Psychiatry Research: Neuroimaging 287 (2019) 31–40

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Network neurobiology of electroconvulsive therapy in patients with depression

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ARTICLE INFO

Keywords:
Brain networks
Electroconvulsive therapy
Graph theory analysis
Depression
Cognitive deficits
Neurobiology

ABSTRACT

Graph theory, a popular analytic tool for resting state fMRI (rsfMRI) has provided important insights in the neurobiology of depression. We aimed to analyze the changes in the network measures of segregation and integration associated with the administration of ECT in patients with depression and to correlate with both clinical response and cognitive deficits. Changes in normalised clustering coefficient (γ), path length (λ) and small-world (σ) index were explored in 17 patients with depressive episode before 1st and after 6th brief-pulse bifrontal ECT (BFECT) sessions. Significant brain regions were then correlated with differences in clinical and cognitive scales. There was significantly increased γ and σ despite significant increase in λ in several brain regions after ECT in patients with depression. The brain areas revealing significant differences in γ before and after ECT were medial left superior frontal gyrus, left paracentral lobule, right pallidum and left inferior frontal operculum; correlating with changes in verbal fluency, HAM-D scores and delayed verbal memory (last two regions) respectively. BFECT reorganized the brain network topology in patients with depression and made it more segregated and less integrated; these correlated with clinical improvement and associated cognitive deficits.

1. Introduction

Electroconvulsive therapy (ECT) is considered as an effective treatment for depression (Lamprecht et al., 2013). Our knowledge about effects of ECT on brain though not completely determined, has advanced in last 8 years with evolution in techniques and analysis of functional neuroimaging (Bolwig, 2014; Nordanskog et al., 2010). Resting state functional MRI (rsfMRI) is a contemporary tool used to understand the disease biology in-vivo because of the ease of image acquisition and spectrum of image analysis platforms (Chen and Glover, 2015; Lee et al., 2013). Graph theory analysis, one of mathematical frameworks for rsfMRI interprets well the small world architecture of brain networks (Bullmore and Sporns, 2009). Here, the brain is assumed as a graph composed of nodes, representing structurally or functionally defined regions of interest (ROI); with edges, representing network connectivity between these nodes. It is usually defined at three levels: measures of segregation (e.g., clustering coefficient, network motifs), measures of integration (e.g., shortest path length, efficiency, small worldness) and measures of influence (e.g., degree, betweenness-centralities, hubs, modularity). These graph measures are used to identify mathematically the effective network/ hubs and global network properties of the brain (Bullmore and Sporns, 2009; Gong and He, 2015; Sporns, 2013).

Graph theory analysis in patients with depression have revealed altered measures of segregation and integration (Gong and He, 2015). This data driven technique has confirmed the disease induced alterations in many nodal regions found in other analytical framework of resting state fMRI (Feng et al., 2016; Kaiser et al., 2015; Mulders et al., 2015; Wang et al., 2016). The nodal regions belonging to frontal cortex included dorsolateral prefrontal cortex (DLPFC) (Jin et al., 2011; Ye et al., 2016; Zhang et al., 2011), superior frontal gyrus (SFG) (Tao et al., 2013), precentral gyrus (Tao et al., 2013) and inferior frontal gyrus (IFG) – specifically frontal operculum (Meng et al., 2014; Sacchet et al., 2014). The other significant areas lie in limbic system [anterior cingulate cortex (ACC) (Sacchet et al., 2014; Ye et al., 2016), amygdala (Jin et al., 2011; Tao et al., 2013; Ye et al., 2016), hippocampus (HC)

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https://doi.org/10.1016/j.pscychresns.2019.03.008
Received 17 August 2018; Received in revised form 16 March 2019; Accepted 19 March 2019
Available online 20 March 2019
0925-4927/

(Ye et al., 2016) and insula (Jin et al., 2011; Tao et al., 2013)] and striatum (Lord et al., 2012; Meng et al., 2014; Zhang et al., 2011). The resting state brain networks whose involvement in depression is supported by graph theory analysis include fronto-parietal, default mode, salience and ventral attention networks (He et al., 2018; Ye et al., 2016; Zhang et al., 2011).

In ECT associated neuroimaging, we could find three studies which utilized graph theory analysis. Considering the findings of these studies, further exploration in this direction is warranted. In one of them, diffusion tensor imaging (DTI) was conducted in 24 patients with first episode drug-naive depression, who received bitemporal ECT (BTECT) (Zeng et al., 2015). The whole brain analysis before 1st and after 8th ECT sessions revealed significant changes in connectivity and nodal strength in few ROIs where post ECT increased connectivity between amygdala and parahippocampal gyrus (PHG) and increased nodal strength in fusiform gyrus (FFG) correlated negatively with improvement in depressive symptoms. However, the second study which was a fMRI study, authors failed to find any correlation between pairwise ROI with change in depressive symptoms during course of right unilateral ECT (RULECT) in 30 patients (Leaver et al., 2016). The same group when analysed only preECT neuroimages in 42 such patients using graph theory found frontoparietal network and subgenual ACC predicting clinical response to RULECT up to 74% (Leaver et al., 2018). Though the method of graph theory analysis was described, specific values of those graph theory measures obtained after analysis and associated p values were not provided in either of the studies by this group.

In ECT-depression studies analysing ROI of functional brain connectivity with Independent Component analysis or seed based, influence of ECT was prominent on intralimbic and limbic-prefrontal network, default mode network, executive control network and functional neuronal connectivity (FNC) of dorsomedial prefrontal cortex (DMPFC), posterior ACC, temporal pole, MTG and subcortical structures (mediodorsal thalamus and ventral basal ganglia) (Abbott et al., 2014, 2013; Bai et al., 2019; Cano et al., 2016; Leaver et al., 2016; Liu et al., 2015; Perrin et al., 2012; Wang et al., 2018; Wei et al., 2014). Many of them found association of improvement of depressive symptoms with some of these specific influenced areas of FNC (Abbott et al., 2014; Bai et al., 2019; Cano et al., 2016; Liu et al., 2015; Wang et al., 2018). But some studies also refuted the correlation between neuroimaging findings and clinical response with ECT (Leaver et al., 2016; Wei et al., 2014; Zhuo and Yu, 2014). In most of the above stated studies, patients received BTECT, RULECT or the electrode placement of ECT was not specified. Since last few years, bifrontal ECT (BFECT) has been considered as a good alternative to BTECT and RULECT (Bjolseth et al., 2015; Dunne and McLoughlin, 2012). Two studies which focused on BFECT found the increase in regional homogeneity (ReHo) and amplitude of low frequency fluctuations (ALFF) of SFG, middle frontal gyrus (MFG) and precentral gyrus (Kong et al., 2017) and increased FNC between fusiform face area and amygdala (Wang et al., 2017a) to be associated with decline in Hamilton depression rating scale (HAMD).

There is some evidence that brain regions critical for therapeutic efficacy may be distinct from regions influencing cognitive side effects. Possibly, frontal and prefrontal cortical regions are also involved in affecting cognition along with medial temporal lobe; influence may vary with electrode placement (Nobler and Sackeim, 2008). The explorations into mechanisms of ECT associated cognitive adverse effects however lags a way behind compared to that of associated clinical response. Its significance should not be debatable considering the presence of cognitive deficits during and until at least 2-weeks post ECT (Semkovska and McLoughlin, 2010; Vasavada et al., 2017). Few structural MRI based ECT studies were conducted but did not find any association between cognitive deficits and cortical/ sub-cortical regions having ECT related significant changes in volume or thickness (Abbott et al., 2014; Bouckaert et al., 2016; Nordanskog et al., 2014). Unfortunately, none of fMRI studies have examined resting state connectivity changes associated with cognitive adverse-effects of ECT.

To summarize, we now better understand the neurobiology of depressive disorder with advancement in brain neuroimaging methods and analysis such as graph theory. The application of graph theory's connectivity model in understanding ECT's mechanisms of action is limited till date and didn't explore cognitive adverse effects. Hence, we aimed to analyze the change in brain network segregation and integration measures after the administration of ECT on 17 patients for the treatment of depressive episode. We also examined if these measures differ with respect to clinical response and cognitive deficits.

2. Methods

2.1. Participants

The study was conducted at an in-patient setting of a tertiary care hospital in Southern India. All participants were recruited in this prospective study after the approval of research protocol by Institute Ethics Committee and after providing a written informed consent. They received a diagnosis of depressive episode of any severity as a first episode or as part of a recurrent depressive or bipolar affective disorder according to ICD-10 (World Health Organization, 1992). All were prescribed BFECT for depression as deemed necessary by their respective treating team of psychiatrists. Pharmacotherapy was decided by the treating team including changing the medications and their dose during the course of ECT. It was neither interfered by us nor was the criterion for inclusion/ exclusion in anyway. Participants of either gender were included and all of them were able to read and write at least one language. None of them received ECT at least six-months prior to recruitment. Patients were excluded if they (i) had any history of alcohol or drug abuse, mental retardation, epilepsy, dementia or any other neurological, or serious physical disease (ii) had any surgical electronic or metal implants and (iii) were not cooperative for neuroimaging or cognitive assessments. MRI scanning, clinical and cognitive assessments were done one or two days prior to the first ECT and then repeated within two days after the sixth or last ECT session, whichever was earlier. We preferred 6th session rather than 8th session as in Zeng et al. (2015) based on the pattern followed in research conducted from our site (Kotresh et al., 2004; Nitturkar et al., 2016; Rakesh et al., 2017). In addition, we conducted analysis of two random months' data of total number of ECT sessions per patient for depressive episode at our ECT services, average number was noted to be 6.44 and 6.72.

2.2. ECT procedure

BFECTs were administered thrice weekly using the NIVIQURE machine (Technonivilac, Bangalore, India) with two lead EEG monitoring. Brief-pulse square-wave stimulation with constant current at 800 mA, 125 bidirectional pulses per second having pulse width of 1.5 ms was used; duration of train was altered to adjust the stimulus dose. All ECTs were administered under anesthetic modification (Thiopentone 2–4 mg/kg & succinylcholine 0.5–1 mg/kg). The concave electrodes were placed bilaterally five centimeters above the outer angle of orbit. During first session, threshold was determined by titration method. Subsequent ECTs was administered at 1.5 times this threshold. The decisions of initiating and stopping ECT was made by the treating team based on clinical response and appearance of adverse event if any.

2.3. Assessments

1 Clinical: The severity of depressive symptoms was assessed by the 17-item Hamilton depression rating scale (HAMD) (Hamilton, 1960).
2 Cognitive:
   a Various domains of memory were assessed by Wechsler Memory Scale (WMS), India (Wechsler and Gurappa

Pushpalatha (NIMHANS), 2011), which is the adaptation of WMS-III (Wechsler, 1997) for the Indian population into different Indian languages and has Indian norms in the form of percentile ranks. In view of possible difficulty in carrying out the complete scale secondary to the underlying depression and available literature about ECT associated cognitive deficits, we decided to use (i) word list, (ii) visual reproduction, (iii) verbal pair associate, (iv) logical memory story, and (v) digit span test of WMS for our study; 1st, 3rd and 4th tests for episodic verbal memory, 2nd test for visual memory and 5th one for working memory. We didn't use any index score. Instead we considered immediate and delayed recall scores for initial 4 tests, learning, recognition and retention scores for initial 2 tests and maximum number of digits under 5th test. Since we didn't have control group and were interested only in pre-post ECT difference, we utilized raw scores.

b Controlled oral word association test (Barry et al., 2008), Stroop test (Golden, 1978) and Tower of London (Shallice, 1982) were used to assess phonemic fluency, response inhibition and planning respectively. All these tests had been adapted for Indian setting (Rao et al., 2004). The sum of all words from three consonants was taken as score for phonemic fluency. The difference of naming time and reading time was considered as Stroop effect score. For Tower of London, the total number of problems with minimum moves was considered as the score.

2.4. Neuroimaging

2.4.1. Data acquisition

A spin echo sequence (TR = 2000 ms, TE = 20 ms; refocusing pulse 90°; slice thickness of 3 mm in an interleaved manner; no of dynamics = 250; FOV_192 × 192 mm, matrix 64 × 64 mm voxels with no gap and voxel size of 3 × 3 × 3 mm) was used to acquire whole brain T2 weighted images in a 3T scanner (SKYRA; Siemens, Erlangen, Germany). A three dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence was acquired (TR = 1900 ms; TE = 2.44 ms; voxel 1 × 1 × 1 mm; matrix 256 × 256 voxels) for spatial registration and segmentation.

2.4.2. Data analysis

The fMRI data preprocessing was carried out using statistical parametric mapping SPM9 (https://www.fil.ion.ucl.ac.uk/spm/) following standard methods. Network analysis was carried out using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). The network correlation matrices are provided in Fig. 1.

2.4.3. Pre-processing

Structural fMRI data pre-processing included realignment, segmentation to remove white matter and cerebrospinal effect, normalisation to MNI152 standard space of 3 × 3 × 3 $mm^{3,}$ motion correction using Friston's 24 motion parameter, and temporal band-pass filtering with 0.01–0.09 Hz (Bharath et al., 2017). Patients were included in the analysis after motion correction. Their head motions between pre and post ECT measures were not significantly different. (Translation (mean ± SD in mm):: pre:1.84 ± 2.77, post:1.61 ± 2.69, *p*: 0.67; Rotation (mean ± SD in radians):: pre: 0.02 ± 0.02, post: 0.03 ± 0.04, *p*: 0.16) using the Artifact Detection Toolbox.

2.4.4. Brain region parcellation

The Automatic Anatomical Labelling atlas was used to parcellate brain into 116] regions. The average of all the voxels in one region of interest was taken as the time series of that ROI.

2.4.5. Graph theory analysis

First, a range of sparsity threshold was determined to ensure the same number of network edges for each participant by retaining only those connections whose edge strengths exceeded a given threshold. This procedure guaranteed that the threshold networks were estimable for small-worldness and also avoided excess network fragmentation at sparser thresholds (Bharath et al., 2017; Fornito et al., 2010). Sparsity was defined as the ratio of the number of actual edges divided by the maximum possible number of edges in a network. The range of sparsity generated here was $0.11 \leq S \leq 0.45$, with an increment of 0.01. Then, normalized clustering coefficient (γ), normalized path length (λ) and small-worldness (σ) were derived by dividing the absolute graph theory metrics data with corresponding metrics data of random networks obtained by randomization across the generated sparsity levels.

For rsfMRI graph measures, time series was correlated region by region using Pearson's correlation and a 116 × 116 matrix was constructed (Fig. 1). The graph theory properties of the functional brain networks were defined on the basis of 116 × 116 Graph in rsfMRI, G (V, E) where G is the non-zero subset with vertices V = anatomical ROIs (nodes "N") and edges E = Internodal correlation coefficient (Fisher's *Z* value) as a connection between nodes were calculated. The small-world parameters (i.e., γ, λ, σ) were calculated over the range of sparsity ($0.11 \leq S \leq 0.45$) using the BCT toolbox (Bharath et al., 2017) and in-house MATLAB scripts (Bharath et al., 2017; Fornito et al., 2010; Rubinov and Sporns, 2010). Here, false discovery rate (FDR) correction was done for multiple comparisons of 116 brain regions.

2.5. Statistical analysis

Clinical and neuropsychological for pre and post ECT assessments of all participants were tested for normality by Shapiro Wilk test. Accordingly, paired *t*-tests or Wilcoxon signed rank test was conducted

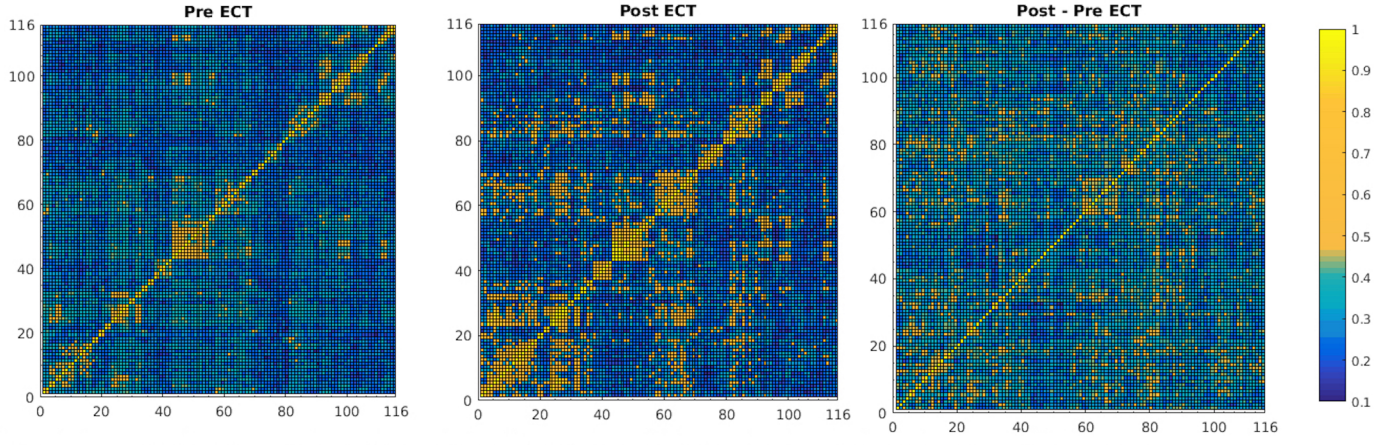

Fig. 1. The average absolute correlation matrix of patients with depression in 116 brain regions based on Automatic Anatomical Labelling status.

Table 1
Socio-demography, clinical features and treatment- Baseline.

Variable		Frequency (%) Mean ± SD
Age		44.8 ± 18.9 years
Gender	Male	7 (41.2%)
	Female	10 (58.8%)
Diagnosis	1st Depressive episode	6 (35.3%)
	Recurrent depressive disorder	6 (35.3%)
	Bipolar affective disorder	5 (29.4%)
Presence of psychotic symptoms		10 (58.8%)
Total duration of illness		8.1 ± 11.1 years
Duration of current episode		4.7 ± 3.2 months
Age at onset of illness		36.7 ± 17.7
No. of ECT sessions		7.2 ± 1.2
Seizure Threshold		130.6 ± 60.9
Antipsychotics		13 (76.5%)
Antidepressants		12 (70.6%)
Mood stabilizer		4 (23.5%)
Benzodiazepine		8 (47.1%)

to assess significant ECT induced changes. For significant variables, the difference in ratings of 2 occasions was also tested for normality. Then, the relationships between significant brain regions and significant clinical and cognitive scores were assessed using Pearson or Spearman Correlation. FDR correction was applied for both pre-post difference and correlation analysis.

3. Results

3.1. Baseline and clinical-cognitive outcome

Data of 17 recruited participants was taken for this graph theory analysis of rsfMRI. 2 participants were excluded because of excessive motion artefacts in neuroimaging. All of them were patients receiving BFECT for their depressive episode. The baseline details are provided in Table 1. It includes socio-demography, clinical features and treatment characteristics. The number of ECT sessions varied between 5 and 11 and 11 out of 17 patients received 6 sessions. Table 2 shows the results of baseline and post 6th ECT clinical assessment and those of neuropsychology. It also indicates the variables where the difference in these 2 time-points' assessments were statistically significant. Here, due to varied degree of cooperation for various cognitive assessments, the sample size varied for each cognitive measures (Table 2). Along with severity of depression, there was significant decline in phonemic fluency after ECT. There was also significant improvement in immediate and delayed word list recall and immediate visual reproduction recall.

3.2. Changes in network typology

The normalised clustering coefficient increased significantly (sparsity level 1–37%) after ECT (Fig. 2). The normalised path length also increased significantly (sparsity 1, 2, 4, 6, 9–11, 26–29, 34–37, 40%) after ECT (Fig. 2). Despite the increase in the pathlength the normalised small worldness increased significantly (sparsity 1, 2, 5–37) after ECT therapy (Fig. 2).

The brain areas which revealed significant differences (FDR adjusted p-values) in clustering coefficient after ECT were the left inferior frontal operculum ($p = 0.0467$), left medial superior frontal gyrus ($p = 0.0382$), left paracentral lobule ($p = 0.0382$) and right pallidum ($p = 0.0382$) (Fig. 3).

3.3. Correlation between brain regions having significant changes in network typology and significant clinical-cognitive outcome (Fig. 4)

On analysis, it was found that change in HAM-D scores was significantly ($p = 0.044$) but negatively correlated ($r = -0.493$) with differences in left paracentral lobule connectivity. The decline in COWA scores was significantly ($p = 0.026$) correlated ($r = 0.534$) with left medial superior frontal gyrus. Delayed wordlist recall showed a positive trend in correlation with right pallidum ($r = 0.482$, $p = 0.050$) and left inferior frontal operculum ($r = 0.468$, $p = 0.058$). All p-values were FDR adjusted.

4. Discussion

The current study utilized graph theory model to examine the change in brain network topology associated with BFECT in patients having a depressive episode. We report significantly increased clustering coefficient and small worldness with increased pathlength after ECT in patients with depression. Several regions in the left frontal lobe along with right pallidum revealed significant changes which correlated with the clinical improvement and change in neuropsychological scores.

4.1. Effect of ECT on global network characteristics

As per our study, there was significant increase in small world typology after 6 BFECT sessions. This differs from Zeng et al. (2015) which found no change in global small word topology of brain after course of 8 ECTs. One reason for this discrepancy could be the nature of measures used in the topological analyses. rsfMRI measures are restricted to gray matter and thus represents functional covariance between regions, while DTI measures used in earlier study represent direct measure of structural connectivity (Korgaonkar et al., 2014); ECT

Table 2
Clinical and cognitive outcome after 6 ECT sessions.

Variable	Pre ECT Mean (SD)	Post 6th ECT Mean (SD)	t/ z value[a]	p
HAM-D ($n = 17$)	24.06 (5.74)	6.59 (7.62)	$t = -9.24$	0.000[b]
Controlled oral word association ($n = 15$)	22.47 (3.20)	14.46 (3.56)	$t = -3.35$	0.002[b]
Immediate word list recall ($n = 17$)	17.24 (11.34)	22.67 (10.35)	$t = 2..49$	0.018[b]
Delayed word list recall ($n = 17$)	5.12 (6.06)	7.88 (6.88)	$t = 2.05$	0.049[b]
Immediate visual reproduction recall ($n = 15$)	47.33 (30.24)	66.20 (27.55)	$t = 3.37$	0.005[b]
Delayed visual reproduction recall ($n = 15$)	32.33 (27.88)	44.27 (34.22)	$t = 1.51$	0.153
Immediate logical memory recall ($n = 16$)	14 (15.14)	17.38 (15.61)	$t = 0.90$	0.382
Delayed logical memory recall ($n = 16$)	6.19 (9.15)	5.69 (9.29)	$t = -0.20$	0.844
Immediate verbal pair associate ($n = 14$)	10.86 (10.33)	9.43 (9.53)	$z = -0.51$	0.609
Delayed verbal pair associate ($n = 14$)	3.3 (4.18)	2.93 (3.39)	$z = -0.72$	0.469
Digit span ($n = 16$)	9.94 (5.63)	10.5 (4.07)	$z = 0.06$	0.954
Stroop test ($n = 9$)	172.38 (83.36)	185.3 (102.23)	$z = 0.30$	0.767
Tower of London: The number of problems with minimum moves ($n = 15$)	7.27 (2.49)	7.4 (2.41)	$t = 0.18$	0.859

[a] t for paired t-test, z for Wilcoxon signed rank test.
[b] statistically significant difference.

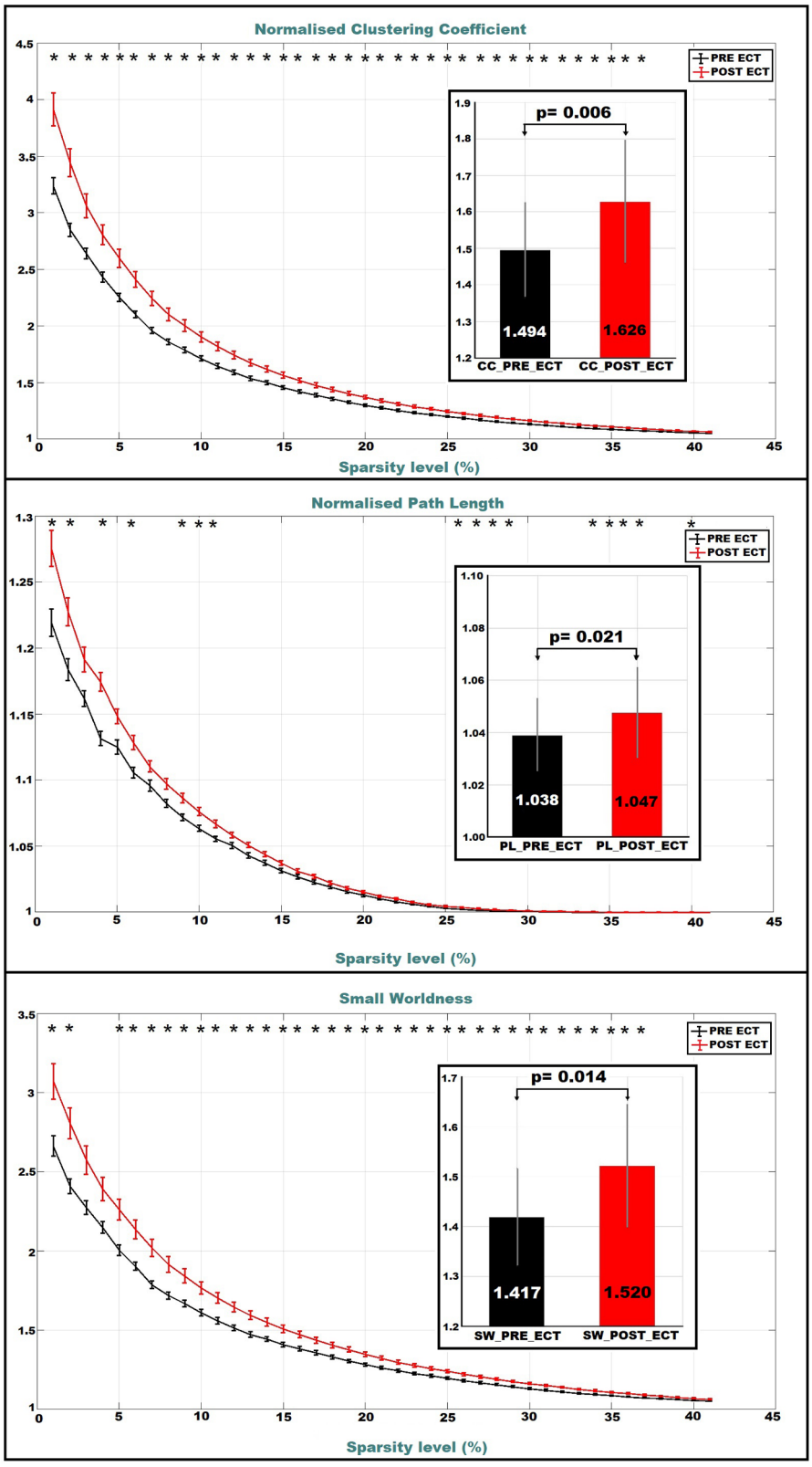

Fig. 2. Brain network typology in Pre-ECT and Post-ECT
* indicates significant ($p < 0.05$, uncorrected) difference between Pre and Post ECT graph theory measure; # indicates FDR corrected; In all bar charts, Y axis denotes the mean of corresponding graph theory measure across all sparsity levels.

might affect earlier mentioned aspects of brain more than the later one. Small worldness is the ratio of clustering coefficient with pathlength and small-worldness index larger than one would have a higher clustering coefficient (i.e., normalized version much >1) and a comparable characteristic path length (i.e., normalized version ~1). This indicates overall efficient information segregation with lower energy cost and higher transmission rate (Liao et al., 2017; Sporns and Zwi, 2004). In our study though there was increase in both clustering coefficient and

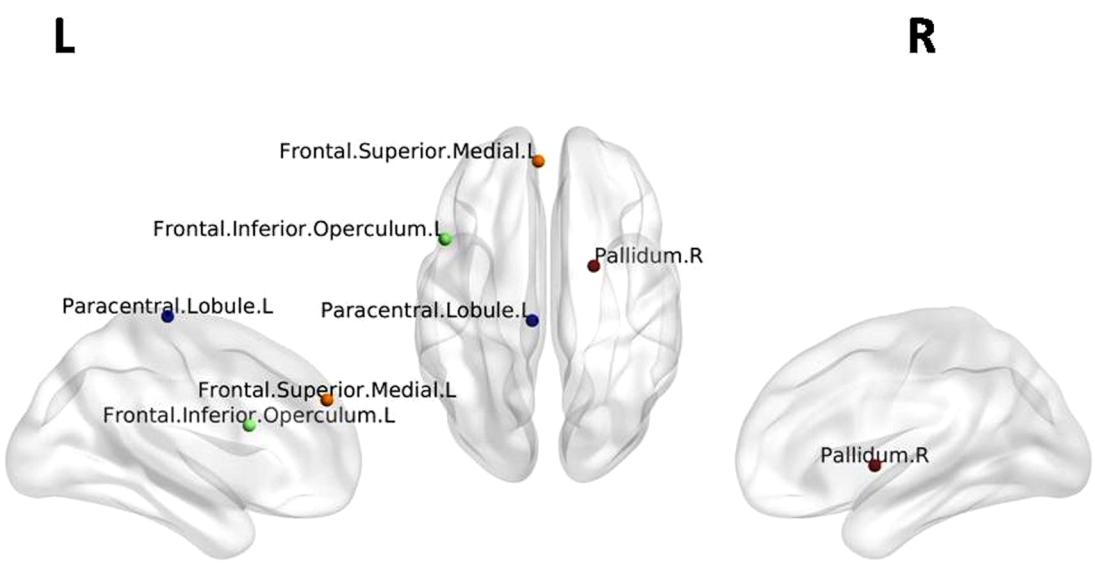

Fig. 3. Nodes with significant differences ($P < 0.05$) in clustering coefficient (CC) between post-ECT and pre-ECT
Nodes (Individual ROIs) are differently coloured according to the strength of CC. Nodes and edges are presented on inflated surface maps by BrainNet Viewer (https://www.nitrc.org/projects/bnv/).

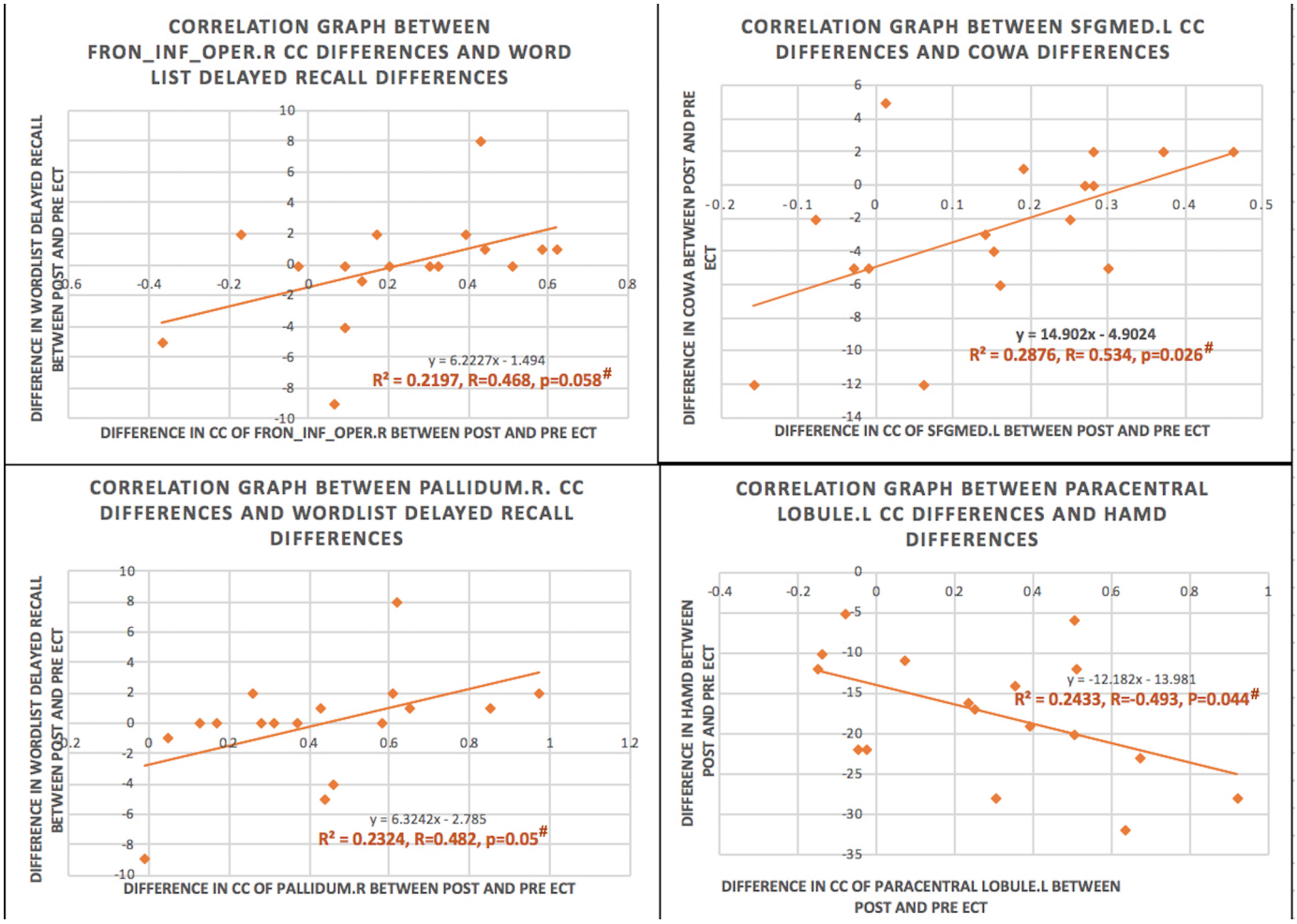

Fig. 4. Correlation graph shows nodal regions having significant correlation between its Δ CC and Δ HAMD/ Δ cognitive function (Δ = Post ECT – Pre ECT)
CC: Clustering coefficient, Front_Inf_Oper.L: Left inferior Frontal operculum, HAMD: Hamilton depression rating scale, Pallidum.R: Right Pallidum, Paracentral lobule.L: Left Paracentral lobule, SFGMed.L: Left Medial Superior Frontal Gyrus.

path-length after the course of ECT, the former surpassed the later resulting in better small world network.

An increased pathlength reflects reduced integration, making global communication between different regions of brain more difficult and reducing global efficiency. Earlier studies of patients with drug naïve depression had reported smaller path lengths and higher global efficiency (Zhang et al., 2011). We found increase in path length post ECT compared to what was present before ECT in our depressed subjects. This matches with the findings of similar increased path length and reduced global efficiency in antidepressants treated depressed patients (Meng et al., 2014). Similarly, findings of disrupted small worldness in past studies of depressed subjects goes well with improvement in small worldness noted in our study during the course of ECT for depression (Jin et al., 2011; Sacchet et al., 2014). Thus, from the results of our study it could be inferred that ECT relates to lesser integration and more segregation of brain connections during its course in depression. Nonetheless, results of some brain-network studies conducted on depression do not go well with our findings (Chen et al., 2016; Wang et al., 2017b; Ye et al., 2016).

There has been some attempt to understand these global changes in brain network typology through other factors altered by psychiatric disorders. In a recent study, dopamine receptor blockage through antipsychotics could modulate reduced global efficiency (increased pathlength) and increased clustering coefficient present in drug naïve schizophrenia (Hadley et al., 2016). Though 59% of our subjects had psychotic symptoms, it is difficult to extrapolate these findings to the results of ECT associated reduced global efficiency (increased pathlength) and increased clustering coefficient noted in our study. ECT is noted to have both antipsychotic related clinical effects and reduction of antipsychotic induced adverse effects; probably due to its differential effects on dopamine activity in different parts of brain (Baldinger et al., 2014). There is a need of graph theory based analysis in more ECT fMRI studies in depressed subjects with and without psychotic features separately.

4.2. Effect of ECT on specific nodal typology and correlation with clinical outcome

The current study suggests four brain regions which were affected during the course of BFECT. Three of them are part of left frontal lobe namely inferior frontal operculum, supero-medial frontal region and paracentral lobule. Significant increase of ReHo and ALFF of frontal lobe (SFG, MFG, and precentral gyrus) by BFECT was also noted in earlier study indicating synchronised oscillations and spontaneous activity of neurons (Kong et al., 2017). However, the predominance of ECT's impact on left side in our study was not supported by this study. One recent rsfMRI based study using SPM software found increased resting-state functional connectivity of DMPFC with left anterior prefrontal cortex with BFECT in the sample of 23 patients having depressive episode (Wang et al., 2018). They also had 25 age and gender matched subjects in control group which had significantly increased FSN in the above nodes compared to patient group. rsfMRI based studies on depression had found predominant effect on one hemisphere more than the other (Lord et al., 2012); left side leading (Iwabuchi et al., 2014; Schlösser et al., 2008; Tao et al., 2013) and right side leading (Meng et al., 2014; Sacchet et al., 2014). Local nodal efficiency of superior (Lord et al., 2012; Meng et al., 2014; Tao et al., 2013) and medial frontal gyrus (Tao et al., 2013), and inferior frontal operculum (Tao et al., 2013) are also implicated in depressive episodes. These frontal and insular regions are integral part of functional networks involved in depression such as anterior default mode network, salience network and central executive network (Mulders et al., 2015).

There is some evidence that activity of paracentral lobule is more in people having depression (Li et al., 2016) and high anxiety traits (Greening and Mitchell, 2015) during exposure to negative emotional pictures (Li et al., 2016) and in resting state as well (Greening and Mitchell, 2015). The thickness of left paracentral gyrus compared to precentral gyurs was recently found to be one of the strongest predictors to lower relapse rate of depression within 6months post ECT in 2 independent samples (Wade et al., 2017). The predictive capacity of its somatosensory component (in relation to ACC) (van Waarde et al., 2015) and left supplementary motor area (Jiang et al., 2017) were also noted to be strong for response to ECT in depression. All these 3 studies used RULECT rather than BFECT as in our study. Paracentral lobule has also been considered as an important "hub controller" (Hagmann et al., 2008) having bidirectional connections with precuneus (Zhang and Li, 2012) which is a core component of human default mode network (Raichle et al., 2001).

With reference to the use of graph theory in ECT, Zeng et al. (2015) found increased nodal strength in FFG with reduction in depressive symptoms whereas Leaver et al. (2016) didn't find correlation between nodal graph theory metrics of any ROI associated with ECT (those ROIs where alteration in resting state FNC from baseline to 2–4 weeks later occurred only in ECT group but not in control group i.e. $ECT_{baseline} \neq ECT_{2–4weeks} = CO_{baseline} = CO_{2–4weeks}$ or $ECT_{2–4weeks} \neq ECT_{baseline} = CO_{baseline} = CO_{2–4weeks}$) and that of ROIs associated with improvement in depressive symptoms. Zeng et al. (2015) noted effect in temporal region with BTECT while our study using BFECT noted effect in frontal region. In the study by Leaver et al. (2018) where RULECT was administered, pre-ECT left frontoparietal network connectivity strength was the best predictor of ECT response to depression. This hints towards the possibility of different brain areas/networks targets with different electrode placements in ECT for providing improvement in depression. However, Leaver et al. (2018) also had provided evidence for the role of left supplementary motor area (part of paracentral lobule) in predicting ECT response. Thus, there may be complex relationship between effects specific to electrode placement in ECT and general effects of ECT leading to reduction in symptoms.

Further, basal ganglia particularly striatum (Bohr et al., 2012; Meng et al., 2014; Ye et al., 2016) did show major significance in many studies on depression with possible disturbance in cortical– striatal–pallidal–thalamic circuit related to reward-hate (Tao et al., 2013), sensory and self-information processing (Iwabuchi et al., 2014; Meyer et al., 2001). In our study, right pallidum had significant increase in clustering coefficient post-ECT. Amygdala, HC, PHG, fusiform gyrus, MTG, precuneus, and thalamus reported to be associated with depression (Gong and He, 2015; Kaiser et al., 2015; Mulders et al., 2015) and its treatment after ECT (Abbott et al., 2013; Cano et al., 2016; Joshi et al., 2016) were not found significant in current study, probably because the global measures did not survive correction in this data driven type of analysis or probably because of the heterogeneous clinical group.

4.3. Correlation of effect of ECT on specific nodal typology and that on cognitive functions

Unlike the earlier studies, the current study found relationship between BFECT associated changes in local brain connectivity and cognitive performance. There was a significant correlation between decline in phonemic fluency and left medial superior frontal connectivity. Very few studies on ECT assessed phonemic fluency (Semkovska and McLoughlin, 2010). Those on BFECT have found reduction in phonemic fluency after course of ECT sessions (Dybedal et al., 2015; Kellner et al., 2010). Left frontal lobe particularly DLPFC, superior frontal cortex and part of inferior frontal cortex play a role in phonemic fluency (Alvarez and Emory, 2006; Klumpp and Deldin, 2010).

Delayed wordlist recall showed a positive trend in correlation with right pallidum ($r = 0.482$, $p = 0.050$) and left frontal inferior operculum ($r = 0.468$, $p = 0.058$). The role of globus pallidus in verbal learning and memory particularly delayed has been investigated. Substance P (Kertes et al., 2009), glutamate as well as GABA (Buchanan et al., 2015) play a role to involve pallidum through cortico-basal ganglia-thalamocortical loop (Wei and Wang, 2016) in verbal

memory deficits. The role of frontal operculum is mostly cited as task control and decision making whether to initiate the process of retrieval and recall of information (Higo et al., 2011). It is probably done through cingulo-opercular network (CON) (Sestieri et al., 2014) and more relevant for verbal than non-verbal memory (Nixon et al., 2004). Although it is implicated bilaterally (Lepage et al., 2000), the evidence is stronger for left side. Since the lower motivation to work on the cognitive task is one of the major causes of poor cognitive performance in depression, we expected the brain region responsible for decision process to have a significant role in ECT associated improvement in depression as well as memory recall.

Our study did not find significant correlation with working memory test scores probably because we only used changes in clustering coefficient for clinical correlation. Other measures like local efficiency, modularity, hubs, and betweeness centrality might be potentially useful. In this regard, it is interesting to note that the increased clustering coefficient after ECT in the paracentral lobule, though correlated with improvement in symptoms, the same phenomenon in the adjacent medial frontal lobe was associated with worsening of language fluency. Thus, the increased clustering in our study could explain both the benefits and cognitive deficits associated with ECT. Hyperconnectivity response probably indicates a neurological disruption (Hillary et al., 2015) and could represent both a compensatory response to increased pathlength and a therapy induced cortical plasticity. Emerging view states that cognition is the result of dynamic integration between distributed large scale networks (Bressler and Menon, 2010) and a more efficient integration is linked to higher IQ (van den Heuvel et al., 2009). We hypothesize that medial frontal lobe was less efficient for cognitive processes due to the increased pathlength between its connections resulting in the observed cognitive deficits. Further studies using global efficiency measures and dynamic connectivity measures might throw more light into mechanisms underlying cognitive deficits after ECT.

4.4. Conclusion and limitations

The current study using graph theory analysis of brain rsfMRI has demonstrated a segregated and less integrated network topology correlating with the clinical improvement and explaining the change in cognitive functions, thus contributing to the understanding of network neurobiology of ECT in patients with depression. It also provides network based evidence that the actions of ECT may not be interpreted separately for clinical outcome and associated cognitive adverse effects. The heterogeneity of ECT induced cognitive deficits in patients with depression does complicate the understanding of ECT induced cognitive deficits. Nonetheless, the use of network analysis in the current study in comparison to earlier fMRI studies of ECT and examination of BFECT rather than BTECT or RULECT might have also made the results of the current study exclusive. In addition, seizure threshold determination method also differed; some studies using titration based (Abbott et al., 2013; Leaver et al., 2016; van Waarde et al., 2015) and some using age based method (Cano et al., 2016; Liu et al., 2015; Zeng et al., 2015). We preferred titration based method considering the evidence for lesser cognitive adverse effects with it (McCall et al., 2000; McClintock et al., 2014).

The study had limitations such as lack of control population (Liu et al., 2015; Perrin et al., 2012; Zeng et al., 2015), heterogeneity of clinical population (first as well as later episodes, unipolar as well as bipolar depression, with or without psychotic features) (Abbott et al., 2013; Cano et al., 2016; Wang et al., 2018), influence of variable pharmacotherapy (Cano et al., 2016; Liu et al., 2015; Perrin et al., 2012; Wang et al., 2018) and smaller sample size (Abbott et al., 2013; Cano et al., 2016; Liu et al., 2015; Perrin et al., 2012; Wang et al., 2018; Wei et al., 2014). In particular, there is some evidence that bipolar depression may differ in global brain graph metrics (higher clustering coefficient, better local efficiency and shorter pathlength (He et al., 2016)) and local graph metrics (stronger clustering and nodal efficiency in prefrontal and mid-frontal, ACC, PCC, STG, PHC and cuneus (He et al., 2016), higher degree of centrality in precuneus and lower in left insula (Li et al., 2017), higher nodal strength in temporal pole and higher nodal efficiency in precuneus (Wang et al., 2017b)) from unipolar depression. At the same time, one of these studies indicated convergent deficits in graph theory related topology in whole brain, DMN and limbic networks in unipolar and bipolar depression and reflects common pathophysiological processes in them (Wang et al., 2017b). These limitations were also present in earlier studies (references cited with the respective limitation); hence highlighting the pragmatic issues of ECT associated neuroimaging studies. Nonetheless, this study being more explorative needs to be followed by more studies on using graph theory analysis to understand mechanisms of ECT in depression while addressing these limitations.

Acknowledgement

This work was supported by Department of Science and Technology, Government of India under the program ‘Cognitive Science Research Initiative’ (SR/CSRI/26/2015).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.03.008.

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