









ORIGINAL ARTICLE

Abnormal functional connectivity patterns in temporal lobe epilepsy—An international ENIGMA-epilepsy study

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Abstract

Objectives: Temporal lobe epilepsy (TLE) impacts multiple brain networks. Aberrant functional connectivity has been demonstrated in resting-state networks (RSNs) that mediate higher brain functions in TLE. This study aimed to identify the reproducible patterns of altered functional connectivity in TLE in a large, international cohort through ENIGMA-Epilepsy.

Methods: Resting-state functional MRI datasets from nine centers across North America, South America, Europe and South Africa, including 442 people with TLE and 387 healthy adults, were analyzed. We examined group differences in whole-brain connectivity in patients compared to controls in seven major RSNs. We also investigated whole-brain connectivity maps for key nodes within the default mode network (DMN). Furthermore, the associations between connectivity patterns and clinical variables were assessed.

Results: We found lower within-network connectivity scores (13.6% on average) and higher between-network connectivity scores (129% on average) in non-limbic RSN in TLE. This pattern was reproducible across all seven sites and most robust for DMN and visual networks. Patterns of connectivity were not associated with age of seizure onset or disease duration and were mostly similar in patients with left and right TLE with a few exceptions; isolated regions of

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high connectivity in left TLE and lower connectivity in right TLE compared to controls.

Significance: We show strong evidence of lower connectivity within most RSNs and higher connectivity outside of these networks that was highly consistent across geographically diverse sites, demonstrating the robustness and generalizability of our findings. The findings demonstrate a consistent disruption of network organization in TLE that may underlie cognitive co-morbidities and seizure propagation patterns observed in this patient population.

Plain Language Summary: In this international ENIGMA-Epilepsy study, resting-state fMRI data from 442 individuals with TLE showed reduced connectivity within major resting-state networks (about 14% lower) and markedly increased connectivity between networks (about 129% higher), compared to 387 healthy controls. These patterns were highly reproducible across sites. Connectivity alterations were not related to age of onset or disease duration and were largely similar across left and right TLE, aside from small, region-specific differences. Overall, the study demonstrates a robust, widespread reorganization of brain network connectivity in TLE, which may help explain associated cognitive difficulties and seizure spread.

KEYWORDS

functional MRI, resting-state functional connectivity, temporal lobe epilepsy

1 | INTRODUCTION

Temporal lobe epilepsy (TLE) is characterized by recurrent focal seizures that originate in the temporal lobes and may involve one or both hemispheres. In TLE, structural and functional abnormalities are present in local and distributed networks throughout the brain.^{1,2} Identifying aberrant networks in patients with TLE is important for understanding the pathophysiology of the disorder.

Resting-state fMRI (rsfMRI) has emerged as a standard technique for investigating network abnormalities in epilepsy.³ Intrinsic synchronized fluctuations in the brain at rest are reliably mapped as sets of functionally connected regions defined as resting-state networks (RSNs).^{4,5} Atypical functional connectivity patterns have been demonstrated with rsfMRI in multiple brain networks in TLE, particularly in temporo-limbic regions and the default mode network (DMN).¹ Although lower connectivity within the DMN is the most consistent finding, both lower and higher connectivity are reported across other networks, including the dorsal and ventral attention networks (DAN and VAN), the visual network (VN) and the frontoparietal networks (FPAR).^{6–10} The variability observed across studies likely reflects small sample sizes and diverging study methods and patient characteristics. Evidence of reproducible and reliable estimates of the magnitude of

Key points

- Resting-state functional connectivity in TLE was studied in 829 participants.
- Lower within-network connectivity was observed in TLE.
- High between-network connectivity in non-limbic resting-state networks was observed in TLE.
- Left TLE was associated with higher connectivity compared to controls.
- Lower connectivity was more frequently detected in right TLE.

group differences across multiple RSNs would afford insight into the mechanisms of seizure generation, nature of cognitive impairments, and other co-morbidities in people with TLE and form a basis for further studies of causation and treatment.

The current study sought to identify resting-state functional connectivity changes associated with TLE in a large international ENIGMA-Epilepsy consortium

dataset, aiming to demonstrate the reproducibility of detected network aberrations across samples. Based on prior structural and functional studies, we hypothesized that functional connectivity of RSNs would be significantly altered in TLE. We predicted that these differences would be characterized by lower within-network connectivity, reflecting a more global network structure and less segregation of RSNs as a result of TLE. Improved understanding of abnormal communication in intrinsic neural networks would improve disease monitoring, in terms of progression and treatment response, and provide insight into disease mechanisms.

2 | MATERIALS AND METHODS

2.1 | Data and participants

Datasets from nine ENIGMA-Epilepsy centers containing resting-state functional MRI were included in this study, with data from 521 adults with TLE and 457 healthy controls (Table S1). All sites obtained local ethics approval. Participants were included if they were ≥ 18 years, had EEG-confirmed TLE (patients), or no seizure history (controls), and had not undergone prior neurosurgery.

2.2 | Data processing

Each site processed their own data locally using HALFpipe (Harmonized AnaLysis of Functional MRI pipeline: <https://github.com/HALFpipe>),¹¹ an enhanced interface to fMRIPrep¹² with harmonized protocols across centers. Standard preprocessing included motion correction, normalization to MNI space, spatial smoothing, denoising and band-pass filtering. Scans with excessive motions were excluded. NeuroCombat (<https://github.com/rpomponio/neuroHarmonize>) was employed to remove variance associated with site from individual voxel-wise whole-brain connectivity maps, while retaining variance associated with age, sex, and group (TLE/control). See [Supplementary Methods](#) for full details.

2.3 | Functional connectivity analysis

The seeds for this study were defined according to the seven-network parcellation by Yeo et al. (Figure S1).⁵ Each seed is the bilateral representation of one of the following networks: DMN, DAN, VAN, FPAR, SMN, VN,

and limbic network (LN). Network-specific whole-brain connectivity maps were constructed by extracting the average BOLD time series from a seed region of interest, as defined by a binary mask image, and using the time series as a regressor in a first-level general linear model (GLM). This results in a whole-brain functional connectivity map, with Z-scores representing connectivity strength between the seed of interest and each voxel in the brain (i.e., seed-to-voxel connectivity). Familywise multiple comparisons correction was performed by setting cluster- and voxel-wise alpha thresholds to 0.05 and 0.001, respectively.

2.3.1 | Whole-brain connectivity analysis

Tests of group differences in specific seeds of interest to whole-brain connectivity were conducted using an analysis of covariance (ANCOVA) framework, as implemented in AFNI's *3dttest++* tool with participant age, sex, and mean framewise displacement included as covariates of no interest.¹³ We examined both between-network and within-network connectivity. Clusters showing significant differential connectivity between the TLE and control groups for a particular network seed were classified as either within-network or between-network alterations. If the cluster overlapped to a greater extent with the mask for the seed network, this was then referred to as *within-network connectivity*. Conversely, those clusters with larger overlap with the masks for networks other than their seed were referred to as *between-network connectivity*. Membership of the networks was defined as the network with which the cluster overlapped to the largest extent.

2.3.2 | Magnitude and reproducibility of RSN differences in TLE

To determine the magnitude of network connectivity differences, we calculated the Cohen's *d* effect size estimates for clusters both within and outside a network by subtracting the mean connectivity in clusters for the controls from the corresponding mean for the patients and dividing the result by the standard deviation of connectivity estimates for the controls. In order to test the reproducibility of our data across samples, we conducted a leave-one-out analysis wherein we iteratively computed the minimum and maximum percent difference and Cohen's *d* estimates for each network after excluding each of the sites individually.

2.3.3 | Seed-based DMN analysis

To refine findings, seed-based analyses were conducted on six key nodes within the DMN (bilateral angular gyrus, anterior cingulate cortex and posterior cingulate cortex/precuneus) that have previously been investigated in TLE.^{7,14-15} Finally, group comparisons were conducted for bilateral DMN subnetwork seeds by using *3dcalc* to sum the whole-brain connectivity maps for the left and right hemisphere versions of each seed pair and then dividing the resulting summed voxel-wise connectivity estimates by two. The [Supplementary Material](#) provides additional detail and shows spatial locations of all seeds.

2.3.4 | RSN correlations with clinical variables

Connectivity estimates were tested for associations with age of seizure onset, duration of illness, and laterality of seizure onset. Analyses were covaried for age, sex, and motion. Detailed models are described in [Supplementary Methods](#).

3 | RESULTS

After harmonization and quality control, the final sample included 829 participants (442 TLE and 387 healthy adults) ([Table 1](#)). The TLE group showed a higher mean age ($p < 0.05$) and greater head motion ($p < 0.001$) and as a result, both were included, in addition to sex, as covariates in the analyses. [Table S2](#) summarizes the resting-state fMRI acquisition details.

TABLE 1 Final sample demographics.

	TLE	HC	Test
<i>N</i>	442	387	
Age	39.4 (13.5)	36.1 (12.7)	$t = 4.5$, $p = 0.027$
Female	0.62	0.60	$\chi^2 = 0.45$, $p = 0.5$
Age at seizure onset (year)	17.3 (13.1)	-	-
Duration of disease (year)	22.7 (16.7)	-	-
Motion	0.17 (0.1)	0.14 (0.1)	$t = 6.53$, $p < 0.001$

Note: For continuous variables, such as age, results are presented as mean (standard deviation).

Abbreviations: HC, healthy controls; *N*, number of participants; TLE, temporal lobe epilepsy.

3.1 | Results from whole-brain connectivity analyses with magnitude and reproducibility of RSN differences

3.1.1 | Default mode network

Whole-brain connectivity analysis

The DMN showed extensive changes in functional connectivity to the rest of the cortex and subcortical brain regions in people with TLE compared to controls. Using bilateral DMN masks as the functional connectivity seed, the TLE group showed lower connectivity to five of the six clusters within the DMN (i.e. within network hypoconnectivity) compared to the control group and higher connectivity to nine of the 10 clusters outside of the DMN (i.e. between network hyperconnectivity). Higher connectivity was shown between the DMN seed and four clusters in the VAN, two clusters in the DAN, one cluster in the SMN, and one cluster in FPAR ([Figure 1](#)). [Table S3](#) summarizes within-network and between-network connectivity for all RSNs.

Magnitude and reproducibility of DMN differences

Within-DMN connectivity was lower for TLE for all seven sites with scan data for both controls and cases (range across sites = -1.475 to -0.132 ; Cohen's $d = -0.50$), whereas connectivity to the DMN from clusters situated in other networks was higher in TLE than in controls across all seven sites (range across sites = 0.162 – 1.015 ; Cohen's $d = 0.59$) (see [Table 2](#)).

3.1.2 | Dorsal attention network

Whole-brain connectivity analysis

Significant differences were noted in functional connectivity patterns within the DAN and between the DAN and other RSN in the TLE group compared to controls. In whole-brain connectivity analyses for the DAN, we found lower connectivity in one cluster within the DAN in the TLE group compared to the control group and higher connectivity in all clusters outside of the DAN and in other RSN. Hyperconnectivity was shown between the DAN and eight clusters in the DMN, four clusters in the SMN, two clusters in the VN, one cluster in the FPAR, and one cluster in the VAN with additional clusters that overlapped the DMN and VAN, DMN and LN, and DMN and FPAR.

Magnitude and reproducibility of DAN differences

Lower connectivity within the DAN was observed in the TLE group in five of the seven sites with both TLE and control participants (range across sites = -0.602 to 1.019 ; Cohen's $d = -0.008$), whereas connectivity to the DAN from clusters

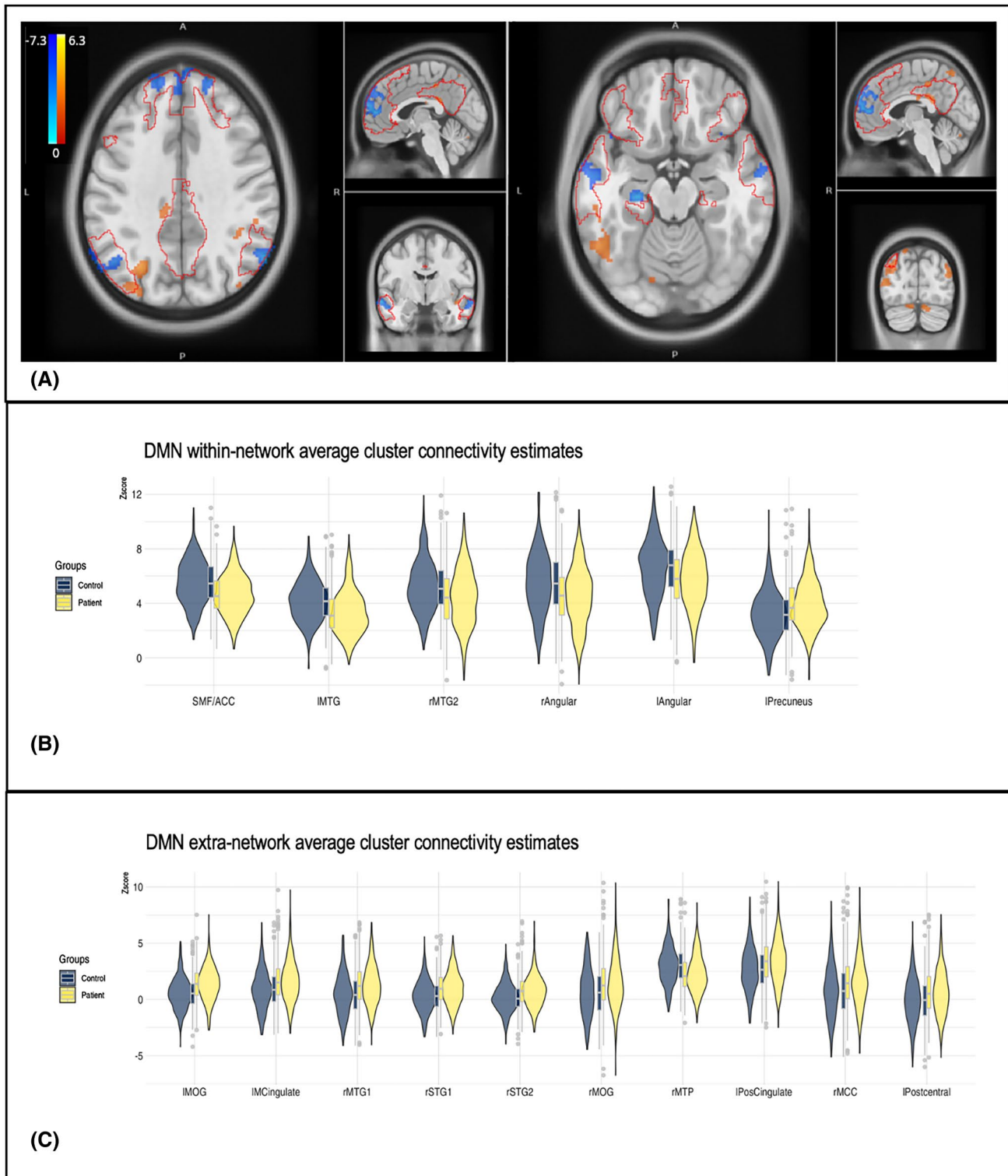


FIGURE 1 (A) Results of group comparison of default mode network (DMN) whole-brain connectivity map. Clusters show regions of higher connectivity (orange) and lower connectivity (blue) to mean DMN signal in patients compared to controls, with cluster and voxel-wise thresholds set at $p < 0.05$ and $p < 0.001$, respectively. The DMN seed mask used for this analysis is outlined in red. (B) DMN within-network and (C) DMN between-network connectivity clusters, Z-scores of connectivity estimates are compared between patients and controls in selected regions showing significant difference. Clusters are named according to AFNI MNI atlas: ACC, anterior cingulate cortex; MOG, medial occipital gyrus; MTG, medial temporal gyrus; STG, superior temporal gyrus.

TABLE 2 Summary of significant within-network and between-network findings across all sites, reported by network.

Network	Within-network clusters			Between-network clusters		
	Higher:Lower	Difference from controls (range)	Cohen's <i>d</i> (range)	Higher:Lower	Difference from controls (range)	Cohen's <i>d</i> (range)
DMN	1:1	−1.475; −0.132	−0.50 (−0.86; −0.42)	9:1	0.162; 1.015	0.59 (0.46; 0.69)
DAN	1:5	−0.602; 1.019	−0.01 (−0.53; 0.02)	21:1	0.340; 0.923	0.69 (0.60; 0.74)
FPAR	0:1	−0.626; −1.526	−0.42 (−0.43; −0.41)	12:1	0.637; 1.109	0.67 (0.60; 0.73)
VAN	0:5	−0.560; −2.216	−0.58 (−0.82; −0.53)	14:0	0.202; 1.163	0.67 (0.63; 0.70)
SMN	0:2	−0.524; −2.039	−0.42 (−0.58; −0.39)	4:0	−0.219; 0.639	0.28 (0.22; 0.32)
VN	0:1	−0.271; −2.049	−0.37 (−0.48; −0.32)	9:0	0.446; 1.304	0.64 (0.62; 0.67)
LN	No clusters	N/A	N/A	5:6	−0.668; 0.046	−0.27 (−0.38; −0.22)

Note: The column labeled higher:lower contains the respective number of clusters that are more/less strongly connected in patients than controls, with cluster and voxel-wise thresholds set at $p < 0.05$ and $p < 0.001$, respectively. The differences from controls in connectivity (range) and corresponding Cohen's *d* are reported for these clusters. A negative difference represents lower connectivity in patients compared to controls. Percentage differences are calculated by subtracting the mean connectivity estimate for patients from controls across all sites. Minimum and maximum estimates from leave one out analyses are provided in parentheses. Network names are according to Yeo 7-network atlas: DMN, default mode network; DAN, dorsal attention network; FPAR, frontoparietal control network; VAN, ventral attention network; SMN, somatomotor network; VN, visual network; and LN, limbic network.

situated in other networks was higher in the TLE group for all seven sites (range across sites = 0.340 to 0.923; Cohen's $d = 0.69$) (Table 2; Figure 2). See [Supplementary Material: TLE versus HC DAN map in MNI space](#).

3.1.3 | Frontal parietal network

Whole-brain connectivity analysis

In the FPAR, there was lower connectivity detected in a single cluster in the left dorsolateral prefrontal cortex (peak $x,y,z = -50.5, 49.5, 1.5$), part of the FPAR network (Figure 2). The TLE group showed higher connectivity in 12 clusters between the FPAR and other RSN, compared to the control group. Higher connectivity was evident between the FPAR and five clusters in the VAN, three clusters in the DAN, three clusters in the VN, and one cluster in the DMN.

Magnitude and reproducibility of FPAR differences

Within-network connectivity of FPAR was lower in patients for all seven sites with case and control scans (range across sites: −0.626 to −1.526; Cohen's $d = -0.42$), whereas connectivity to the FPAR from clusters situated in other networks was higher in cases than controls across all seven sites (range across sites: 0.637–1.109; Cohen's $d = 0.67$). See [Supplementary Material](#) for the complete set of clusters.

3.1.4 | Ventral attention network

Whole-brain connectivity analysis

Using bilateral VAN masks as the functional connectivity seed, the TLE group showed lower connectivity to all

five clusters within the network compared to the control group and higher connectivity to all 14 clusters between the VAN and other RSN. Higher connectivity was shown between the VAN and three clusters in the DMN; two clusters in the FPAR; two clusters in the VN; one in the SMN; and two clusters overlapping the DAN, FPAR, and VN (Figure 1).

Magnitude and reproducibility of VAN differences

In the VAN, lower connectivity was noted in the TLE group for all five within-network clusters and for all seven sites (range across sites: −0.560 to −2.216; Cohen's $d = -0.58$). In the clusters outside of the network, higher between-network connectivity was observed in TLE compared to controls for all seven sites (range across sites: 0.202–1.163; Cohen's $d = 0.67$).

3.1.5 | Sensory motor network

Whole-brain connectivity analysis

In the SMN, two within-network clusters showed lower connectivity in the TLE group compared to the controls, and connectivity between the SMN and other RSNs showed higher connectivity in the TLE group. Higher network connectivity was evident between the SMN and one cluster in the DAN, one in the VN, one in the FPAR, and one cluster overlapping the FPAR and VAN.

Magnitude and reproducibility of SMN differences

Within-network connectivity was lower in the TLE group for all seven sites (range across sites: −0.524 to −2.039; Cohen's $d = -0.42$). Connectivity to the SMN from other networks was higher in the TLE group for

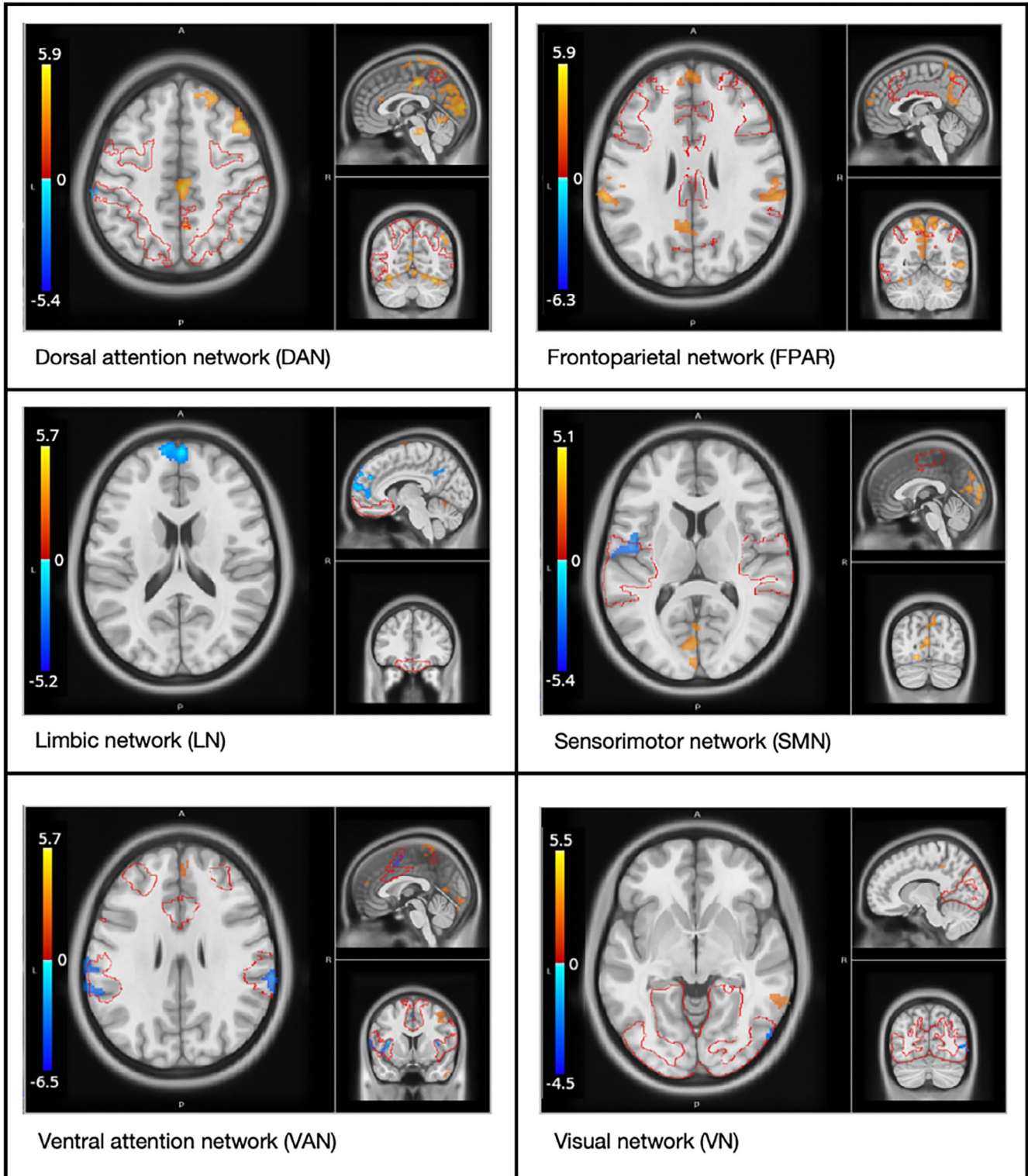


FIGURE 2 Group comparison of whole-brain connectivity maps for the remaining six networks from the seven-network Yeo et al.⁵ Clusters show regions of higher connectivity (orange) and lower connectivity (blue) in patients compared to controls, with cluster and voxel-wise thresholds set at $p < 0.05$ and $p < 0.001$, respectively. Red outline of original seed mask displayed.

five of the seven sites (range across sites: -0.219 to 0.639 ; Cohen's $d = 0.28$).

3.1.6 | Visual network

Whole-brain connectivity analysis

A single, within-network, cluster showed lower connectivity in the TLE group compared to the controls and higher connectivity was shown for all clusters between the VN and other RSN. Higher connectivity was shown between the VN and three clusters in the FPAR, two clusters in the SMN, two clusters in the DAN and one cluster in the VAN.

Magnitude and reproducibility of VN differences

Within-network connectivity was lower in TLE patients for all seven sites (range across sites: -0.271 to -2.049 ; Cohen's $d = -0.37$), and higher connectivity was evident in TLE to clusters outside the network for all seven sites (range across sites: 0.446 – 1.304 ; Cohen's $d = 0.64$).

3.1.7 | Limbic network

Whole-brain connectivity analysis

No within-network clusters were detected for the LN and the majority (6/11) of the clusters that fell outside of this network demonstrated lower connectivity in the TLE group. Moreover, all the lower connected clusters form part of the DMN.

Magnitude and reproducibility of LN differences

Between-network connectivity was lower in the TLE group for six of the seven sites with scans acquired for both groups (range across sites: -0.668 to 0.046 ; Cohen's $d = -0.27$). See [Supplementary Material](#): TLE versus HC Limbic map in MNI space.

3.2 | Seed-based analyses of the DMN sub-regions

Functional connectivity maps for the three DMN subregion seeds (bilateral angular gyrus, ACC and precuneus) demonstrated lower within-network connectivity in cases for the majority of significant clusters. Notably, a consistent pattern of lower connectivity with both the left and right hippocampus was evident for all three seeds (see [Table S2](#)). After cluster-wise correction for multiple comparisons, we did not find any associations with age of seizures onset or duration of epilepsy.

3.3 | RSN correlations with clinical variables

Patterns of network connectivity were not associated with age of seizure onset or disease duration, but some differences were observed between patients with left and right TLE, after correcting for age, sex, and subject motion. Patients with left TLE showed higher DMN and LN connectivity to a region in visual cortex compared to healthy controls. Those with right TLE demonstrated lower connectivity in this cluster for the DMN only, relative to both healthy controls and those with left TLE. Moreover, in those with right TLE, lower connectivity was observed between the SMN and a subcortical cluster in the left caudate head/nucleus accumbens region, relative to both healthy controls, and, to a lesser and non-significant extent, to those with left TLE. There were no significant differences between left and right TLE in demographic and other clinical characteristics, or subject motion estimates ([Table S4](#)).

4 | DISCUSSION

This study provides the largest resting-state fMRI analysis of TLE to date. The novelty of our results lies in the detection of robust patterns across sites, and large-scale confirmation of RSN disruption, advancing the field beyond single-center studies that are focused on DMN and/or limbic networks. The large sample size provides statistical power for detecting globally relevant changes that cannot be achieved in smaller, single-center studies, while the heterogeneity of our multi-center dataset achieves greater generalizability of our findings. Overall, we showed that aberrations in functional connectivity reach beyond previously studied LN and DMN. Our results demonstrate a robust pattern of widespread abnormalities in functional connectivity in TLE characterized by lower within-network connectivity and higher between-network connectivity in the majority of RSNs. This potentially reflects a compensatory mechanism or pathological reorganization. Importantly, this pattern was highly reproducible across sites.

4.1 | Reproducibility and generalizability: Advantages of a global multi-site dataset

We postulate that our findings represent a reduced differentiation between RSNs and an increased integration of non-limbic RSNs. Prior studies showing similar changes in

the so-called “integration-segregation axis”¹⁶ have proposed that this pattern represents a compensatory mechanism in TLE to isolate disruptive interictal or ictal effects^{16,17} or pathological re-wiring in the presence of repetitive seizures. However, the mechanisms underlying these changes remain speculative as studies have not demonstrated any consistent advantages or disadvantages of these patterns. A network-based analysis of structural alterations in the ENIGMA-Epilepsy dataset also suggested a global change in network organization, notably with more integration of DMN regions in contrast to more regularization of limbic regions.¹⁸ Here, using resting-state fMRI, we showed comparable findings in TLE.

Overall, our large, multi-center analysis demonstrated aberrations in all RSNs that were reproducible across sites and showed medium to large effect sizes with leave-one-center-out reiterations. The alterations in functional connectivity found in our study demonstrate functional changes that are comparable to structural connectivity differences observed in prior studies, whereby patients show a less modular, more regularized network pattern in TLE compared to controls. This level of reproducibility is hard to demonstrate in smaller rsfMRI studies and is critical to building reliable neuroimaging biomarkers.

4.2 | Reduced segregation and increased integration of non-limbic networks

The dynamic resting brain can be viewed with a duality of segregation and integration of RSNs relative to each other. While each region is primarily affiliated with one of the seven networks (within-network connectivity), there are variable degrees of integration with other RSNs (between-network connectivity).

Lower within-network connectivity of non-limbic RSNs, most prominently seen in DMN, VAN, and FPAR, reflects a loss of network-specific functional specialization or segregation. Perturbations in DMN connectivity are well described in TLE and are proposed as a possible clinical diagnostic marker.^{19,20} Reduced connectivity in TLE has been linked to higher seizure frequency and longer disease duration, and connectivity has also been shown to fluctuate in response to interictal discharges.²¹ These findings were further supported by the seed-based analyses of the six key network nodes and consistent with the current literature pointing to DMN hypoconnectivity in TLE.^{6,17,21–26}

Network changes across non-limbic networks have implications in cognitive dysfunctions in TLE, as regions physiologically tasked with certain processes become less exclusive to their strongest affiliation (i.e., their atlas-derived RSN label). Our findings may inform future studies

identifying the cognitive phenotypes in people with TLE, where research shows a broad range of impairments in language, memory, executive functioning, attention/processing speed, and visuospatial ability that differ across individual patients.²⁷ The DMN has particularly been linked to episodic memory, negative rumination, and self-referential thought, and lower within-network connectivity has been associated with poor executive functioning as well as global cognitive impairment.²⁸

Unlike DMN, DAN is considered a task-positive network, involved in volitional orienting of visuospatial attention, and engaged when externally directing attention.^{27,29} Likewise, the aberrations noted in the FPAR network are relevant, given the high prevalence of executive dysfunction in TLE.³⁰ The FPAR network is implicated in higher order functioning such as sustained attention, complex problem-solving, and working memory and is supported by prior reports in TLE.^{26,31–32}

These non-limbic networks all showed widespread hyperconnectivity with regions outside their network boundaries. This increased integration may reflect compensatory adaptations or maladaptive connections. In particular, hyperconnectivity from DMN and VAN to task-positive and sensory networks could indicate reorganization. Notably, these findings remained robust across sites in our leave-one-center-out method.

Within the sensory/unimodal to association/transmodal gradient model,³³ SMN and VN are considered the most segregated and anatomically isolated networks. Lower within-network connectivity in these RSNs hence supports the whole-brain network reorganization hypothesis and is in line with prior observations of structural and functional changes.^{19,34–36} It is important to note that our findings reflect localized differences in specific clusters, rather than uniform reductions across entire networks. For example, in the DMN, we observed reduced connectivity between the network seed and clusters in the superior medial frontal gyrus, angular gyrus, and middle temporal gyrus—areas known to support memory, semantic integration, and self-referential thought and commonly implicated in TLE. Similar region-specific reductions were found in VAN, DAN, FPAR, SMN, and VN, involving key nodes related to attention, executive function, and sensory processing. These findings suggest that functional aberration is more apparent in selective hubs within RSNs, rather than affecting entire networks uniformly.

4.3 | Isolation of the limbic network

In contrast to the reduced segregation and increased integration seen across other RSNs, LN exhibited reduced between-network connectivity, particularly to the DMN.

Notably, no significant within-network clusters were detected, despite isolation from other RSNs. This unique pattern in LN, with a central role in ictal and interictal manifestations of TLE, could represent either a protective adaptation aimed at containing epileptiform activity, or a pathological disconnect contributing to impaired communication with associative and regulatory circuits. Pronounced reductions in connectivity between mesial temporal structures and key hubs of the DMN have been shown in individuals with mesial TLE, consistent with impairments in episodic memory and self-referential processing, which is less pronounced in non-lesional and neocortical TLE.^{37–39} Structural connectivity studies provide further evidence of this reduced between-network connectivity, showing disrupted white matter pathways linking the LN to broader cortical systems, while reduced integrity in mesial temporal projections—including the fornix, parahippocampal cingulum, and uncinate fasciculus—as well as cingulum-mediated pathways supporting LN–DMN communication, has been shown in diffusion MRI.⁴⁰ These abnormalities frequently extend beyond the temporal lobe, reflecting widespread network involvement.^{34,40–42} Future studies should assess how this isolation evolves with disease severity, progression, and its role in predicting treatment response.

4.4 | Default mode network subregion connectivity and hippocampal interaction

To refine our interpretations, we performed seed-based analyses of six key DMN nodes and consistently found reduced connectivity between these subregions and the hippocampus. This hippocampal hypoconnectivity underscores the centrality of mesial temporal dysfunction in TLE. This approach partially addresses the limitations of bilateral network seeds by revealing regionally specific patterns of disconnection. Our findings suggest hippocampal disconnection and warrant follow-up studies building on this finding. In DMN subregion analysis, we also found higher seed-based functional connectivity for the left posterior cingulate cortex and precuneus to DMN, which is consistent with prior reports.^{20,22,25,43} The posterior cingulate cortex is a central hub of DMN and subserves a variety of cognitive functions, especially those linked with long-term memory and working memory.⁴⁴ Previous ENIGMA-Epilepsy studies have identified cortical thickness changes in these regions in patients with TLE.³¹ Here, we provide fMRI evidence for the robust alterations in these functional subnetworks. Future studies may compare structural and functional changes in relation to disease severity or clinical phenotypes to better characterize these changes.

4.5 | Left and right TLE show difference in connectivity patterns

While connectivity patterns were largely similar between left and right TLE, a few differences were observed. Our results suggested opposing influences of laterality on intrinsic connectivity of the brain in people with TLE, most apparent for the DMN: we found relatively greater connectivity to a cluster in the right lingual gyrus in left TLE, while right TLE showed lower connectivity to the same cluster compared to controls. Differences between left and right TLE have been demonstrated in functional and structural analyses in the past, suggesting that the two major TLE subgroups are not mere mirror images of the same disease.^{45–47} Two factors are relevant to this distinction: (1) the human brain is highly lateralized, most prominently in developmental gene expression as well as function, such as language and handedness, as well as other cognitive functions that are less frequently assessed in this regard; and (2) detected changes may represent a different compensatory mechanism in contralateral temporal lobe structures.

4.6 | Limitations and future directions

Despite the advantages of large multi-site analysis in providing higher analytical power, our analysis comes with several inherent limitations. First, data were collected retrospectively from clinical and research centers, which may introduce selection bias. Second, we were not able to collect all relevant clinical covariates such as medication, race/ethnicity, or seizure frequency, or other potential confounds. It is possible that some of the clusters of significant differences between patients and controls represent the effect of medication or other uncontrolled variables. Additionally, while mesial temporal sclerosis is a known clinical contributor to connectivity alterations in TLE, imaging confirmation was available for only a subset of our cohort. As such, we could not assess its effects directly, but we recognize this as a critical factor for stratification in future studies that all of these variables could influence connectivity patterns. Third, the use of unilateral seeds could reveal hemisphere-specific patterns; however, the use of bilateral seeds allowed us to evaluate symmetrical network architectures and interactions between homologous regions.

The study of functional connectivity is limited by factors such as inter-subject variability of clinical characteristics which may affect network properties, an inherent limitation when studying heterogeneous samples. Site-to-site variability can also limit interpretability of our findings, including differing criteria for the selection of patients receiving

resting state imaging and differing patient management and data collection protocols. However, all imaging data were harmonized using the same pre- and postprocessing approach, as well as the same quality control metrics, reducing cross-site methodological variance. Future studies are underway to collect additional clinical data and correlate abnormal connectivity with neuropsychological and/or seizure outcomes to better understand how atypical functional network architecture impacts disease course and clinical outcomes.

In conclusion, our large, multi-site study provides strong evidence that TLE is associated with a reproducible pattern of functional network disruption with widespread brain involvement. Our results support the hypothesis of a more regularized, less modular network organization in TLE that may explain a range of clinical and cognitive co-morbidities and could eventually be used to guide treatment planning or evaluate treatment response.

AUTHOR CONTRIBUTIONS

Victoria Ives-Deliperi: Conceptualization (lead); investigation (equal); methodology (lead); project administration (lead); resources (equal); visualization (equal); writing—original draft (lead). **Jonathan Ipser:** Conceptualization (equal); formal analysis (lead); data curation (lead); investigation (lead); methodology (equal); software (lead); visualization (lead); project administration (equal); reviewing and editing (equal). **James T. Butler:** Conceptualization (equal), methodology (equal), resources (equal), supervision (supportive), reviewing and editing (supportive). **Heath Pardoe:** Data curation (equal); formal analysis (equal); investigation (equal); resources (equal); reviewing and editing (equal). **Hamid Soltanian-Zadeh:** Data curation (equal); investigation (equal); resources (equal); reviewing and editing (equal). **Christian Rummel:** Data curation (equal); formal analysis (equal); investigation (equal); resources (equal); reviewing and editing (equal). **Roland Wiest:** Reviewing and editing (supportive). **Simon S. Keller:** Reviewing and editing (supportive). **Barbara A. K. Kreilkamp:** Data curation (equal); formal analysis (equal); investigation (equal); resources (equal); reviewing and editing (equal). **Anna Elisabetta Vaudano:** Data curation (equal); formal analysis (equal); investigation (equal); resources (equal); reviewing and editing (equal). **Alice Ballerini:** Reviewing and editing (supportive). **Stefano Meletti:** Reviewing and editing (supportive). **Gerard Hall:** Reviewing and editing (supportive). **Peter Taylor:** Reviewing and editing (supportive). **Luis Concha:** Data curation (equal); formal analysis (equal); investigation (equal); resources (equal); reviewing and editing (equal). **Alfonso Fajardo-Valdez:** Data curation (equal); formal analysis (equal); investigation (equal); resources (equal); reviewing and editing

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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