Identification of abnormal closed-loop pathways in patients with MRI-negative drug-resistant epilepsy

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Abstract

To identify abnormal changes in closed-loop pathways among magnetic resonance imaging-negative drug-resistant epilepsy (MRI−DRE) patients and to examine the associations of these abnormalities with emotional and cognitive impairments. A total of 26 patients with MRI−DRE and 26 healthy controls (HCs) were included in this study. Causal brain networks and temporal-lag brain networks were constructed from rs-fMRI data, and the Johnson algorithm was used to identify stable closed-loop pathways. Abnormal closed-loop pathways in the MRI−DRE group were identified by comparison with HCs, and associations with indicators of cognitive and emotional impairments were examined using Pearson correlation analysis. The results reveal that the abnormal stable closed-loop pathways were distributed across frontal, parietal, and occipital lobes, and included altered FC values both within and between cerebral hemispheres. Four abnormal closed-loop pathways in the occipital lobe were associated with emotional and cognitive impairments. These abnormalities may serve as biomarkers for diagnosis and guidance of individualized treatments for MRI−DRE.

Introduction

Epilepsy is characterized by spontaneous recurrent seizures due to abnormal neural network activity (Royer et al., 2022). Numerous antiepileptic drugs (AEDs) with heterogenous modes of action are available to suppress epileptic seizures, and about 63.7% of patients can achieve seizure-free status using AEDs, especially when treatment is initiated early in the disease course (Chen et al., 2018). However, approximately one-third of patients do not achieve seizures-free status even after two or more antiepileptic drug regimens, known as drug-resistant epilepsy (DRE) (Kwan et al., 2011). Further, many of these patients show no signs of neuroanatomic abnormalities on brain magnetic resonance images that could help identify the locations of seizure initiation and propagation for non-pharmaceutical treatment (termed magnetic resonance imaging-negative DRE, MRI−DRE). Recent functional MRI (fMRI) studies indicate that recurrent seizure activity results from abnormalities in brain network organization and connectivity, which may be useful biomarkers to guide clinical diagnosis and treatment (Shi et al., 2019; Sinha et al., 2020).

Resting state functional MRI (rs-fMRI) is an advanced non-invasive neuroimaging technique that can reveal the intrinsic connectivity of functional brain networks (Hao Zhang, 2022), including differences in patients compared to matched healthy controls. Further, rs-fMRI can be combined with other modalities such as diffusion tensor imaging (DTI), magnetoencephalogram (MEG), and electroencephalogram (EEG) to reveal the precise associations among abnormal network activity, structural reorganization, and clinical impairments (Abdallah et al., 2022; Ebrahimzadeh et al., 2019; Huang et al., 2020). Brain network analysis is widely employed to identify potential biomarkers for the diagnosis and treatment of epilepsy (Larivière et al., 2021). Existing brain network models can be roughly divided into correlation brain networks and causal brain network (Hernán F J González, 2022; Pang et al., 2022). The causal brain network with directional information is more suitable for the analysis of closed-loop pathways mechanism at the brain region level. On the one hand, compared with many conventional functional connectivity, causal brain networks can provide additional information on the direction of information flow and may be more helpful in distinguishing disease features. On the other hand, direction information is the basis of judging whether the loop exists. While causal brain networks analysis has been limited to small-scale networks, whole-brain causal network analysis can be achieved by including temporal-lag brain network analysis (Xia et al., 2023).

Most major brain networks include closed-loop pathways. These pathways can be detected as early as 18–22 weeks of gestation and increase in number, especially in the cortex, as neuronal populations expand during development (McConnell et al., 1994; Tau and Peterson, 2010). These closed-loop pathways are critical for normal brain function and are implicated in various brain disorders. For instance, stress-related circuits involving the cortex and hypothalamus include closed loops (Kataoka et al., 2020), while closed-loop pathways in the medial prefrontal cortex are implicated in fear and anxiety (Chen et al., 2021). In a rat seizure model, closed-loop pathways between the hippocampus and medial prefrontal cortex (mPFC) are involved in dysfunctional spatial cognition (Niedecker et al., 2021). Closed-loop pathways related to seizures can also be activated or inhibited by other networks and pathways, such as the basal ganglia–thalamocortical and the cerebellum–thalamocortical pathways (Gong et al., 2021; He et al., 2020). Therefore, identifying aberrant closed-loop pathways may provide feasible targets for clinical intervention.

Patients with epilepsy frequently exhibit comorbid cognitive, emotional, social, and (or) mnemonic impairments (Keezer et al., 2016). However, the network abnormalities underlying these impairments are less clear than those involved in motor and languages deficits, which have been mapped extensively in epilepsy patients for many decades (Catalino et al., 2020). Thus, despite the high prevalence of comorbidities in the human epilepsy population, little is known about the underlying mechanisms (Aguilar et al., 2018), hampering diagnosis and treatment.

Most previous studies on closed-loop pathways in epilepsy have been limited to the neuronal level or focused only on known closed-loop pathways, while there is a lack of research on closed-loop pathway abnormalities in epilepsy at the whole brain network level. The current study analyzed functional closed-loop pathways at the whole-brain level and explored the potential associations with cognitive and emotional impairments in MRI−DRE patients.

Materials and methods

Participants
Patients with MRI-negative epilepsy were evaluated at the Department of Functional Neurosurgery, Nanjing Brain Hospital, from May 2021 to March 2023. A total of 52 subjects were considered as study candidates, including 26 MRI−DRE patients and 26 healthy controls (HCs). The MRI−DRE patients were selected according to the following criteria: (1) diagnosis of DRE by two senior epilepsy center physicians based on the 2017 International League Against Epilepsy seizure classification guidelines (Fisher et al., 2017); (2) negative head MRI after admission; (3) right-handed; (4) 15–65 years of age; (5) full cooperation with head MRI examinations; (6) no history of hypertension, diabetes, congenital mental impairment, or hypoxic–ischemic encephalopathy. The HC participants were selected according to the following criteria: (1) volunteered for the study; (2) right-handed; (3) 15–65 years of age; (4) no neurological disease, neurological dysfunction, or serious physical illness.

Clinical psychological assessments

Clinical assessments were performed by two trained psychologists from the Department of Functional Neurosurgery, Nanjing Brain Hospital. Cognitive status was evaluated using the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) (Lin et al., 2021), while emotional status was evaluated using the Hamilton Anxiety Rating (HAMA) and Hamilton Depression Rating (HAMD) (Darabyan et al., 2016).

Image acquisition

All MRI data were collected using a 3.0-T superconducting MRI system (AWP166156, Prisma, Simens). Structural MRI data were obtained using a 3D T1WI sequence with the following parameters: repetition time (TR) = 2300 ms; echo time (TE) = 2.29 ms; inversion time (TI) = 450 ms; field of view (FOV) = 256 × 256 mm²; matrix = 256 × 256; flip angle = 8°; scanning layer number = 192; layer thickness = 1 mm, no interval, sagittal scanning covering the whole brain. The rs-fMRI scanning parameters were as follows: TR = 2000 ms, TE = 25 ms, FOV = 240 mm × 240 mm, RM = 64 × 64, ST = 3 mm, FA = 90°, 0.5 mm gap, 40 transverse slices, interleaved, and 240 volumes.

Data processing

Data were processed using Statistical Parametric Mapping (SPM12) running in MATLAB R2013b (MathWorks, Natick, USA). Processing included the following steps: (1) Conversion of DICOM format image files to NIFTI image files using Dcm2nii software; (2) Exclusion of the first and last 10 rs-fMRI volumes to remove noise signals and interference caused by head movements; (3) Correction for the acquisition time delay between slices; (4) Removal of images with head translation > 2 mm or rotation > 2°; (5) Band-pass filtering (0.01–0.08 Hz) to reduce the influence of physiological noise; (6) Registration of rs-MRI data to T1 structural images and conversion to standard Montreal Neurological Institute (MNI) space; (7) Resampling to 2 mm × 2 mm × 2 mm voxel size; (8) Spatial smoothing using a Gaussian kernel of 6-mm full-width at half maximum (FWHM); (9) Extraction of time series for each brain region from preprocessed images according to the Anatomical Automatic Labeling (AAL) atlas.

Construction of causal brain and temporal-lag brain networks

Causal brain network modeling was conducted as described (Xia et al., 2023). Briefly, a deep learning model was used to simultaneously infer causal associations between activities in different brain regions according to temporal-lag (time delay in transmission). The details are shown in Fig. 1. Unlike many previous brain network modeling methods, this method can model nonlinear interactions between brain regions.

Identification of closed-loop pathways

Closed-loop pathways were identified using the algorithm proposed by Johnson (Johnson, 1975). This algorithm can find all simple circuits in a binary adjacency graph without repeated nodes except for the first and last vertices (i.e., closed loops). The time complexity of the algorithm is defined by $O((n+e)(c+1))$, where $n$ denotes the number of nodes, $e$ denotes the number of connected edges, and $c$ denotes the number of simple closed-loop pathways.

Statistical analysis

Demographic and clinical variables were analyzed and compared using Statistical Product and Service Solutions 26 (SPSS 26). All datasets were first examined for normality using the Kolmogorov–Smirnov test. According to test results, none of the continuous demographic and clinical variables were normally distributed, and so are expressed as the mean ± standard deviation. Means were compared using the independent samples t-test, and variables differing between groups were included as covariables in subsequent correlation analyses. The gender ratio was compared between groups by chi-squared test.

The aim of this study is to identify abnormal closed-loop pathways in MRI−DRE and associations with cognitive and emotional impairments. However, due to the high inherent heterogeneity among subjects, only closed-loop pathways shared by many subjects are suitable as biological markers. Therefore, we defined closed-loop pathways found in at least 85% of the HC group as stable closed-loop pathways for comparison (Xia et al., 2023). First, the mean network connectivity strengths in the HC group were obtained and those with weights ≥ 0.85 were set to 1, while those with weights < 0.85 were set to 0, yielding binary networks. These binary networks were then analyzed using the Johnson algorithm to identify closed-loop pathways. Only those found in 85% of HCs were retained for group comparisons (Fig. 2). The edge strengths of these stable
closed-loop pathways conformed to normal distribution and were compared between groups by two-sample t-test. Second, correlations between the average weight of each stable closed-loop pathway and clinical symptoms (HAMA and HAMD scores for emotional impairments and MoCA and MMSE scores for cognitive impairments) were examined in the MRI-DRE group, and z-score was used to correct for multiple comparisons. Age, gender and years of education were all included as covariates in the correlation analysis using the multivariate Granger causality toolbox (MVGC) (Barnett and Seth, 2014). Finally, the potential association between different clinical symptoms of MRI-DRE was deeply explored.

Results

Participant characteristics

A total of 52 subjects were included in the final analysis, 26 patients with MRI-DRE and 26 healthy controls (HCs). The baseline demographic and clinical features of all subjects are summarized in Table 1. Neither average age or gender ratio differed between groups (p > 0.05), while years of education was significantly greater in the HC group.

Stable closed-loop pathways

A total of 89 stable closed-loop pathways were identified and these closed-loop pathways could be divided into seven independent clusters based on nodal and edge composition (Fig. 2). The left part of Fig. 2 shows the functional connectivity (FC) graph, where the same color indicates that the two connected brain structures are in the same area (e.g., green indicates that both structures are within the occipital lobe), while gray indicates that the two brain structures are in different areas. The right side of Fig. 2 shows these same seven independent clusters based on functional network topology.

As indicated by Fig. 2, there were more interactive connections within the same area than across areas. Of the 7 clusters, two were confined to the frontal lobe, while the remaining five spanned multiple lobes, including four encompassing frontal and occipital lobes. Four closed-loop pathways were simple circuits with only two brain regions involved, while the remaining three were complex circuits involving more than two brain regions. Of these, the circuit labelled number 5 was the most complex, although it mainly involved the occipital lobe.

Comparison of causal brain and temporal-lag brain networks between groups

We then identified connected edges associated with these stable closed-loop pathways that differed significantly between MRI-DRE and HC groups by two-sample t-test. Results are visualized in Fig. 3, where nodes of the same color are from the same cluster, and nodes differing in color are from different clusters. Again, the causal brain network is shown on the left side and the temporal-lag brain network on the right side.

Abnormal functional connections in the MRI-DRE group were located primarily in the occipital, frontal, and parietal lobes with no obvious laterality. In addition, the number of abnormal functional connected edges was much greater within than across hemispheres. Some abnormal functionally connected edges appeared in both the causal network and the temporal-lag brain network, such as SMG.R→IFGoperc.R and PCL.L→PreCG.R. Finally, the abnormal closed-loop pathway SOG.R→LING.L→SOG.R appeared in both the causal and temporal-lag brain networks.

Clinical psychological correlation analysis

Four closed-loop pathways, all located in the occipital lobe, were significantly correlated with clinical indicators. Of these, SOG.R→MOG.R→SOG.R (r = 0.56, p = 0.005), SOG.L→LING.L→SOG.L (r = 0.519, p = 0.011), and SOG.L→MOG.L→SOG.L (r = 0.519, p = 0.005) were correlated with cognitive impairment, and SOG.L→CUN.L→LING.R→CUN.R→SOG.L (r = 0.441, p = 0.035) with anxiety (Fig. 4). The average weights of the edges within SOG.L→LING.L→SOG.L, SOG.L→CUN.L→LING.R→CUN.R→SOG.L, and SOG.L→MOG.L→SOG.L were positively correlated with clinical indicators, while the mean edge weight of SOG.R→MOG.R→SOG.R was negatively correlated with clinical indicators. Moreover, all of these pathways include the superior occipital gyrus (SOG) as a node.

Comparison of clinical psychology-related circuits Interactions

Finally, we calculated the interaction strength among the three closed-loop pathways found by the causal network (Fig. 4). There was no significant interaction between closed-loop pathways SOG.L→LING.L→SOG.L and SOG.L→CUN.L→LING.R→CUN.R→SOG.L as these pathways share a common node (SOG.L), which can lead to unsolvability during operation. Interaction strengths were greatest between the closed-loop pathways SOG.R→MOG.R→SOG.R and SOG.L→CUN.L→LING.R→CUN.R→SOG.L (0.079 and 0.074), while weaker interactions were found between SOG.R→MOG.R→SOG.R and SOG.L→LING.L→SOG.L (0.037 and 0.059, respectively). The results are shown in Table 2.

Discussion

Several meta-analyses have concluded that functional brain networks are quantitatively altered in epilepsy and that these changes are potential biomarkers for diagnosis and treatment (Dharan et al., 2021; Slinger et al., 2022). While closed-loop pathway analysis has been applied to
examine changes in brain networks associated with motor dysfunction (Sharifi et al., 2022), this is the first study to apply closed-loop pathway analysis of rs-fMRI data to epilepsy at the whole-brain level, and further to examine the associations of these pathway changes with comorbid anxiety, depression, and cognitive dysfunction. Indeed, multiple closed-loop pathways involving structures within the frontal, parietal, and occipital lobes were altered in MRI^-DRE patients, and the magnitudes of these alterations in occipital lobe closed-loop pathways were associated with clinical indicators of emotional and cognitive dysfunction.

Temporal lobe epilepsy showed a significant reduction in clustering coefficient in the occipital lobe (Sone et al., 2016). Accumulated source imaging (ASI) analysis suggests that activity in the frontal and parietal lobes is a major driver of seizures (Sun et al., 2021). These findings suggest that the widespread brain network disorders involving frontal lobe, parietal lobe and occipital lobe in epilepsy, which is consistent with the results of the study. Previous studies have shown that abnormal discharges in the central region are closely associated with seizures generation (Akiyama et al., 2006). In the study, the present of abnormal FC in the central region (PCL.L→PreCG.R) may be an important trigger for seizures.

Brain regions with shared or cooperative functions tend to be more strongly connected, forming a functional cluster in network connectivity analysis. In turn, brain networks are composed of several clusters of densely connected brain regions (Li et al., 2021). In a rodent model of epilepsy, interconnected neuron clusters were reported to form large-scale brain networks contributing to epileptic comorbidities (Li et al., 2019). The current study also identified seven independent clusters of abnormal FC in MRI^-DRE patients. As the subjects selected in the study all lacked structural abnormalities detectable by MRI, these clustered regions likely contributed to DRE pathogenesis and may ultimately lead to structural lesions. Moreover, these abnormalities may serve as valuable biomarkers for the early clinical diagnosis and treatment of MRI^-DRE.

There are aberrant thalamocortical pathway in epilepsy patients, which may contribute to the imbalance in excitatory versus inhibitory drive triggering seizures (Gong et al., 2021). Reduced inhibitory output from the basal ganglia and concomitant thalamus synchronization are also directly implicated in the transition from focal seizure activity to bilateral tonic-clonic seizures (He et al., 2020). Highly excitable limbic pathway circuits also contribute to generalized epilepsy (Chen et al., 2021). We identified multiple abnormal closed-loop pathways, including PCL.L→PreCG.R and SOG.R→LING.L→SOG.R, in both the causal brain network and temporal-lag brain network, indicating these abnormal functional connections and closed-loop pathways are relatively stable in MRI^-DRE. Collectively, these findings support the notion that epilepsy is a disorder of whole-brain networks rather than of individual brain areas (Courtiol et al., 2020; Royer et al., 2022).

Further analyses revealed significant correlations of abnormalities in four closed-loop pathways, all including the superior occipital gyrus (SOG) as a node, with cognitive and emotional impairments. The SOG is a component of the dorsal attention network (DAN) (Spreng et al., 2013), and a previous study reported that DAN dysfunction was the most strongly predictive of cognitive decline compared to other brain networks (Jiang et al., 2022). In addition, FC strength between the DAN and default mode network (DMN) was negatively correlated with anxiety (Duan et al., 2020), suggesting that DAN dysfunction may contribute to both emotional and cognitive deficits in MRI^-DRE. Based on the current results, it is reasonable to speculate that modulation of occipital closed-loop pathways are a promising target for the purpose of improving patients’ emotion and cognition impairment in MRI^-DRE (e.g., modulation of SOG FC using neurostimulation, stereotactic EEG, or targeted drugs). (Aicua Rapun et al., 2019; Liang et al., 2022; Wang et al., 2022)

Changes in closed-loop pathways including the SOG plus either middle occipital gyrus (MOG) or lingual gyrus (LING) were also correlated with cognitive dysfunction. These findings are consistent with previous studies reporting that cognitively impaired elderly with white matter hyperintensities exhibited reduced amplitude of low-frequency fluctuations in the MOG and that abnormal thickness of the LING was associated with social cognitive deficits in myotonic dystrophy type 1 patients (Serra et al., 2020; Xing et al., 2022). Further, bilateral LING activity was reduced in patients with generalized anxiety disorder (Cui et al., 2022), while changes in FC between the parahippocampal gyrus and both posterior cingulate cortex and cuneus (CUN) were strongly associated with trait anxiety (Wu et al., 2019). Consistent with these findings as well, changes in the closed-loop pathway including SOG, LING, and CUN were associated with anxiety. Targeted closed-loop pathway interventions may therefore improve both emotional and cognitive function in epilepsy patients.

The occipital lobe is mainly involved in the regulation of visual function (Rosenke et al., 2018), but also contributes to emotional and cognitive functions. Graph theory analysis revealed that impaired emotional regulation was associated with significantly lower nodal and modular network metrics in the occipital lobe (Liu et al., 2022). White matter hyperintensity volume in the occipital lobe and fractional anisotropy of the forceps major, an occipital association tract, were also associated with cognitive dysfunction (Wang et al., 2020). Similarly, we found that altered closed-loop pathways in the occipital lobe were significantly correlated with emotional and cognitive dysfunction in MRI^-DRE, and the abnormal FC pathways in the occipital lobe were correlated with psychotic symptom severity. The current findings thus demonstrate the utility of whole-brain closed-loop pathway analysis for identifying novel pathomechanisms of epilepsy, although additional studies are needed for verification.

Early-life status epileptics in rats can lead to both cognitive and emotional impairment, indicating that both cognitive and emotional networks are disrupted by epilepsy (Mikulecká et al., 2019), and we found a positive interaction between the cognitive and emotional closed-loop pathways. Although the interaction was not strong (i.e., severe emotional impairment does not necessarily predict greater cognitive impairment) (Keezer et al., 2016), this finding is consistent with the frequent comorbid cognitive and emotional impairments observed among patients with epilepsy. This
findings also further supports the reliability of closed-loop pathway analysis. We infer that concurrent emotional and cognitive impairments in epilepsy patients are associated with disease progression and that early control of emotional and cognitive impairments may improve prognosis.

Conclusions

This study provides the first evidence that closed-loop pathways in frontal, parietal, and occipital lobes are altered in MRI-DRE. These findings confirm that epilepsy is primarily a neural network disorder rather than a disease associated with local brain lesions, and suggest that seizures can result from abnormal FC in the central region. In addition, we identified four functional closed-loop pathways significantly associated with emotional and cognitive impairments. These altered closed-loop pathways may be neural biomarkers to assist in the diagnosis and treatment of MRI-DRE. Moreover, interventions targeting these pathways may relieve comorbid clinical symptoms, including psychiatric impairments, in addition to seizure activity.

Declarations

Ethical approval The Ethics Committee of Nanjing Brain Hospital approved the study (No. 2021-KY018-01), and all subjects provided informed written consent to voluntarily participate.

Conflict of Interest All authors disclose no conflicts of interest.

Authors’ contributions All the authors contributed to the conception and design of the study. JB, NR, and HZ performed material preparation, data collection, and data analysis. JB and HY wrote the first draft of the manuscript and YW prepared figures 1-4. All the authors revised the draft manuscript. All authors have read and approved the final version of this manuscript.

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Data availability All data generated and analyzed in the study are included in this paper. The transcripts from which this manuscript was developed are available on request from the corresponding author.

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References


### Tables

**Table 1** Baseline clinical and demographic characteristics of MRI−DRE and HCs group participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MRI−DRE</th>
<th>HCs</th>
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<td>AEDs (types)</td>
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AEDs, antiepileptic drugs; MRI−DRE, magnetic resonance imaging-negative drug-resistant epilepsy; HCs, healthy controls

**Table 2** Interactions between closed-loop pathways associated with cognitive impairment and affective disorders based on the causal brain network
### Figures

#### Fig. 1

**Construction of causal and temporal-lag brain networks.** Regional signal values were extracted from fMRI data, and both causal effect and temporal-lag values between brain regions were estimated based on a structural learning model.

#### Fig. 2

**Figure 2**
Identification of stable closed-loop pathways. The left side shows the binary functional connectivity graph. A total of 89 stable closed-loop pathways were identified in the healthy control brain. The same color indicates that the two connected brain structures are within the same area, while gray indicates that the two connected brain structures are in different areas. The right shows the seven independent clusters based on functional network topology.

**Fig. 3**

Closed-loop pathways with significant differences in mean edge values between MRI-DRE and HC groups. The left shows the connected edges of stable closed-loop pathways with significant differences in causal brain network values between MRI-DRE and HC groups, while the right side shows stable closed-loop pathways with significant differences in temporal-lag brain network values between MRI-DRE and HC groups. Nodes of different colors are from different clusters (consistent with the seven clusters shown in Fig. 2).
Figure 4

Relationships between closed-loop pathway abnormalities and clinical indicators. (A-C) The horizontal axis in the graph represents the mean weight of all functional connected edges related to a given closed-loop pathway in the causal brain network. (D) The horizontal axis in the graph represents the mean weight of all functional connected edges related to a given closed-loop pathway in the temporal-lag brain network.