

# Functional and Structural Networks Decoupling in GTCS and Its Reorganization by Drugs

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## Research Article

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# Abstract

## Objective:

The present study aims to investigate the potential disturbance of functional and structural large-scale networks in drug-naive patients with generalized tonic-clonic seizures (GTCS) and the effects of drugs-receiving.

## Methods:

In this study, 41 patients with GTCS, including 21 drug-naive patients and 20 patients with antiepileptic drugs (AEDs), and 29 healthy controls were recruited to construct large-scale brain networks based on the resting-state functional magnetic resonance imaging (fMRI) and diffusion tensor image (DTI). The structural and functional connectivity and the coupling between structure and function were further investigated to identify the network features that responded to drugs.

## Results:

Drug-naive patients showed extensively enhanced functional and structural connections compared with controls. Especially, abnormally enhanced connections between the default mode network (DMN) and the frontal parietal network (FPN) were observed. Besides, drug-receiving patients showed similar functional connection strength to that of the control group. However, drug-receiving and drug-naive patients demonstrated similar alterations in the structural network. Moreover, the structural and functional coupling was decreased in connections within DMN and DMN with other networks, and drug-receiving could reverse the decrease.

## Significance:

These findings identified the pattern alteration of structural and functional connectivity in GTCS patients. AEDs treatment benefit for the seizures might originate from the effects of the functional network rather than the structural network. However, it can improve the abnormal brain network by affecting the coupling relationship. The coupling of structural and functional connectivity might be used to evaluate the efficacy of AEDs.

## Key Points

1, The connectivity among DMN, FPN, Limbic, and their connections with other networks were enhanced in drug-naive patients, while the increase was remised with drug-receiving.

2, Both patient groups showed stable alterations of structural connection among DMN, FPN, and VN relative to healthy controls.

3, The structural and functional coupling was decreased in connections within DMN and DMN with other networks, and drug-receiving could reverse the decrease.

## Introduction

Epilepsy is one of the most common and chronic neurological disorders (G. Avanzini et al., 2012; Thurman et al., 2011) and about 65 million people were affected in the world (Thurman et al., 2011). Generalized tonic-clonic seizures (GTCS) is a type of epilepsy characterized by muscle contractions, sudden loss of consciousness (Jallon & Latour, 2005; Marini, King, Archer, Newton, & Berkovic, 2003), with generalized spike-wave discharge (GSWD) (Broutian et al., 2020; Li, Chen, & Huang, 2020). Until now, antiepileptic drugs (AEDs) are common treatments for epilepsy. However, it is not clear how the AEDs affect brain networks of patients with epilepsy, which is a greatly important issue for investigating potential pathomechanism and therapy targets.

The human brain is a complex network constituted based on functional and structural connectivity among brain regions. Recently, neuroimaging tools are rapidly evolving and have been used to examine the underlying neural mechanisms of epilepsy (Galovic et al., 2019; Wandschneider et al., 2017). Resting-state functional magnetic resonance imaging (rs-fMRI) demonstrated synchronous low-frequency fluctuations of blood oxygenation level-dependent (BOLD) signals of brain regions, which were thought to reflect synchronous neural activities (Biswal, Yetkin, Haughton, & Hyde, 1995). Specifically, accumulated studies found that the entire brain was affected through the thalamocortical and corticocortical connectivity (Aghakhani et al., 2004; Blumenfeld et al., 2003; Gotman et al., 2005). Functional connectivity (FC) is the statistical correlation between different brain regions in terms of information processing and structural connectivity (SC) (Esposito, Bortoletto, & Miniussi, 2020). Diffusion tensor image (DTI) is often used to construct the SC based on the white matter traction, and to investigate the mechanism in healthy brain and/or disorders (Gong et al., 2019; Jiang et al., 2020; Xue et al., 2014). In addition, the relationship between function and structure attracted a lot of attention in the studies of brain connectivity. SC shapes different connection patterns of FC and the FC reflects the SC architecture (Z. J. Wang, Dai, Gong, Zhou, & He, 2015). The previous study has demonstrated that the function-structure coupling was altered in patients with generalized epilepsy (Zhang et al., 2011). Patients with GTCS showed disrupted functional reorganization of the default mode network (DMN) and the dorsal attention network (DAN) (Z. G. Wang et al., 2011). In addition, abnormal structural network organization has also been observed in GTCS, which was related to the extent of hypoxia in brain sites serving vital functions (Allen et al., 2020). Zhang et al., further proved that the small-world topology showed a downward trend in functional and structural networks in patients with GTCS (Zhang et al., 2011). In all, studying multidimensional profiles of the epileptic network could greatly contribute to understanding the pathomechanism of disease.

Recently, the network-level weighted correlation probability (NWCP) was proposed to achieve the multimodal fusion of neuroimages on the network level in our previous study (Sisi Jiang et al., 2021). Here, NWCP was firstly used to integrate structural and functional networks in patients with epilepsy. To

investigate the disturbance of multimodal characteristics of brain networks in GTCS and to uncover the potential treatment effects of AEDs on the brain, resting-state fMRI and diffusion tensor imaging data of drug-naïve and drug-receiving patients with GTCS were collected to construct functional and structural networks in this study. The connectivity strength was next investigated and compared between groups. Finally, the coupling between functional and structural networks was further evaluated using NWCP.

## Method

### 1. Subjects

In this study, patients were recruited from the department of the West China Hospital (from June 2015 to June 2019), and diagnosed with GTCS based on the clinical and seizures semiology information consistent with the International League Against Epilepsy guidelines (Engel, 2001) by neurologists (LY). From our database, we selected 21 patients as the drug-naïve patients (DNP) group, who were newly diagnosed. And the other patients received antiepileptic drugs as the drug (Keppra) receiving patients (DRP) group. A sample of twenty-nine 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 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. 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.

Table 1  
Demographic of all subjects

	DNP	DRP	HC	P value
Gender(male/female)	21(12/9)	20(6/14)	29(13/16)	0.216 <sup>a</sup>
Age(year)	26.5±14.2	24.7±10.5	25.3±8.9	0.868 <sup>b</sup>
Age at onset(year)	22.7±15.9	20±11.5	-	0.544 <sup>c</sup>
Handedness(right/left)	21/0	20/0	29/0	NaN <sup>a</sup>
Duration(years)	3.8±6.2	4.7±4.7	-	0.628 <sup>c</sup>
Abbreviations; DNP: drug-naïve patients, who were newly diagnosed; DRP: drug receiving patients; HC: healthy controls (gender-matched control group)				
<sup>a</sup> Chi-square test.				
<sup>b</sup> One-way analysis of variance.				
<sup>c</sup> Two-sample t-test.				

## 2. Data Acquisition

All subjects underwent MRI scanning in the 3-Tesla MRI scanner (GE DISCOVERY MR750). High-resolution T1-weighted images were obtained by 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<sup>2</sup>; matrix size = 256 × 256; and slice thickness = 1mm (no gap). Resting-state functional data were obtained by using a gradient-echo echo-planar imaging sequence. The main scanning parameters were as follows: TR = 2 s; TE = 30 ms; flip angle = 90°; FOV = 24 × 24 cm<sup>2</sup>; matrix size = 64 × 64; slice thickness = 4 mm (no gap); slice number = 35; and scanning time lasting 510s (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 mm \* 2 mm \* 2 mm, b-value = 1000s/mm<sup>2</sup>; FOV = 256 mm\*256 mm, three b0 images with 64 non-co-linear diffusion directions per shell. The acquisition time was 10 min.

## 3. Data preprocessing

Preprocessing of the fMRI dataset was performed using the NIT software package. The fMRI 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>), 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 non-linearly registered to the FMRIB58\_FA template. Then, an inverse warping transformation from the standard space to the native dMRI space can be obtained.

## 4. Network analysis

Based on the above steps, the FC matrix and the SC matrix were obtained. The different brain region is defined as the nodes of the network, and the value in the matrix is the connection strength of pairwise nodes. Therefore, networks of the fMRI dataset and the DTI dataset were constructed.

### 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. Regional time series were calculated by averaging

all voxel time series within the region. Pearson's correlation coefficient was calculated between each pair of regions. Finally, Fisher r-to-z was used to obtain a 90\*90 FC matrix for each subject.

## 4.2 Structural network

The AAL template was registered to individual native space by using the inverse transformation obtained above. For each subject, the whole brain (excluding the cerebellum) was partitioned into 90 regions based on the AAL template. Each region was defined as a brain network node. The WM pathways were reconstructed using the deterministic streamline tracking algorithm. A streamline was terminated when it reached another voxel with: (a) an FA value lower than 0.2 (reflecting low levels of preferred diffusion, often gray matter voxels), (b) when the streamline exceeded the brain mask (i.e., gray and white matter voxels), or (c) when the trajectory of the streamline made a turn sharper than 35 degrees. In this study, the mean of the FA values of streamlines connecting two regions was computed to assess the strength of the structural connections. Then, a 90\*90 symmetric SC matrix for each subject was obtained.

To reduce false positives of structural connections, a nonparametric one-tailed sign test was performed in both three groups separately. For each edge of the structural networks, the sign test was performed with the null hypothesis that there was no structural connection. Then the Bonferroni method was used to correct for multiple comparisons at  $p < 0.05$ . Then, a binarized group-level structural connection network for each group was generated to capture the underlying structural connection patterns. Next, a combined mask of SC of three groups, which was only included the common connection of all groups, was generated to restrict further between-group comparisons.

## 4.3 Coupling analysis of functional network and structural network

To discover the coupling between the functional and structural networks, the subject-covariate relationship was measured using NWCP. First, Based on previous literature(Yeo et al., 2011), we divided brain regions into eight functional networks (visual network, VN; Limbic network, LN; somatomotor network, SMN; default mode network, DMN; dorsal network, DAN; frontoparietal network, FPN; ventral attention network, VAN; subcortical network, SCN). Then, the NWCP was individually defined in three groups by the following formula:(Sisi Jiang et al., 2021)

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

Where  $N_i$ ,  $N_j$  represents  $i$ th or  $j$ th network ( $i, j \leq 8$ ), and  $m, n$  is the node in a certain network ( $N_i$  or  $N_j$ ). The Pearson coefficient ( $C_{m,n}$ ) is calculated between the FC and SC connecting node  $m$  and node  $n$ , and  $C_{sig}$  is a part of  $C_{m,n}$  which is significant ( $p < 0.05$ ). And all of the  $C_{m,n}$  values are taking the absolute value before NWCP calculating here. If  $i=j$ , the NWCP value measures the within-network coupling relationship and else is the between-network coupling relationship. A higher NWCP value implies a stronger

association between FC and SC between networks. Finally, the NWCP between networks and within the network were statistical tests respectively.

## 5. Statistical analysis

For the comparisons of the network of functional or structural connections, the ANOVA ( $p < 0.001$ ) and post-hoc analysis ( $p < 0.01$ ) were used to detect between-group differences of the strength of FC and SC. The result is displayed by the BrainNet toolbox (Xia, Wang, & He, 2013) and the Circos toolkit (Krzywinski et al., 2009).

The statistics of the coupling relationship between functional and structural networks were detected using nonparametric permutation tests (10000 iterations). Specifically, the data of the two groups was shuffled, FC and SC respectively, then the shuffled set reclassified them into two groups and recalculated the NWCP. Significance was set at  $p < 0.05$ .

# Results

## 1. Functional network

### 1.1 Connectivity comparisons

Compared with the HC group, the DNP group showed a trend of enhanced FC, predominantly including connections involving the right triangular inferior frontal gyrus and the right middle temporal gyrus (Figure 1). However, the functional connection strength of the DRP group tended to be like that of the HC group. In the network consisting of different edges, we found that the right triangular inferior frontal gyrus acted as a hub region. In addition, the functional connections in the DRP group were generally decreased relative to the DNP, mainly including the right middle temporal gyrus and the right medial superior frontal gyrus.

At the network-level, the DMN of the DNP group showed remarkably enhanced connectivity with the FPN and VN. The increased connectivity between the FPN and VN was also observed in the DNP relative to controls. Meanwhile, the connections between SCN and the limbic network showed a downward trend in the DNP. Compared with HC, the DRP showed increased FC between DMN and FPN and decreased FC between the SMN and limbic network.

Compared with the DNP, the DRP demonstrated distributed decreased FC between networks, mainly including FC between DMN and FPN, between VN and DMN, and between VN and FPN. Besides, increased FC between SCN and the limbic network was observed in the DRP.

## 2. Structural network

Compared with the HC group, the left medial occipital gyri demonstrated the enhanced FC in the DNP group or the DRP group. When the DRP group was compared with the DNP group, a difference was found

in the connection between the right medial cingulum and putamen.

Some common differences were observed in the DNP group and the DRP group compared with the HC group at the network-level (Figure 2), which were connections between VN and FPN (increased), DMN and FPN (increased), the connection between VAN and DMN (decreased). Moreover, connections between VAN and SCN (decreased) and SMN and limbic network (increased) also altered in the DNP group.

### **3. Coupling analysis of functional and structural networks**

Figure 3 demonstrates the different coupling of FC and SC in between groups. Compared with the HC, the DNP showed decreased coupling within the DMN and coupling between the DMN and VAN. Besides, both the DNP and DRP demonstrated decreased coupling between the Limbic and SMN. Compared with the DNP, the DRP showed decreased coupling between the DMN and Limbic and increased coupling within DMN.

## **Discussion**

AEDs, as a common choice for epileptic patients in clinical practice, play an important role in the different transmitter systems to achieve remission of seizures. The distinct regions might be affected by AEDs, so network analysis would provide a new sight to investigate the influence of AEDs. The present study based on noninvasive brain imaging and brain network analysis characterized alterations of functional and structural connectivity and their coupling in patients with and without receiving AEDs. We found that both patient groups showed a stable increase in structural connection strength among DMN, FPN, and VN relative to healthy controls, suggesting that the structural alteration observed in GTCS patients was obstinate even through receiving AEDs. The DNP group showed the significantly widely enhanced functional connectivity, involving the DMN, FPN, limbic network, and VN, but only one connection between DMN and FPN was heightened in the DRP group. Thus, the functional connectivity would be sensitive to AEDs. In addition, the structural and functional coupling was decreased in connections within DMN, between DMN and VAN, and between the limbic network and SMN. However, patients with AEDs showed decreased coupling in only one connection between limbic network and SMN, and the coupling within DMN was significantly increased compared with patients without AEDs. In all, the present findings suggested that medical treatment might be more effective in improving functional abnormalities rather than structural connections. Consistent SC abnormality in the DNP and DRP groups indicated that the structural abnormality might be a fundamental phenomenon of the disease. Furthermore, AEDs could reverse the alteration of structural and functional coupling in epilepsy.

In previous studies (Parsons, Bowden, Vogrin, & D'Souza, 2020; Zanao, Lopes, de Campos, Yasuda, & Cendes, 2019), it has been reported that abnormally connectivity was observed between the DMN and other functional networks during interictal discharges, thus, the DMN is considered to associate with the generation of epileptic discharges (Jiang, Li, Liu, Yao, & Luo, 2021). Accumulated studies based on the electroencephalogram have suggested that enhanced FC might be a crucial feature corresponding to epileptic cortical discharges (Adeli, Zhou, & Dadmehr, 2003; Schevon et al., 2007), which was consistent

with the theory "Neurons that fire together, Wire Together" by Donald Hebb et al.(Hebb, 1949). Matching this view, the current work also identified the enhancement of functional connectivity within DMN and that between DMN and the other networks in patient groups. This widespread enhancement of connections might be a byproduct of the rapid transmission of electrical signals through the brain during seizures(Dixon et al., 2018; Wei et al., 2015). Besides, the present results showed a specifically increased functional and structural connection between DMN and FPN in the DRP group, implying that the cortical changes caused by the epileptic activation were not completely ameliorated by the medicine, and these brain regions might still be affected by the epileptic disorder, but for the area without effects of epileptic activation, the medicine has obvious improvement effect. Consistent with previous findings, our results indicated that the medical treatments have a potential effect to affect the interaction of the DMN with the other networks. However, compared with the HC group, higher connectivity strength between DMN and FPN in the DNP group was found not only in functional networks but also in structural networks. Moreover, the DRP group had the same abnormal alterations as the DNP group. These phenomena unaffected by drugs might represent a fundamental pathologic brain state in patients with GTCS. Therefore, we speculate that medication was easier to affect FC to alleviate the disease than to structural networks. This might be one of the reasons why curing epilepsy is difficult. In addition, the synergy between functional and structural networks is very important, which maintains physiological activities. The stable structural and functional connection between FMN and FPN in patients with and without AEDs might contribute to the reasons why patients who received antiepileptic drugs were more likely to remain seizures.

FPN is also one of the higher-order networks of the brain, which is responsible for executing cognitive control functions, such as work memory and attention selection(Corbetta, 1998; Vincent, Kahn, Snyder, Raichle, & Buckner, 2011). The enhanced connection between FPN and the other networks such as VN and limbic might reflect the intrinsic information over-integration between the generation and propagation networks of epileptic activities. A common phenomenon related to this alteration is that patients with epilepsy usually lose their sense of the environment and the ability to control themselves during seizures(Thurman et al., 2011). Increased functional connections were also observed in this work between the FPN and the limbic network in patients with GTCS. Since the limbic network is related to emotional cognition(Delfino-Pereira et al., 2020; Hayes & Northoff, 2011), such enhancement might explain the phenomenon of cognitive impairment accompanied by epilepsy. Besides(Krzeminski et al., 2020; Weng et al., 2020), this study also found abnormally enhanced connections within the primary networks, mainly including the limbic network, SMN, and VN. Both SMN and VN are important components of the primary-sensory perceptual cortices(Roland et al., 2017). It has been demonstrated that the coordination of visual and motor activities is associated with the synchrony of certain nerve rhythms(P. Avanzini et al., 2012; Muthukumaraswamy, Johnson, Gaetz, & Cheyne, 2004), however, this synchronicity might be disrupted by epileptic discharges, and the resulting phenomenon was abnormally enhanced connections within the primary networks(Hebb, 1949). These phenomena might be reasons why abnormal behavior existed in patients with epilepsy, such as convulsions and absence.

The fusion of multimodal provides an effective instrument to integrate the advantage of different neuroimages(Sisi Jiang et al., 2021; Qin et al., 2021). The fusion on the network-level might be adaptive for the disorders of the brain network(Sisi Jiang et al., 2021). Our previous study proposed the NWCP focused on the static and dynamic functional connections [18], which would reflect the coupling between structural and functional connectivity. The previous findings suggested that AEDs might be able to modulate the brain function of patients with GTCS. However, the effect of the drug on the structural network might be weak. The structural and functional coupling was only decreased in connections between the limbic network and SMN in GTCS in addition to connections within DMN and between DMN and VAN, reflecting antagonism of alteration of functional and structural networks in the DNP group. The limbic network and sensory-motor cortex were also important for generalized epilepsy. For example, limbic may take part in the generalized discharges generation(Badawy, Jackson, Berkovic, & Macdonell, 2013; Badawy, Lai, Vogrin, & Cook, 2013; Moguilner et al., 2017), and SMN may be related to motor symptoms in GTCS(Jiang et al., 2020). Thus, the structural and functional decoupling between the limbic network and SMN was comprehensible. Interestingly, patients with AEDs also showed the decreased coupling of this connection, supporting the importance of the connection on epilepsy. In addition, coupling within DMN was significantly increased compared to patients with AEDs to ones without AEDs. Therefore, we suggested that medical treatment can improve the abnormal brain network by affecting the structural and functional coupling relationship.

There are still some limitations in our study. First, due to the present study being a cross-sectional study, a comparison is lacking between before and after medication treatment. Although patients with or without treatment were collected, it is necessary for a longitudinal study. Because individual differences can be avoided. Then, the differences are not quantified in the cognitive evaluation between groups so that the effects of treatment on cognitive changes are not clear. Finally, we will recruit more subjects to increase the stability of our results.

## **Conclusion**

Broadly enhanced brain connectivity might make the interactions between different brain regions more sensitive in generalized epileptic patients with GTCS. Therefore, when abnormal physiological changes appeared in one or several regions, these changes can spread to neighboring and distant brain regions quickly. Moreover, the coupling of structural and functional networks was affected by epileptic action, and the structural and functional decoupling might play a crucial role in generalized epilepsy. AEDs treatment benefits the seizures that might originate from the effects of functional networks rather than structural networks. However, it can improve the abnormal brain network by affecting the coupling relationship. The structural and functional network coupling might be used to evaluate the efficacy of AEDs.

## **Declarations**

### **Ethical Approval**

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

### **Consent to Participate**

Written informed consent was signed by each participant before MRI scanning.

### **Consent to Publish**

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

### **Authors 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 Liand Sisi Jiang undertook the data analysis; Haonan Pei, Shuai Mai, Sisi Jiang and Cheng Luo wrote and revised the manuscript. All authors reviewed the manuscript and approved the final manuscript.

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### **Competing Interests**

None of the authors have a conflict of interest to declare.

### **Availability of data and materials**

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

### **Disclosures**

There is no conflict of interest.

**Written informed consent** was signed by each participant before MRI scanning.

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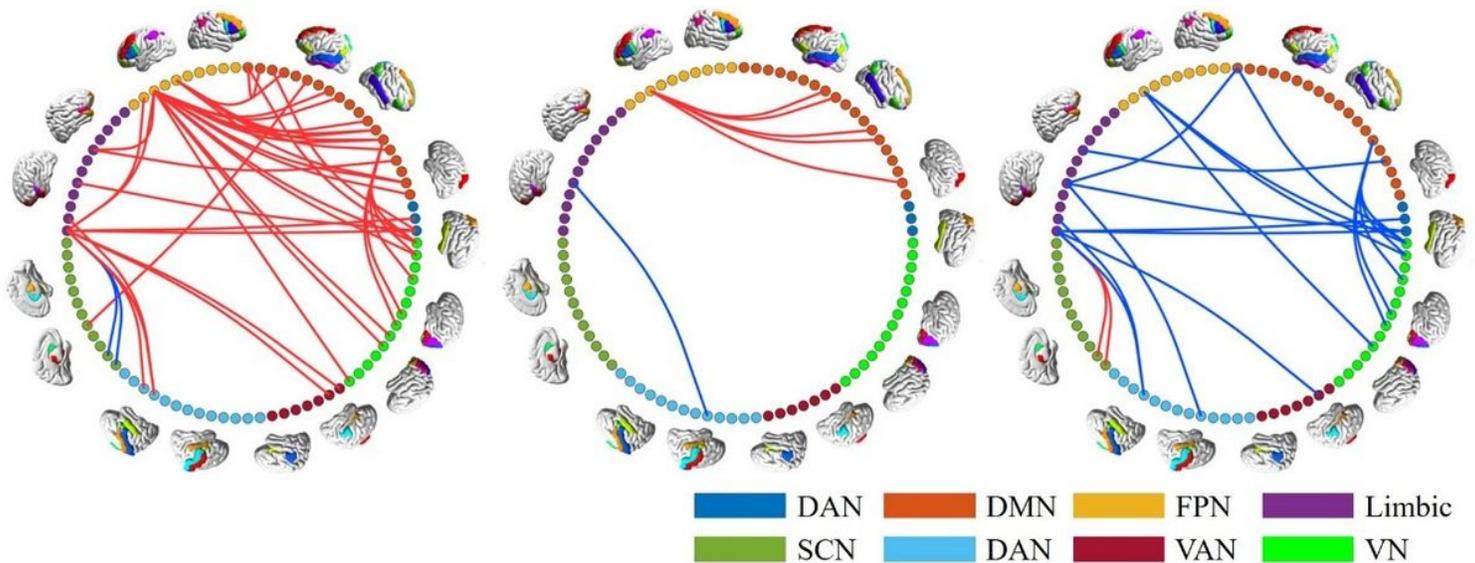
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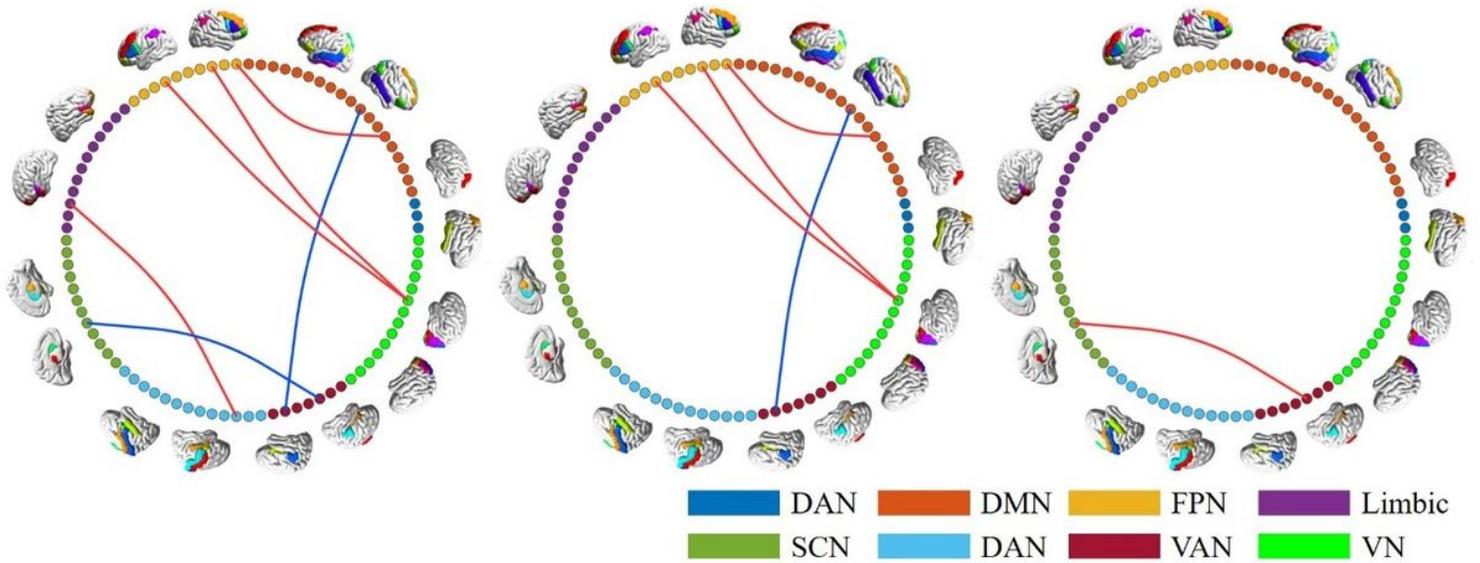
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## Figures



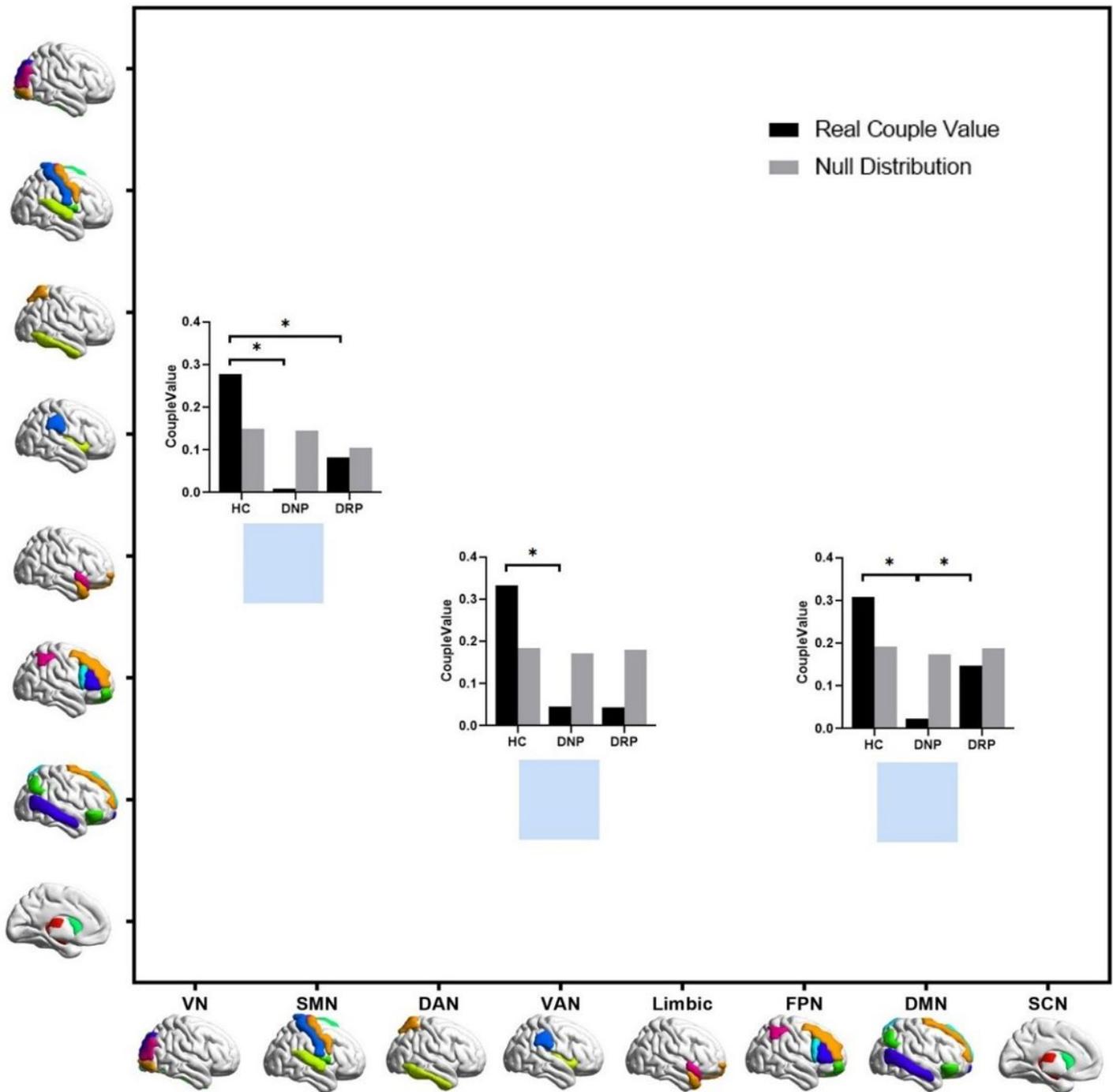
**Figure 1**

Abnormal changes within the functional network. (A) shows some abnormal changes in the DNP group compared with the HC group; (B) shows interesting changes in the DRP group compared with the HC group, and we can observe the differences between the DNP group and the DRP group in the (C). The Red line implies the enhanced connection, and the blue line is the weak connection.



**Figure 2**

Abnormal changes within the Structural network. (A) shows some abnormal changes in the DNP group compared with the HC group; (B) shows changes in the DRP group compared with the HC group, and we can observe the differences between the DNP group and the DRP group in the (C). The Red line implies the enhanced connection, and the blue line is the weak connection.



**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. \*  $p < 0.05$

## Supplementary Files

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