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Striatum- and Cerebellum-Modulated Epileptic Networks Varying Across States with and without Interictal Epileptic Discharges

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Idiopathic generalized epilepsy (IGE) is characterized by cryptogenic etiology and the striatum and cerebellum are recognized as modulators of epileptic network. We collected simultaneous electroencephalogram and functional magnetic resonance imaging data from 145 patients with IGE, 34 of whom recorded interictal epileptic discharges (IEDs) during scanning. In states without IEDs, hierarchical connectivity was performed to search core cortical regions which might be potentially modulated by striatum and cerebellum. Node–node and edge–edge moderation models were constructed to depict direct and indirect moderation effects in states with and without IEDs. Patients showed increased hierarchical connectivity with sensorimotor cortices (SMC) and decreased connectivity with regions in the default mode network (DMN). In the state without IEDs, striatum, cerebellum, and thalamus were linked to weaken the interactions of regions in the salience network (SN) with DMN and SMC. In periods with IEDs, overall increased moderation effects on the interaction between regions in SN and DMN, and between regions in DMN and SMC were observed. The thalamus and striatum were implicated in weakening interactions between regions in SN and SMC. The striatum and cerebellum moderated the cortical interaction among DMN, SN, and SMC in alliance with the thalamus, contributing to the dysfunction in states with and without IEDs in IGE. The current work revealed state-specific modulation effects of striatum and cerebellum on thalamocortical circuits and uncovered the potential core cortical targets which might contribute to develop new clinical neuromodulation techniques.

Keywords: Idiopathic generalized epilepsy; striatum; cerebellum; hierarchical connectivity; moderation; interictal epileptic discharges.

1. Introduction

Idiopathic generalized epilepsy (IGE) is characterized by paroxysmal spontaneous generalized spike-wave discharges seen with scalp EEG.[1] IGE is a brain network disease, and functional abnormalities have been identified in distributed regions.[2] The thalamocortical network is responsible for the generation and propagation of generalized spike-wave discharges and abnormal behaviors in patients.[3,4] The thalamocortical circuit plays an important role in the epileptic brain network, but it is not specific enough. To further elucidate the underlying networks, it is necessary to explore brain circuits related to the specific state of IGE.

Animal studies, computational models, and human imaging studies have provided abundant evidence that the striatum and cerebellum have critical regulatory effects on the thalamocortical network.[5–7] The striatum and cerebellum have been recognized as modulators of epileptic networks.[8,9] The potential physiological basis of the striatum's modulation effects on epilepsy depends on its regulation of the gamma-aminobutyric acid (GABA) and glutamate (Glu) system.[10] Besides, the cerebellum has also been revealed to act effectively in stopping epileptic discharges when receiving high-frequency electric stimulation.[5] A projection pathway of the cerebellum–thalamus–cerebrum is proposed to be

responsible for this effect. Specific cerebellar afferent and efferent projections have been demonstrated to be related to the disturbance in the epileptic network.[11,12] Moreover, neuromodulation techniques based on these recognized modulators in the epileptic network are also being developed.[13,14]

The functional interaction between the striatum/cerebellum and extensive cerebral cortices is the key to revealing the pathology of epilepsy. Accumulated neuroimaging studies have suggested complex dysconnectivity patterns in various epilepsies, to which the striatum and cerebellum contributed much.[15,16] However, previous multimodal studies mainly focused on the overall strength of interaction and ignored the hierarchical architecture of functional connectivity (FC). Recently, using a step-wise connectivity approach, a known connectivity stream has been revealed from primary cortices to the default mode network (DMN) in the healthy,[17] and specific brain network hierarchy was investigated in attention-deficit/hyperactivity disorder.[18] The stepwise functional connectivity (SFC) analysis with specific seeds showed specific hierarchical architecture under distinctive conditions and contributed to revealing the peculiarity of brain networks under distinct phenomena.[19] Therefore, by defining appropriate seeds, the hierarchical connectivity analysis could uncover specific functional architectures of distinct diseases.[20,21] Thus, we presume the hierarchical architecture of the epileptic modulator might help to uncover specific core regions in IGE.

The connectivity features of brain networks can reflect different emotional and cognitive states of the brain under both normal physiological and pathological conditions.[22–24] Besides, state-specific EEG and MRI profiles contribute to the diagnosis and clinical interventions of neurological and psychiatric disorders.[25–27] The EEG features are more directly relevant to epilepsy research, such as predicting seizures in patients.[28,29] Therefore, we aim to analyze the brain network mechanisms of epilepsy by integrating both the states of discharge and non-discharge using EEG and fMRI data. Interictal epileptic discharges (IEDs) usually occur suddenly and disrupt the brain network architecture.[30] In previous simultaneous EEG–fMRI studies, it is found that the characteristics of the brain network show distinct differences in the state with and without IEDs.[31,32]

Modulation effects of the striatum and cerebellum are expected to be different in periods with and without IEDs. However, the specific modulation effects of the cerebellum and striatum on epileptic brain networks in states with and without IEDs have not been characterized in human brain imaging studies so far. Therefore, we collected fMRI data with simultaneous EEG, aiming to characterize epileptic networks derived from striatal and cerebellar modulation effects. This study first identified core cortical networks hierarchically connecting to the striatum and cerebellum. Then, to uncover the potential modulation effects, we employed moderation models to explore how the striatum and cerebellum affect the cortical–cortical interactions in states with and without IEDs using a linear interaction model. A detailed analysis flowchart is illustrated in Fig. 1. Based on the hypothesis of pathological mechanism and relying on the signal analysis technology of nervous system, this research aims to solve the problem of the modulation of brain network in epilepsy, which might contribute to develop new clinical neuromodulation techniques.

2. Methods

2.1. *Participants*

One hundred and forty-five patients with IGE were collected. All patients were diagnosed as IGE according to the epilepsy classification of the International League Against Epilepsy. All patients in this study had generalized tonic–clonic seizures as the main seizure type. One hundred and fourteen healthy controls were recruited. No participants had brain lesions or other neurological disorders. The diagnosis of patients and the marking of IEDs were independently performed by two experienced clinicians (Q.L. and S.W.). In this study, a total of 34 patients showed IEDs during scanning, while the remaining 111 patients showed no discharges. Detailed information on the participants is shown in Table 1.

2.2. *Data acquisition*

MRI data were acquired on a 3T GE scanner with an eight-channel-phased array head coil (EXCITE, GE, Milwaukee, WI). Resting-state functional data were acquired using an echo-planar imaging sequence (echo time = 30 ms, repetition time = 2000 ms,

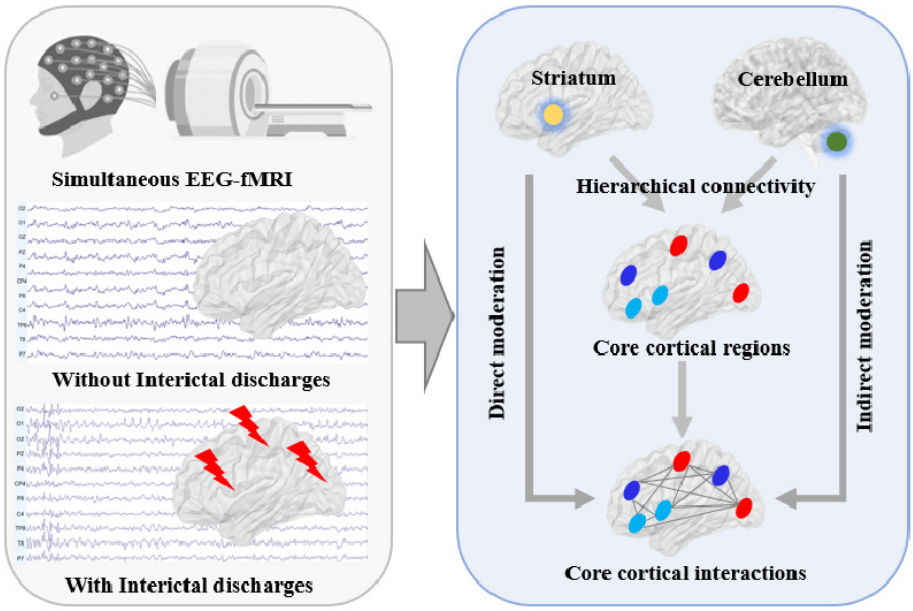


Fig. 1. Schematic overview of the analytical pipeline. The striatum and cerebellum were selected as seeds of analysis because of their recognized modulation roles in the epileptic network. The resting-state fMRI data were divided according to the presence and absence of IEDs during the scan. Striatal and cerebellar hierarchical connectivity is depicted by step-wise FC and modulation effects are depicted by multiple moderation models.

data matrix $= 64 \times 64$, flip angle $= 90°$, slice thickness $= 4$ mm (no gap)). Electroencephalogram (EEG) during fMRI was acquired using a 64-channel MR-compatible EEG cap (Neuroscan, Charlotte, NC) with an amplifier (Neuroscan, synAmps2) outside the scanning room. A reference was set on the Fcz according to the 10–20 standard system. The EEG sampling rate was 5000 Hz. All subjects were asked to close their eyes without falling asleep. Each scan lasts 400 s, generating 200 volumes.

2.3. *Preprocessing*

A self-developed software package NIT was used for preprocessing fMRI data.[33] The first five volumes of each run were discarded and slice-timing correction,

Table 1. Study cohort demographics of IGE and control participants.

	IGE				
Characteristic	fMRI scan without IEDs	fMRI scan with IEDs	HC	p-value[a]	p-value[b]
Number	111	34	114	—	—
Age (year)	25.9 ± 7.7	25.3 ± 7.8	26.1 ± 7.6	0.65	0.58
Gender (M:F)	60:51	19:15	72:42	0.85	0.17
AED (with: without)	74:37	22:12	—	0.83	—
Age at onset (year)	19.9 ± 8.6	20.8 ± 8.2	—	0.53	—
Duration (year)	6.2 ± 7.9	4.5 ± 5.3	—	0.26	—

[a]A comparison between IGE with and without IEDs.
[b]A comparison between IGE and HC.
Notes: IGE: idiopathic generalized epilepsy; IEDs: interictal epileptic discharges; HC: healthy controls; AED: antiepileptic drugs.
Two fMRI datasets with and without IEDs come from two independent samples. We collected 145 patients here.

realignment, and spatial normalization to the Montreal Neurological Institute template were conducted successively. Then, 24 head-motion parameters, white matter, and cerebrospinal fluid signals were regressed. Finally, the fMRI data were filtered in the 0.01–0.1 Hz band. Preprocessed data were down-sampled to 6 mm isotropic voxels for the computational efficiency of the following hierarchical connectivity analysis. Curry 7 software (Compumedics Neuroscan) was used to preprocess the EEG data. The MR gradient artifacts and ballistocardiac were removed using template artifact subtraction.[34] Then, processed EEG data were bandpass filtered (1–45 Hz) and down-sampled to 250 Hz. The onset and offset of IEDs were first marked by S.W. and subsequently confirmed by Q.L.

2.4. *Hierarchical connectivity analysis in patients without IEDs during the scan*

To identify core cortical regions connecting to the striatum and cerebellum, we performed a hierarchical connectivity analysis in resting-state fMRI data without IEDs using a recently-developed SFC approach which detects connectivity streams with consideration of successive numbers of "link-step" distances.[18,19] The seeds interact with easily connected regions via short-distance connections, and with core brain regions (so-called regions with hubness) via longer-distance connections. We defined the cerebellum and striatum as seeds and calculated SFC up to 20-step distances. The value of SFC was employed to evaluate the strength of hierarchical connectivity. For a given voxel, we recorded the distance at which it is first significantly ($p < 0.05$, FWE corrected) connected to the seed, which was defined as the preferred link-step distance. Network-level preferred link-step distance was calculated by the average of all voxels in a given network. Moreover, we further explored the spatial scope in each step. The number of voxels significantly ($p < 0.05$, FWE corrected) linked with the seed at each step was recorded as the spatial scope of connectivity. Network-level preferred link-step distance and spatial scope were z-scored and compared between groups. The network-level spatial scope was calculated by the ratio of the number of significantly connected voxels to the whole voxel number in the network. Seven network templates were defined according to the work of Yeo *et al.*[35] T-tests were used to detect case-control differences in SFC strength, distance, and scope. Regions with significant case-control differences in hierarchical connectivity analysis were defined as seed regions in the following moderation analysis.

2.5. *Direct and indirect moderation analysis in patients without IEDs during the scan*

Direct moderation was identified by constructing node–node moderation models with time courses (TC) of nodes as variables (Fig. 2(a)). Specifically, the TC of cortical regions act as independent and dependent variables. Particularly, the striatum and cerebellum significantly connected with the thalamus, and the thalamocortical circuit played crucial roles in IGE, thus we also employed the thalamus as a modulator in the moderation analysis. Thus, the TC of the thalamus, striatum, and cerebellum were extracted to act as moderators in the node–node moderation model. The node–node moderation portrayed a three-node moderation clique (chain-like clique). The positive moderation effect signifies that the modulator can strengthen the relationship between dependent and independent variables. Negative modulation indicates a weakening role. For the within- and between-groups significant node–node moderation cliques, one-sample and two-sample t-tests were used for the β_{inter} values ($p < 0.05$, uncorrected). Group comparison statistics were performed only if there was a significant node–node moderating effect within at least one group.

The relationship between two regions can be described not only by the direct relationship between the two regional signals themselves but also by the indirect relationship between them and one or more common regional connections. Such an analysis is already available in brain network studies.[36,37] In this study, to further uncover indirect moderation effects, edge–edge moderation models were constructed with the connectivity series across subjects as variables (Fig. 2(b)). The edge–edge moderation model aims to discover such an indirect moderation clique, that if region i and region j both connect to a region k, then the association between i and j can be moderated by k-related connections. Based on the hypothesis of this study, we, therefore, defined that

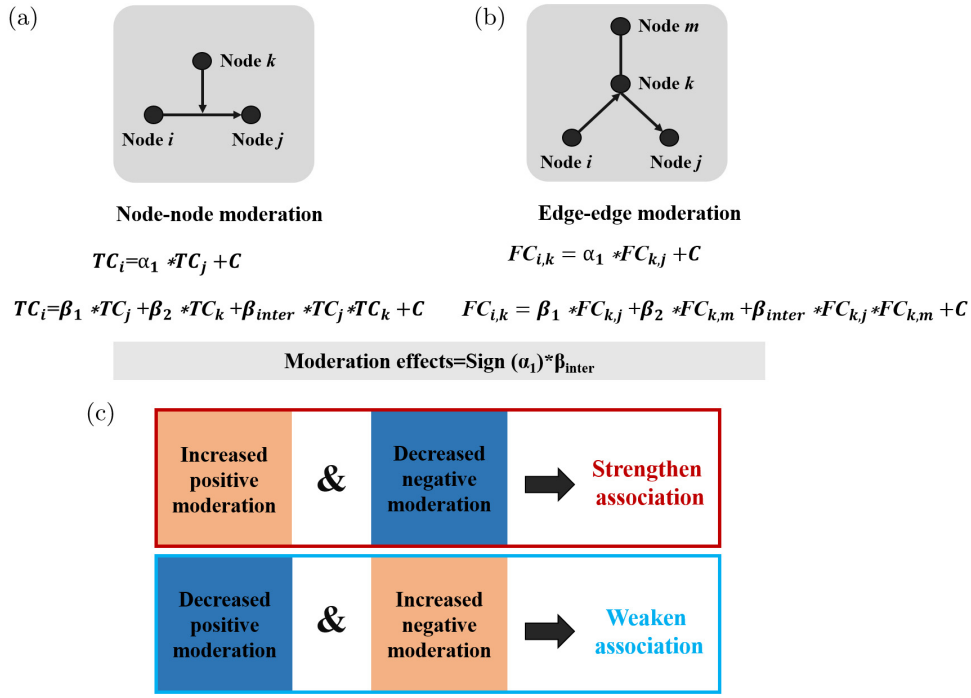


Fig. 2. Construction of moderation models. (a) A node–node moderation clique was created by a general linear model, based on the interaction of TC between regions. (b) An edge–edge moderation clique was created by a general linear model, based on the interaction of FC between edges. Notably, to avoid the influence of multicollinearity on the main effect, we use the regression coefficient in the model without interaction terms as the reference for the main effect. C, residual; β, regression coefficient. The subscripts i, j, k, and m represent different brain regions. $FC_{i,k}$ represents the FC between region i and j. (c) In case-control comparisons, both the increased positive moderation and decreased negative moderation indicate a role in strengthening association between variables, and both the decreased positive moderation and increased negative moderation indicate a role in weakening association between variables.

region k must be a region of the striatum, cerebellum, or thalamus. The edge–edge moderation portrayed a four-node moderation clique (star-like clique), illustrating that one node moderates the interaction between the other two nodes through another node. To test the significance of the edge–edge moderation, the interaction item with $p < 0.05$ (without correction) was first considered a possible moderation effect. To further verify the reliability, 10,000 times sampling without replacement (sampling 50 subjects each time) was performed within the group to access the occurrence probability of significant star-like cliques ($p < 0.05$, uncorrected). The moderating effect was considered significant within the group only if the occurrence probability was greater than 0.6 in bootstrapping. Only the moderating effects that were significant within at least one group were compared between groups. Significant between-group differences in edge–edge moderation were detected using a permutation test, randomly assigning participants 10,000 times. Notably, in case-control comparisons, both the increased positive moderation and decreased negative moderation indicate a role in strengthening association between variables, and both the decreased positive moderation and increased negative moderation indicate a role in weakening association between variables (Fig. 2(c)).

2.6. *Direct and indirect moderation analysis in patients with IEDs during the scan*

In the frequency band from 0.01 Hz to 0.1 Hz, a window length less than $1/f$ (= 100 s) doesn't cover the signals at the lowest frequency, which seems inappropriate for a correlation analysis.[38] Thus, we chose a window length of 50 TR for moderation analysis in the period with IEDs, to include information about the stages of discharge generation, propagation, and termination. We selected

consecutive periods of data with the IEDs located in the center of the window. The selected period must meet the condition that there is no discharge except for the central IEDs. Finally, 28 patients met the criteria and were further analyzed. In all selected patients, the average discharge time is 9 s, and the shortest discharge time is 2 s. If a patient has multiple IEDs and can extract multiple periods that meet the criteria, we will average different data windows. Then, the node–node, and edge–edge moderation models were constructed using the windowed data.

To detect significant moderation effects in periods with IEDs relative to periods without IEDs and HC, we first segmented all data into periods and then randomly selected one period from each subject 10,000 times, resulting in 10,000 sampled groups of patients without IEDs and 10,000 sampled groups of HC. Case-control comparisons of node–node (t-test) and edge–edge (permutation test) moderation were conducted 10,000 times. We set a more stringent statistical threshold to avoid false positive results. Of the 10,000 comparisons, only those showing significance in at least 95% of them will be retained. Case-control differences were finally characterized by averaged differences across 10,000 comparisons.

2.7. *IEDs-induced functional connectivity*

In each subject, a modulation model was constructed with IEDs events as the moderator, aiming to illustrate the connectivity modulated by epileptic discharges. Significant IEDs-modulated connectivity was determined by comparing it with a null model constructed by randomly scrambling the correspondence between IEDs events and subjects 10,000 times.

3. Results

3.1. *Case-control differences of the SFC*

Notably, the hierarchical architecture is defined by functional profiles in this work, which is a physiology not an anatomy, reflecting potential information flow pathways. In HC, the striatum and cerebellum are both convergently connected to cortical regions in the DMN and attention network. However, the striatum and cerebellum convergently connected to cortical sensorimotor network (SMN) and visual network in patients with IGE (Fig. S1). Abnormal strength of SFC was observed in IGE ($p < 0.05$, FDR corrected; Figs. 3(a) and 3(b)). Since the case-control differences in SFC strength become stable after step 5, we only demonstrated the first five steps ($p < 0.05$, FDR corrected; Figs. 3(a) and 3(b)). The striatum showed increased connectivity with the anterior cingulate cortex (ACC) at short link-step distances (steps 1–3) and increased connectivity with the visual cortices (VC), decreased connectivity with the mesial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and insula at relatively long link-step distances (steps 4 and 5). The cerebellum showed increased connectivity with VC and decreased connectivity with the MPFC and PCC at almost all distances (except step 1). Meanwhile, the cerebellum showed increased connectivity with the sensorimotor cortices (SMC) and decreased connectivity with the insula at long distances (steps 4 and 5).

The striatum connected to the SMN with shrunken spatial scope in relatively short link-step distances and extended spatial scope in long link-step distances. In contrast to the SMN, the striatum is connected to the DMN with extended spatial scope in short distances and shrunken spatial scope in long distances. The cerebellum connected to the SMN with extended spatial scope in relatively long link-step distances ($p < 0.001$; Fig. 3(c)).

3.2. *Moderation effects in fMRI data without IEDs*

Based on case-control comparisons of SFC, the MPFC, PCC, SMC, VC, ACC, and insula were selected as cortical nodes for the moderation analysis. There are five different node–node moderation effects between HC and IGE ($p < 0.001$, uncorrected; Fig. 4(a)). Decreased thalamic negative moderation on the connectivity from SMC to ACC and decreased striatal negative moderation on the connectivity from MPFC to PCC were found in IGE. Patients also showed increased cerebellar negative node–node moderation on bidirectional connectivity between ACC and MPFC, and connectivity from SMC to ACC ($p_{\text{perm}} < 0.001$, uncorrected). The thalamus showed increased negative moderation on connectivity from SMC to ACC through the

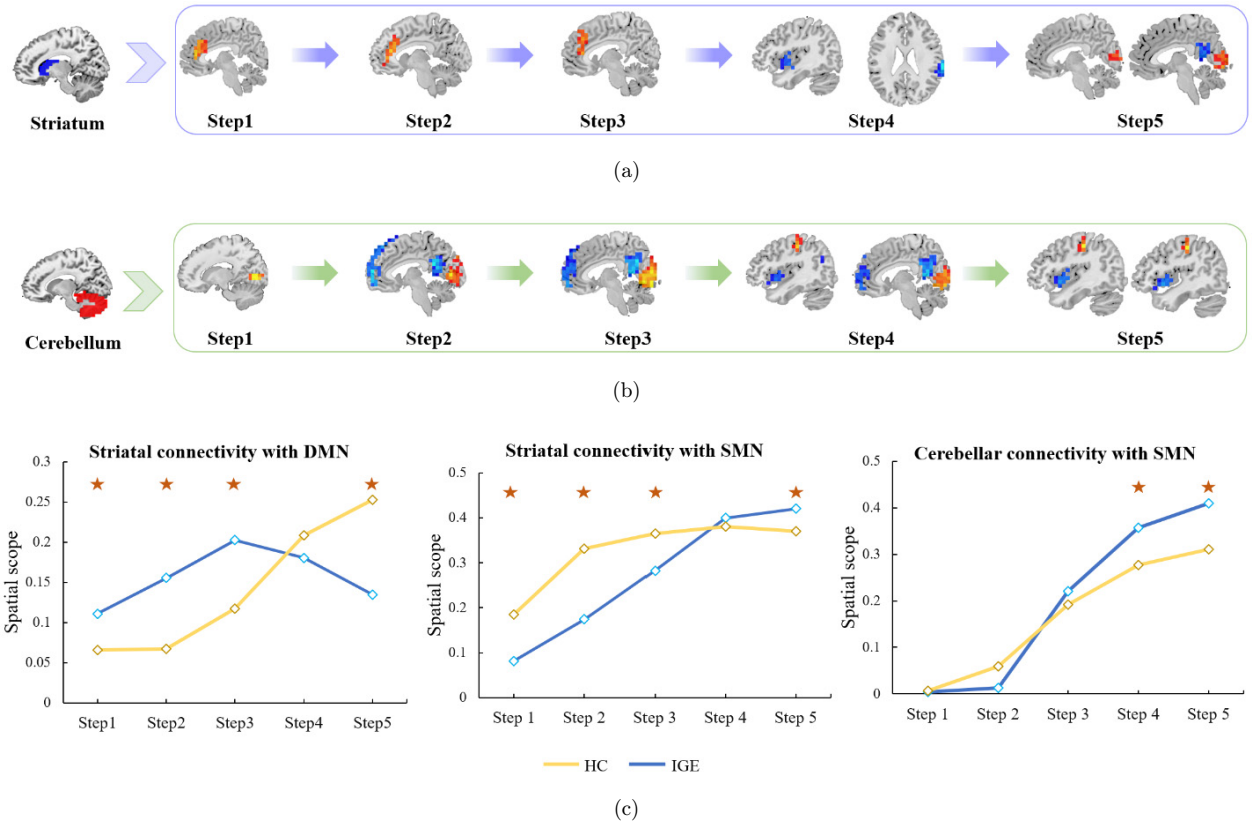
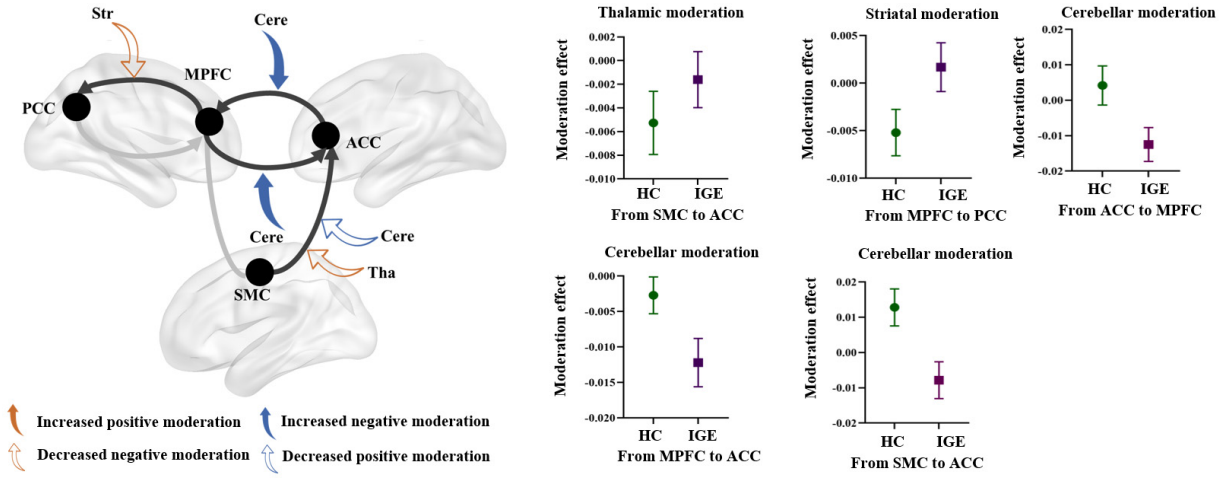


Fig. 3. (Color online) Characteristics of the abnormal hierarchical connectivity. Patients with IGE showed abnormal step-wise connectivity strength seeding at the striatum (a) and the cerebellum (b) compared with the HC ($p < 0.05$, FDR corrected). (c) Case-control differences of the spatial scope. The red asterisk (*) indicates $p < 0.001$ without correction.

cerebellum and the cerebellum showed decreased positive moderation on connectivity from PCC to the insula through the striatum. Besides, the thalamus showed reversed negative moderation on connectivity from MPFC to PCC through the striatum, and the striatum showed reversed negative moderation on connectivity from PCC to the insula through the thalamus (Fig. 4(b)).

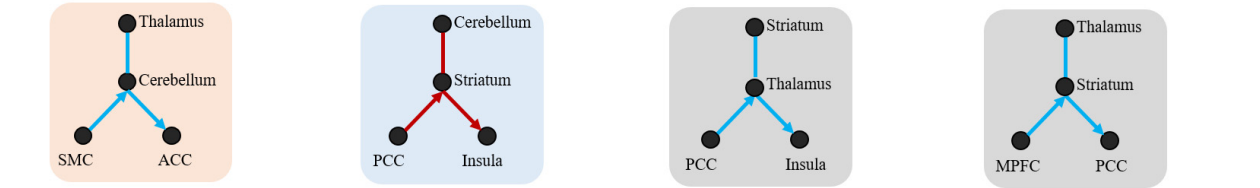
3.3. *Moderation effects of IEDs on cortical interaction*

According to the rule that the discharge must be in the center of the data segment, the IEDs that occur within 20 s after the start of the scan and within 20 s before the end of the scan are not available. Finally, the fMRI data of 28 patients with IEDs were further analyzed. Compared to periods without IEDs, increased node–node and edge–edge moderations were observed in periods with IEDs. The connectivity from PCC to the insula and the connectivity from the SMC to the insula were negatively moderated by the thalamus, and the connectivity from the ACC to the insula was positively moderated by the thalamus and striatum ($p < 0.001$, uncorrected; Fig. 5(a)). Four indirect increased positive moderation effects were recognized in periods with IEDs in contrast to periods without IEDs ($p < 0.001$, uncorrected; Fig. 5(b)). The cerebellum positively moderated the connectivity from PCC to SMC through the striatum and positively moderated the connectivity from the MPFC to PCC through the thalamus. The striatum positively moderated the connectivity from the PCC to the insula through the cerebellum. The thalamus positively moderated the connectivity from the PCC to the Insula through the cerebellum. The thalamus also positively moderated the connectivity from the PCC to the insula through the cerebellum. Moreover, relative to HC, patients with IEDs also showed predominantly increased node–node and edge–edge



Direct moderation in states without IEDs relative to HC

(a)



Increased negative moderation	Decreased positive moderation	Reversed negative moderation	Reversed negative moderation
HC: Moderation effect =-0.56;	HC: Moderation effect =0.94(*)	HC: Moderation effect =1.66 (*)	HC: Moderation effect =0.86 (*) ;
IGE: Moderation effect =0.69 (*)	IGE: Moderation effect =0.12 (*)	IGE: Moderation effect = -0.15 (*)	IGE: Moderation effect =-0.53 (*)

Indirect moderation in states without IEDs relative to HC

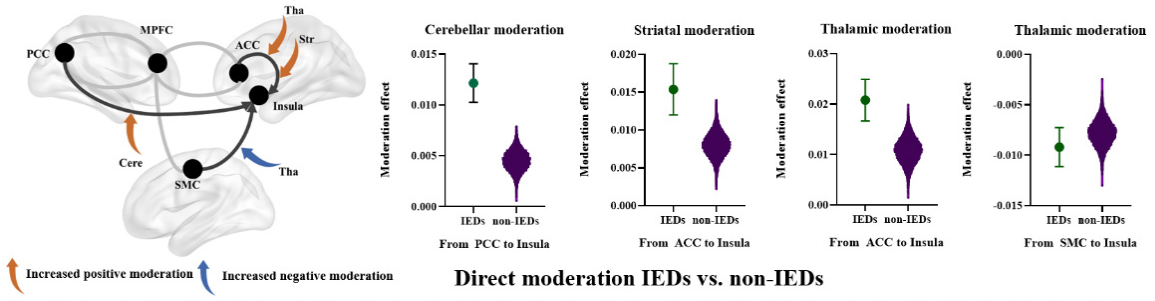
(b)

Fig. 4. (Color online) Moderation in IGE in periods without IEDs compared with the HC. (a) Case-control comparison of node–node moderation effects ($p < 0.001$, uncorrected). (b) Edge–edge indirect moderation in IGE without IEDs relative to the HC ($p_{\text{perm}} < 0.001$, uncorrected). The red asterisk (*) indicates $p < 0.05$ without correction. The red star-like moderation clique indicates a positive moderation effect, and the blue star-like moderation clique indicates a negative moderation effect. The orange square background indicates increased moderation, the blue square background indicates decreased moderation, and the gray square background indicates reversed moderation.

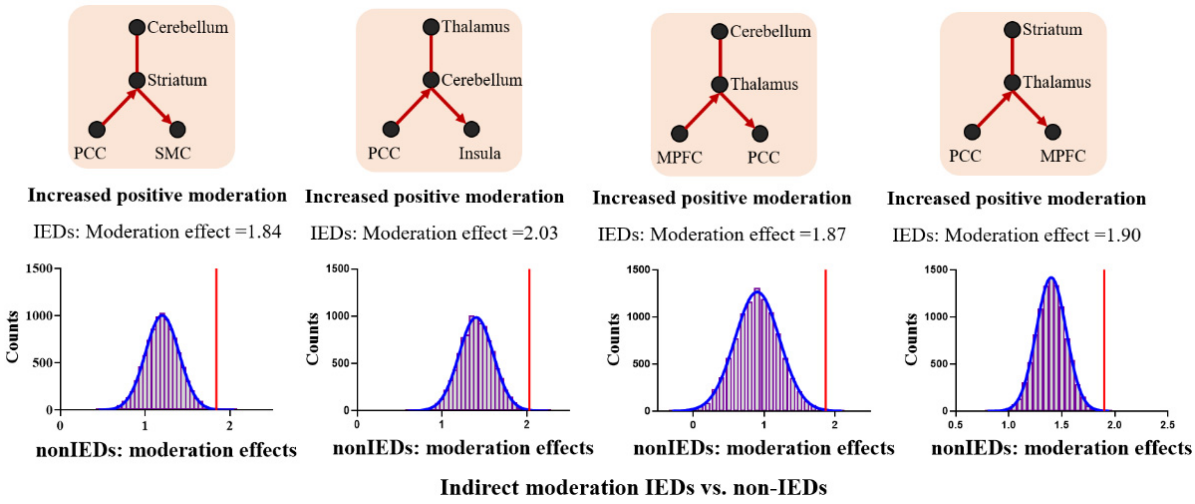
moderation effects (Figs. S2 and S3). The FC induced by IEDs was characterized by convolving the discharge moment as an event with the HRF function and then introducing a linear regression model. Compared with a permuted null model, we found that IEDs induced significant ($p_{\text{perm}} < 0.01$, uncorrected) positive connectivity from PCC to SMC (Fig. 6).

4. Discussion

Inspired by the recognized modulation role of the striatum and cerebellum in epileptic networks, this study investigated how they affect the epileptic network in different brain states (with and without IEDs) in IGE. We collected fMRI data with simultaneous EEG from patients with IGE. This work provided evidence that the striatum and cerebellum are abnormally hierarchically connected with SMC and regions in the DMN and regions in salience network (SN). Then, in the state without IEDs, the cerebellum and striatum played moderation roles in weakening DMN–SN and SN–SMC interactions. Interestingly, the thalamus directly strengthened the SMC–ACC interaction but indirectly weakened SMC—ACC through the cerebellum. Overall enhanced moderations on the over-interaction in



(a)



(b)

Fig. 5. Moderation in periods with IEDs compared without IEDs. (a) Node–node moderation in periods with IEDs relative to periods without IEDs ($p < 0.001$, uncorrected). (b) Edge–edge indirect moderation in periods with IEDs relative to periods without IEDs ($p_{\text{perm}} < 0.001$, uncorrected). The frequency diagram plot on the last line shows distribution of the moderation effects in 10,000 sampled periods without IEDs.

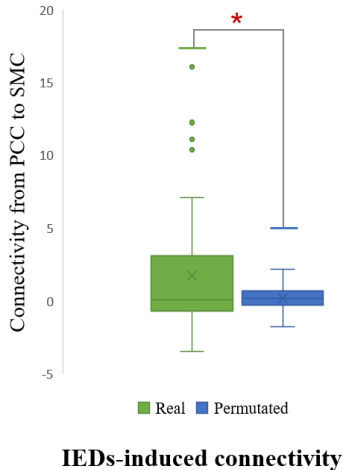


Fig. 6. IEDs-induced connectivity. The IEDs evoked significant connectivity from PCC to SMC ($p_{\text{perm}} < 0.01$, uncorrected).

DMN–SMC and DMN–SN were observed in states with IEDs. Meanwhile, the SN–SMC interaction was negatively moderated by the striatum and cerebellum. Moreover, the epileptic discharges also directly modulated the connectivity from PCC to SMC (Fig. 7). It is noteworthy that our work provides evidence from a physiological prospective not an anatomical prospective to uncover the state-specific effects of striatum and cerebellum on the thalamocortical circuits.

The abnormality of regions in SMN is usually linked to the motor symptoms of patients with epilepsy. Hyperexcitability of the motor cortex was inferred to contribute to the susceptibility of the epileptic brain.[39] Increased functional integration of the SMC in epilepsy was inferred to contribute to the

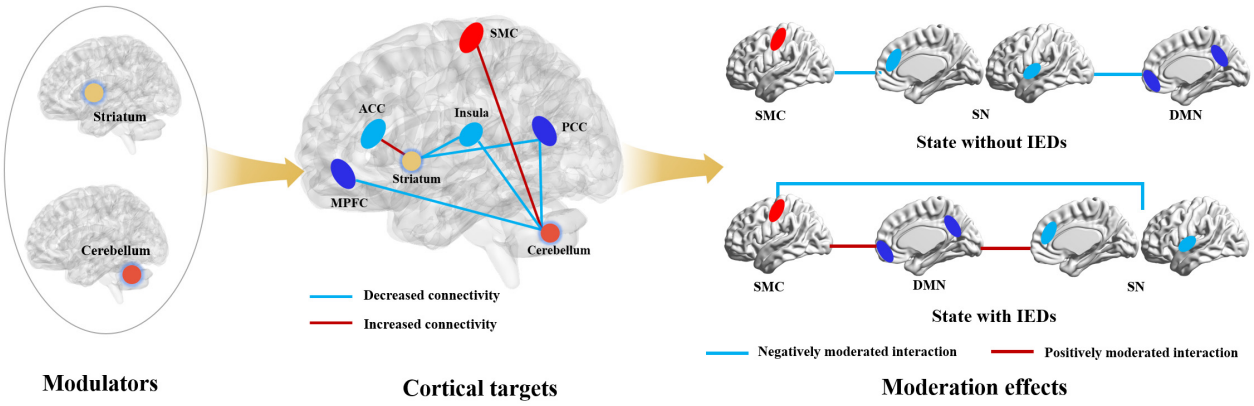


Fig. 7. Summary of the modulation effects in patients with IGE in different states. Patients showed increased hierarchical connectivity with SMC and decreased connectivity with regions in the DMN. The striatum, cerebellum, and thalamus negatively moderated the interactions of regions in the SN with DMN and SMC in the state without IEDs. Positive moderation effects on the interaction between regions in SN and DMN, and between regions in DMN and SMC, and negative moderation on interactions between regions in SN and SMC were observed in periods with IEDs.

vulnerability of the epileptic brain.[40] We also found hierarchical hyper-connectivity between SMC and striatum and cerebellum at relatively longer link-step distances, supporting the susceptibility of the SMC in IGE. Hierarchical connectivity studies have demonstrated an information flow stream from lower-order (regions in the SMN) to so-called hub cortices (regions in the DMN).[18,19] However, we found the extended spatial scope and prolonged link distance of the SMN, which consistently supported its "over-hubness", implying that the IGE was trapped in motor signal processing. In other words, SMN has taken the place of DMN in the central position in patients with IGE. As known, the activity of the DMN played a crucial role in the generation and propagation of generalized epileptic activities, which have been demonstrated to be suspended during the interictal period.[3] Long-term recurrent discharges might have impaired the overall function of the DMN.[41,42] In this study, we revealed hierarchical hypo-connectivity between regions in the DMN and striatum and cerebellum from medium to long link-step distances, indicating cascading effects along with the primary to higher-order function continuum, which might be related to the long-term and recurrent functional suspension of the basic brain state in seizures. Moreover, in this study, we also found significantly extended spatial scope between DMN and striatum in a relatively short link distance and shrunken spatial scope in a relatively longer link distance, providing evidence to suggest the "under-hubness" of DMN in IGE.

The SN consists of the anterior cingulate cortex ACC and the insula and is responding the differentiating relevant stimuli and irrelevant stimuli and assigning salience to stimuli-focused information.[43] Besides, the SN also coordinates behavior-relevant networks away from the DMN.[44,45] Meanwhile, the striatum could cooperate with the SN, affect the state shifting of the brain during attention tasks,[46] and moderate the deactivation of the DMN through dopamine-predominated pathways.[47] In periods without IEDs, we found the thalamus negatively moderated the interaction within DMN through the striatum, which might be responsible for the disconnectivity of DMN.[48] A previous study of vague nerve stimulation indicated that the balance between the DMN and SN played a core role in treatment in patients with epilepsy.[49] Consistently, in this study, the striatum, cerebellum, and thalamus played roles in weakening the interaction between regions in the DMN and SN, implying a reduced control over internal self-referential activities. Meanwhile, the cerebellum and thalamus also played roles in weakening the interaction between the regions in SN and SMC, contributing to the loss of control of the sensorimotor information in states without IEDs. Decreased suppression of the cerebellum has been

identified to be a cause of increased somatosensory, which is responsible for motor abnormalities in epilepsy.[50] Moreover, motor hyperactivation during cognitive tasks has been widely recognized in patients with generalized epilepsy, suggesting an easily motivated motor state when processing external salient stimuli.[51] Our findings further supported and supplemented the involvement of SN in the abnormal processing of sensorimotor information. In all, these findings profiled a metastable brain state characterized by the striatum, cerebellum, and thalamus weakening on the SN–SMN and SN–DMN interactions in IGE, which contribute to the susceptibility and vulnerability of the epileptic network.

Most of the evidence that the cerebellum and striatum regulate epileptic discharges is from invasive animal experiments,[52] but there are few results from imaging studies. We found the thalamus, striatum, and cerebellum together contributed to strengthening the interaction between regions in DMN and SMN, and between DMN and SN, resulting in enhanced interactions in the epileptic network in periods with IEDs, which was in line with the dynamic over-synchronization of epileptic networks evoked by the IEDs.[3,53] The interaction between the striatum and thalamus was suggested to be related to the presence of seizure generalization.[54] A previous study suggested that the thalamus and striatum might be facilitators of the generation and propagation of IEDs by weakening the monitoring of regions in SN on the SMC.[55] Consistently, we also found that the thalamus and striatum played roles in weakening the interaction between regions in SN and SMC. Taken together, the present findings further supported that the thalamus, striatum, and cerebellum contributed to the over-interacted network in periods with IEDs and the loss of control of SN on SMC in periods with IEDs in IGE.

Previous EEG–fMRI studies revealed dynamic brain network states in human generalized spike-wave discharges, illustrating brain network evolution in pro-ictal, pre-ictal, ictal, and post-ictal periods.[31] Tangwiriyasakul *et al.* recognized gradually elevated synchrony from the SMC to posterior precuneus regions, which was referred to contribute to a state predisposing to discharge onset. Consistently, we also found that the IEDs positively modulated (strengthening) the connectivity from PCC to SMC, indicating a driving role of the PCC in the epileptic brain,[56] which might trigger an over-synchrony motor brain state facilitating the generation of generalized spike-wave discharges.[57] Combining moderation effects in states with and without IEDs, we further suggested the over-interaction between DMN and SMC might be a crucial feature determining the presence of epileptic discharges.

However, it is worth noting that the scalp EEG signals may not capture all epileptic discharge events, and there may be epileptic discharges that are not visible. Therefore, the recorded discharges may have some inaccuracies, affecting the characterization of the true modulation effects of the discharge state. Additionally, in our study, some patients may have had epileptic discharges during the scanning but were classified into the group without discharges, introducing potential errors in statistical comparisons. Fortunately, our study has a moderately large sample size, providing some tolerance for errors. Therefore, we believe that the results of this study are stable and have reference value.

5. Limitations

There were several limitations in our study. First, the average discharge time within one window is only 9 s, which may cause low detection efficiency. According to previous studies, abnormal brain functional activities last for a relatively long period.[31] Thus, our study reveals to a certain extent the moderation effect in the whole process of the generation, propagation, and termination of the IEDs. Besides, this study did not provide more detailed information on the clinical manifestations of the patients, such as seizure frequency. Additionally, the fMRI data with IEDs were observed in a relatively small sample. Moreover, when calculating the modulation effects of IEDs on connectivity, we used the traditional classical hemodynamic response function without considering individual and regional differences. This study focused on the striatum and cerebellum, but other brain regions involved in epileptic networks may be overlooked. It's necessary to study modulation effects in the whole brain in the future work. Finally, although we uncovered the moderation effects in states with and without IEDs, it is insufficient to describe the causal relationship between the IEDs and altered functional interactions.

6. Conclusion

Taken together, driven by the modulation role of the striatum and cerebellum, this study designed a framework to investigate the striatal and cerebellar modulation effects on the epileptic network. A core cortical network consisting of regions in DMN, SN, and SMC was recognized to be a potential modulation target of the striatum and cerebellum. A metastable state without IEDs was characterized by the striatum and cerebellum playing roles in weakening SN–DMN and SN–SMC interactions in alliance with the thalamus. Overall increased moderation effects on cortical interactions were observed in the disrupted state with IEDs. The abnormal interaction between DMN and SMC might be a crucial characteristic difference in the states with and without IEDs. Moreover, the PCC seems to be a trigger to fire the SMC during the period of discharges.

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