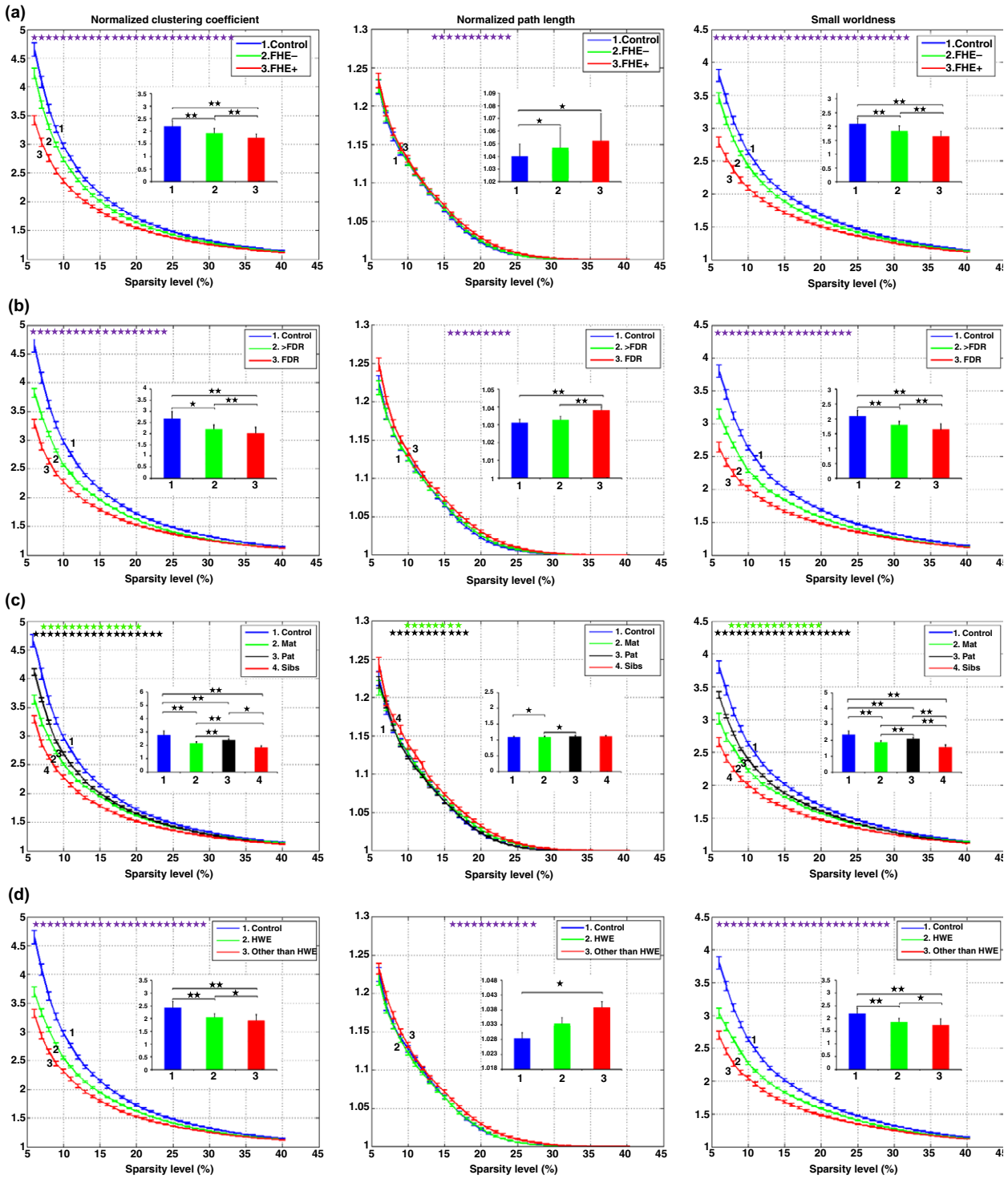

Figure 2 Graphical representations of the results. The first column of graphs represents the normalized clustering coefficient, the second column of graphs represents the normalized path length and the third column of graphs represents the small worldness (sparsity 6%–40%) between 1.controls and (a) 3.FHE+ versus 2.FHE−, (b) 3.FDR versus 2. > FDR, (c) the difference between 4.Sibs with 3.Mat and 2.Pat groups and (d) 2.FHE of HWE versus 3.FHE other than HWE. Inset bar graphs for each graph demonstrate the overall group effect and a comparison between the groups. $*P < 0.05$, $**P < 0.005$. [Colour figure can be viewed at wileyonlinelibrary.com].

Table 3 Group-wise results with brain regions having significant decrease in normalized clustering coefficient: (a) represents the regions that had higher γ in FHE+ compared to FHE−; (b) represents the regions that had higher γ in FDRs compared to >FDR; (c) represents the regions that had higher γ in Sibs compared to Mat and Pat groups together; (d) represents the regions that had higher γ in FHE of HWE compared to FHE other than HWE

SL. no.	Brain area	*X* (coor)	*Y* (coor)	*Z* (coor)	*P* Value
(a) Brain region differences between FHE+ and FHE−					
1	Right inferior frontal gyrus	28	28	−16	0.0005
2	Right superior frontal gyrus	12	16	60	0.0005
3	Right middle temporal gyrus	52	−12	−8	0.0006
4	Right superior temporal gyrus	64	−52	12	0.0007
5	Right postcentral gyrus	52	−12	52	0.0006
6	Right anterior cingulate	8	16	−8	0.0008
7	Right caudate	16	4	16	0.0005
8	Left precentral gyrus	−60	0	24	0.0005
9	Left superior temporal gyrus	−52	−8	4	0.0002
(b) Brain region differences between FDRs versus >FDR					
1	Right superior temporal gyrus	64	−52	12	0.005
2	Left inferior frontal gyrus	−52	16	0	0.004
3	Left superior temporal gyrus	−60	−44	8	0.005
(c) Brain region differences between Mat, Pat and Sibs groups					
1	Right inferior frontal gyrus^{p}	56	24	20	0.005
2	Right transverse temporal gyrus^{mp}	68	−16	12	0.004
3	Right fusiform gyrus^{p}	32	−36	−16	0.005
4	Right insula^{mp}	44	−12	12	0.002
5	Left middle frontal gyrus^{mp}	−32	0	56	0.005
6	Left superior temporal gyrus^{m}	−48	−36	16	0.002
7	Left precentral gyrus^{m}	−60	0	24	0.004
(d) Brain region differences between affected relatives having HWE or other than HWE					
1	Right medial frontal gyrus	4	44	28	0.005
2	Right parahippocampal gyrus	8	−8	−8	0.004

coor, coordinates; FDR, first degree relative; FHE, family history of epilepsy; HWE, hot water epilepsy; m, maternal; Mat, probands with affected maternal relatives; p, paternal; Pat, probands with affected paternal relatives; Sibs, probands with affected siblings.

reduces in the end stage [30]. As cross-sectional studies group these chronological connectivity abnormalities induced by the disease into one, they further induce variability in results. Whole brain analysis is another factor that has produced variable results [31], probably reflecting disease related dynamic changes in some areas and compensatory response related changes in other areas. Longitudinal studies and ROI analysis in areas known to be affected by disease are other ways to reduce the heterogeneity in the results [15]. EEG studies demonstrate increased clustering coefficient and path length during ictal discharges compared to the interictal phase [32,33]. Whether interictal discharges in addition can also be responsible for the variability in hemodynamic network connectivity is unknown at this time.

There are few studies that have looked at the influence of the degree of relationship on the clinical patterns of epilepsy. It has been noted that having affected FDRs is associated with higher odds of diagnosing epilepsy in patients, particularly if the seizures are of the same phenomenology [34], which supports the findings of the present study which reveals higher network disruption in first degree affected relatives. Similarly the disease expression is more severe in siblings consistent with the current results. Reduced network characteristics in probands with a history of multiple types of epilepsy in the family could indicate an influence of a higher number and degree of pathological genes as is evident in epilepsies having a polygenic inheritance pattern [35,36]. In the background of reproducible results from the functional connectome using healthy rsfMRI data in a multi-center study including 1414 subjects [37], our results support the notion that this technique could provide insights into genetic patterns, similar to whole genome analysis which led to several important discoveries in breast cancer, diabetes etc. Such methods are especially important in diseases like epilepsy as they can help in objectively evaluating the heterogeneity associated with clinical phenotypes, environmental factors and the genetic and allelic polymorphisms that influence the susceptibility to epilepsy. Objective measures could in turn help in deriving methods which can predict individual risk for epilepsy and reduce the dependence on population-based risk estimates.

The temporofrontal differences could be specific to the type of epilepsy as HWE is known to be geographically confined [38,39]. Since the differences observed in this study are between two groups of patients with HWE, the difference is unlikely to be only limited to HWE. Application of these methods in universally available epilepsy groups like TLE will be required to get better clinical acceptance for this finding. Clinical application will become more accurate when correlated with genetic analysis including unaffected family members and twins to ascertain gene–environment interactions associated with HWE. Despite these limitations the knowledge that there are abnormal networks which can be visualized in patients having a relative with epilepsy in the family is an important finding in understanding the neurobiology of HWE.

Conclusion

Our findings demonstrate that HWE patients carry the burden of inheritance susceptibility as functional connectivity abnormalities proportional to the degree of the relationship in the temporofrontal regions. Such evidence if applied to more common epilepsies could assist in visualizing and quantifying factors that make people more vulnerable to epilepsy.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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