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SYSTEMATIC REVIEW ARTICLE

Voxel-wise Functional Connectivity of the Default Mode Network in Epilepsies: A Systematic Review and Meta-Analysis

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Abstract: ***Background*:** Default Mode Network (DMN) is recognized to be involved in the generation and propagation of epileptic activities in various epilepsies. Converging evidence has suggested disturbed Functional Connectivity (FC) in epilepsies, which was inferred to be related to underlying pathological mechanisms. However, abnormal changes of FC in DMN revealed by different studies are controversial, which obscures the role of DMN in distinct epilepsies.

***Objective*:** The present work aims to investigate the voxel-wise FC in DMN across epilepsies.

***Methods*:** A systematic review was conducted on 22 published articles before October 2020, indexed in PubMed and Web of Science. A meta-analysis with a random-effect model was performed using the effect-size signed differential mapping approach. Subgroup analyses were performed in three groups: Idiopathic Generalized Epilepsy (IGE), mixed Temporal Lobe Epilepsy (TLE), and mixed Focal Epilepsy (FE) with different foci.

***Results*:** The meta-analysis suggested commonly decreased FC in mesial prefrontal cortices across different epilepsies. Additionally decreased FC in posterior DMN was observed in IGE. The TLE showed decreased FC in temporal lobe regions and increased FC in the dorsal posterior cingulate cortex. Interestingly, an opposite finding in the ventral and dorsal middle frontal gyrus was observed in TLE. The FE demonstrated increased FC in the cuneus.

***Conclusion*:** The current findings revealed both common and specific alterations of FC in DMN across different epilepsies, highlighting the contribution of these dysfunctions to epileptic activities and cognitive behaviors in patients. Furthermore, the current study provided powerful evidence to support DMN as a potential candidate for effective intervention in epilepsy.

ARTICLE HISTORY

Received: December 28, 2020
Revised: February 24, 2021
Accepted: March 18, 2021

DOI:
10.2174/1570159X19666210325130624

Keywords: Default mode network, resting state, functional connectivity, idiopathic generalized epilepsy, temporal lobe epilepsy, functional magnetic resonance imaging.

1. INTRODUCTION

In recent years, functional magnetic resonance imaging (fMRI) has been widely used in brain function researches, making a great contribution to the understanding of the underlying physiological mechanism from the mesoscale view [1-3]. Remarkably, multiple brain networks are consecutively proposed as continuous or discrete brain structures with spontaneous synchronized activities in a resting state and adapted in a specific task state [4]. Of the many brain networks, there is a particularly striking network called the Default Mode Network (DMN), which has attracted a lot of attention, penetrating into many domains of nervous system research [5, 6]. The most core regions of the DMN include the ventral and dorsal medial prefrontal cortex (vMPFC and dMPFC), the Posterior Cingulate Cortex (PCC), and the bilateral angular gyrus [5]. The spatial pattern of the DMN can be identified by the independent component analysis and voxel-wise Functional Connectivity (FC) approaches. The voxel-wise FC analysis is mainly implemented by seeding at the MPFC or PCC, which has been demonstrated to be valid by the previous studies [7]. The DMN is active in the resting state and silent in the task state, which is recognized to be responsible for maintaining the normal intrinsic activity of the brain and involved in advanced cognitive performance [5, 8]. Besides, the DMN has been studied in-depth in vari-

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1570-159X/22 $65.00+.00

ous neuropsychological diseases, such as Alzheimer's disease [9], schizophrenia [10], and epilepsy [11].

Epilepsy is a type of neurological disorder characterized by recurrent and spontaneous seizures caused by abnormal and excessive synchronization activity of a large number of neurons. In terms of the spatial distribution of the origin of epileptic discharges, epilepsy can be divided into Generalized Epilepsy (GE) and Focal Epilepsy (FE) [12]. A seminal study by Gotman *et al*. suggested a suspension state of the DMN in the generation and propagation of Generalized Spike-Wave Discharges (GSWD) by means of simultaneous EEG-fMRI [13], which provided evidence to relate the activity of the DMN to epileptic discharges. Besides, subsequent researches on many types of epilepsy, such as Temporal Lobe Epilepsy (TLE), also revealed the contribution of the DMN to epileptic discharges. Although the epileptic discharge is transient, the damage caused by repeated seizures over a long period of time to brain function is cumulative. Epileptic discharges significantly disturb the information communication of the brain, which can be measured by the FC analysis. The FC is a measurement reflecting the synchronization of spontaneous neuronal activity of different regions by capturing the temporal correlations or statistical dependency [14, 15]. Accumulated previous studies onFC have provided significant evidence to reveal the physiopathologic mechanism underlying epilepsy. A study based on the fMRI data without interictal discharges revealed the disturbed FC in the DMN, which further suggested that the role of the DMN might not only limit to epileptic discharges [16]. Moreover, a potential association between the DMN and cognitive impairment of patients with epilepsy is also revealed by a large number of fMRI studies, based on various cognitive tasks, such as working memory, executive control [17-19]. In all, the DMN plays a crucial role in epileptic discharges, and its functional connective profile has a profound influence on the brain function of patients.

Over the years, converging researches have been conducted to investigate the FC of DMN in various types of epilepsy. By subjective instinct, many of these findings seem to point in a broadly consistent direction, but the definitive conclusion is unknown. A meta-analysis is an approach that can help us effectively review and integrate previous studies and draw a conclusion through them. In the present review, we focused on the voxel-wise resting-state FC of DMN in patients with epilepsy and aimed to provide a reference for future intervention studies in epilepsy.

2. METHODS

2.1. Search Strategies

By using PubMed and Web of Science, we conducted a comprehensive literature search of studies published up to October 2020 using the keywords 'epilep*' or 'seizur*', 'default network' or 'default mode network', 'rest*', 'function*', and 'connect*'. Besides, manual searching of the reference lists of the obtained articles was also performed. A systematic approach compliant with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was adopted.

2.2. Eligibility Criteria

A study was excluded for the following reasons: 1) it was not a resting-state fMRI study, 2) it was not a voxel-wise analysis, 3) there was no healthy control (HC) group, 4) there was no statistical analysis, 5) it was not a human research, 6) the patients involved in the study had comorbid conditions, 7) the study did not report coordinates 8) it evaluated directional functional connectivity, 9) it used entirely overlapping samples, and the same DMN map was reported in another publication.

2.3. Data Extraction

One reviewer (SSJ) searched the literature and screened all titles and abstracts. Then, for all potentially relevant articles, full-text versions were retrieved and further screened by two reviewers (SSJ and HCL). The data extraction was performed by SSJ and checked by HCL. Once a study was selected, the following variables were recorded: epilepsy type, sample sizes, the mean age of subjects, gender, mean illness duration, seizure frequency, and antiepileptic drugs. Some studies did not report the last two variables. The coordinates with statistically significant differences were extracted, including the direction of the alteration (patient > HC, patient < HC) and the effect size (T value, if the original studies reported the z-value or p-value, they were transformed to T value).

2.4. Effect Size Signed Differential Mapping Meta-analysis

In the present study, the meta-analysis was performed using the effect size signed differential mapping (ES-SDM) software (http://www.sdmproject.com) in a standard process [40, 41].

A preprocessing procedure was performed for each study to generate a map of effect size values (known as Hedge's d) and a map of variances according to the extracted peak voxels, which was then integrated into the following meta-analysis. Specifically, the t-values of peak voxels are straight forwardly converted to unbiased effect sizes and variances. If the t-value is not available, such as z-values reported in some studies or corresponding p-values of statistics, these studies can be included as long as they can be converted to t-values.

For each study, the voxels close to peak voxels were assigned a value depending on the distance to the close peak voxel by applying a normalized Gaussian kernel function (FWHM = 20 mm) [41]. It has been demonstrated that the value of FWHM of 20 mm can optimally balance the sensitivity and specificity of the meta-analysis. Notably, the kernel is weighted by the effect size of the peak voxel in the ES-SDM. When a voxel is assigned values by more than one peak voxel, a square of distance weighted average value was calculated. All studies included in the meta-analysis are combined with a random-effects model, weighted by the inverse of the sum of variance and the between-study heterogeneity by means of DerSimonian-Laird estimator [42].

Statistical significance was determined using a nonparametric randomization test, which randomizes the location of the voxels within the gray matter of the whole brain. In the present study, only the differences that survived a voxel-

level (height) threshold of p-value < 0.001 and a cluster-level (extent) threshold of 23 voxels were reported [41].

A jack-knife analysis was performed to assess the reliability and stability of the results, which does meta-analysis iteratively with one study left out in one iteration until every study was removed. In this work, clusters that showed significant differences in more than 80% of the iterations were considered to be robust. Besides, the publication bias was also taken into consideration by means of the Egger test and funnel test.

The Q test, H test, and the I-square statistic were used to test the heterogeneity of the effect size across the studies [43]. The Q test depicts the weighted sum of squares of mean deviation of the effect size, which is easily affected by the number of studies of meta-analysis. The H test adjusts the Q test by t, considering the degree of freedom. I-square is another development statistic measurement assessing the percentage of variation of effect size induced by different studies in total variation.

Moreover, the subgroup analysis was also conducted in different types of epilepsy. Furthermore, the meta-regression analysis was performed to assess the potential effects of duration and onset age of illness on the amount of FC alteration. For the reduction of spurious relations, the significance level was set at p < 0.0001 [41].

3. RESULTS

3.1. Study Selection

According to the keywords, 106 papers were searched on Web of Science and 103 papers on PubMed. Then, 48 duplicates were removed, after which 161 studies remained. Next, 107 studies were removed after screening the abstracts. Further full-text assessment was elaboratively performed in 54 studies. Then, 17 studies not voxel-wise FC, 13 studies without statistic coordinates, 1 study not resting state, and one case report study were further excluded from the meta-analysis. In total, 22 papers finally met the eligibility criteria, including 28 between-group comparisons. The literature search methods and results are shown in Fig. (**1**). Detailed information of the studies is shown in Table **1**, including age, gender, and duration of the illness.

3.2. Study Characteristics

The demographic information of patients and controls varied across different studies. There are seven studies that described "age- and gender-matched" HC without the explicit information of HC. The total sample included 659 patients with epilepsy (316 females and 343 males) and 709 healthy subjects. Six studies included two groups of patients and performed statistical comparisons with the same HC group. According to the types of epilepsy, three subgroups could be divided with enough number of studies for separate meta-analysis. There are 6 between-group comparisons in the IGE group, 14 comparisons in the TLE group, and 8 comparisons in the FE group. In the IGE group, 2 groups of GTCS, 1 group of JME, 2 groups of AS, and 1 group of IGE (without explicit clarification of subtypes of IGE) were included. The mixed TLE group included 5 groups of patients with left origins, 4 groups with right origins, and 5 groups of mixed patients with left and/or right epileptic origins. Notably, 9 clarified unilateral TLE were further gathered in a separate subgroup analysis. 2 studies on the patients with BECTS, one study in the FLE, and one study on a group FE without explicit subgroup classification were gathered into a mixed FE group.

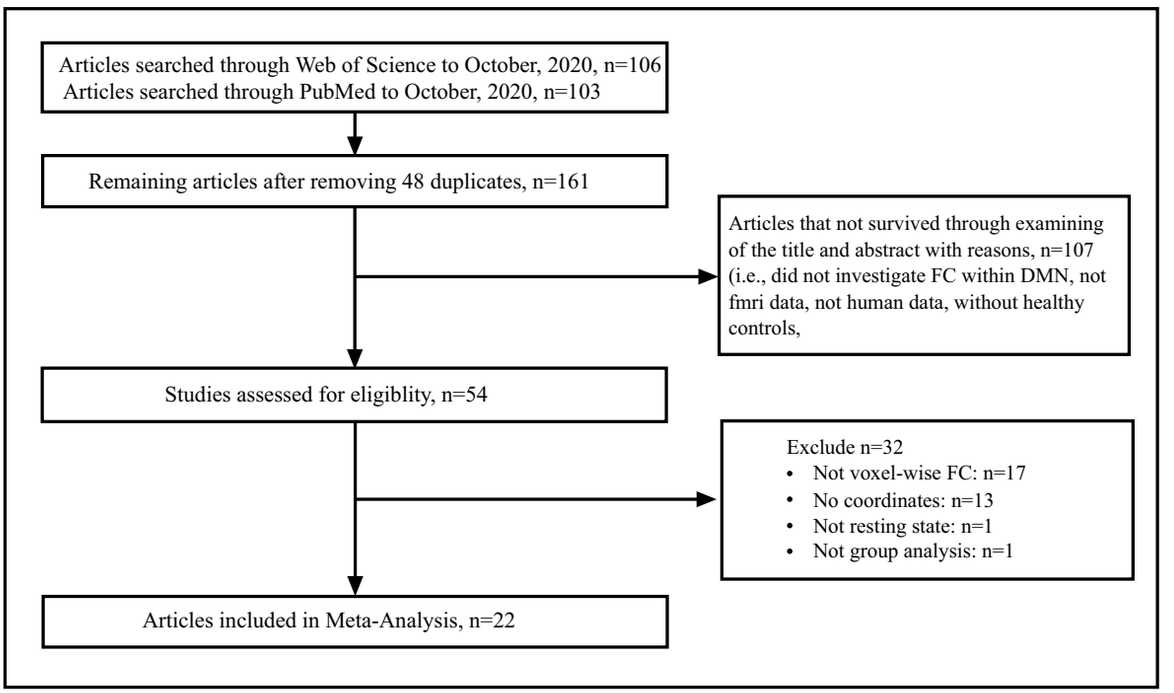

Fig. (1). Articles identification and selection flowchart.

Table 1. Characteristics of epilepsy studies included in the meta-analysis.

Study	Epilepsy Patients					HC		
	Epilepsy Type	N	Age (mean)	Duration (year)	Gender (M:F)	N	Age (mean)	Gender (M:F)
Zhang *et al*. (2010) [20]	lmTLE	25	23.3	10.5	14:11	29	24.5	16:13
	rmTLE	27	25.8	9.7	16:11	29	24.5	16:13
Liao *et al*. (2011) [21]	mTLE	20	26.3	8.98	10:10	20	26.2	NAN
Wang *et al*. (2011) [22]	GTCS	16	23.37	10.62	7:9	16	27.93	8:8
Luo *et al*. (2012) [23]	TLE	7	17.86	NAN	4:3	14	NAN	NAN
	FE	9	16.22	NAN	5:4	14	NAN	NAN
Luo *et al*. (2011) [11]	AE	12	13.67	6.92	9:3	14	NAN	NAN
Widjaja *et al*. (2012) [24]	MRE	11	14.1	5.4	3:8	14	NAN	NAN
Mankinena *et al*. (2012) [25]	TLE	21	11.7	2.5	10:11	21	NAN	NAN
Haneef *et al*. (2012) [26]	rTLE	11	40.2	17.6	7:4	13	33.3	9:4
	lTLE	12	36.2	17.6	9:3	13	33.3	9:4
Kay *et al*. (2013) [27]	IGE	60	31.5	15.5	25:35	38	NAN	NAN
Dou cet *et al*. (2014) [28]	lTLE	13	44.47	19.7	4:9	14	NAN	NAN
	rTLE	16	41.01	19.57	7:9	14	NAN	NAN
Cao *et al*. (2014) [29]	FLE	46	26	9.2	21:25	46	25.3	22:24
Xiao *et al*. (2015) [30]	BECT	15	8.7	1.4	10:5	15	NAN	9:6
Wei *et al*. (2015) [31]	GTCS	27	24.9	7.76	19:8	29	26.93	17:12
Shih *et al*. (2016) [32]	lmTLE	15	36.87	23.47	9:6	15	36.33	8:7
Li *et al*. (2017) [33]	JME	20	18.2	11.1	7:13	21	18.3	9:12
	AE	21	12	NAN	9:12	21	18.3	9:12
Li *et al*. (2017) [34]	BECT	20	9	1.94	7:13	28	10	15:13
Wang *et al*. (2017) [35]	IS	13	2.92	2.20	10:3	35	2.5	22:13
Hu *et al*. (2017) [36]	FE	62	27.9	NAN	32:30	64	29.1	35:29
Jiang *et al*. (2018) [37]	MRE	19	23.11	8.26	10:9	21	22.17	12:9
Zanao *et al*. (2019) [38]	lTLE	46	45.37	32.4	16:30	59	43.64	22:37
	rTLE	42	46.45	29.6	11:31	59	43.64	22:37
Zhang *et al*. (2020) [39]	TLE	16	29.63	9.13	8:8	17	27.76	11:6
Zhang *et al*. (2020) [19]	rTLE	27	29.89	7.87	13:14	20	27.70	12:8

Abbreviations: AE: absence epilepsy, GTCS: generalized tonic-clonic seizures, JME: juvenile myoclonic epilepsy, lmTLE: left mesial temporal lobe epilepsy, rmTLE: right mesial temporal lobe epilepsy, lTLE: left temporal lobe epilepsy, rTLE: right temporal lobe epilepsy, FLE: frontal lobe epilepsy, BECT: benign epilepsy with centrotemporal spikes, MRE: medically refractory epilepsy, IS: infantile spasms.

The mean age of all patients was 25, the mean age of the IGE group was 21, the mean age of the TLE group was 33, and the mean age of the mixed FE group was 17. Most of the included studies tend to report the duration of disease more than the onset age of the disease. There are three studies that did not report the duration of the disease. The mean duration of disease of all 19 studies was 12.27 years, the mean duration of IGE was 10.38 years, the mean duration of TLE was 16.5 years, and the mean duration of the mixed FE was 4.73. The mean onset age of the patients was calculated manually by subtracting age from the course of the disease. However, most studies did not clarify that the onset age of the disease defined depends on the age of the first seizure or the age of diagnosis as epilepsy. Besides, only six studies reported the frequency of seizures of patients. No study was performed in a group of drug-naïve patients. In most of the studies of patients with antiepileptic drugs (AED), the explicit information of types and dosage of drugs is unclear. Moreover, some studies mixed drug-naïve and drug-receiving patients in one patient group.

3.3. Meta-Analysis

The meta-analysis based on all recruited researches, including various types of epilepsy, suggested significantly decreased FC in mesial prefrontal cortex (MPFC) (peak at

MNI (2, 52, 2); SDM = -0.25; Q =5 6; I^2 = 47), bilateral angular gyrus (AG) (left: peak at MNI (-48, -58, 33); SDM = -0.15; Q = 33; I^2 = 9; right: peak at MNI (48,-68,23); SDM = -0.13; Q = 37; I^2 = 18), left hippocampus (lHipp) (peak at MNI (-29, -11, -23); SDM = -0.13; Q = 31; I^2 = 4) and increased FC in bilateral cuneus cortex (cuneus) (left: peak at MNI (-13, -76, 33); SDM = 0.13; Q = 74; I^2 = 60; right: peak at MNI (10, -78, 34); SDM = 0.11; Q = 68; I^2 = 56) and dorsal posterior cingulate cortex (dPCC) (peak at MNI (-5, -27, 47); SDM = 0.06; Q = 28; I^2 = 31) (Fig. **2**). The Egger tests on all above reported regions showed no significant publication bias (p > 0.05).

After screening the types of epilepsy in the meta-analysis, two categories could be investigated through different researches: Idiopathic Generalized Epilepsy (IGE) and Temporal Lobe Epilepsy (TLE). Notably, the TLE group includes the lmTLE, rmTLE, lTLE, and rTLE. Eight studies (8 between-group comparisons) were performed on patients with IGE and 12 studies (14 between-group comparisons) on patients with TLE. Specifically, for the mixed TLE group, we performed an additional analysis on studies with clarified unilateral foci. We kept the coordinates of studies with left foci unchanged and left-right flipped the coordinates of studies with right foci. After this process, we could investigate the alterations of FC in the ipsilateral and contralateral regions of epileptogenic foci.

The subgroup analysis in the IGE revealed decreased FC in a cluster, including dorsal anterior cingulate cortex and mesial prefrontal cortex (dACC/dMPFC) (peak at MNI (0, 30, 22); SDM =- 0.23; Q = 9; I^2 = 36) and bilateral AG (left: peak at MNI (-41, -76, 30); SDM = -0.3; Q = 8; I^2 = 27; right: peak at MNI (41, -74, 31); SDM = -0.32; Q = 7; I^2 = 15), and increased FC in the right superior frontal gyrus (rSFG) (peak at MNI (31, 63, 7); SDM = 0.17; Q = 14; I2 = 57)) (Fig. **3A**). Considering the limited number of studies. *i.e.*, less than 10, we did not perform the Egger test but the funnel plot was presented for the visual inspection of the publication bias (p-value > 0.05).

In the present study, the TLE group demonstrated decreased FC in the MPFC (peak at MNI (1, 50, 1); SDM = -0.25; Q = 26; I^2 = 50), bilateral mesial temporal regions (left: peak at MNI (-31, -11, -29); SDM = -0.21; Q = 21; I^2 = 38; right: peak at MNI (63, -23, -12); SDM = -0.13; Q = 16; I^2 = 19), left ventral middle frontal gyrus (vMFG) (peak at MNI (-30, 43, 37); SDM = -0.13; Q = 15; I^2 = 10), and increased FC in the dPCC (peak at MNI (0, -40, 51); SDM = 0.09; Q = 14; I^2 = 46) and the left dorsal middle frontal gyrus (dMFG) (peak at MNI (-28, 28, 49); SDM = 0.12; Q = 14; I^2 = 7) (Fig. **3B**). Similarly, the Egger test was conducted and demonstrated no significant publication bias. In the mixed FE group, decreased FC was observed in ventral MPFC (vMPFC) (peak at MNI (3, 57, 10); SDM = -0.45; Q = 21; I^2 = 72) and the left lateral parietal cortex (l LPC) (peak at MNI (-60, -47, 29); SDM = -0.17; Q = 6; I^2 = 2). Besides, the mixed FE group also demonstrated increased FC in bilateral cuneus (left: peak at MNI (-11, -75, 30); SDM = 0.41; Q = 42; I^2 = 85; right: peak at MNI (11, -76, 34); SDM = 0.38; Q = 36; I^2 = 83) (Fig. **3C**).

With subgroup analysis in unilateral TLE, we further identified the decreased FC in the bilateral temporal lobe

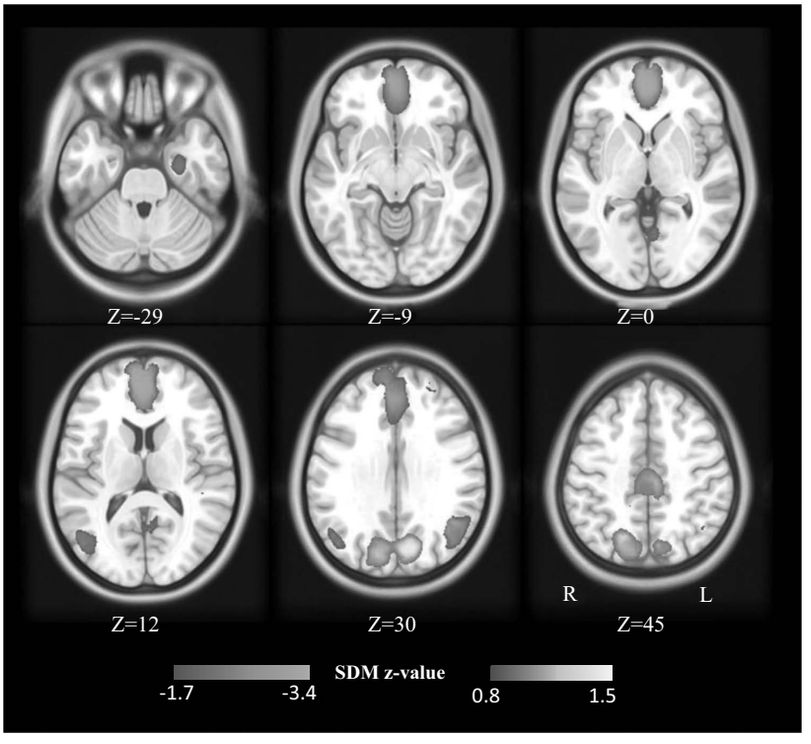

Fig. (2). Meta-analysis in published researches across all types of epilepsy; The warm color represents increased FC in epilepsy, and the cold color represents decreased FC in epilepsy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

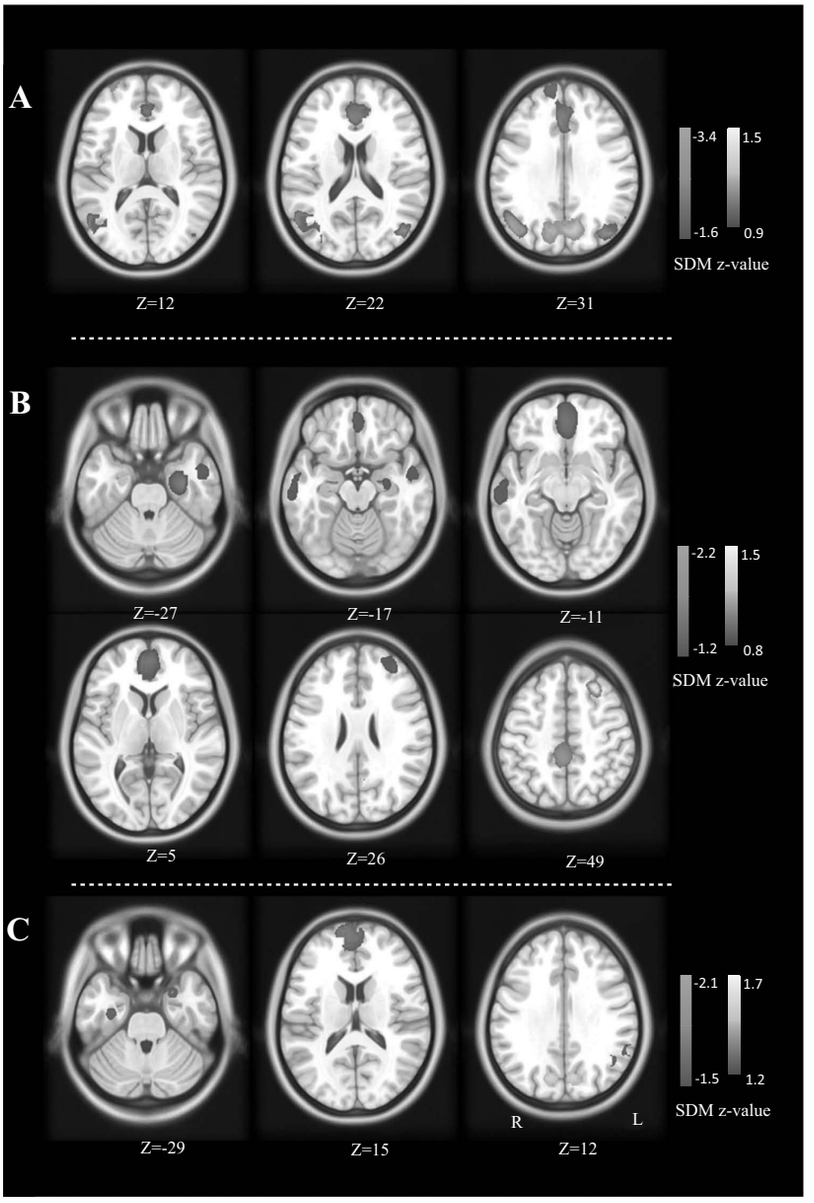

Fig. (3). Meta-analysis in subgroups of epilepsy in IGE (**A**), TLE (**B**), and mixed FE (**C**); The warm color represents increased FC in epilepsy, and the cold color represents decreased FC in epilepsy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

regions and increased FC in contralateral extratemporal regions, including dMFG and a cluster in the temporoparietal junction areas (Fig. **4**).

The jack-knife process was performed for the above analyses to validate the current results. It was suggested that the regions with significant between-group differences preserved with reproducibility of more than 80%.

Furthermore, the meta-regression analysis revealed a significant association between the FC and clinical features (duration and onset age of disease) (Fig. **5**). In the whole group, a negative correlation was observed between the FC of the right angular gyrus (rAG) and the duration. In the IGE group, both the FC of bilateral AG decreased (deteriorated) along with the duration of disease. Besides, the tendency of decreased FC in the vMFG and increased FC in the dMFG accompanied by longer duration was observed in the TLE group. Moreover, the TLE group also showed a significant correlation between the onset age of the disease, the FC in vMFG, and a cluster in the temporal pole. No significant correlation was found in the mixed FE group.

4. DISCUSSION

In the present study, we have assessed the disturbed FC in the DMN in patients with epilepsy through a meta-analysis. The meta-analysis of all selected studies and subgroup analysis confirmed the common hypoconnectivity in the MPFC across different types of epilepsy, which was inferred to be related to the suspension of intrinsic brain states caused by epileptic discharges. Specifically, the IGE de-

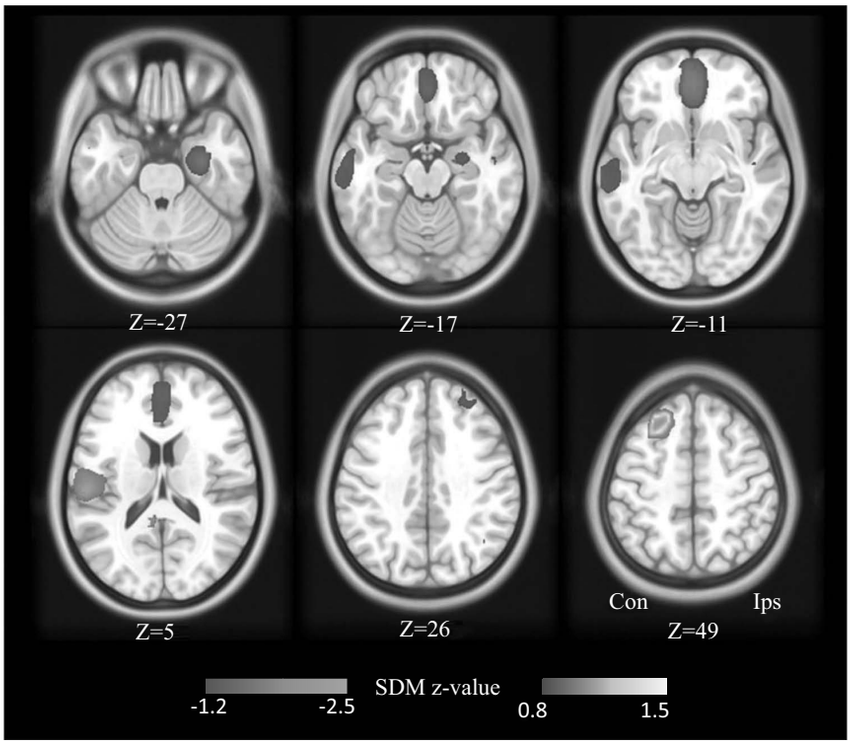

Fig. (4). Meta-analysis in subgroups of unilateral TLE; The warm color represents increased FC in epilepsy, and the cold color represents decreased FC in epilepsy. Ips, ipsilateral side of foci; Con, contralateral side of foci. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

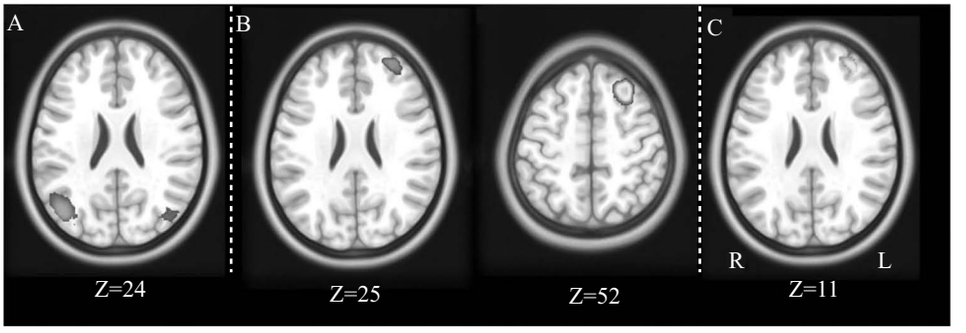

Fig. (5). Correlation between FC and duration and onset age of the disease;Negative correlation between FC of the bilateral AG and duration in IGE (**A**); negative correlation in the FC of the vMFG and the dMFG negatively and positively correlated with the duration in TLE, respectively (**B**); a positive correlation between vMFG and the onset age of diseased in TLE (**C**); The warm color represents a positive correlation, and the cold color represents a negative correlation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

creased in the dMPFC/dACC while the TLE and the mixed FE group decreased in the vMPFC, implying a potential distinction in the different types of epilepsy. Besides, the decreased FC of AG in the IGE further indicated the loss of the ability of information integration in IGE, contributing the declined arousal level to appropriately respond to the external stimulus. In TLE, specifically decreased FC in temporal structures was expected to be associated with the epileptic network responsible for the generation and propagation of discharges and cognition deficits. Moreover, increased FC of the dPCC and the opposite changes of FC were observed in the dMFG and vMFG in TLE, which is an interesting and unexpected finding with several speculative interpretations. In all, the present study highlighted a crucial role of the DMN across epilepsies, providing a reliable reference for the intervention target of therapy.

4.1. Common Hypoconnectivity in the MPFC in Epilepsies

The MPFC is a crucial higher-order region participating in numerous behaviors and cognitive functions, including attention, memory, decision-making, executive control *etc*. [44, 45]. Its activity has been demonstrated to be suspended

during the generation and propagation of epileptic activities in different epilepsies [13, 46]. The deactivation of the MPFC was viewed to be responsible for the reduced responsiveness to the external environment during interictal discharges [47]. We further hypothesize that the long-term inhibition induced by epileptic discharges accumulates gradually, manifested as weakening of functional interaction. In the present meta-analysis, the hypoconnectivity in all types of epilepsy reflected a weak within-network communication, implying insufficient functional integration in the basic brain state [27, 48]. Since most of the researches included in the meta-analysis used resting-state BOLD-fMRI without simultaneous EEG specifying the interictal epileptic discharges, theoretically speaking, we could not completely eliminate the potential influence of interictal discharges on the observed effects. However, with consideration of the resting-state data process instead of an activation analysis in these included studies, the observed effect could not be totally interpreted by potential interictal discharges. Thus, we tend to infer this hypoconnectivity to be a sustained feature of the epileptic brain. In a previous study, decreased FC of DMN in the baseline without interictal discharges supported our view [49]. In all, deactivation during the instantaneous discharge reflects the inhibition effect of the basic state of the brain and is referred to be related to responsiveness, which seems to be a common pathomechanism in various epilepsies [49]. With the accumulation of seizures, the transient inhibition of DMN caused by epileptic discharge gradually develops to long-term chronic injury of brain function, which might be characterized by the hypoconnectivity phenomenon in the basic brain state. Furthermore, core regions of the DMN might be putative targets for the efficient intervention, and the connective profile might be potentially modulated to achieve good effects of therapy.

Notably, the IGE and TLE showed hypoconnectivity in the dorsal and ventral structures of the mesial frontal lobe, respectively. Multiple studies have indicated that the dorsal and ventral MPFC play different roles in the execution and inhibition of actions [50, 51]. Although these studies are mainly based on the performance of these two brain regions in the rewarding-related task state, the potentially distinct yet complementary role of ventral and dorsal MPFC was also implied in the resting-state state [52, 53]. The clear pathogenesis for epilepsy is the imbalance between excitability and inhibition. The distinctive disruption of connectivity in ventral and dorsal MPFC might be a specific feature underlying the physiopathologic mechanism in different types of epilepsy. Up till now, few studies focused on the balancing role of vMPFC and dMPFC in epilepsies, and more convincing evidence is still needed to clarify the potential distinctions across different epilepsies.

4.2. Specific Hypoconnectivity in the AG in IGE

The significantly inhibited activity of AG accompanied by epileptic discharges was also observed in IGE in the previous studies, and the present meta-analysis also revealed decreased FC in this region. The AG is an important region in the inferior parietal lobe and plays a crucial role in the arousal system, which is essential for visuospatial awareness [54, 55]. Besides, the AG acts as a connective hub for integrating global information [56]. It has been demonstrated that the angular regions greatly contribute to the adaption of global brain connectivity to respond to the increasing external demands [57], contributing to the shifting of the attention towards salient and active events [58]. In patients with IGE, the deactivation of AG during epileptic discharges was viewed to be related to the decreased arousal level. Moreover, the hypoconnectivity of AG might reflect its decreased ability to integrate multi-modal information of the brain, which might be responsible for various cognitive behavior in IGE. Furthermore, our meta-regression analysis suggested a significant negative correlation between the decreased FC of AG and the duration of disease, which indicated that the disturbance of the functionality of AG gradually accumulates along with the recurrent seizures, providing evidence supporting our previous hypothesis.

4.3. Specific Hypoconnectivity in the TLE

The above-mentioned regions demonstrated decreased activity during epileptic discharges and decreased FC in the resting state, which seems to reach an agreement of suppression and loss of functionality of the DMN in patients. In epilepsy, the discharge-caused activation is a short-term state, and the overall FC profile in the resting state is a cumulative manifestation associated with various pathological factors, such as the course of the disease and the onset age. The regional activity and connectivity profiles may be consistent or opposite in different regions. Although the temporal lobe network (TLN) and MPFC both showed reduced FC in TLE, the responses to epileptic discharges were reversed. The TLN is positively activated and the MPFC is suppressed during the generation and propagation of epileptic activities in patients with TLE [59, 60]. This phenomenon might imply the different roles of the two in the pathological mechanism of TLE.

The interictal epileptic discharges have been reported to induce the activation of TLN, of which the neuronal activity is affected through synaptic connections at a close distance [59]. It seems relatively easy to understand the explicit involvement of TLN in the generation and spreading discharges. The present findings revealed significantly decreased FC in the ipsilateral hippocampus of foci in TLE, further suggesting potential damage caused by the epileptic activities. A previous study investigated the thalamocortical FC in the states with and without epileptic discharges in TLE. Decreased FC between the thalamus and the TLN was observed during the ictal period, while it was not observed in the non-ictal period [61], suggesting that the TLN have distinct functional profiles in different periods. During the resting state, the hippocampus (the most common region of origin) showed increased FC with the regions in the temporal lobe and decreased FC with other regions of the DMN [62], which further indicated a different role of the TLN from the other regions of the DMN. The active and connective profiles of the TLN seem to correspond to distinct disruptions of the epileptic brain in TLE. Moreover, memory deficiency is most frequently involved in patients with TLE, which has often been associated with aberrant FC in the DMN [17]. In all, it could be inferred that the TLN presented transient increased neural activity due to the epileptic discharges and long-term decreased FC along with the accumulation of sei-

zures, which might greatly contribute to the memory-predominant cognition impairment.

4.4. Hyperconnectivity in the dPCC in TLE

The dPCC is an area that has received little attention in epilepsy researches. In epilepsies, epileptic discharges-induced abnormal activity is hardly observed in the dPCC, which implied that the dPCC might not be directly involved in the generation and propagation of epileptic activities. The dPCC has abundant interaction with multiple brain networks and is active in functional systems. In the present study, we provide three possible considerations for the hyperconnectivity of dPCC in the TLE, including an over-high level of arousal, a visual stimulus-induced over-motion response, and compensation for memory deficits.

In a previous study, electrostimulation of the white matter directly serving the dPCC led to the behavioral unresponsiveness accompanied by a disconnectivity pattern [63], which referred the dPCC to the involvement of maintaining consciousness to recognize the external environment [64]. Previous studies in consciousness-related disorders usually reported altered FC of the dPCC, which further supported the assumption [64]. Besides, the PCC has been demonstrated to have a critical role in information integration among multiple functional systems in the condition that the state of consciousness is changed by drugs or natural sleep [65-67]. In the present study, we referred that the hyperconnectivity in the dPCC might represent a high level of arousal in patients with TLE, which facilitates the epileptic brain to be in an excitable and vulnerable state facing external stimulus. This interpretation could be further supported by a fact revealed by disease studies suggesting that the dPCC has a crucial role in maintaining arousal and awareness [55]. Besides, the dPCC plays a significant role in the visuospatial function, receiving inputs from the dorsal visual stream [68], which greatly contributes to the arousal and conscious system. It has been demonstrated that the dPCC has a close association with the sensorimotor network and adjusts motion according to the visuospatial needs *via* the dorsal multisensory stream. Thus, we also speculated that the increased FC in the dPCC might reflect an over-enhanced response of the motor system to primary visual inputs, which might be related to the photosensitiveness of patients with epilepsy [69]. However, the clinical evaluation of photosensitiveness of patients lacks in the studies that are included in the present study, which needs to be verified with more evidence.

The memory deficiency is one of the most common cognitive impairments in patients with TLE in the previous studies [70]. It is generally recognized that mesial temporal lobe regions make a predominant contribution to the memory deficiency [71]. However, there are still some other regions that might play important roles in memory processing. The activation of dPCC when performing personal episodic memory tasks suggested a possible contribution to higher-level cognition [72]. Besides, the dPCC has been suggested to be involved in the parietal memory system [73]. In the present study, the TLE showed increased FC in the dPCC, suggesting enhanced functionality, which might imply a compensatory phenomenon in memory function competing with the decreased FC in the TLN.

4.5. Unbalanced Dysconnectivity in Prefrontal Regions in TLE

Interestingly, the present meta-analysis found opposite FC alterations in the ipsilateral dMFG (increased) and contralateral vMFG (decreased) of the foci in patients with TLE. The dysfunction of the two regions aggravates along with the duration of disease, indicating potential long-term pathologic accumulation. The opposite alterations implied that the two regions might be affected differentially in the epileptic brain state. However, it is hard to interpret this phenomenon with specific pathological mechanisms. More focused studies are needed to address this issue. Besides, we found that the vMFG tends to have higher FC in patients with later-onset age of the disease. It has been recognized that the relationship between the plasticity of the brain and age shows an inverted U-shaped curve [74, 75]. Consistently, in previous disease searches, it has been proposed that the patients with early-onset age might have a better capacity to adapt to the disease and might recognize the brain network to some extent [76, 77]. The prefrontal cortices have been suggested to be highly malleable in multiple conditions [78]. In TLE, the FC of the vMFG might be modulated by the plasticity of the brain.

4.6. Hyperconnectivity in the Cuneus in FE

The mixed FE group included various focal epilepsies with different origins of epileptic discharges. By considering the intrinsic heterogeneity between diseases, the present findings of FE need to be taken with caution. Specifically, high heterogeneity was observed in the increased FC of the cuneus. The anterosuperior parieto-occipital sulcus divides the cuneus from the precuneus. Moreover, the precuneus is a core node of the posterior DMN, and the cuneus adjacent to the precuneus is included in the cluster of the posterior DMN, which is referred to relatively less separately. It is interesting to find the hyperconnectivity in the cuneus in patients with FE and no alterations in the precuneus in the current study. A delayed coactivation of the cuneus and the primary visual cortex in visual stimulus indicated a modulation effect of the cuneus on the visual information processing [79]. The hyperconnectivity in cuneus suggested an over-processing for the visual inputs in patients with epilepsy [80]. Although the currently included papers in the meta-analysis donot investigate the photosensitivity of patients, converging previous studies indicated a high proportion of photosensitivity in patients with epilepsy [81]. In all, we viewed this hyperconnectivity of cuneus in IGE to be a hypersensitive characteristic of the over-reaction to the external visual information in the basic state.

There are several limitations of the present meta-analysis. Firstly, the clinical information for the patients is relatively insufficient. We could not obtain the information of AED, the response to the drugs, and the frequency of seizure. Secondly, the studies of drug-naïve patients are also lacking. Thirdly, the ES-SDM approach used in the present study is based on the reported coordinates of previous studies rather than the raw imaging data, which might induce inaccuracy of the final results. Forthly, the preprocessing and statistical significance (with or without multiple comparisons correction) are not totally consistent across the studies. Although

the ES-SDM algorithm can compensate for this difference to some extent, potential artificial confounds might still exaggerate the heterogeneity between studies.

CONCLUSION

The present meta-analysis systematically reviewed the studies investigating the FC of DMN in epilepsy, revealing both common and specific alterations in distinct types of epilepsy. The current findings suggested commonly decreased FC of MPFC, highlighting its role in the generation and propagation of epileptic activities. Additional involvement of the posterior DMN and temporal lobe regions was observed in the IGE and TLE, respectively. Besides, increased FC in the dPCC and opposite dysfunction in the prefrontal cortex were referred to contribute to the specific pathomechanism in TLE. Moreover, the increased FC of the cuneus in the FE was viewed to be related to the potential visual hypersensitivity of patients. In all, this study provided evidence for the FC of DMN epilepsies and contributed to the understanding of the underlying mechanism for potentially effective intervention.

LIST OF ABBREVIATIONS

AE	=	Absence epilepsy
AED	=	Antiepileptic drugs
AG	=	Angular gyrus
DMN	=	Default mode network
dorsal ACC	=	Anterior cingulate cortex
FC	=	Functional connectivity
FE	=	Focal epilepsy
GSWD	=	Generalized spike-wave discharges
GTCS	=	Generalized tonic-clonic seizures
IGE	=	Idiopathic generalized epilepsy
JME	=	Juvenile myoclonic epilepsy
MFG	=	Middle frontal gtrus
MPFC	=	Mesial prefrontal cortex
PCC	=	Posterior cingulate cortex
TLE	=	Temporal lobe epilepsy

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

A systematic approach compliant with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was adopted.

FUNDING

This work was supported by the grant from the National Key R&D Program of China (2018YFA0701400), the National Nature Science Foundation of China (U2033217, 61933003, 81960249 and 81771822), and the CAMS Innovation Fund for Medical Sciences (CIFMS) (No.2019-I2M-5-039).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We thank Professor Jean Gotman for his valuable comments on this manuscript.

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