Effect of Temporal Lobe Epilepsy on Auditory-motor Integration for Vocal Pitch Regulation: Evidence from Brain Functional Network Analysis

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***Abstract*—Temporal lobe epilepsy (TLE) is a medically refractory focal epilepsy associated with structural deficits. Considerable evidence has revealed that patients with TLE also exhibit deficits in functional connectivity. Previous research has shown that patients with TLE exhibit decreased performance in speech sound perception and auditory-motor integration for voice control, which might be related to the compromised brain network connectivity. However, the specific nature of functional connectivity within and across brain regions remains largely unknown. To answer this question, we extended previous research from examining the topological properties of the entire brain network to the intra- and inter-regional communications of different brain regions. Patients with TLE and healthy controls were recruited to perform a pitch reflex task, during which electroencephalograph (EEG) data were acquired to construct graphical brain networks. Compared with healthy controls, inter-regional and cross-hemispheric connections were reduced in patients with TLE, whose functional networks were primarily composed of intra-regional connections. Significant differences in network parameters (betweenness centrality, modularity, and functional integration) as well as network hubs between the two groups further supported our findings that TLE is associated with alterations in functional connectivity during auditory-motor integration.**

I. INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common form of medically refractory focal epilepsy characterized by an early age of onset [1] and sclerosis in the mesial temporal lobes [2]. A growing body of research has shown structural deficits associated with TLE by using voxel-based morphometry (VBM) [3], diffusion tensor imaging (DTI) [4], and functional magnetic resonance imaging (fMRI) [5]. TLE is associated with a significant volume loss of the thalamus, cerebral hemispheres, and cerebellum [3] or abnormalities in white matter fiber tracts [4], and epileptogenic lateralization [5]. Therefore, TLE is generally thought to be a systemic disorder due to its widespread structural damage.

Besides structural deficits, functional neuroimaging studies have also shown that TLE has disrupted functional connectivity within certain networks involving the temporal, parietal, and frontal cortices [6-12]. For example, Liao et al. [6] found that region-wise functional connectivity within the medial temporal lobes was significantly increased in patients with TLE, with that within the frontal and parietal lobes significantly decreased. Moreover, a decreased cross-regional functional connectivity between frontal and parietal lobes was found in the patient group. Graph-theoretical analysis of corticography recordings further revealed an association between longer TLE duration and lower temporal lobe functional connectivity and more random neural network configuration [6-8].

These alterations in the structural and functional networks tend to have a negative impact on cognitive function of patients with TLE [13]. In the case of auditory processing, TLE patients exhibited decreased performance in temporal ordering and dichotic listening tasks [14], as well as impairment in processing rapid sequential auditory information [15]. Besides, TLE patients produced MMN with increased latencies due to their impaired pre-attentive processing of sounds [16], or difficulties in auditory processing associated with novelty discrimination [17]. Across different auditory tasks, there was a negative correlation between latency of auditory cortical responses and TLE onset [19,20]. These studies suggest that patients with TLE are associated with deficits in central auditory processing, which may influence speech motor control.

Speech motor control refers to the systems and strategies that regulate the production of speech [21], which relies on sensory feedback, especially auditory feedback [22,23]. Current theories and models posit that this process engages a distributed network involving frontal, parietal, and temporal cortices, where incoming auditory feedback is compared with predictions generated from "efference copies" of motor commands [24-29]. Discrepancies between incoming and

actual feedback lead to feedback prediction errors. Sensory areas then respond by conveying such discrepancies to motor regions, and ongoing speech output is adjusted to correct for the perceived vocal errors.

A well-studied experimental paradigm that examines the mechanism of speech motor control is frequency altered feedback (FAF) [30,31]. In such experiments, speakers produce sustained vowels while hearing their voice auditory feedback unexpectedly pitch-shifted up or down. Speakers respond to voice feedback perturbations by producing compensatory responses in an opposite direction to the perturbations.

Our team [36] found that patients with TLE produced significantly larger compensations in their vocal responses but smaller amplitudes in P2 responses to vocal pitch errors (1/2 or 2 semitones upward) as compared to healthy controls. Moreover the graph-theoretical analysis revealed that patients with TLE exhibited a disrupted neuronal network with a significant increase of clustering coefficients and path lengths. These findings provided evidence that patients with TLE have atypical integration of auditory feedback into the vocal motor system, and the functional network configuration differs between TLE patients and healthy controls. Yet, the previous study provided an initial insight into the reconfiguration of functional network during auditory-motor integration for vocal control in TLE patients. Speech motor control, however, is a specialized and integrated system which is inherently dynamic with rich patterns of regional interactions. Brain regions must interact with one another in a time-varying fashion to enable its complex functions [37]. To date, the specific nature of the transient communications among different brain regions throughout the course of auditory-motor integration is largely unknown. As well much less is known about the compromised transient dynamics of regional interactions associated with TLE.

In this connection, we attempted to address this knowledge gap by extending our research from the global topological properties of the whole brain network to the intra- and inter-regional communications of different brain regions during auditory-motor integration. Based on the constructed brain network, six regions of interest (ROI) were defined to compare the intra- and inter-regional connectivity between the two groups. After which network parameters including betweenness centrality (BetC), modularity (Mod) and functional integration (FI), and hubs were defined and computed to further analyze the differences in their functional network. This approach offers an opportunity to understand the topological and organizational properties of an interconnected functional network, going beyond its global efficiency towards the integrity of the dynamic mechanism that governs inter-regional communication. Further advantages of such approach is that it provides a better understanding of the regional interactions, and will help us detect the cognitive dysfunction associated with TLE, which is crucial for clinical decision making.

II. MATERIALS AND METHODS

A. Participants

Patients were recruited from the Department of Neurology at The First Affiliated Hospital of Sun Yat-sen University in China, including 28 patients (10 females and 18 males; mean age = 27.32 ± 5.96 years: 11 left-sided, 17 right-sided). All patients met the following inclusion criteria: Full Scale IQ > 80 and no apparent intellectual disability or attention disorders prior to onset of seizure; no history of temporal lobectomy; and epileptic spikes in the bilateral frontotemporal or temporal lobes. Eligibility criteria for age-matched healthy controls (10 females and 18 males; mean age = 25.79 ± 5.92 years) included normal IQ, normal structural brain imaging, and absence of speech, hearing, language, or neurological disorders. Each participant passed a bilateral screening test to verify the hearing status. Informed consent was obtained from all participants and the study was approved by the institutional board for human research of The First Affiliated Hospital at Sun Yat-sen University.

B. Experimental Setup

The experiment was carried out in a sound-attenuated booth. Participants heard their self-voice feedback with a gain of 10 dB sound pressure level (SPL) relative to their vocal output. Participants were instructed to produce the vowel /u/ for approximately 5-6 seconds at their conversational pitch and loudness level, while listening to their voice unexpectedly pitch-shifted upwards 50 or 200 cents (100 cents = 1 semitone). During each vocalization, 5 pitch shifts (200 ms duration) were presented with an inter-stimulus interval of 700-900 ms and the first one occurred 500-1000 ms after the vocal onset. Participants produced 40 consecutive vocalizations, resulting in 100 +50-cent trials and 100 +200-cent trials.

Participant's voice was picked up by a dynamic microphone (model DM2200, Takstar Inc.), amplified by a MOTU Ultralite Mk3 firewire audio interface, and pitch-shifted by the Harmonizer controlled by a MIDI program (Max/MSP, v.5.0 by Cycling 74). The pitch-shifted signals were finally amplified by an ICON NeoAmp headphone amplifier and fed back to participants through insert earphones (ER1-14 A, Etymotic Research Inc.). The transistor-transistor logic (TTL) pulses were generated to mark the onset of each pitch perturbation, and sent to the EEG recording system via a synch DIN cable. The original and pitch-shifted voice signals as well as the TTL pulses were digitized with a sampling frequency of 10 kHz by a PowerLab A/D converter (model ML880, AD Instruments), and recorded using LabChart software (v.7.0 by AD Instruments).

C. EEG Data Acquisition and Analyses

The EEG data were recorded using a 64-electrode Geodesic Sensor Net (Electrical Geodesics Inc.) with 1 kHz sampling rate and referenced against the vertex (Cz). The signals were amplified by a Net Amps 300 amplifier (Electrical Geodesics Inc.) and recorded onto a Macintosh computer. During the

online recording, impedances of individual sensors were kept below 50 kΩ.

Offline signal processing was carried out using NetStation software. Raw data were band-passed filtered (1-20 Hz) and segmented with a window of -200 ms before and 500 ms after the onset of the pitch shift. Data were then re-referenced to the average of the electrodes on each mastoid, and baseline-corrected. Recorded trials with excessive muscular activity, eye blinks, or other activities beyond the range of -50 to 50 μv were rejected. On average, 81% of trials were retained for further analyses. In accordance with previous studies [38,39], two time windows were analyzed, corresponding to the epochs of the N1 and P2: 80-180 ms and 160-280 ms after the onset of the pitch shift.

D. Graphical Network Construction

A graph is a basic topographical representation of a network consisting of nodes (vertices) and connections between these nodes (edges) [40]. In the current study, the graphical network analysis was performed using HERMES software on the EEG data in the theta band (3-8 Hz). The first step of graphical network construction is to evaluate the correlation between each pair of electrodes by computing a synchronization matrix with the SL. The SL is a measure to detect linear and nonlinear interdependencies between two time series *X* and *Y*, which is defined as:

$$\mathrm{SL} = \frac{1}{N(N-w)P_{ref}} \sum_{i=1}^{N} \sum_{j=i+w}^{N-w} \theta(r_x - |X_i - X_j|)\, \theta(r_y - |Y_i - Y_j|)$$

where X_i and Y_i are converted from the time series *X* and *Y* as a serious of state space vectors, r_x and r_y denote the cutoff distance. The SL ranges between P_{ref} (set as 0.01 in the current study) and 1, and was calculated between all pair-wise combinations of EEG channels, which result in a square N × N matrix of size 64.

The next step of graphical network construction is to convert the N × N matrix into an unweighted binary graph *G*. In general, if the SL between a pair of channels *i* and *j* exceeds a given threshold *T,* an edge is assumed to exist; otherwise no edge exists. The subgraph G_i is defined as the set of nodes that are directly connected to the *i*th node with an edge. The degree of connectivity, *K*, is defined as the average of the degrees of all the nodes k_i in the subgraph G_i:

$$\mathrm{K} = \frac{1}{N} \sum_{i \in G} k_i$$

In the current study, the graphical network was constructed by selecting the appropriate threshold *T* (refer to [36]) for TLE patients and healthy controls respectively. To control the influence of the degree of connectivity, several fixed values of *K* (*K* = 9, 10, 11, 12) were applied. The synchronization matrix of each group was then converted to its corresponding binary graph. The binary graph of TLE patients and healthy controls were then compared. Six regions of interest (ROI) based on the electrodes on the scalp surface: frontal (F), central (C), occipital (O), left temporal (LT), right temporal (RT) and parietal (P) lobe, were defined for further connectivity analysis.

E. Brain Functional Network Characteristics

Three relevant network characteristics including betweenness centrality (BetC), modularity (Mod) and functional integration (FI) were calculated in the current study to further reveal the difference in functional connectivity between TLE patients and healthy controls. Betweenness centrality measures the potentiality in controlling communication between other nodes in the rest of the network [41], which ranges from 0 to 1. A node with higher betweenness centrality would have more control over the network, and thus plays a dominant role in information transfer. Modularity reflects the concentration of edges within modules compared with random distribution of links between all nodes regardless of modules. Functional integration measures the ratio of cross-hemisphere functional connectivity to the whole brain network functional connectivity, which is in the range of 0 to 1. In general, brain network with higher functional integration has more cross-hemisphere functional connectivity.

F. Brain Functional Network Hub

The hub within each ROI was determined on the basis of the predefined network parameters. Specifically, a hub is defined as a node that is attached to larger number of edges than the other nodes, thus it occupies a central position in the overall organization of the network [41-43]. Hubs can be detected using numerous graph measures, which include node degree (degree centrality), betweenness centrality, clustering coefficient and characteristic path length, respectively defined as the number of edges maintained by the node, the number of short communication paths that the node participate in, the degree to which nodes tend to cluster together, and the average distance (the length of the shortest path) between the node and the rest of the work.

It is often advantageous to detect hubs by aggregating ranks across different measures [41]. Hence, in the current study, hubs were determined if more than two of the following criteria were met: (i) the degree centrality of the node is more than one standard deviation above the mean degree centrality of the other nodes ($DC_i > mean + SD$); (ii) the betweenness centrality of the node is more than one standard deviation above the mean betweenness centrality of the other nodes ($BC_i > mean + SD$); (iii) the clustering coefficient of the node is lower than one standard deviation below the mean clustering coefficient of the network ($CC_i < mean - SD$); and (iv) the characteristic path length of the node is shorter than one standard deviation below the mean characteristic path length of the other nodes ($L_i < mean - SD$).

Based on the graphical network constructed with SL matrix, hubs in the functional network were determined for both the patients with TLE and healthy controls following the above-mentioned rules when *K* was set as 9, 10, 11, and 12, respectively. To compare the hubs within each group, permutation test was performed.

III. RESULTS

A. Mean SL Values Within and Between ROIs

Figure 1 shows T-bar plots of mean SL values within and across ROIs as a function of stimulus and group. A Wilcoxon signed-rank test conducted on the mean SL values revealed that in response to pitch shifts of +50 cents, the mean SL value of patients with TLE was significant greater than that of the healthy controls within frontal, central, parietal, right temporal, and occipital lobe, and between frontal and central lobe, fontal and left temporal lobe, frontal and right temporal lobe, central and right temporal lobe, parietal and left temporal lobe, parietal and right temporal lobe, parietal and occipital lobe, left temporal and occipital lobe, and right temporal and occipital lobe. In terms of vocal response to pitch shifts of +200 cents, significant differences of the mean SL value between the two groups were found within and across similar ROIs, but not between frontal and right temporal lobe, as compared to the vocal responses to +50 cents pitch shifts.

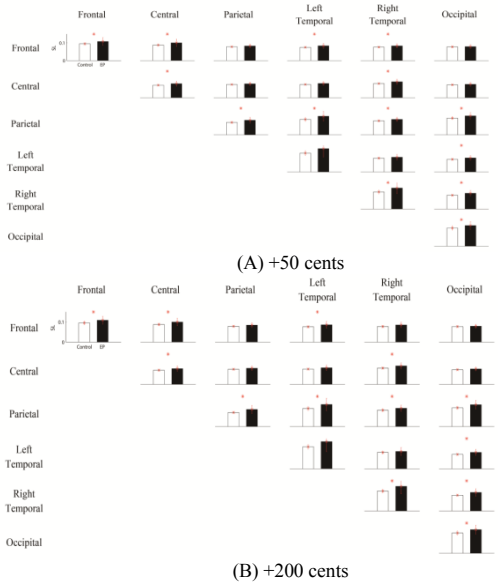

Fig. 1 T-bar plots of mean SL values within and across ROIs in response to pitch shifts of (A) +50 cents and (B) +200 cents. The white bars and black bars denote the mean SL values of healthy controls and TLE patients, respectively. Red asterisks indicate where the difference between the two groups is significant ($p < 0.05$).

B. Graphical network construction

The graphical network was constructed for each of the K value (K = 9, 10, 11, 12), which is shown in Figure 2. Inter-regional connections linking frontal and occipital lobe, left and right temporal lobe, and temporal to occipital lobe were mainly found in healthy controls. Such connections did exist in the patient group, but they were relatively rare compared to intra-regional connections. These results provided direct evidence that the functional connectivity within and among

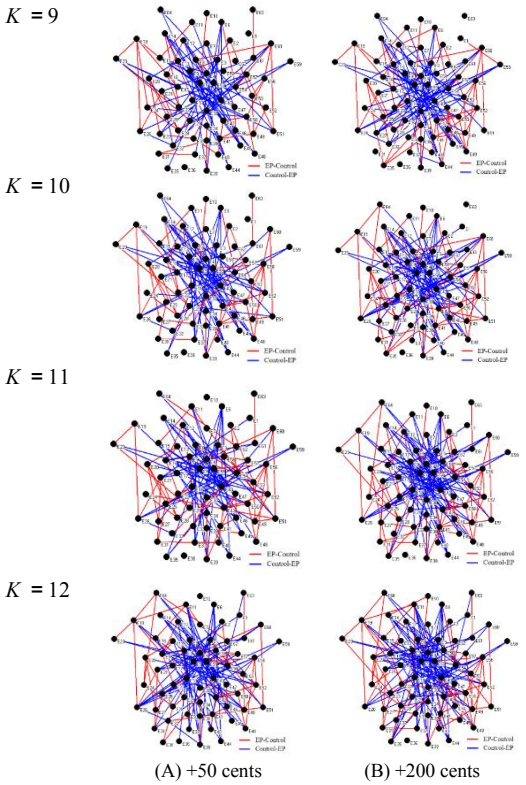

Fig. 2 Graphical networks in the case of (A) +50 cents and (B) +200 cents pitch shifts constructed based on the electrodes (black dots) on the scalp surface when K values were set as 9, 10, 11, and 12. Red lines denote the edges existing in TLE patients but not in the healthy controls, and blue lines denote the reverse condition.

different brain regions during the course of auditory-motor integration were in different patterns across the two groups.

C. Brain Functional Network Characteristics

Graphical network is an intuitive approach to present the differences of functional connectivity between TLE patients and healthy controls. To further investigate the altered functional network in the patient group, three functional network parameters, betweenness centrality, modularity, and functional integration, were calculated in the case of +50 cents and +200 cents pitch shifts as a function of *K*, and summarized in Table 1, together with a between-group comparison.

As can be seen in Table 1, TLE patients presented significantly increased betweenness centrality but reduced functional integration compared with healthy controls in both cases (i.e., +50 cents and +200 cents pitch shifts) regardless of *K*. In terms of modularity, significant group differences were found when $K = 9$, 10, and 11, but only in the case of +200 cents pitch shifts. These results are consistent with the graphical network, and demonstrate group differences in brain functional network with more detailed evidence.

Table 1: Brian functional network parameters as a function of K

Brain functional network parameters		+50 cents		+200 cents	
		Control	TLE	Control	TLE
K = 9	BetC	0.0253	0.0280(*)	0.0254	0.0280(*)
	Mod	0.4585	0.4766	0.4554	0.4859(*)
	FI	0.2601	0.2177(*)	0.2727	0.2256(*)
K = 10	BetC	0.0232	0.0256(*)	0.0233	0.0254(*)
	Mod	0.4345	0.4542	0.4334	0.4635(*)
	FI	0.2814	0.2392(*)	0.2942	0.2418(*)
K = 11	BetC	0.0215	0.0233(*)	0.0215	0.0234(*)
	Mod	0.4149	0.4341	0.4126	0.4413(*)
	FI	0.3008	0.2537(*)	0.3142	0.2575(*)
K = 12	BetC	0.0200	0.0215(*)	0.0202	0.0216(*)
	Mod	0.3982	0.4177	0.3961	0.4150
	FI	0.3157	0.2662(*)	0.3281	0.2713(*)

Note: asterisks indicate where the difference between the two groups is significant (*t*-test, $p < 0.05$); BetC: betweenness centrality; Mod: modularity; FI = Functional Integration.

D. Brain Functional Network Hub Analysis

A between-group comparison of hubs was conducted by a permutation test, and the results are displayed in Table 2(A) and 2(B). As shown in the tables, the degree centrality, betweenness centrality, clustering coefficient, and characteristic path length were significantly changed (decrease/increase) in certain hubs in the patient group, which supported our hypothesis that TLE alters the brain functional network during auditory-motor integration.

Table 2(A): Sig. difference in hub: +50 cents

Hub measures	Sig. decrease in TLE		Sig. increase in TLE	
	Hub	Region	Hub	Region
DC	9	Central (L)	54	Central (R)
	13	Frontal	56	Temporal (R)
	14	Frontal		
	45	Occipital		
BC			27	Temporal (L)
			45	Occipital
CC			6	Frontal
L			6	Frontal
			9	Central (L)
			37	Occipital (L)

Note: L = left; R = right; DC = degree centrality; BC = betweenness centrality; CC = clustering coefficient; L = characteristic path length.

Table 2(B): Sig. difference in hub: +200 cents

Hub measures	Sig. decrease in TLE		Sig. increase in TLE	
	Hub	Region	Hub	Region
DC	9	Central	41	Occipital (R)
BC	6	Frontal	27	Temporal (L)
			41	Occipital (R)
CC	41	Occipital (R)	6	Frontal (L)
	60	Frontal (R)		
L	27	Temporal (L)	6	Frontal (L)
	41	Occipital (R)	9	Central
	57	Temporal (R)	15	Frontal
			37	Occipital (L)

Note: L = left; R = right; DC = degree centrality; BC = betweenness centrality; CC = clustering coefficient; L = characteristic path length.

IV. DISCUSSION

The current study investigated whether patients with TLE exhibited disruptions in the functional connectivity that supports auditory-motor integration within and across brain regions. The present study served as an extension to our previous study [36] by focusing on the global efficiency of the brain functional network to the mechanisms that govern intra- and inter-regional communications. As expected, when exposed to pitch feedback perturbations, patients with TLE exhibited different topological properties within and across certain networks as compared to healthy controls, further supporting our previous finding that that TLE is associated with a functional decline of sensorimotor control of vocal production.

One primary finding from the current study is the significantly increased mean SL values within/between certain brain regions in patients with TLE. As highly synchronized EEG signals within brain regions suggest topological alterations in the functional network towards a more regularized configuration, this is in line with our previous finding of a higher coefficient C and longer absolute path length L in patients with TLE compared to healthy controls in the auditory-motor processing of pitch feedback errors. The direction of topological alterations in functional networks was also revealed by our findings in graphical network, network parameters and hubs.

Significantly increased functional connectivity within certain regions in patients with TLE is also reflected by the higher values of betweenness centrality and modularity of their functional network, indicating a stronger local specialization in TLE. This finding indicated that TLE is associated with a stronger local specialization. On the other hand, the rarely found inter-regional connectivity and the significantly lower functional integration associated with TLE may indicate less efficient information interactions between interconnected brain regions, making the speed of signal propagation slower. Hub is the node with a significantly larger number of links in comparison with other nodes in the network, and plays a crucial role in information transfer. As compared to healthy controls, significant change in network hubs associated with TLE may suggest that information transfer become less efficient in the functional network of patients with TLE.

Considering that the small-world brain favors a selection of maximizing cost efficiency of both local specialization and global interaction in large-scale networks, increased intra-regional connectivity and decreased inter-regional connectivity associated with TLE may disrupt this optimal balance in information processing, leading to atypical auditory-motor integration for voice control. Based on the dual stream model of speech processing [44-48], the auditory dorsal stream supports an interaction between auditory and motor representations of speech. With the progress made in the neural organization of sensorimotor integration, a network of brain regions involved in this process has been identified, where superior temporal sulcus (STS) regions code sensory-based representations of speech, the motor regions code

motor-based representations of speech, and Sylvian parietal-temporal (Spt) area serves as a sensory-motor integration system[49-50]. Alterations in functional network may have a negative effect on the integration of auditory and motor representations of speech, and thus lead to abnormal pitch reflex behavior in patients with TLE.

Overall, changes in graphical network parameters and hubs found in the study reflect a less optimal topological organization in patients with TLE, considering their functional connectivity both within and across different brain regions. The topological alterations observed closely resemble those found in graph-theoretical analysis of EEG or fMRI signals in the interictal phase [12,51] or during focal seizures [52,53]. A different pattern of network disruption in patients with TLE (i.e., a more random network with a lower coefficient C and shorter absolute path length L) was reported in some studies [6,7], and the discrepancy in the findings may stem from the different experimental paradigms or inclusion criteria of subjects.

The current study provides further evidence that patients with TLE have a disrupted topology of the brain functional networks supporting auditory-motor integration during vocal pitch regulation. Note that we defined ROIs and applied them to study the inter-regional connectivity between patients with TLE and healthy controls. The interaction between specific brain regions involved in the dorsal stream throughout the course of auditory-motor integration, however, is out of the scope of our discussion. Therefore, the construction of brain functional network based on the cerebral cortex by source reconstruction will be conducted in future work.

V. Conclusion

This study demonstrated the disrupted topology of the brain functional networks that support auditory-motor integration for vocal pitch control in patients with TLE. The results showed that patients with TLE tended to have increased intra-regional connectivity and reduced inter-regional connectivity in their functional network, reflected by alterations in network parameters as well as network hubs. These results will help us detect the cognitive dysfunctions associated with TLE.

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