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Disruptions in modular structure and network integration of language-related network predict language performance in temporal lobe epilepsy: Evidence from graph-based analysis

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ABSTRACT

Objective: Temporal lobe epilepsy (TLE) is a network disorder that alters the total organization of the language-related network. Task-based functional magnetic resonance imaging (fMRI) aimed at functional connectivity is a direct method to investigate how the network is reorganized. However, such studies are scarce and represented mostly by the resting-state analysis of the individual connections between regions. To fill this gap, we used a graph-based analysis, which allows us to cover the total language-related network changes, such as disruptions in an integration/segregation balance, during a language task in TLE.
Methods: We collected task-based fMRI data with sentence completion from 19 healthy controls and 28 people with left TLE. Using graph-based analysis, we estimated how the language-related network segregated into modules and tested whether they differed between groups. We evaluated the total network integration and the integration within modules. To assess intermodular integration, we considered the number and location of connector hubs—regions with high connectivity.
Results: The language-related network was differently segregated during language processing in the groups. While healthy controls showed a module consisting of left perisylvian regions, people with TLE exhibited a bilateral module formed by the anterior language-related areas and a module in the left temporal lobe, reflecting hyperconnectivity within the epileptic focus. As a consequence of this reorganization, there was a statistical tendency that the dominance of the intramodular integration over the total network integration was greater in TLE, which predicted language performance. The increase in the number of connector hubs in the right hemisphere, in turn, was compensatory in TLE.
Significance: Our study provides insights into the reorganization of the language-related network in TLE, revealing specific network changes in segregation and integration. It confirms reduced global connectivity and compensation across the healthy hemisphere, commonly observed in epilepsy. These findings advance the understanding of the network-based reorganizational processes underlying language processing in TLE.

1. Introduction

Temporal lobe epilepsy (TLE) is a common partial-onset epilepsy with seizures arising from the temporal lobe [1]. As the temporal lobe belongs to the language-related network, TLE, as a network disorder, may modify its organization [2]. This was mainly confirmed by studies using functional magnetic resonance imaging (fMRI). While fMRI activation reported an engagement of additional regions in both hemispheres during language tasks in TLE (for review, see [3]), it does not cover the interaction between areas. Thus, these reorganizational processes remain unclear [4].

An alternative method to study reorganization is functional connectivity (FC), which examines the communication between areas based on fMRI timeseries [5]. Previous studies, mostly using resting-state fMRI [6], revealed unique patterns of FC between language-related regions in TLE [7]. These patterns reflected both

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a decrease [8,9] and an increase [10] in FC between language-related regions. Although resting-state fMRI to a large extent characterizes task-based networks, including the language-related network [11], it still provides restricted information about such networks without performing tasks [12]. Thus, task-based fMRI aimed at FC is a direct way of analyzing the language-related network [13] and its reorganization in TLE [14].

Task-based fMRI studies exploring reorganization within the language-related network in TLE are limited (for review, see [15]). Using a seed-based approach, Vlooswijk et al. [16] and Trimmel et al. [17] found a decrease in FC within frontotemporal areas in people with TLE. Takaya et al. [18] and Foesleitner et al. [19] revealed similar results, compensated by enhanced FC within the left frontoparietal areas and between the left temporal and right temporoparietal areas. These findings consistently highlighted the reduction in FC between the perisylvian language areas in TLE. However, the seed-based approach can only show shifts in individual pairwise connections within the network in TLE. To complement previous results, a graph-based analysis is required to represent the topological changes in the language-related network [6].

The graph-based analysis considers a network as a set of nodes and edges representing the regions and interregional connections. This approach allows us to gain insights into integration/segregation balance within the language-related network in healthy controls and its disruption in TLE [20,21]. The segregation of the network into modules allows for specialized processing within each module [22], whereas the integration between modules required for higher-order cognitive functions, including language, is implemented via connector hubs, the nodes with high intermodular connectivity [23]. As TLE appears as diminished long-range connections and hyperconnectivity within the epileptic focus [24], it may lead to disruptions in the modular structure and connector hubs, reflecting the impact of seizures or compensatory mechanisms and resulting in less efficient cognitive performance [25]. The graph-based metrics can indicate these connectivity disruptions. Both global and local efficiency characterize the total network integration and integration within modules, whereas their difference can reveal integration/segregation imbalance. Therefore, we conducted the graph-based analysis focusing on the integration/segregation balance in TLE, to better understand its disruption.

Previously, Banjac et al. [26] reported the altered integration/segregation balance in TLE using fMRI tasks based on the dynamic interaction between language and memory [27]. While the segregation was characterized by modules with anatomically closer areas and diminished long-range connections, a shift in the intermodular integration was shown as an increase in the number of connector hubs within non-language systems during the tasks. These changes related to connector hubs can be interpreted as potential compensation due to the observed modular reorganization, aligning with previous studies [28–30]. However, Banjac et al. [26] prioritized global changes in the integrated language-and-memory network rather than within its two subsystems. As a result, the obtained changes did not correlate with language performance in TLE. That suggests that previous analysis might lack sensitivity to more subtle changes within each network. Sensitivity can be gained by analyzing the networks separately, thus, identifying the modular structure of the language-related network and its connector hubs without the influence of non-language systems. However, to our knowledge, no graph-based studies specifically focused on it.

Overall, the present study aimed to investigate changes within the language-related network in TLE by applying graph-based analysis to task-based fMRI. In fMRI, we used a sentence completion task [31], that engages core language processing in the anterior and posterior language-related regions while minimizing the influence of other cognitive systems, including memory [32,33]. We expected that this approach would provide insights into the reorganization specifically within the language-related network in TLE and predict language performance. As reorganization progresses over time in TLE [24], we also tested the association between epilepsy duration and network reorganization, and its impact on predicting language performance.

2. Material and methods

2.1. Participants

Twenty-eight people with drug-resistant left TLE participated in the study (14 females; age: mean = 37.6, *SD* = 6.2, range = 28–50; age of onset: mean = 14.3, *SD* = 10.6, range = 0–42; duration: mean = 21.6, *SD* = 13.3, range = 4–50). All were right-handed native Russian speakers. They underwent presurgical assessment including neurological examination, interictal/ictal video-EEG monitoring, and magnetic resonance imaging (MRI) to define seizure onset zones, at the National Medical and Surgical Center named after N.I. Pirogov (Moscow, Russian Federation). MRI indicated sclerosis in the left hippocampus (n = 20; one of these participants also had focal cortical dysplasia in the insular cortex in both hemispheres), sclerosis in both hippocampi (n = 1), gliosis in the left temporal lobe (TL) (n = 4), encephaloceles in the left TL (n = 1) or both TLs (n = 1); two participants were MR-negative (n = 2). Table 1 summarizes the demographic, clinical, and behavioral characteristics of people with TLE.

Nineteen controls participated in the study (15 females; age: mean = 40.7, *SD* = 6.5, range = 30–53). All were right-handed native Russian speakers with no history of psychiatric or neurological diseases. They underwent scanning at the National Medical and Surgical Center named after N.I. Pirogov (Moscow, Russian Federation). All people with TLE and controls gave written informed consent. The study was approved by the ethical committee of the National Medical and Surgical Center named after N.I. Pirogov.

2.2. Language task

Participants performed a block-designed language paradigm with alternating experimental and baseline blocks [31]. The experimental block was a sentence completion task, in which participants had to read aloud a visually presented sentence and complete it with a semantically and grammatically appropriate final word (direct object of the verb; for example, *Umnaya sosedka prochla* ... – "*A clever neighbor read* ..."). During the baseline block, participants had to read aloud one syllable repeated three times (for example, *Peeeee peeeeeeeeee peeeeeee peeeeeee*...) and repeat this syllable one more time. Each block lasted 21 s and consisted of three stimuli presented for 5 s and separated by an interstimulus interval when an exclamation mark was presented for 2 s. The scanning session included 120 stimuli (60 in the experimental blocks and 60 in the baseline blocks), and lasted 14 min 56 s.

2.3. Magnetic resonance imaging acquisition

We acquired MRI data on a 3 T Siemens Magnetom Skyra MRI scanner with a 20-channel head coil. First, structural T1-images were obtained using a 3D gradient-echo (MP-RAGE) sequence with TR = 2200 ms; TE = 2.4 ms; flip angle = 8°. Each T1-image contained 144 axial slices (no gap) with FOV = 320 × 320 mm^2 and spatial resolution = 1.0 × 1.0 × 1.0 mm^3. Then, fMRI data (128 functional

Table 1
Demographic, clinical, and behavioral characteristics of people with TLE.

ID	Demographic characteristics			Clinical characteristics			Behavioral characteristics	
	Age, gender	**Diagnosis**	**Handedness**	**Pre-operative MRI/ Pathology**	**Age of onset, years**	**Epilepsy duration, years**	**Response accuracy, %**	**Response time, ms**
1	36, F	TLE-L	R	HS-L	7	29	91.7	559.1
2	32, M	TLE-L	R	MRI-negative	21	11	66.7	625.7
3	34, F	TLE-L	R	EC; TL-L	22	12	78.4	741.4
4	45, M	TLE-L	R	FCD; InsL-L/R HS; L	5	40	91.5	772.8
5	44, M	TLE-L	R	HS-L	19	25	71.7	704.9
6	35, F	TLE-L	R	HS-L	10	25	*NA*	*NA*
7	35, M	TLE-L	R	Gliosis; TL-L	0	35	88.3	574.9
8	30, M	TLE-L	R	HS-L	23	7	91.7	563.5
9	47, M	TLE-L	R	HS-L	7	40	15.0	673.6
10	46, F	TLE-L	R	Gliosis; TL-L	42	4	88.1	543.2
11	44, M	TLE-L	R	HS-L	0	44	93.3	614.2
12	50, M	TLE-L	R	HS-L	0	50	60.0	522.9
13	32, F	TLE-L	R	HS-L	0	32	*NA*	*NA*
14	35, F	TLE-L	R	MRI-negative	12	23	78.3	668.9
15	32, M	TLE-L	R	HS-L/R	28	7	55.0	553.0
16	42, M	TLE-L	R	HS-L	19	23	81.7	601.3
17	35, F	TLE-L	R	EC; TL-L/R	29	6	88.3	571.7
18	37, M	TLE-L	R	Gliosis; TL-L	30	7	65.0	627.1
19	48, F	TLE-L	R	HS-L	7	41	*NA*	*NA*
20	34, F	TLE-L	R	HS-L	1	33	*NA*	*NA*
21	33, M	TLE-L	R	HS-L	2	31	55.2	534.4
22	35, F	TLE-L	R	HS-L	2	33	91.7	613.4
23	39, F	TLE-L	R	HS-L	19	20	96.7	470.1
24	28, M	TLE-L	R	Gliosis; TL-L	18	10	91.7	412.5
25	43, F	TLE-L	R	HS-L	14	29	95.0	476.4
26	41, F	TLE-L	R	HS-L	18	23	98.3	613.3
27	29, F	TLE-L	R	HS-L	1	28	96.7	447.7
28	33, M	TLE-L	R	HS-L	24	9	86.7	586.4

Note. F/M = female/male; L/R = left/right; TL/InsL = temporal/insular lobe; TLE = temporal lobe epilepsy; FCD = focal cortical dysplasia; EC = encephalocele; HS = hippocampal sclerosis; *NA* = not available.

volumes) were collected during the language task using an EPI sequence with TR = 7000 ms; TE = 30 ms; flip angle = 90°. Each functional image contained 30 axial slices (no gap) with FOV = 2 05 × 205 mm^2 and spatial resolution = 3.0 × 3.0 × 3.75 mm^3. We applied sparse sampling acquisition to record the participant's overt responses in intervals equal to TR delay = 5000 ms.

2.4. Behavioral data

Auditory responses were recorded and transcribed for all participants, except for two controls and four people with TLE due to technical errors. *Response accuracy* (*RA*) was assessed by two independent raters as the ratio of correct responses to the total number of responses. Responses were considered correct if they represented grammatically and semantically appropriate sentence completions. *Response time* (*RT*) was assessed by one rater using Praat, version 6.3.09 (https://www.fon.hum.uva.nl/praat/) as an interval between the start of the stimulus presentation and the response completion. Details of the estimation of *RA* and *RT* are presented in Elin et al. [31]. To test whether *RA* and *RT* differed between the groups, we used Mann-Whitney *U* tests.

2.5. fMRI preprocessing

We discarded the first eight volumes of task-based fMRI data corresponding to task instructions and despiked the remaining volumes in AFNI-21.3.13 [34] with *3dDespike*. We preprocessed T1-images and task-based fMRI data using fMRIPrep-20.2.6 [35]. Details of the pipeline are presented in the Supplementary Methods. Briefly, correction for intensity non-uniformity, skull stripping, and brain tissue segmentation of cerebrospinal fluid, white matter, and grey matter were performed on T1-images. Skull stripping, slice-timing, and fieldmap-less susceptibility distortion correction were performed on fMRI data. T1-images and fMRI data were spatially normalized to the MNI template. Following the denoising strategy for task-based FC [36], we regressed out 24 realignment parameters of head motion (six rotational and translational parameters, temporal derivatives, and their squared terms), global signal, and the top five anatomical components for white matter with the top five anatomical components for cerebrospinal fluid obtained from the principal component analysis. To account for signal drifts, we excluded 18 discrete cosine-basis regressors. fMRI data were smoothed with a 6-mm FWHM isotropic Gaussian kernel.

2.6. Graph-based analysis of the language-related network

The language-related network was defined as 36 ROIs comprised of 18 core language-related regions in the left hemisphere, taken from Labache et al. [37], and their homologs. We averaged functional time-series extracted from preprocessed fMRI data in AFNI with *3dmaskdump* across all voxels within each ROI. We performed the *correlational psychophysiological interaction (cPPI)* on the timeseries using the '*cPPI*' toolbox [38] in MATLAB R2021a (MathWorks; Natick, MA, USA). For each ROI, timeseries were first deconvolved with the canonical *hemodynamic response function (HRF)* to represent the underlying neural activity [39]. Then, the deconvolved timeseries were multiplied with the design variable (sentence completion > syllables) and convolved back with the canonical *HRF* to form a *cPPI* term. Thus, we calculated an undirected symmetrical connectivity 36 × 36 matrix for each participant containing partial correlations across all pairs of the 36 ROIs. The correlational coefficients within each matrix, except for the diagonal elements, were Fisher-transformed to *z*-scores. We set their negative values to zero [40], leaving only positive weighted values in the connectivity matrices.

2.6.1. Graph-based system segregation

To identify the modular structure of the language-related network in each group, we applied the Louvain algorithm to the connectivity matrices. To increase the robustness of the results, we repeated the algorithm at a set of proportional thresholds (range = 1–99% in 1% increment [41]) and implemented the consensus approach [42]. Thus, we obtained a stable structure at the individual level. To obtain the final modular structure for each group, we again implemented the consensus approach across all participants.

For people with TLE, we extracted the *modularity index* (*Q*), which measures the degree of network division into modules obtained across all thresholds. Then, we correlated *Q* with language performance. To compare the modular structures between the groups, we used the *variation of information* (*VIn*), a measure of the information required to represent two partitions through each other [43]. We obtained the significance of *VIn* through a permutation procedure. Details of the modular structure detection and their comparison are presented in the Supplementary Methods.

2.6.2. Graph-based system integration

After the modular structure detection in each group, we applied a set of proportional thresholds (range = 5–20% in 5% increment) to each connectivity matrix to remove spurious connections [6]. We calculated the graph-based metrics on matrices obtained at each threshold, then averaged the results across the set of thresholds [44].

For each participant, we estimated *global efficiency* (E_{glob}) and *local efficiency* (E_{loc}) as metrics of the total network integration and averaged intramodular integration, respectively [45]. We also measured the *integration-segregation balance* (*IS*) [10] as the difference between E_{glob} and E_{loc}.

To examine intermodular integration, we identified connector hubs using the *participant coefficient (PC)* and *intra-community degree (z)* metrics [46]. Details of the metric estimation are presented in the Supplementary Methods. Nodes with *PC* and *z* values higher than 0 were defined as connector hubs. We extracted the number of connector hubs in both hemispheres (N_{hubs}), the left (N_{hubs}-*L*) and right (N_{hubs}-*R*) hemisphere. At the group level, we identified a node as a connector hub if the frequency of its occurrence as a connector hub across participants was found to be an outlier. According to Leys et al. [47], we used *median absolute deviation (MAD)* for robust outlier detection. The threshold of the detection was the sum of the median and 2.5 times the *MAD*, which was considered to be moderately conservative [47].

2.7. Statistical analyses

All statistical analyses were performed in RStudio, version 4.2.0 (https://www.rstudio.com). To test whether epilepsy duration and age of onset were associated with *Q*, E_{glob}, E_{loc}, *IS*, N_{hubs}, N_{hubs}-*L*, and N_{hubs}-*R* in people with TLE, Pearson's correlation coefficients were calculated, with the level of significance adjusted for seven tests, $\alpha = 0.05/14 = 3.5 \times 10^{-3}$ (Bonferroni correction). To test whether E_{glob}, E_{loc}, *IS*, N_{hubs}, N_{hubs}-*L*, and N_{hubs}-*R* differed between controls and people with TLE, two-sample *t*-tests were used, with the level of significance adjusted for six tests, $\alpha = 0.05/6 = 0.008$ (Bonferroni correction).

To assess the association between language performance (*RA*, *RT*) and the graph-based metrics, as well as their interaction with epilepsy duration in TLE, we used two multiple linear regressions. As epilepsy duration was correlated with age of onset ($r = -0.89$, $p < 0.001$), we did not consider the interaction of the graph-based metrics with age of onset in the multiple linear regressions. Given that *IS* and N_{hubs} represented linear combinations of E_{glob} with E_{loc}, and N_{hubs}-*L* with N_{hubs}-*R*, respectively, multicollinearity could have resulted in the false-negative inferences in the regressions while considering all graph-based metrics [48]. Therefore, we first estimated the multicollinearity of all graph-based metrics using the squared generalized variance inflation factor ($GVIF^{(1/(2\times df))}$) [48]. According to Dormann et al. [49], we used a value of $GVIF^{(1/(2\times df))} = 5$ as a threshold that indicated multicollinearity.

2.8. Data and code availability

The raw datasets are not publicly available due to containing sensitive personal information. Preprocessed data can be found online at DOI (https://doi.org/10.17605/OSF.IO/F4JR3). The code is publicly available (https://github.com/vkarpychev/Graph-analysis-of-language-network).

3. Results

3.1. Demographic and behavioral characteristics

A two-sample *t*-test revealed no significant difference between controls and people with TLE in age ($t_{(46)} = 1.7$, $p = 0.09$) and a chi-square test revealed no significant difference in gender distribution ($\chi^2_{(1,48)} = 3.3$, $p = 0.07$). Mann-Whitney *U* tests revealed that *RA* was significantly higher in controls ($M = 98.1\%$, $SD = 13.4\%$) than people with TLE ($M = 79.9\%$, $SD = 19.3\%$), $z = 4.3$, $p < 0.001$. No difference was found in *RT* between controls ($M = 609.2$ s, $SD = 79.6$ s) and people with TLE ($M = 586.5$ s, $SD = 88.3$ s), $z = 0.70$, $p = 0.48$.

3.2. Graph-based analysis of the language-related network

3.2.1. Graph-based system segregation

Fig. 1 shows the modular structures and connectivity matrices within the language-related network. The language-related network in both groups was segregated into four modules. We found no difference in $VIn = 0.38$, $p = 0.41$ between the modular structures in the groups. However, both groups had unique modules. Controls found a left-lateralized module (module-3) comprising perisylvian language areas, except for two regions in the right superior temporal lobe. People with TLE, in turn, reported a unique module consisting of areas in the left temporal lobe only (module-4). Table S1 presents the modular structures for both groups. No associations were found between *Q* and epilepsy duration, $r = -0.03$, $p = 0.89$, as well as age of onset, $r = 0.03$, $p = 0.89$.

3.2.2. Graph-based system integration

No association was found between E_{glob}, E_{loc}, *IS*, N_{hubs}, N_{hubs}-*L*, N_{hubs}-*R* and epilepsy duration, as well as age of onset in people with TLE (Fig. 2). Table 2 presents the results of two-sample *t*-tests comparing the graph-based metrics between controls and people with TLE. N_{hubs}-*R* was significantly lower in controls ($M = 3.1$, $SD = 1.2$) than people with TLE ($M = 4.7$, $SD = 1.7$), $t_{(45)} = -3.5$, $p < 0.001$. Differences in *IS* and N_{hubs} reached the significance level $\alpha = 0.05$, but not the Bonferroni-corrected significance level ($\alpha = 0.008$). Fig. 2 shows the distributions of the graph-based metrics.

Distributions of the graph-based metrics and their correlations to epilepsy duration.

E_{glob} = global efficiency; E_{loc} = local efficiency; *IS* = integration-segregation balance; N_{hubs} = the number of connector hubs; N_{hubs}-*L* = the number of connector hubs in the left hemisphere; N_{hubs}-*R* = the number of connector hubs in the right hemisphere; ED = epilepsy duration; AO = age of onset.

*Difference significant at α = 0.008 Bonferroni-corrected.

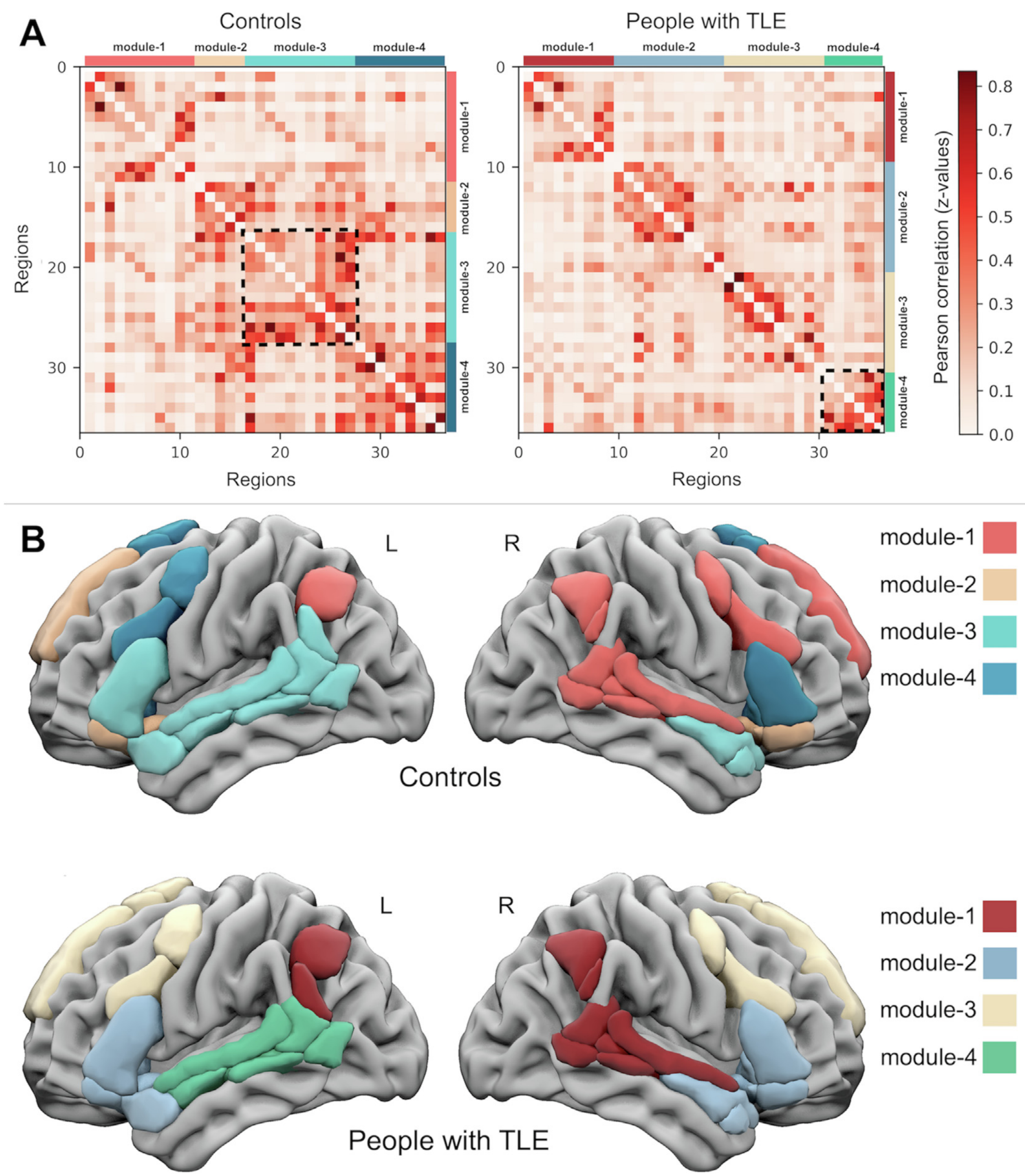

Fig. 1. Modular structures of the language-related network in healthy controls and people with TLE. (A) Connectivity matrices averaged across participants in each group and across a set of proportional thresholds (range = 1–99% in 1% increment). Dotted squares indicate unique modules for each group: module-3 in healthy controls, module-4 in people with TLE. (B) Spatial distribution of the modular structure in each group. Each color indicates a single module in each group.

In controls, the connector hubs identified as outliers using *MAD* [47] were pars opercularis and two regions in the superior temporal sulcus (STS) in the left hemisphere, as well as supramarginal gyrus and a region in STS in the right hemisphere. In people with TLE, connector hubs were the precentral gyrus and two regions in STS in the left hemisphere, as well as the anterior insula in the right hemisphere. Fig. 3 shows the identified connector hubs.

3.2.3. Associations of language performance with the graph-based metrics in people with TLE

We estimated $GVIF^{(1/(2\times df))}$ of all graph-based metrics. The values of $GVIF^{(1/(2\times df))} > 10^5$ for N_{hubs}-*L*, N_{hubs}-*R*, and N_{hubs}; $GVIF^{(1/(2\times df))} = 17.8$ for E_{glob}; 32.6 for E_{loc}; 31.7 for *IS* exceeded the threshold ($GVIF^{(1/(2\times df))} = 5$), indicating the multicollinearity. Given that *IS* and N_{hubs} represented linear combinations of E_{glob} with E_{loc}, and N_{hubs}-*L* with N_{hubs}-*R*, respectively, we removed E_{glob}, E_{loc}, and N_{hubs}-*L*, N_{hubs}-*R* to avoid multicollinearity resulting in false-negative inferences in the multiple linear regressions.

Thus, we built two multiple linear regressions with either *RA* or *RT* as dependent variables and the graph-based metrics (*Q*, *IS*, N_{hubs}), as well as their interaction with epilepsy duration as independent variables. We mean-centered all graph-based metrics and adjusted the level of significance for two multiple linear regressions, $\alpha = 0.05/2 = 0.025$ (Bonferroni correction). Table 3 presents the results of the multiple linear regressions examining the associations of *RA* and *RT* with the graph-based metrics in people with TLE. We did not detect multicollinearity in these multiple linear regressions. Greater *RA* was significantly associated with higher *IS* ($\beta = 454.4$, $SE = 164.1$, $t_{(14)} = 2.8$, $p = 0.014$) and higher value of interaction between *IS* and epilepsy duration ($\beta = 580.4$, $SE = 153.0$, $t_{(14)} = 3.8$, $p = 0.002$): that is, the reduction in *IS* with epilepsy duration predicted lower *RA*. There were no associations between *RT* and the graph-based metrics.

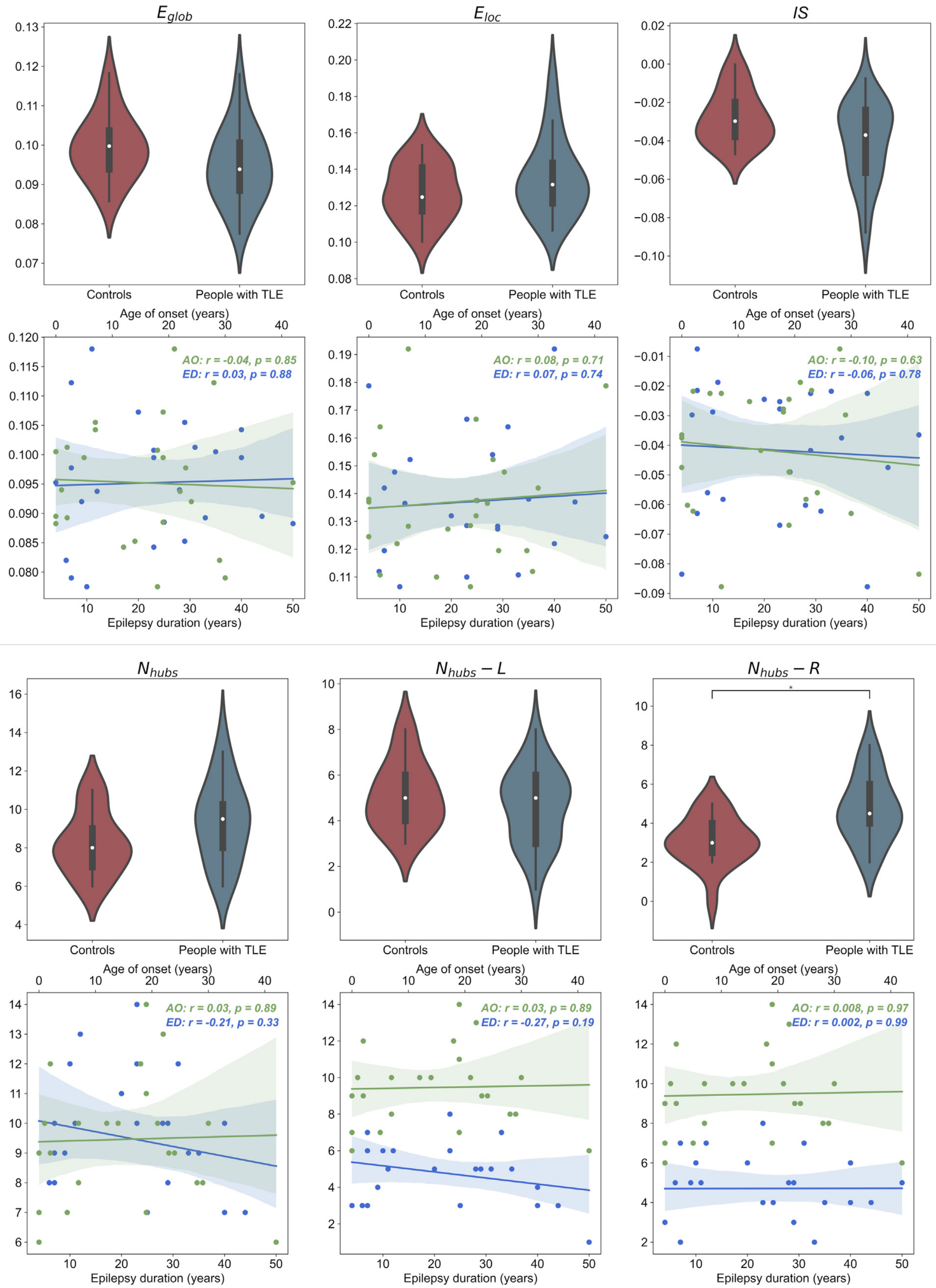

Fig. 2. Graph-based metrics between healthy controls and people with TLE. E_{glob} = global efficiency; E_{loc} = local efficiency; IS = integration-segregation balance; N_{hubs} = the number of connector hubs; N_{hubs}-L = the number of connector hubs in the left hemisphere; N_{hubs}-R = the number of connector hubs in the right hemisphere; ED = epilepsy duration; AO = age of onset.
*Difference significant at α = .008 Bonferroni-corrected.

Table 2
Results of two-sample *t*-tests comparing the graph-based metrics of the language-related network between healthy controls and people with TLE.

Graph-based metrics	Controls		People with TLE		$T_{(45)}$	*p*
	M	*SD*	*M*	*SD*		
E_{glob}	0.10	0.01	0.09	0.01	1.8	0.08
E_{loc}	0.13	0.01	0.13	0.02	−1.4	0.18
IS	−0.03	0.01	−0.04	0.02	2.3	0.02
N_{hubs}	8.2	1.6	9.4	2.1	−2.0	0.05
N_{hubs} -*L*	5.1	1.5	4.6	1.7	1.0	0.33
N_{hubs} -*R*	3.1	1.2	4.7	1.7	−3.5	< 0.001*

Note. E_{glob} = global efficiency; E_{loc} = local efficiency; *IS* = integration-segregation balance; N_{hubs} = the number of connector hubs; N_{hubs}-*L* = the number of connector hubs in the left hemisphere; N_{hubs}-*R* = the number of connector hubs in the right hemisphere.
* Difference significant at α = 0.008 Bonferroni-corrected.

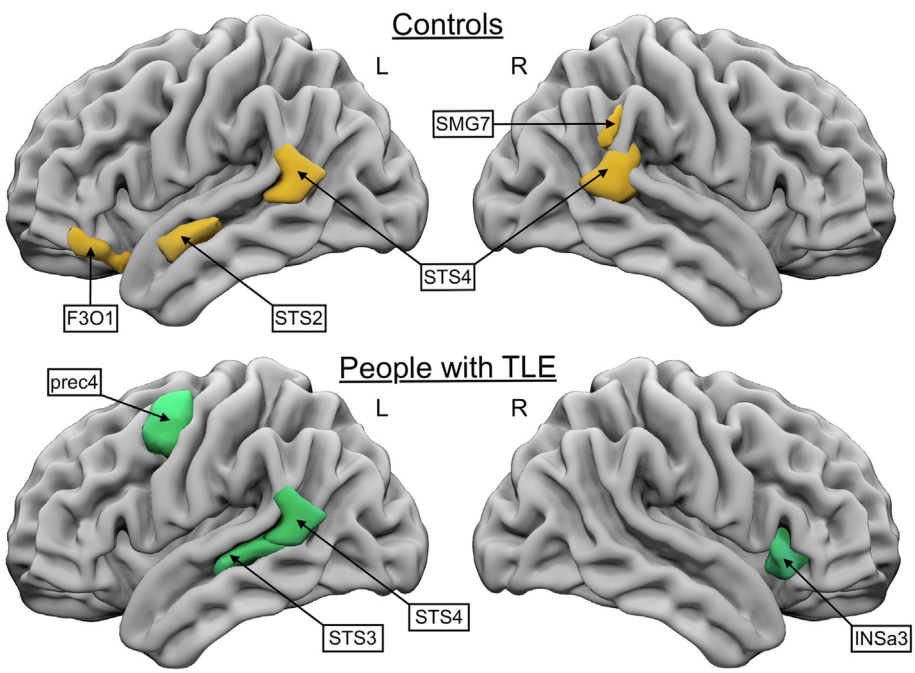

Fig. 3. Connector hubs in healthy controls and people with TLE. F3O1 = pars opercularis; STS2, STS3, STS4 = areas in the superior temporal sulcus; SMG7 = supramarginal gyrus; prec4 = precentral sulcus; INSa3 = anterior insula.

Table 3
Results of the multiple linear regressions examining the associations of *RA* and *RT* with the graph-based metrics in people with TLE.

	β	*SE*	$t_{(14)}$	*p*	$GVIF^{(1/(2\times df))}$
RA					
(Intercept)	81.3	3.2	25.5	<0.001*	*NA*
IS	454.4	164.1	2.8	0.014*	1.29
Q	76.8	50.1	1.5	0.14	1.21
N_{hubs}	1.9	1.6	1.1	0.27	1.28
duration	2.4	4.2	0.6	0.58	1.85
IS × *duration*	580.4	153.0	3.8	0.002*	1.26
Q × *duration*	−31.62	49.25	−0.6	0.53	1.34
N_{hubs} × *duration*	1.80	1.98	0.9	0.38	2.05
RT					
(Intercept)	584.3	21.4	27.3	<0.001*	–
IS	−375.9	1102.8	−0.3	0.74	–
Q	−130.6	336.5	−0.4	0.70	–
N_{hubs}	−1.4	11.0	−0.1	0.90	–
duration	3.39	28.4	0.12	0.91	–
IS × *duration*	55.9	1028.4	0.05	0.96	–
Q × *duration*	236.4	331.0	0.7	0.49	–
N_{hubs} × *duration*	−4.47	13.3	−0.3	0.74	–

Note. RA = response accuracy; *RT* = response time; *IS* = integration-segregation balance (E_{glob} − E_{loc}); *Q* = modularity index; N_{hubs} = the number of connector hubs; *duration* = epilepsy duration; *SE* = standard error; $GVIF^{(1/(2\times df))}$ = squared generalized variance inflation factor (identical values for two multiple linear regressions); *NA* = not available.
* Predictors significant at α = 0.025 Bonferroni-corrected.

4. Discussion

The study investigated the reorganization of the language-related network in people with TLE. Applying graph-based analysis to task-based fMRI, we found how the language-related network was segregated into modules in each group and compared integration in the total network and within the modules between the groups. Differences in the intermodular integration were assessed by comparing the number and location of connector hubs [20,21]. To increase the sensitivity to characteristics of the language-related network, we used a sentence completion task engaging core language processing. Given that TLE affects language functions [50], we analyzed the relation between the graph-based metrics and language performance in people with TLE.

We first explored the effect of TLE on the segregation into modules in the language-related network. We found no difference in the *variance of information* (*VIn*) between the modular structures of the groups [43]. While *VIn*, as a quantitative metric, does not reflect the role of the regions, perisylvian language areas were segregated differently in the groups. During language processing in controls, perisylvian language areas, including pars triangularis, the supramarginal gyrus, and regions of the superior and middle temporal gyri, are grouped into a left-lateralized module. Consistent with the reduced role of long-range connections in TLE [24,26], we did not find such module in people with TLE. Instead, part of perisylvian language areas – pars triangularis, pars opercularis, and anterior regions in the superior temporal gyrus, together with their homologs, formed a bilateral module. This suggests potential compensation with the right hemisphere involvement [28]. The posterior language-related areas close to the epileptic focus, in turn, formed a unique left-lateralized module. Thus, these changes in the modular structure in TLE were indicative of diminished long-range connections and hyperconnectivity within the epileptic focus [24].

These altered connectivity patterns observed in our study in TLE are thought to be interrelated and enhanced with epilepsy duration and seizure frequency [24]. Our results were consistently supported by previous studies [10,51,52] and can be interpreted in line with "*the network inhibition hypothesis*" [53]. According to this hypothesis, during the propagation of ictal activity beyond the temporal lobe to the subcortical structures – thalamus and brainstem reticular activation system, their excitatory signals to the neocortex become disrupted [51]. Due to this altered input, the neocortex shifts into the deactivated state. Under recurrent seizures, it leads to connectivity reorganization over time with reduced long-range connections. Conversely, there appears to be hyperconnectivity within the epileptic focus in TLE. Even though hyperconnectivity can be explained by growing new synapses and axonal sprouting [54], the mechanisms underlying the diminished long-range connections are not fully understood. It is unclear whether they reflect a direct consequence of ictal activity or an adaptive mechanism to prevent seizure propagation [24].

Despite this connectivity reorganization under recurrent seizures, we revealed no difference in the network integration (E_{glob}) and averaged intramodular integration (E_{loc}) between controls and people with TLE based on their modular structures. These findings are consistent with Roger et al. [10], who found no difference in E_{glob} and E_{loc} within the language-and-memory network between these groups using resting-state fMRI. However, we observed that *IS*, the contrast between E_{glob} and E_{loc}, was shifted more to E_{loc} in people with TLE, which did not reach significance after multiple testing corrections. Thus, we found a statistical tendency that the dominance of the intramodular integration over the total network integration was greater in TLE. To our knowledge, no graph-based studies revealed such imbalance within the language-related network. However, this is consistent with a common observation of reduced global connectivity [20,24] and increased local connectivity in epilepsy represented, respectively, by E_{glob} and E_{loc} in our study. The increased local connectivity is, in turn, indicative of hyperconnectivity within the epileptic focus described above, as well as greater total network segregation in epilepsy [55,56]. As both phenomena were mostly confirmed using resting-state fMRI [8–10] (for review, see [15]), further graph-based studies need to confirm this statistical tendency of the alteration in TLE relying on task-based fMRI [14].

We described the intermodular integration via connector hubs found in the left temporal lobe in both groups. In people with TLE, additional connector hubs were the precentral gyrus in the left hemisphere and anterior insula in the right hemisphere, whereas pars opercularis in the left hemisphere and supramarginal gyrus with a region in STS in the right hemisphere were connector hubs only in healthy controls. Moreover, the groups differed in the number of connector hubs (N_{hubs}). While there was no difference in the left hemisphere, their number in the right hemisphere (N_{hubs}-R) significantly increased in people with TLE. Together, this supports the idea that TLE primarily disrupts the functioning of hubs due to the high cost of their connecting role [57,58]. The increase of N_{hubs}-R agrees with Banjac et al. [26], who reported such gain in the dorsal attention network in TLE during language and memory tasks. This reflects an engagement of additional non-language systems, including the right hemisphere [28], accompanied by a decrease in FC within the left frontotemporal areas [16–19]. Although this increase in N_{hubs}-R did not predict language performance in our study, it can serve as compensation, because bilateral reorganization was shown to be associated with greater cognitive performance [29,30]. However, the exact role of such reorganization in left TLE remains unclear. Given the left-hemispheric lateralization of language processing, Takaya et al. [18] pointed out that enhanced FC within left frontoparietal areas can be more likely compensation than bilateral reorganization. Further studies are needed to clarify the compensatory mechanism in TLE.

Finally, considering the graph-based segregation and integration metrics, we found that reduced *IS*, that is, a shift towards the intramodular integration relative to total network integration, predicted lower *RA* in TLE. Moreover, the greater reduction in *IS* with epilepsy duration predicted lower *RA*. This is consistent with Vlooswijk et al. [16] and Trimmel et al. [17], who, using seed-based fMRI, reported that FC predicted language performance. However, in contrast to the graph-based analysis, seed-based fMRI focused only on individual pairwise connections [6]. Applying the graph-based analysis to resting-state fMRI, Roger et al. [10] reported that the individual integration of the regions within the language-and-memory network predicted cognitive performance, whereas the network changes did not. Struck et al. [52] reported the opposite effect of the network changes. Both reduced global clustering coefficient and increased rich club proportion, as the graph-based metrics, predicted lower multi-domain cognitive performance in TLE. As both metrics represented the total network integration and segregation into modules, our prediction of *RA* is consistent with Struck et al. [52]. These results align with "*the network inhibition hypothesis*" [53], which posits that recurrent seizures affect the connectivity organization, including long-range connections, required for higher-order cognitive functions [24]. But, in contrast to Struck et al. [52], we used task-based fMRI instead of resting-state fMRI. Thus, we complemented previous studies by providing evidence for the relation between network changes and language performance during a task in TLE. To our knowledge, only one study previously applied the graph-based analysis to language task-based fMRI but did not find such an association in TLE [26]. While Banjac et al. [26] considered the language-and-memory network based on the dynamic interaction between both functions, we focused on core language processing and respective networks via sentence completion in fMRI. As a result, we gained sensitivity to more subtle changes within the language-related network in TLE, allowing to predict language performance.

We acknowledge some limitations in our study. Due to the limited sample size, we did not investigate differences in the reorganization depending on the underlying pathologies of TLE [19]. Therefore, further studies need to specify our findings regarding the pathologies. Also, we did not consider seizure frequency and anti-epileptic medications as predictors, but they may influence the graph-based metrics [16]. Although we followed a common practice of removing negative connections from the connectivity matrices according to Wang et al. [40], such connections may provide relevant information about network organization [59]. Finally, our results were dependent on the choice of proportional thresholds applied to the connectivity matrices [60]. However, we believe that averaging the graph-based metrics across different proportional thresholds minimized the potential bias related to thresholding. Further studies should address these limitations.

5. Conclusions

This is the first graph-based study that specifically investigated language-related network reorganization in TLE using task-based fMRI. During core language processing, people with TLE exhibited a bilateral module formed by the anterior language-related areas and a module in the left temporal lobe, reflecting hyperconnectivity within the epileptic focus. However, they did not show a left-lateralized module consisting of left perisylvian language areas found in healthy controls. As a consequence of this reorganization, we observed a statistical tendency that a shift towards the intramodular integration relatively the total network integration was greater in TLE, which predicted language performance, as well as possible compensation via the increase in the number of connector hubs in the right hemisphere.

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CRediT authorship contribution statement

Victor Karpychev: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Writing – original draft. **Svetlana Malyutina:** Methodology, Investigation, Data curation, Validation, Writing – review & editing. **Anna Zhuravleva:** Investigation, Data curation, Formal analysis. **Oleg Bronov:** Data curation, Resources. **Vasiliy Kuzin:** Data curation, Resources. **Aleksei Marinets:** Data curation, Resources. **Olga Dragoy:** Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

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