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ORIGINAL ARTICLE

Functional and structural networks decoupling in generalized tonic–clonic seizures and its reorganization by drugs

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Abstract

Objective: To investigate potential functional and structural large-scale network disturbances in untreated patients with generalized tonic–clonic seizures (GTCS) and the effects of antiseizure drugs.

Methods: In this study, 41 patients with GTCS, comprising 21 untreated patients and 20 patients who received antiseizure medications (ASMs), and 29 healthy controls were recruited to construct large-scale brain networks based on resting-state functional magnetic resonance imaging and diffusion tensor imaging. Structural and functional connectivity and network-level weighted correlation probability (NWCP) were further investigated to identify network features that corresponded to response to ASMs.

Results: Untreated patients showed more extensive enhancement of functional and structural connections than controls. Specifically, we observed abnormally enhanced connections between the default mode network (DMN) and the frontal–parietal network. In addition, treated patients showed similar functional connection strength to that of the control group. However, all patients exhibited similar

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structural network alterations. Moreover, the NWCP value was lower for connections within the DMN and between the DMN and other networks in the untreated patients; receiving ASMs could reverse this pattern.

Significance: Our study identified alterations in structural and functional connectivity in patients with GTCS. The influence of ASMs may be more noticeable within the functional network; moreover, abnormalities in both the functional and structural coupling state may be improved by ASM treatment. Therefore, the coupling state of structural and functional connectivity may be used as an indicator of the efficacy of ASMs.

KEYWORDS

antiseizure medications, connectivity, coupling degree, epilepsy, MRI

1 | INTRODUCTION

Epilepsy is one of the most common chronic neurologic disorders[1,2] and affects approximately 70 million people globally.[3] Generalized tonic–clonic seizures (GTCS) is a type of epilepsy and accounts for 20%–55% of all epilepsies.[4] GTCS is characterized by muscle contractions and sudden loss of consciousness,[5,6] with generalized spike–wave discharge.[7,8]

Moreover, in patients with GTCS, widespread abnormal functional activity has been detected throughout the brain,[9] and it has been suggested that both primary and high-order brain networks are involved.[10,11] Most GTCSs can be effectively controlled by antiseizure medications (ASMs). However, approximately 20%–30% of patients fail to achieve remission from GTCSs.[12] Therefore, understanding the pathophysiology of GTCSs and exploring the effects of ASMs on the brain is crucial to the development of more effective treatments for patients with GTCS. Recently, our understanding of GTCSs has deepened owing to the application of noninvasive neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), which explore different aspects,[13–15] such as functional connectivity and structural connectivity. However, several questions remain unsolved.

Accumulating evidence from multimodal brain studies has suggested that the topological organization of structural and functional brain networks is disrupted in patients with GTCS.[10,16,17] For example, studies have reported disruption of the functional reorganization of the default mode network (DMN)[17,18] and a relationship between abnormal structural network organization and the extent of hypoxia in brain regions serving vital functions.[19] In addition, one study found that the small-world topology of patients with GTCS showed weaker connectivity in the functional and structural networks.[20] The relationship between function and structure has also been a significant focus of studies on brain connectivity. A previous study demonstrated that function–structure coupling is altered in patients with generalized epilepsy.[20] Although numerous studies have explored various aspects of brain states in GTCS patients,[21–23] the pathomechanism of the disease remains elusive because most of these studies did not group according to medication status. Furthermore, the effect of medication status on functional and structural network organization and the coupling of these two networks have not yet been comprehensively analyzed.[16] It remains unclear how ASMs affect brain networks in patients with GTCS, which is a crucial element in investigations of the potential pathomechanism of GTCS and therapy targets.

Recently, network-level weighted correlation probability (NWCP) has been proposed to analyze neuroimage data at the network level.[24] Because of its potential

Key Points

- The functional connectivity, among DMN, FPN, limbic, and their connections with other networks, were enhanced in untreated patients, while the increase was relieved in drug-receiving patients.
- Both patient groups showed stable alterations of structural connection among DMN, FPN, and VN relative to healthy controls.
- The structural and functional coupling degree was decreased within DMN and between DMN with other networks, and drug-receiving could reverse the decrease.

for achieving multimodal data fusion, we modified and adapted this method in this study. To investigate disturbances in the multimodal characteristics of brain networks in patients with GTCS and to uncover the potential treatment effects of ASMs on the brain, we acquired resting-state fMRI and DTI data from drug-naive and ASM-treated patients with GTCS and constructed functional and structural brain networks. The coupling state between the functional and structural networks was further evaluated using the NWCP method. This is the first study to use the NWCP method to integrate structural and functional networks in patients with epilepsy.

2 | MATERIALS AND METHODS

2.1 | Subjects

In this study, patients were recruited from the department of the West China Hospital from 2016 to 2021, and diagnosed with GTCS based on the clinical and seizures semiology information consistent with the International League Against Epilepsy guidelines[25] by neurologists (LY). We selected 21 patients with GTCS from the database as the untreated patients (−) group, who were newly diagnosed and had not yet received medication. And the other patients with GTCS received ASMs (Levetiracetam). A sample of 29 healthy subjects was also included in this study as age and gender-matched control group (HC group). There were no differences between groups in age or gender. The demographic information of these patients was detailed in Table 1. The inclusion criteria included: (a) without other neurologic psychological disorders; (b) no developmental disabilities; (c) normal routine brain MRI scans; (d) Patients who were treated with levetiracetam alone; and (e) the head motion criterion of 3 mm and 3°. This study was approved by the ethical committee of the University of Electronic Science and Technology of China. Written informed consent was obtained from each subject.

2.2 | Data acquisition

All subjects underwent MRI scanning in the 3-Tesla MRI scanner (GE DISCOVERY MR750). High-resolution T1-weighted images were obtained using a three-dimensional fast spoiled gradient-echo sequence. The scanning parameters included: repetition time (TR) = 6.008 ms; echo time (TE) = 1.984 ms; flip angle = 90°; field of view (FOV) = 25.6 × 25.6 cm^2; matrix size = 256 × 256; and slice thickness = 1 mm (no gap). Resting-state functional data were obtained using a gradient-echo echo-planar imaging sequence. The main scanning parameters were as follows: TR = 2000 ms; TE = 30 ms; flip angle = 90°; FOV = 24 × 24 cm^2; matrix size = 64 × 64; slice thickness = 4 mm (no gap); slice number = 35; and scanning time lasting 510 s (255 volumes). During scanning, subjects were required to close eyes without falling asleep. DTI data were acquired using the spin echo pulse sequence: 76 slices, TR = 8500 ms, TE = 70 ms, voxel size = 2 * 2 * 2 mm, b-value = 1000 s/mm^2; FOV = 256 * 256 mm, three b0 images with 64 non-colinear diffusion directions per shell. The acquisition time was 10 min.

2.3 | Data preprocessing

Preprocessing of the fMRI dataset was performed using the NIT software package[26] and SPM12 toolbox (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). The fMRI data preprocessing included the following steps: (a) discarding the first five volumes, (b) slice-timing correction, (c) realignment, (d) normalized to the Montreal Neurological Institute space by using the EPI template, (e) linear detrending, and (f) regressing out the nuisance signals (including 24-parameter motion correction, white matter signals, and the mean cerebrospinal fluid signals).

Image preprocessing steps of all DTI images were performed using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki),

TABLE 1 Demographic information of all subjects.

	Untreated patients	Treated patients	Healthy controls	*P* value
Gender (male/female)	21 (12/9)	20 (6/14)	29 (13/16)	0.216[a]
Age (years)	26.5 ± 14.2	24.7 ± 10.5	25.3 ± 8.9	0.868[b]
Age at onset (years)	22.7 ± 15.9	20 ± 11.5	–	0.544[c]
Handedness (right/left)	21/0	20/0	29/0	NaN[a]
Duration (years)	3.8 ± 6.2	4.7 ± 4.7	–	0.628[c]

[a] Chi-square test.

[b] One-way analysis of variance.

[c] Two-sample *t* test.

including brain extraction, motion, and eddy current corrections. Then, the fractional anisotropy (FA) of each voxel was computed. Higher values of FA indicate more directionally restricted diffusion of water molecules, and lower levels of FA are commonly represented WM damage. The affine transformation was used to co-register FA images in native space to the T1-weighted image of FSL. And structural images were nonlinearly registered to the FMRIB58_FA template. Then, an inverse warping transformation from the standard space to the native dMRI space can be obtained.

2.4 | Network analysis

2.4.1 | Functional network

For each subject, the whole brain (excluding the cerebellum) was segmented into 90 regions according to the automated anatomical labeling (AAL) template.[27] Regional time series were calculated by averaging all voxel time series within given region. Pearson's correlation coefficient and the Fisher-z transformation were used to describe the functional relationship between each pair of regions. Functional connectivity defines statistical dependencies which exhibits the strength of the functional connection between two regions in a given state.[28] All the FC values were retained in the later coupling analysis.

2.4.2 | Structural network

The AAL template was registered to individual native space using the inverse transformation obtained above and divided the whole brain (excluding the cerebellum) into 90 regions. The white matter (WM) pathways were reconstructed using the deterministic streamline tracking algorithm.[29] The mean of the fractional anisotropy (FA) values was computed to assess the relationship between different regions, and we obtained a 90*90 symmetrical SC matrix for each subject. Because the deterministic streamline tracking algorithm can introduce false connections, we further processed the structural connection matrix. To identify highly consistent structural connections across different groups, a nonparametric one-tailed sign test was performed for the three groups separately, and the union of the results of each group was used to describe the consistency.[30] The union mask was used as a threshold rule for the structural connectivity matrices and to generate sparse connectivity matrices for subsequent analyses.

2.4.3 | Coupling analysis of the functional and structural networks

The coupling between the functional and structural networks was measured using the modified NWCP method. This method determines the degree of collaborative change among brain networks, where a high NWCP value indicates high consistency between networks.

First, based on a previous literature,[31] brain regions were divided into eight functional networks (visual network, VN; limbic network, Limbic; sensorimotor network, SMN; DMN; dorsal network, DAN; frontoparietal network, FPN; ventral attention network, VAN; and subcortical network, SCN). The modified NWCP was individually defined by using formula[24]:

$$NWCP_{i,j} = \frac{\sum_{\substack{m \in N_i \\ n \in N_j}} |C|_{sig_{m,n}}}{\sum_{\substack{m \in N_i \\ n \in N_j}} |C|_{m,n}}$$

where N_i, N_j represents the ith or jth network ($i, j \leq 8$). To calculate parameter C, the functional and structural connection vectors were constructed. The functional connection values between two nodes of all subjects were extracted to form a functional connection vector. The same process was followed to obtain the structural connection vector. The Csig is the Pearson coefficient that is significant ($P < 0.05$). All $C_{m,n}$ values are absolute values before NWCP calculating here. If $i = j$, the NWCP value measures the within-network coupling relationship, otherwise, it measures the between-network coupling relationship. A higher NWCP value indicates a stronger association between FC and SC between networks.

2.5 | Statistical analysis

For the comparisons of functional and structural connections, a one-way analysis of variance ($P < 0.001$) and post hoc analyses (Student's t test, $P < 0.01$) were used to detect between-group differences in the strengths of FC and SC. The results were visualized using the BrainNet toolbox[32] and the Circos toolkit.[33]

The statistics of the coupling relationship between functional and structural networks were calculated using nonparametric permutation tests (10 000 iterations). Specifically, the data of the two groups were shuffled for FC and SC separately, the shuffled set was then

reclassified into two groups, and the NWCP was recalculated. Significance was set at $P < 0.05$.

3 | RESULTS

3.1 | Functional network comparisons

Compared with the healthy control (HC) group, untreated patients showed a pattern of more enhanced FC, predominantly in the connections involving the right triangular inferior frontal gyrus and the right middle temporal gyrus (Figure 1). However, the functional connection strength of treated patients did not significantly differ from that of the HC group. For the complex interactions between brain regions, we found that the right triangular inferior frontal gyrus acted as a key region. In addition, the functional connections of treated patients were generally lower than those of untreated patients and included the right middle temporal and right medial superior frontal gyri.

At the network level, the connectivity of the DMN regions of interest (ROIs) to the FPN and VN ROIs was significantly stronger in the untreated patients than in the HC group (Figure 1). Moreover, higher connectivity between the FPN ROIs and VN ROIs was also observed in the untreated patients relative to the HC group. In contrast, the connections between the SCN ROIs and the limbic ROIs showed the weaker connectivity in untreated patients. Compared with the HC group, treated patients showed higher FC between the DMN ROIs and FPN ROIs and decreased FC between the SMN ROIs and Limbic ROIs.

Compared with untreated patients, treated patients exhibited significantly lower FC between ROIs belonging to different networks, primarily within the DMN, FPN, and VN. Furthermore, higher FC between the SCN ROIs and the limbic ROIs was observed.

3.2 | Structural network comparisons

Compared with the HC group, the untreated and treated patients showed higher SC in the left medial occipital gyri. There was also a significant difference between the untreated and treated patients in the SC between the right medial cingulum and putamen.

We observed similar differences between the untreated and treated patients and the HC group (Figure 2): higher SC between the VN and FPN and between the DMN and FPN and lower SC between the VAN and DMN. Moreover, connections between the VAN ROIs and the SCN ROIs were lower, and those between the SMN ROIs and the limbic ROIs were higher, in untreated patients than in the HCs.

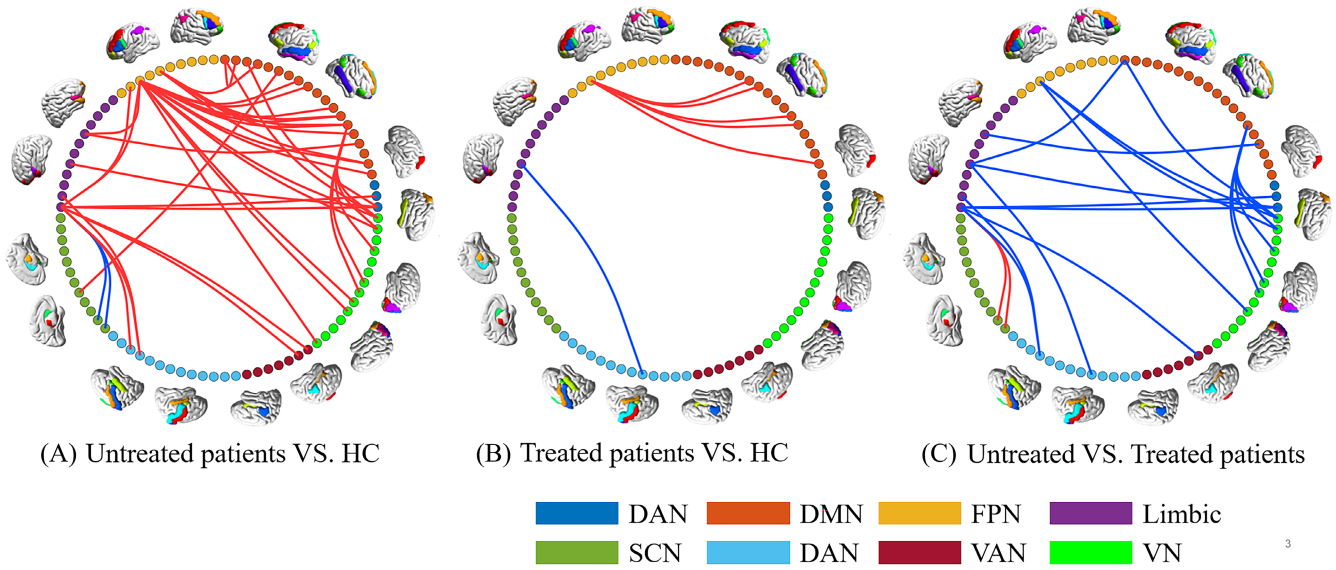

FIGURE 1 Regions with significant differences in ROI-wise functional connectivity. (A) shows alterations between regions in untreated patients compared with the HC group; (B) shows interesting alterations in functional networks in treated patients compared with the HC group, and we can observe the differences between untreated patients and treated patients in the (C). The red line implies the enhanced connection, and the blue line is the weak connection. DAN, dorsal network; DMN, default mode network; FPN, frontoparietal network; HC, healthy controls; Limbic, limbic network; SCN, subcortical network; SMN, sensorimotor network; VAN, ventral attention network; VN, visual network.

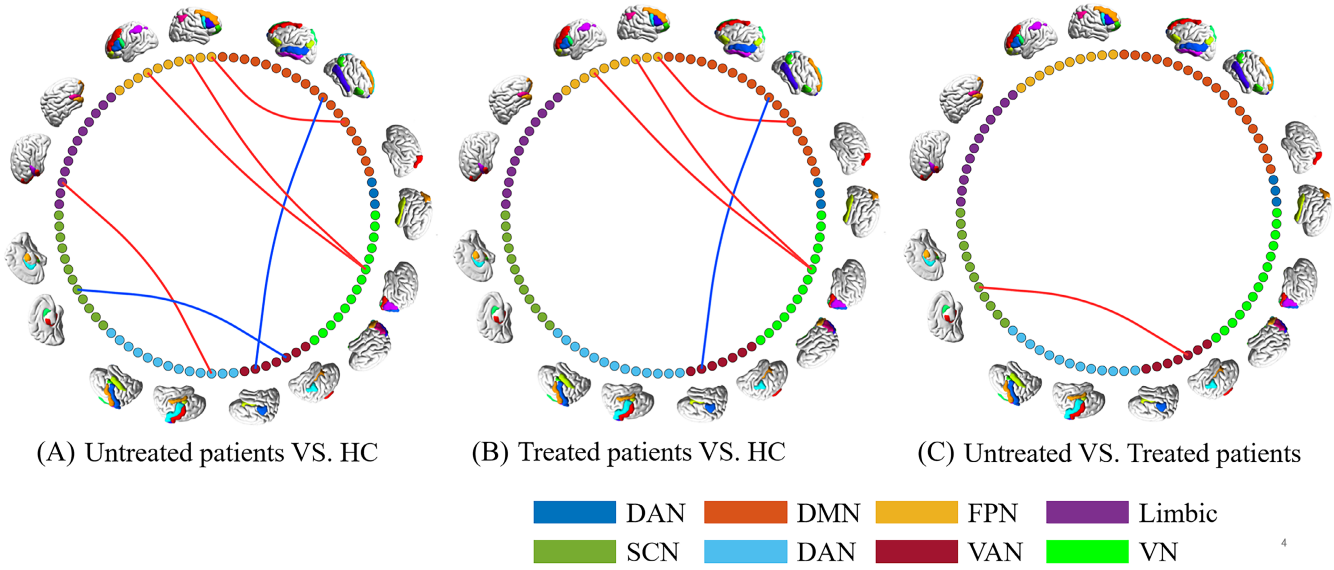

FIGURE 2 Regions with significant differences in ROI-wise structural connectivity. The red line implies the enhanced connection, and the blue line is the weak connection. DAN, dorsal network; DMN, default mode network; FPN, frontoparietal network; HC, healthy controls; Limbic, Limbic network; SCN, subcortical network; SMN, sensorimotor network; VAN, ventral attention network; VN, visual network.

3.3 | Coupling analysis of functional and structural networks

Figure 3 illustrates the difference in coupling between FC and SC. Compared with the HC group, untreated patients showed a lower degree of coupling within the DMN and between the DMN and VAN. However, all patients showed a lower degree of coupling between the limbic network and the SMN. Compared with untreated patients, treated patients showed a lower degree of coupling between the DMN and limbic network and a higher degree of coupling within the DMN.

4 | DISCUSSION

ASM is a common treatment option for patients with epilepsy to achieve seizure remission. Distinct brain regions are likely affected by ASMs; therefore, network analysis is a suitable method to investigate the effect of ASMs. This study based on noninvasive brain imaging and brain network analysis characterized alterations in FC and SC and their degree of coupling in both treated and untreated patients. We found that (a) both patient groups showed a consistently higher structural connection strength between the ROIs of the DMN, FPN, and VN relative to HCs; (b) untreated patients showed a significantly higher FC than HCs within regions involving the DMN, FPN, limbic network, and VN, although only the connection between the DMN ROIs and FPN ROIs was higher in treated patients; (c) the degree of structural and functional coupling was lower within the DMN, between the DMN and VAN, and between the limbic network and SMN in untreated patients than in the HC group, although treated patients showed a lower degree of coupling in only one connection between the limbic network and SMN. Overall, the present findings suggest that ASMs are more effective in improving functional abnormalities than structural connections. Consistent SC abnormalities across all patients indicated that structural abnormality may be a fundamental phenomenon of epilepsy. Furthermore, ASMs may reverse the alterations in the degree of structural and functional coupling in epilepsy.

In line with a previous study,[34,35] we observed higher connectivity between the DMN and other functional networks and within the DMN in patients than in HCs. The DMN is thought to be associated with the generation of epileptic discharges,[36] and the widespread enhancement of connections in patients may be a byproduct of the rapid transmission of electrical signals through the brain during a discharge.[37,38] When we compared the treated patients with the HC group, we showed higher functional and structural connections between the DMN and FPN in the patients. However, the differences that we observed between the untreated patients and the HC group were not apparent in the comparison between the treated patients and the HC group. This finding suggests that the DMN and FPN are more impacted by the disease than other brain regions. These connections that were unaffected by treatment may represent a fundamental pathological brain state in patients with GTCS. Therefore, we speculate that ASMs can improve brain states and have a greater positive impact on functional networks than on structural

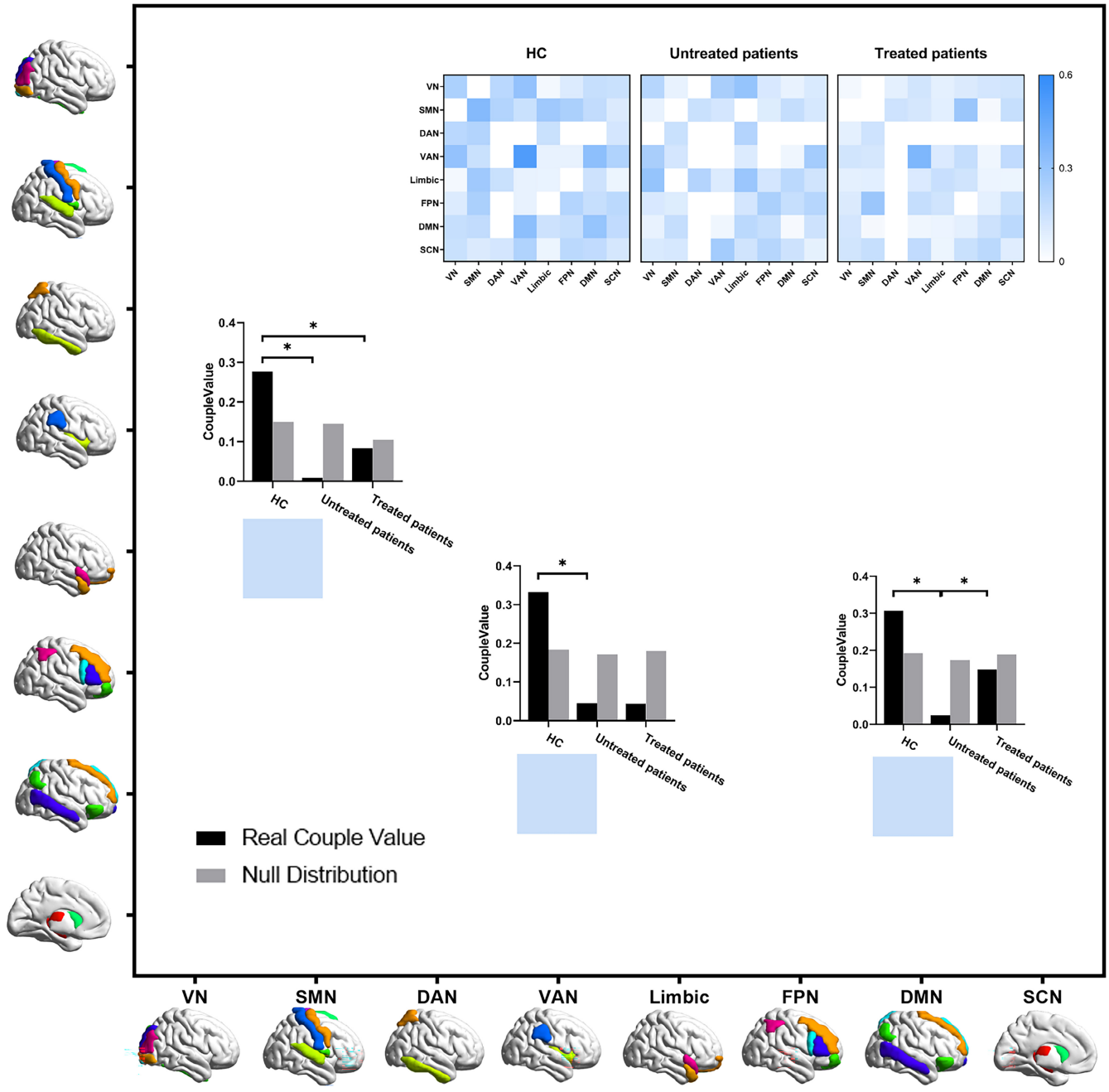

FIGURE 3 Abnormal changes of coupling of functional and structural networks. Black columns represent true coupling values. The gray columns represent the mean of the null distribution. The blue squares represent significant differences between groups. The color in the upper right diagram represents the strength of the coupling. *$P < 0.05$. DAN, dorsal network; DMN, default mode network; FPN, frontoparietal network; HC, healthy controls; Limbic, limbic network; SCN, subcortical network; SMN, sensorimotor network; VAN, ventral attention network; VN, visual network.

networks to alleviate the disease. This may be one reason why effectively treating epilepsy is difficult.

The FPN is a higher order brain network that is responsible for executing cognitive control functions, such as working memory and attention selection.[39,40] The enhanced connection between the FPN ROIs and ROIs of other networks, such as the VN and limbic network, in patients with epilepsy may reflect intrinsic information overintegration. A common phenomenon of epilepsy that may be related to this alteration is the loss of patients' sense of environment and self-control during seizures.[2,41,42] We also found abnormally enhanced connections within the primary networks, predominantly in the limbic network, SMN, and VN.[43,44] The SMN and VN are key components of the primary-sensory perceptual cortices.[45] It has been shown that the coordination

of visual and motor activities is associated with the synchrony of certain neural rhythms.[46,47] In patients with epilepsy, the abnormal discharge characteristics may result in abnormal neural rhythms, and this may manifest as abnormally enhanced connections within the primary network, as we observed in this study.[48] A previous study revealed structural connectivity abnormalities within the SMN and occipital lobe in individuals with photosensitive characteristic in the idiopathic generalized epilepsies.[49] Photosensitive epilepsy is commonly seen in patients with idiopathic generalized epilepsies, ranging from 30% to 90%,[50] and various studies have reported evidence for both occipital and more widespread cortical hyperexcitability in those with photosensitive epilepsy.[50,51] In line with this, we found that the structural connections between the occipital lobe in the VN and the FPN region were significantly stronger, and the connections between the FPN and DMN were stronger in patients than in HCs. These findings further suggest that abnormal connections between the occipital lobe and the DMN and FPN are a physiological mechanism of photosensitivity in those with idiopathic generalized epilepsies. However, we did not specifically collect data on photosensitivity characteristics; therefore, further research is needed to explore the physiological mechanism underlying photosensitivity.

The synergy between functional and structural networks is crucial in the maintenance of physiological activities. Multimodal fusion provides an effective instrument for integrating the advantages of various neuroimaging methods to explore the relationship between brain networks.[24,52] We observed that functional and structural coupling was only lower in connections between the limbic network and SMN in GTCS patients than in HCs, in addition to connections within the DMN and between the DMN and VAN, which reflects the discordance between functional and structural networks in untreated patients. The limbic network and SMN are also important for generalized epilepsy. For example, the limbic network is thought to be involved in generalized discharge generation,[53–55] and the SMN is considered to be related to the motor symptoms of GTCS.[56] This would explain the structural and functional decoupling between the limbic network and the SMN we observed. Interestingly, patients taking ASMs also showed a lower degree of coupling of this connection, which supports the importance of this connection in epilepsy. In addition, coupling within the DMN was significantly higher in patients taking ASMs than in those not taking ASMs. Therefore, we speculate that ASM improves brain function by restoring the structural and functional coupling relationship.

ASMs may influence brain activity in epileptogenic regions,[57] as shown by fMRI activation pattern changes[58,59] and structural remodeling.[60] This study yielded similar findings in functional networks, such as alterations in functional connections involving the DMN and FPN, although structural connections appeared to be less affected by ASMs than functional connections. These findings further suggest that functional networks are more sensitive to ASMs, whereas structural network changes are latent and subtle. By exploring the coupling status of functional and structural networks, we found that the interaction between functional and structural networks was affected by ASMs. The coupling status of multiple networks was disrupted in untreated patients, with DMN as the core, whereas in patients taking medication, the coupling status was improved. Because ASMs can affect cortical activity,[57] structure–function coupling likely shows that alterations in functional connections reflect underlying changes in structural connections. These results complement existing neuroimaging findings. Furthermore, our study provides an effective research method for exploring changes in functional and structural networks, which can be applied to analyses of other drugs or disease subtypes.

Our study has several limitations. First, because our study was a cross-sectional study, we are lacking a pre–post medication treatment comparison within the patient group. Although we included both treated and untreated patients, a longitudinal study is necessary to account for individual differences. Additionally, differences in cognitive abilities between groups were not evaluated; thus, the effects of treatment on cognition are unclear. We also require a larger sample size to improve the stability of our results. Finally, the modified NWCP method was used to combine different modes of data to explore brain network alterations. Although this does not pose any mathematical problem, the relevance of this method to physiological significance requires further research.

5 | CONCLUSION

Broadly enhanced brain connectivity may indicate that the communication between different brain regions is more active in patients with GTCS. This phenomenon suggests that highly synchronized brain networks are the foundation for how epileptic activity spreads throughout the brain. Moreover, the coupling of structural and functional networks was affected by epileptic action, and thus, structural and functional decoupling may play a crucial role in generalized epilepsy. Although the effect of ASMs may be more obvious in functional networks, the abnormal coupling of the functional and structural networks may be improved by ASM treatment. Therefore, the degree of coupling between the structural and functional networks may serve as an indicator to evaluate the efficacy of ASMs. However, further study is needed to better understand the effects of ASMs.

AUTHOR CONTRIBUTIONS

Cheng Luo and Liang Yu designed the study and supervised the project; Shuai Ma and Liang Yu managed the experiments and data collection; Haonian Pei, Zetao Liu, Yuehao Wang, Zhihuan Yang, Qifu Li, and Sisi Jiang undertook the data analysis; Haonan Pei, Shuai Mai, Sisi Jiang, and Cheng Luo wrote and revised the article. All authors reviewed the article and approved the final article.

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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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CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or nonfinancial interests to disclose.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Ethics Committee of the Clinical Hospital of Chengdu Brain Science Institute approved this study.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

CONSENT TO PUBLISH

This work does not include materials from participants that require consent to publish.

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REFERENCES

1. Avanzini G, Manganotti P, Meletti S, Moshé SL, Panzica F, Wolf P, et al. The system epilepsies: a pathophysiological hypothesis. Epilepsia. 2012;53(5):771–778.
2. Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia. 2011;52:2–26.
3. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet. 2019;393(10172):689–701.
4. Gastaut H, Gastaut JL, Gonçalves e Silva GE, Fernandez Sanchez GR. Relative frequency of different types of epilepsy: a study employing the classification of the international league against epilepsy. Epilepsia. 1975;16(3):457–461.
5. Jallon P, Latour P. Epidemiology of idiopathic generalized epilepsies. Epilepsia. 2005;46:10–14.
6. Marini C, King MA, Archer JS, Newton MR, Berkovic SF. Idiopathic generalised epilepsy of adult onset: clinical syndromes and genetics. J Neurol Neurosurg Psychiatry. 2003;74(2):192–196.
7. Broutian A, Dolgova S, Belyakova-Bodina A, Abramova A, Lukianova A, Noskova T. Bitemporal independent 3-Hz spike-and-waves in adult patient with idiopathic generalized epilepsy and graves disease. Clin Neurophysiol Pract. 2020;5:206–208.
8. Li Y, Chen Q, Huang W. Disrupted topological properties of functional networks in epileptic children with generalized tonic-clonic seizures. Brain Behav. 2020;10:e01890.
9. Assenza G, Lanzone J, Dubbioso R, Coppola A, Boscarino M, Ricci L, et al. Thalamic and cortical hyperexcitability in juvenile myoclonic epilepsy. Clin Neurophysiol. 2020;131(8):2041–2046.
10. Jia X, Xie Y, Dong D, Pei H, Jiang S, Ma S, et al. Reconfiguration of dynamic large-scale brain network functional connectivity in generalized tonic-clonic seizures. Hum Brain Mapp. 2020;41(1):67–79.
11. Laufs H. Functional imaging of seizures and epilepsy: evolution from zones to networks. Curr Opin Neurol. 2012;25(2):194–200.
12. Zu M, Fu L, Hu M, Cao X, Wang L, Zhang J, et al. Amplitude of low-frequency fluctuation with different clinical outcomes in patients with generalized tonic-Clonic seizures. Front Psych. 2022;13:847366.
13. Galovic M, van Dooren VQH, Postma TS, Vos SB, Caciagli L, Borzì G, et al. Progressive cortical thinning in patients with focal epilepsy. JAMA Neurol. 2019;76(10):1230–1239.
14. Wandschneider B, Burdett J, Townsend L, Hill A, Thompson PJ, Duncan JS, et al. Effect of topiramate and zonisamide on fMRI cognitive networks. Neurology. 2017;88(12):1165–1171.
15. Yao D, Qin Y, Zhang Y. From psychosomatic medicine, brain–computer interface to brain–apparatus communication. Brain-Apparatus Commun. 2022;1(1):66–88.
16. Wang Z, Larivière S, Xu Q, Vos de Wael R, Hong SJ, Wang Z, et al. Community-informed connectomics of the thalamocortical system in generalized epilepsy. Neurology. 2019;93(11):e1112–e1122.
17. Zhang Y, Huang G, Liu M, Li M, Wang Z, Wang R, et al. Functional and structural connective disturbance of the primary and default network in patients with generalized tonic-clonic seizures. Epilepsy Res. 2021;174:106595.
18. Wang ZG, Lu GM, Zhang ZQ, Zhong YA, Jiao Q, Zhang ZJ, et al. Altered resting state networks in epileptic patients with generalized tonic-clonic seizures. Brain Res. 2011;1374:134–141.

19. Allen LA, Harper RM, Vos SB, Scott CA, Lacuey N, Vilella L, et al. Peri-ictal hypoxia is related to extent of regional brain volume loss accompanying generalized tonic-clonic seizures. Epilepsia. 2020;61(8):1570–1580.
20. Zhang ZQ, Liao W, Chen HF, Mantini D, Ding JR, Xu Q, et al. Altered functional-structural coupling of large-scale brain networks in idiopathic generalized epilepsy. Brain. 2011;134:2912–2928.
21. Wang Z, Wang X, Rong R, Xu Y, Zhang B, Wang Z. Impaired hippocampal functional connectivity in patients with drug resistant, generalized tonic-clonic seizures. Neuroreport. 2019;30(10):700–706.
22. Ji G-J, Zhang Z, Xu Q, Zang Y-F, Liao W, Lu G. Generalized tonic-clonic seizures: aberrant interhemispheric functional and anatomical connectivity. Radiology. 2014;271(3):839–847.
23. Quan L, Liu X, Cui R, Li X, Liu C, Yang R, et al. Interaction effects of action real-time strategy game experience and trait anxiety on brain functions measured via EEG rhythm. Brain-Apparatus Commun. 2023;2:1–14.
24. Jiang S, Li H, Pei H, Liu L, Li Z, Chen Y, et al. Connective profiles and antagonism between dynamic and static connectivity underlying generalized epilepsy. Brain Struct Funct. 2021;226:1423–1435.
25. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–530.
26. Dong L, Luo C, Liu X, Jiang S, Li F, Feng H, et al. Neuroscience information toolbox: an open source toolbox for EEG-fMRI multimodal fusion analysis. Front Neuroinform. 2018;12:56.
27. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage. 2002;15(1):273–289.
28. Esposito R, Bortoletto M, Miniussi C. Integrating TMS, EEG, and MRI as an approach for studying brain connectivity. Neuroscientist. 2020;16:471–486.
29. Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol. 1999;45(2):265–269.
30. Yan T, Wang W, Yang L, Chen K, Chen R, Han Y. Rich club disturbances of the human connectome from subjective cognitive decline to Alzheimer's disease. Theranostics. 2018;8(12):3237–3255.
31. Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011;106(3):1125–1165.
32. Xia MR, Wang JH, He Y. BrainNet viewer: a network visualization tool for human brain connectomics. PLoS One. 2013;8(7):15.
33. Krzywinski M, Schein J, Birol I, Connors J, Gascoyne R, Horsman D, et al. Circos: an information aesthetic for comparative genomics. Genome Res. 2009;19(9):1639–1645.
34. Zanao TA, Lopes TM, de Campos BM, Yasuda CL, Cendes F. Patterns of default mode network in temporal lobe epilepsy with and without hippocampal sclerosis. Epilepsy Behav. 2019;121:106523.
35. Parsons N, Bowden SC, Vogrin S, D'Souza WJ. Default mode network dysfunction in idiopathic generalised epilepsy. Epilepsy Res. 2020;159:8.
36. Jiang S, Li H, Liu L, Yao D, Luo C. Voxel-wise functional connectivity of the default mode network in epilepsies: a systematic review and meta-analysis. Curr Neuropharmacol. 2021;20:254–266.
37. Wei HL, An J, Zeng LL, Shen H, Qiu SJ, Hu DW. Altered functional connectivity among default, attention, and control networks in idiopathic generalized epilepsy. Epilepsy Behav. 2015;46:118–125.
38. Dixon ML, de la Vega A, Mills C, Andrews-Hanna J, Spreng RN, Cole MW, et al. Heterogeneity within the frontoparietal control network and its relationship to the default and dorsal attention networks. Proc Natl Acad Sci U S A. 2018;115(7):E1598–E1607.
39. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity (vol 100, pg 3328, 2008). J Neurophysiol. 2011;105(3):1427.
40. Corbetta M. Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems? Proc Natl Acad Sci U S A. 1998;95(3):831–838.
41. Delfino-Pereira P, Bertti-Dutra P, Del Vecchio F, de Oliveira JAC, Medeiros DDC, Cestari DM, et al. Behavioral and EEGraphic characterization of the anticonvulsant effects of the predator odor (TMT) in the amygdala rapid kindling, a model of temporal lobe epilepsy. Front Neurol. 2020;11:586724.
42. Hayes DJ, Northoff G. Identifying a network of brain regions involved in aversion-related processing: a cross-species translational investigation. Front Integr Neurosci. 2011;5:49.
43. Krzeminski D, Masuda N, Hamandi K, Singh KD, Routley B, Zhang J. Energy landscape of resting magnetoencephalography reveals fronto-parietal network impairments in epilepsy. Netw Neurosci. 2020;4(2):374–396.
44. Weng Y, Larivière S, Caciagli L, Vos de Wael R, Rodríguez-Cruces R, Royer J, et al. Macroscale and microcircuit dissociation of focal and generalized human epilepsies. Commun Biol. 2020;3(1):244.
45. Roland JL, Griffin N, Hacker CD, Vellimana AK, Akbari SH, Shimony JS, et al. Resting-state functional magnetic resonance imaging for surgical planning in pediatric patients: a preliminary experience. J Neurosurg Pediatr. 2017;20(6):583–590.
46. Muthukumaraswamy SD, Johnson BW, Gaetz WC, Cheyne DO. Modulation of neuromagnetic oscillatory activity during the observation of oro-facial movements. Neurol Clin Neurophysiol. 2004;2004:2.
47. Avanzini P, Fabbri-Destro M, Dalla Volta R, Daprati E, Rizzolatti G, Cantalupo G. The dynamics of sensorimotor cortical oscillations during the observation of hand movements: An EEG study. PLoS One. 2012;7(5):e37534.
48. Hebb DO. The organization of behavior: a neuropsychological theory. NY: Wiley; 1949.
49. Groppa S, Moeller F, Siebner H, Wolff S, Riedel C, Deuschl G, et al. White matter microstructural changes of thalamocortical networks in photosensitivity and idiopathic generalized epilepsy. Epilepsia. 2012;53(4):668–676.

50. Lopes MA, Bhatia S, Brimble G, Zhang J, Hamandi K. A computational biomarker of photosensitive epilepsy from interictal EEG. eNeuro. 2022;9(3):ENEURO.0486-21.2022.
51. Padmanaban V, Inati S, Ksendzovsky A, Zaghloul K. Clinical advances in photosensitive epilepsy. Brain Res. 2019;1703:18–25.
52. Qin Y, Zhang N, Chen Y, Tan Y, Dong L, Xu P, et al. How alpha rhythm spatiotemporally acts upon the thalamus-default mode circuit in idiopathic generalized epilepsy. IEEE Trans Biomed Eng. 2021;68(4):1282–1292.
53. Moguilner S, García AM, Mikulan E, del Carmen GM, Vaucheret E, Amarillo Y, et al. An unaware agenda: interictal consciousness impairments in epileptic patients. Neurosci Conscious. 2017;3(1):niw024.
54. Badawy RA, Lai A, Vogrin SJ, Cook MJ. Subcortical epilepsy? Neurology. 2013;80(20):1901–1907.
55. Badawy RA, Jackson GD, Berkovic SF, Macdonell RA. Cortical excitability and refractory epilepsy: a three-year longitudinal transcranial magnetic stimulation study. Int J Neural Syst. 2013;23(1):1250030.
56. Jiang S, Li X, Li Z, Chang X, Chen Y, Huang Y, et al. Cerebellocerebral connectivity in idiopathic generalized epilepsy. Eur Radiol. 2020;30(7):3924–3933.
57. Xu Q, Hu Z, Yang F, Bernhardt BC, Zhang Q, Stufflebeaskm SM, et al. Resting state signal latency assesses the propagation of intrinsic activations and estimates anti-epileptic effect of levetiracetam in Rolandic epilepsy. Brain Res Bull. 2020;162:125–131.
58. Wandschneider B, Stretton J, Sidhu M, Centeno M, Kozák LR, Symms M, et al. Levetiracetam reduces abnormal network activations in temporal lobe epilepsy. Neurology. 2014;83(17):1508–1512.
59. Bakker A, Albert MS, Krauss G, Speck CL, Gallagher M. Response of the medial temporal lobe network in amnestic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance. NeuroImage Clin. 2015;7:688–698.
60. Tang Y, Yu X, Zhang X, Xia W, Wu X, Zou X, et al. Single-dose intravenous administration of antiepileptic drugs induces rapid and reversible remodeling in the brain: evidence from a voxel-based morphometry evaluation of valproate and levetiracetam in rhesus monkeys. Neuroscience. 2015;303:595–603.

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