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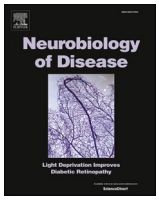

Different connectivity patterns of MRI-negative drug-resistant epilepsy and drug-sensitive epilepsy in cerebellar and subcortical-cortical regions

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ABSTRACT

Controlling cerebellar output may reduce seizure frequency. However, the involvement of the cerebellum in the development of drug resistance remains unclear. This study aims to elucidate the cerebellar-subcortical/cortical connectivity in drug resistance mechanisms using a multimodal approach. We utilized connectivity to select moderation and mediation models to further investigate the contact between the alteration of cerebellar-subcortical/cortical connectivity and drug resistance, taking into account the effect of duration. We compared MRI-negative individuals with drug-resistant epilepsy (DRE), drug-sensitive epilepsy, and healthy controls. The findings revealed a decoupling of connectivity between the cerebellum and subcortical nuclei in DRE. The deviation re sults support the crucial connected role of SCN and cerebellum for drug resistance in epilepsy. Additionally, the results suggest that this increased hyperconnectivity between subcortical and cortical regions, influenced by the cerebellum and the duration of the disease, possibly playing a key role in the development of drug resistance in epilepsy. The thalamus and middle occipital gyrus emerged as particularly significant regions in this context.

1. Introduction

Drug-resistant epilepsy (DRE) remains a significant challenge for medical practitioners, patients' families, and society at large. Despite a broad array of antiseizure medications (ASMs) that effectively control seizures, one-third of epilepsy patients develop DRE (GBD 2016 Neurology Collaborators, 2019). Beyond the seizures, associated issues such as social isolation, stigmatization, and unemployment cause substantial distress (Hohmann et al., 2024). The underlying mechanisms of drug resistance in epilepsy, however, remain poorly understood.

Advances in magnetic resonance imaging (MRI) studies on the pathogenesis of epilepsy have highlighted the critical role of the thalamocortical circuit in the onset and progression of the disease (Warsi et al., 2022). Neuromodulation techniques, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS), have been shown to reduce seizures by modulating this circuit (Gouveia et al., 2024). Previous studies have revealed abnormalities in the functional and structural integration of the cerebellum, basal ganglia, and thalamus, which influence the excitation-inhibition balance in patients with idiopathic generalized epilepsy (IGE) (Gong et al., 2021). These findings suggest

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that interactions among the cerebellum, subcortical nuclei, and cerebral cortex play a role in epilepsy pathogenesis. Optogenetic studies have demonstrated that activating Purkinje cells in the cerebellar cortex in epilepsy models can inhibit seizures by exciting the deep cerebellar nuclei (DCN), which then send inhibitory signals to the thalamus (Krook-Magnuson et al., 2014). Interictal epileptic discharges have shown that the cerebellum, striatum, and thalamus jointly regulate cortical network interactions in IGE (Jiang et al., 2024a). The cerebellum and subcortical nuclei are thus crucial in seizure regulation. Additionally, the cerebellum is implicated not only in seizure activity but also in the development of drug resistance (Ibdali et al., 2021). The prevalence of DRE associated with cerebellar degeneration is notably high at 87.2% (Ibdali et al., 2021). In DBS studies, patients with DRE showed strong structural connectivity (SC) between the thalamus and several brain regions including the brainstem, basal ganglia, cerebellum, primary sensorimotor areas, and premotor areas. This extensive structural connectivity may enable the brain to desynchronize, suggesting the cerebellum as a significant clinical target for neuromodulation in DRE (Remore et al., 2023).

Using functional connectivity (FC), studies have identified alterations in cortical networks between DRE and healthy controls (Bacon et al., 2023; Ding et al., 2023). However, unimodal analyses are often insufficient for exploring the mechanisms of drug resistance. SC lays the groundwork for FC (Straathof et al., 2019). It has been observed that connectivity within the default mode network (DMN) correlates with poor surgical outcomes in temporal lobe epilepsy, based on SC-FC coupling analyses (Zhou et al., 2024). Therefore, building on previous research, this study posits that in DRE, there is abnormal connectivity between the cerebellum, subcortical nuclei, and cortical regions. We enrolled MRI-negative participants with DRE and drug-sensitive epilepsy (DSE). Employing a multimodal approach, we integrated structure-function coupling analysis to clarify the role of cerebellar-subcortical/cortical connectivity in drug resistance mechanisms. To further dissect the interactions among nodes and edges, we utilized both moderated and mediated models based on our connectivity findings, incorporating disease information into our analysis. A detailed flowchart is presented in Fig. 1.

2. Materials and methods

The study received approval from the Ethics Committee of the First Affiliated Hospital of Hainan Medical University. All participants provided signed informed consent.

2.1. Participants

Participants for this study were recruited from the Department of Neurology at the First Affiliated Hospital of Hainan Medical University. We included individuals with DRE, DSE, and healthy controls (HC), matched by gender and age. All patients met the ILAE diagnostic criteria for epilepsy (Scheffer et al., 2017). The baseline was *Time1*, and *Time2* was one year after taking ASMs, during which the ASMs protocol remained unchanged. Patients were followed for 12 months. 50% Responder: patients having a decrease in seizure frequency of ≥50% (Touma et al., 2022). In this study, patients whose seizure frequency at Time 2 was reduced by more than 50% compared to that at Time 1 were defined as DSE. Those who took two ASMs regularly and correctly but failed to achieve sustained seizure freedom were classified as DRE (Perucca et al., 2023). The seizure type of all included subjects was epilepsy with Generalized Tonic-Clonic Seizures Alone (GTCA) or focal to bilateral tonic-clonic seizures (FBTCS). The exclusion criteria applied to all patients included: T1 structural image and T2 Flair image revealed any lesions or structural abnormalities such as hippocampal sclerosis; Contraindications to MRI, such as metallic implants or claustrophobia; Subjects had a history of epilepsy surgery; A history of traumatic brain injuries or drug abuse; The Subjects had stroke, Alzheimer's disease, Parkinson's disease, anxiety, depression, and schizophrenia.

2.2. Image acquisition

MRI data were collected at *Time2* using a 3 T MRI scanner (Discovery MR750, GE). During scans, subjects were instructed to relax, close their eyes, and avoid any specific mental activities while staying awake. T1WI was performed using a T1-3DFSPGR sequence with these parameters: TR = 6.012 ms, TE = 1.968 ms, flip angle (FA) = 9°, matrix = 256 × 256, field of view (FOV) = 25.6 cm × 25.6 cm, layer thickness = 1 mm, and

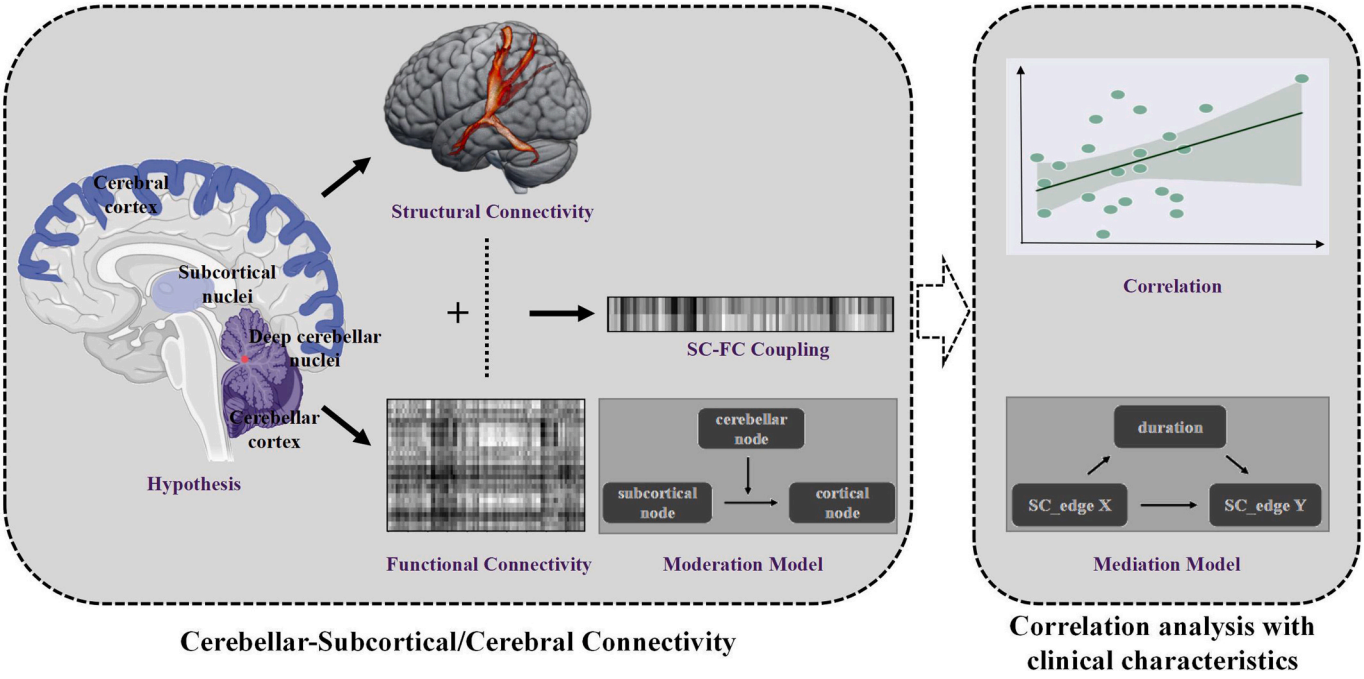

Fig. 1. Hypothesis and flowchart of the analysis. SC: Structural Connectivity; FC: Functional Connectivity.

152 consecutive layers were scanned in axial position. Functional MRI (fMRI) was conducted using an echo planar imaging (EPI) sequence with parameters: TR = 2000 ms, TE = 30 ms, FA = 90°, FOV = 24 cm × 24 cm, matrix = 64 × 64, layer thickness = 4 mm, gap = 0.4 mm, and 255 whole-brain images were acquired each session. Diffusion tensor imaging (DTI) was acquired with an echo planar imaging sequence with parameters: TR = 8500 ms, TE = 63 ms, FA = 90°, single-shot, FOV = 25.6 cm × 25.6 cm, matrix = 128 × 128, layer thickness = 2 mm, 77 consecutive layers were scanned in axial position, with 3 b0 (b = 0) and 64 diffusion-weighted (b = 1000s/mm^2) whole-brain images.

2.3. Data preprocessing

In this study, DiffusionToolkit (https://trackvis.org/dtk/) was used to preprocess the DTI data. Initially, non-brain tissue was removed using the brain extraction tool (BET) in FSL. For each subject, 64 whole brain diffusion-weighted images were registered to an average B0 image without diffusion-weighted using affine transformations to correct for head motion. Eddy current correction was then performed using the eddy tool in FSL to address eddy distortion and magnetic susceptibility artifacts.

Preprocessing of the fMRI data was conducted using the NIT software package (https://www.neuro.uestc.edu.cn/NIT.html). The preprocessing steps included: (1) discarding the initial five time points to ensure magnetic field stability; (2) performing time layer correction and estimating head movement, excluding participants with head motions exceeding 3 mm or 3° in any direction; (3) conducting spatial normalization by using EPI templates to MNI space and resampling each voxel to 3 × 3 × 3 mm^3; (4) applying Gaussian smoothing with a smoothing kernel of 6 mm to enhance the signal-to-noise ratio; (5) regressing out 24 head movement parameters (including 6 translation/rotations in x/ y/ z directions at each time point, 6 head motion parameters at the previous time point, and the square terms corresponding to the 12 head motion parameters mentioned above), white matter (WM), and cerebrospinal fluid (CSF) signals to reduce physiological noise interference (WM and CSF come from prior templates in statistical parametric mapping); and (6) employing a bandpass filter (0.01–0.08 Hz).

2.4. Probabilistic fiber tracking between dentate nuclei and cerebrum

To evaluate the SC from the cerebellum to the cerebral cortex, bilateral dentate nuclei were selected as seed regions and the cerebral cortices as the target regions with waypoints at the superior cerebellar peduncle and thalamus on the same side as the dentate nucleus. This study's probabilistic fiber tracking primarily utilized the anatomical basis of cerebellar efferent fibers. The main efferent fibers of the cerebellum originate from the dentate nucleus, pass through the SCP, ascend to the thalamus, and ultimately project to the vast cerebral cortex (Dum and Strick, 2003; Jiang et al., 2020). All regions in the present study were extracted from the JHU-MNI (Johns Hopkins University-Montreal Neurologic Institute) atlas. Probabilistic tractography was performed to estimate fiber connectivity. Using the bedpostx tool, Markov chain Monte Carlo (MCMC) sampling was applied to estimate fiber orientation distributions in each voxel. Probabilistic tractography was then conducted using probtrackx to map the probabilistic pathways between regions of interest. For a more accurate calculation of SC between the two regions, 5000 iterations of tracking were performed for each voxel in the seed region, using the following parameters: curvature threshold = 0.2, a maximum number of steps = 2000, step length = 0.5 mm. The number of fiber tracts from the dentate nucleus to the cerebral cortex was considered the SC value for the two regions, and each participant received an SC matrix. Due to varying voxel counts in the regions of interest across participants, the SC matrix was standardized based on the total number of streamlines (waytotal) during actual tracing for each participant. Finally, between-group comparisons were conducted using individual permutation-based statistical testing (10,000 replacements, $p < 0.05$).

2.5. FC between cerebellum and cerebrum

To explore the interaction between the cerebellum and cerebrum, their connectivity profile was assessed. Initially, the average time series from cerebellar and cerebral regions were extracted to calculate FC using Pearson correlation. Additionally, bilateral dentate nuclei were included in the cerebellum. Each participant obtained an FC matrix. This matrix was then transformed to *Z*-scores using the Fisher r-to-z transformation, resulting in a zFC matrix for each participant. Intra-group statistical analysis was performed using a one-sample *t*-test. The 1 × 3 one-way analysis of variance (*ANOVA*) ($p < 0.05$) was used to determine if there were differences in zFC results among the three groups (HC, DRE, DSE). Then, *post hoc* analysis was performed on edges with significant changes in *ANOVA* to explore pairwise between-group differences through independent two-sample t-test with Bonferroni correction ($p < 0.05$).

2.6. Structure-function coupling analysis

To define dentate nuclei-specific structure-function coupling, population covariation was employed. Specifically, FC and SC values for the same edge from each participant were concatenated into respective one-dimensional vectors. Pearson correlation was then used to calculate the correlation between FC and SC, producing a correlation matrix for each group. Inter-group comparisons were conducted using individual permutation-based statistical testing (10,000 iterations, $p < 0.05$).

2.7. Moderation analysis of cerebellum on subcortical and cortical cortex

Direct moderation was identified by constructing a node-node moderation model with time series (TS) of nodes as variables. Specifically, the TS from subcortical regions served as the independent variable, the TS from the cortical region acted as the dependent variable, and the cerebellum was employed as the moderating variable. This node-node moderation indicates a three-node moderation clique (Jiang et al., 2024a). A positive moderation effect means that the moderator strengthens the relationship between the dependent and independent variables. Conversely, a negative moderation effect signifies a weakening role. For significant node-node moderation cliques, intra-group statistics were performed using a one-sample *t*-test, and the 1 × 3 one-way *ANOVA* was applied for inter-group comparisons ($p < 0.001$), with two-sample *t*-tests (Bonferroni-adjusted, $p < 0.005$) for *post hoc* analysis were conducted on edges with significant changes in *ANOVA*.

2.8. Correlational analysis of cerebellar-cerebral connectivity and clinical characteristics

Correlation Analysis: This study explored the correlation between intergroup abnormal values (abnormal SC and regression coefficients β in the moderation model) and illness duration, as well as age of onset. Gender and seizure type were controlled as covariates to mitigate confounding effects.

Mediation Model Analysis: Duration served as a mediating factor in this analysis. The independent and dependent variables were identified from the edges showing significant differences in the SC analysis. To prevent selection bias, all included edges were analyzed alternately as independent and dependent variables. The mediation analysis was conducted using model 4 in the Process 4.2 procedure of SPSS 26.0. After confirming a significant total effect (c), the indirect effect (ab) was tested using the Bootstrap method. A mediation effect was determined by assessing the direct effect (c'). If ab is significant and c' is not, this indicates full mediation. If one of a*b and c' is positive and the other negative, it denotes a suppression effect.

3. Results

3.1. Demographic information and clinical characteristics

A total of 72 subjects, including 22 DREs (12 females, mean age: 29.3 ± 9.4 years, type: 7 IGEs and 15 TLEs), 23 DSEs (15 females, mean age: 27.7 ± 13.5 years, type: 17 IGEs and 6 TLEs), and 27 HCs (12 females, mean age: 30.5 ± 11.3 years), participated in this study. No structural lesions were detected on T1 images in any participants. The duration was statistically different between DRE and DSE ($p < 0.05$). There were no group differences in age of onset, and detailed demographic data are shown in Table 1, Supplementary Table S1.

3.2. The SC analysis of the cerebellum-cerebrum

The SC analysis from the bilateral dentate nuclei to the cerebrum showed that SC in DRE was reduced in SCN and LN (right pallidum, left paraHippocampal, left amygdala, and left middle temporal pole) compared to DSE, as illustrated in Fig. 2A. Unlike in comparisons with HC, DRE displayed more altered regions than DSE, involving all eight brain networks with a similar distribution of regions, as depicted in Fig. 2B-C. There were also regions with increased SC in the DRE compared to HC comparison, particularly in the parietal lobes (right superior parietal gyrus, right supramarginal gyrus). Detailed results are provided in Supplementary Table S2.

3.3. The FC analysis of the cerebellum-cerebrum

We defined the cerebellar cortex and bilateral dentate nuclei as regions of interest (ROI) and calculated FC with cerebral regions. Compared to DSE, DRE exhibited decreased FC in the cerebellum with cortical regions (DMN and DAN) and increased FC with the SCN (left putamen, right putamen, left pallidum, and right pallidum), as shown in Fig. 3A. In comparison to HC, DSE demonstrated increased FC between the cerebellum and LN, VAN, and SMN, and decreased FC with DMN, FPN, and VN, as illustrated in Fig. 3C. DRE showed more extensive FC increases with LN, VAN, and SMN compared to HC, while reductions in FC were more pronounced with DMN, FPN, and VN; regions of the VAN also experienced FC reductions, as detailed in Fig. 3B. Notably, the subcortical nuclei region, absent in the DSE *versus* HC comparison, corresponded with the structural connectivity results. Detailed results are available in Supplementary Table S3. After regression of covariates (gender, age and disease duration), the key results of SCN in DRE were not affected compared with DSE. Detailed results are available in Supplementary Table S4.

3.4. The SC-FC coupling analysis of the cerebellum-cerebrum

To elucidate differences in SC-FC coupling between the cerebellum and cerebrum across different groups, further analysis was conducted. The results revealed no significant differences between DRE and DSE. Compared to HC, DRE displayed significantly decreased SC-FC coupling for right dentate nuclei and left olfactory, while DSE showed significantly increased SC-FC coupling for right dentate nuclei and left medial superior frontal gyrus, as shown in Supplementary Fig. S1 and Supplementary Table S5.

Table 1
Demographic information and clinical characteristics.

	DRE	DSE	HC	*p* value
	(*n* = 22)	(*n* = 23)	(*n* = 27)	
Age(year)	29.3 ± 9.4	27.7 ± 13.5	30.5 ± 11.3	0.751[a]
Gender(M/F)	10/12	8/15	15/12	0.339[b]
Duration(year)	15.5(8.75, 20.5)	5(3,10)		**0.005**[c]
Age of onset(year)	12.5(8, 19.25)	15(11,30)		0.134[c]

Note: DRE, Drug resistant epilepsy; DSE, Drug sensitive epilepsy; HC, Healthy control; F, Female; M, Male.
[a] *One-way ANOVA*.
[b] *Pearson Chi-square* test.
[c] *Mann-Whitney U* test.

3.5. Moderation analysis of cerebellum on subcortical and cortical cortex

We observed changes in cerebellar connectivity to subcortical and cortical regions related to drug resistance mechanisms. To further explore the role of the cerebellum in these mechanisms, we employed moderation analysis to examine its effects on subcortical and cortical regions. The moderation analysis comparing DRE and DSE yielded five significant results. The moderating variables were left cerebellum 4–5, right cerebellum 4–5, right cerebellum 6, and vermis 6; the independent variables were right caudate, right thalamus, right hippocampus, and right pallidum; and the dependent variables were left middle occipital gyrus, right superior frontal gyrus, and left fusiform gyrus, as illustrated in Fig. 4A-B and detailed in Supplementary Table S6. A one-sample *t*-test revealed a significant positive moderation effect in all five cases for DRE, a negative significant moderation effect in three cases for DSE, and no moderation effects for HC, as depicted in Fig. 4A-B and Supplementary Table S6. These moderation models also confirmed a positive correlation between the TS of subcortical and cortical ROI in both DRE and DSE, as shown in Fig. 4A and Supplementary Table S7. Additionally, we analyzed the correlation between β and clinical variables (duration, age at onset), controlling for gender and seizure type. The results indicated a positive correlation between β and duration in two models for DRE and one model for DSE, as shown in Fig. 4C.

3.6. Correlations between structural connectivity and clinical variables

To mitigate the effects of gender and seizure type on the results, these variables were regressed before performing correlation analysis of SC. In DRE, a positive correlation was observed between SC (right dentate nuclei pass right thalamus to left medial superior frontal gyrus) and duration, and a negative correlation between SC (left dentate nuclei pass left thalamus to left hippocampus) and age of onset, as depicted in Fig. 5A. In DSE, positive correlations were found between SC (left dentate nuclei pass left thalamus to left amygdala), SC (left dentate nuclei pass left thalamus to left middle temporal pole) and duration, and a negative correlation between SC (right dentate nuclei pass right thalamus to left superior occipital gyrus) and age of onset, as illustrated in Supplementary Fig. S2.

3.7. Mediation model analysis of duration and cerebellar-cerebral SC

The previously noted inter-group differences in duration and its correlation with SC changes suggest that duration may play a crucial role in cerebellar-cerebral SC alterations. Therefore, mediation model analysis was used to evaluate the mediation effect of duration on SC edges. In DSE, SC of left dentate nuclei and left superior occipital gyrus had a positive effect on SC of left dentate nuclei and left middle temporal pole through duration, and SC of left dentate nuclei and left middle occipital gyrus positively influenced SC of left dentate nuclei and left amygdala through duration. However, these effects were not significant in DRE. Detailed results are provided in Fig. 5B and Supplementary Table S8. To further assess the mediation effect, Pearson correlations were calculated for SC of left dentate nuclei and left superior occipital gyrus and SC of left dentate nuclei and left middle temporal pole, as well as SC of left dentate nuclei and left middle occipital gyrus and SC of left dentate nuclei and left amygdala in HC, with none of the results showing significance, as detailed in Supplementary Table S9.

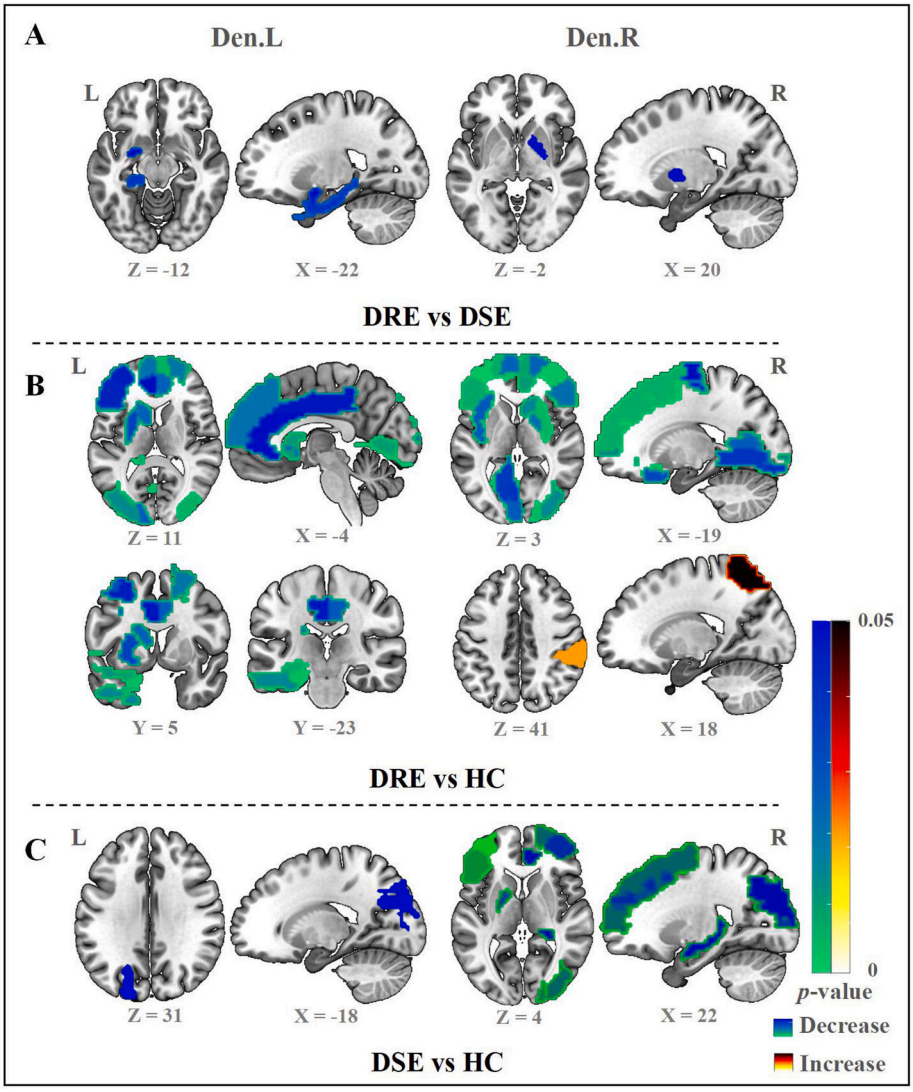

Fig. 2. SC analysis of the cerebellum (dentate nuclei) and cerebrum. (A-C) shows inter-group results for SC. SC decreases are indicated by cool colours and SC increases by warm colours. R: Right; L: Left; Den: Dentate nuclei; DRE: Drug resistant epilepsy; DSE: Drug sensitive epilepsy; HC: Healthy control.

4. Discussion

In this study, we analyzed, for the first time, the differences in cerebellar-subcortical/cortical connectivity between DRE and DSE from a multimodal perspective. The results indicated that FC within the cerebellar-cortical network was reduced. Interestingly, FC increased between the cerebellum and SCN, but decreased in the SC. The deviation results support the connected specificity of SCN and cerebellum in the SC and FC analysis of drug resistance in epilepsy. Structure-function coupling analyses demonstrated a significantly lower coupling between the right dentate nuclei and the left olfactory regions in DRE compared to HC, highlighting distinct interactions between the cerebellum and both subcortical nuclei and the cerebral cortex in DRE and DSE. Building on this crucial finding, our moderation models revealed that cerebellar cortical regions in DRE positively modulate subcortical and cortical connectivity. Conversely, in DSE, these cerebellar cortical regions have a negative moderation effect on the same connectivities. Additionally, the importance of the duration of the disease was underscored. A full mediation effect of disease duration was confirmed in the mediation model of SC for DSE, whereas this effect was absent in DRE. This difference underlines the variable impact of duration on connectivity patterns in these disorders.

4.1. The decoupling and unbalanced connectivity of cerebellar and subcortical/cortical regions in DRE

In previous studies, extensive connectivity changes in DRE compared to healthy individuals have consistently been observed (Bernhardt et al., 2016). This is confirmed by our results, where altered connectivity in DRE occurs across multiple resting-state brain networks. Notably, both SC and FC between the cerebellum and DMN were reduced in both DRE and DSE. A study on drug-naïve children with epilepsy showed reduced gray matter volume and diminished FC in DMN regions (Deng et al., 2024). Combined with our findings, this suggests that DMN impairment may manifest early in epilepsy and worsen as the disease progresses, potentially influenced by the cerebellum. Patients who achieved seizure remission through VNS displayed brain network reorganization, characterized by inhibition of hyperactivation in the SN (equivalent to the VAN in this study) and activation of the DMN, involving the cerebellum, thalamus, and striatum (Wang et al., 2016). The cerebellum enhances the speed of information processing in the brain by increasing functional activity with the frontal lobes (Halko et al., 2014). This indicates that seizure remission may be related to the balance between the networks, which was also demonstrated in our results with reduced FC in the cerebellum and DMN and increased FC in the cerebellum and VAN.

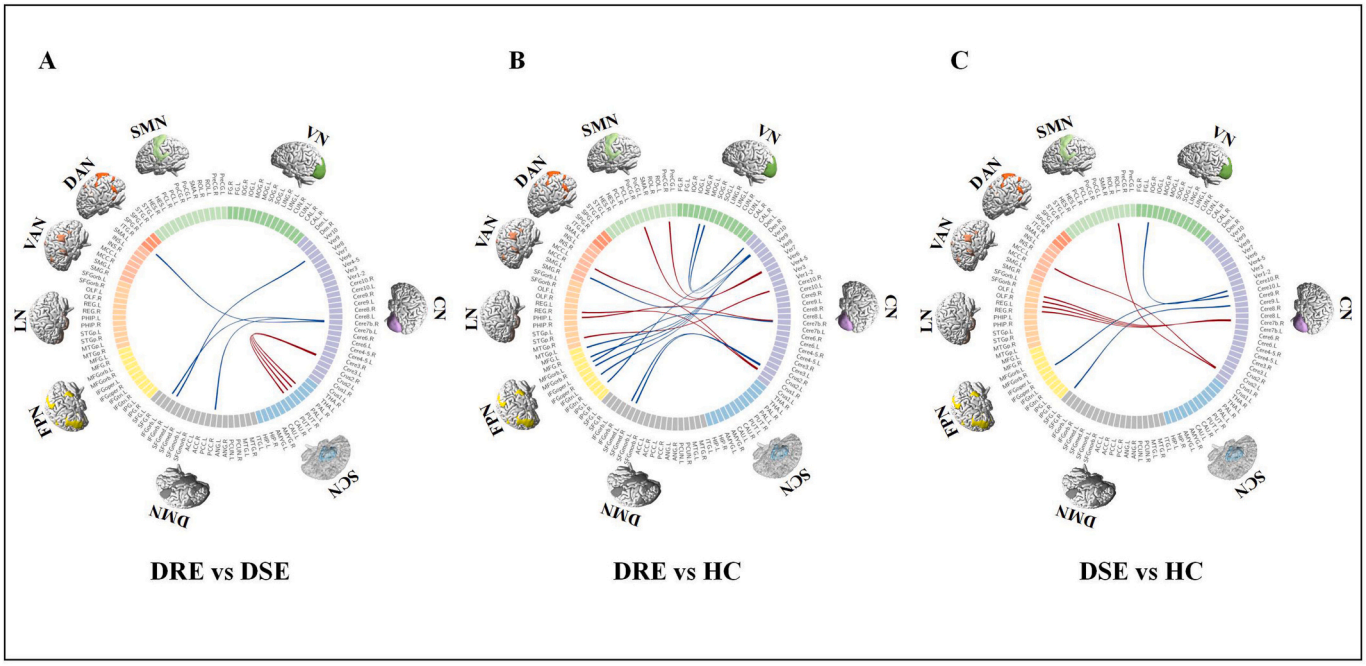

Fig. 3. FC analysis of the cerebellum (cerebellar cortex, dentate nuclei) and cerebrum. (A-C) shows inter-group results for FC. FC decreases are indicated by cool colours and FC increases by warm colours. DMN: Default model network; FPN: Frontoparietal network; LN: Limbic network; VAN: Ventral attention network; DAN: Dorsal attention network; SMN: Sensorimotor network; VN: Visual network; CN: Cerebellar network; SCN: Subcortical network; DRE: Drug resistant epilepsy; DSE: Drug sensitive epilepsy; HC: Healthy control.

Other results, such as altered connectivity in the SMN, have been observed in the DRE and DSE. The cerebellum's influence on the functional activity of the thalamus and motor cortex is well-documented, with the sensorimotor cortex often remaining hyperexcitable in epilepsy patients (Proville et al., 2014; Badawy et al., 2007). SMN activation in DRE, even during non-task conditions, was noted, suggesting that increased positive FC between the cerebellum and SMN in DRE may reflect a persistent state of seizure readiness (Nourski et al., 2024; Trimmel et al., 2021). Moreover, decreases in SC and FC in the VN were also observed and will be discussed further in the section on the moderation model.

From the analysis, the regions affected in DRE encompass almost the entire brain. Merely identifying differences between cortical networks and healthy controls does not fully elucidate the mechanisms of drug resistance in DRE. We observed no significant changes in connectivity between cerebellar and subcortical regions in DSE, in either FC or SC. However, when comparing DRE and DSE, connectivity within the cerebellar network (CN) and the SCN showed a decrease in SC and an increase in FC. Excessive connectivity and synchronization of brain regions, including epileptogenic zones, are recognized as central components of the epilepsy network (Wilke et al., 2011; Varotto et al., 2012). The joint action of cerebellar and subcortical nuclei in inter-network interactions, particularly between the DMN-SMN and DMN-SN, is crucial for inducing epileptic network synchronization (Jiang et al., 2024a). An article has reported a common lesion-related epilepsy network, in which the FC change of the basal ganglia and cerebellum is associated with remission after deep brain stimulation (Schaper et al., 2023). We believe that alterations in FC between the cerebellum and subcortical regions may be a key factor contributing to the complex changes in cortical networks, potentially playing a significant role in the development of drug resistance in epilepsy. The reduction in SC between these regions is considered a consequence of epileptic damage. Previous research has highlighted the cerebellum's role in suppressing seizures (Streng and Krook-Magnuson, 2021). Structural and morphological damage to the cerebellum is well-documented in DRE (Hellwig et al., 2013; Riederer et al., 2008). Disease factors can lead to increased functional activity among vital regions and cause structural damage (Fornito et al., 2015; Vanasse et al., 2021). This manifestation of structural and functional decoupling underscores the significance of altered connectivity between the cerebellum and subcortical nuclei in the mechanisms of drug resistance. Our deviation analysis revealed that the differences between IGE and TLE did not significantly affect the crucial connected role of SCN and cerebellum in drug-resistant epilepsy.

Further investigation into SC-FC coupling between the cerebellum and cerebrum revealed no differences between DRE and DSE. However, since only the dentate nuclei were considered from the cerebellum, this is insufficient to explain the SC-FC coupling between the entire cerebellum and cerebrum. In DRE, lesions often show reduced SC-FC coupling between regions prior to surgery (Johnson et al., 2023). Findings indicate that the strength of inter-network SC-FC coupling is higher in patients who achieve seizure freedom following DRE surgery (Li et al., 2022). Our results identified an increase in one edge in DSE and a decrease in another edge in DRE, aligning with previous findings regarding coupling strength.

4.2. The cerebellum is involved in hyperconnectivity between subcortical and cortical regions in the DRE

The inclusion of the hippocampus, striatum, and thalamus in the subcortical nuclei in this study highlighted that cerebellar modulation in DRE enhances the influence of the subcortical nuclei on the cerebral cortex. During the intermediate phase of seizures, cortical and striatal activity desynchronizes, while the onset and terminal phases are characterized by synchrony and hyper-synchrony (Aupy et al., 2019). This repetitive disruption of the balance between the cerebral cortex and the striatum may contribute to the recurrence of seizures. The cerebellum and striatum exhibit synchronized neuronal activity during movement, facilitating sensory prediction and motor control (Kameda et al., 2023). The interactions among the cerebellum, thalamus, and motor regions play a crucial role in the development and propagation of seizures (Rubio et al., 2023). In line with our findings, we propose that the cerebellum disrupts this subcortical-cortical synchronization of activity.

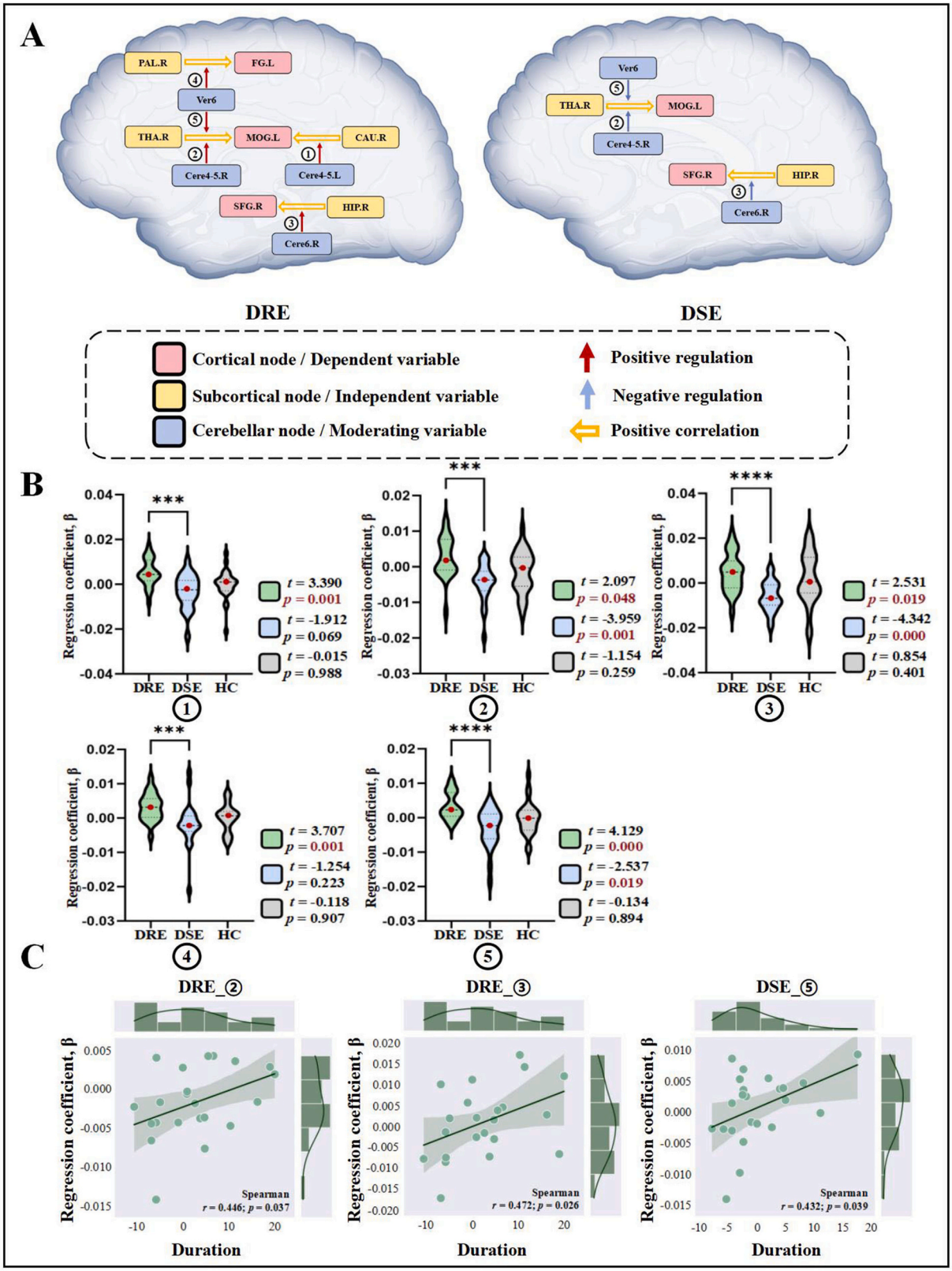

Fig. 4. Moderation analysis of cerebellum on subcortical and cortical cortex. (A) Analysis of five moderation models within the DRE, DSE groups. (B) Differences between groups of five moderation models of DRE *vs* DSE, *t* and *p* are one-sample *t*-tests for DRE, DSE and HC. (C) Correlation analysis of the regression coefficient (β) of the moderation models with duration and age of onset after controlling for variables (gender, seizure type). R: Right; L: Left; PAL: Pallidum; THA: Thalamus; CAU: Caudate; HIP: Hippocampus; FG: Fusiform gyrus; MOG: Middle occipital gyrus; SFG: Superior frontal gyrus; Ver6: Vermis 6; Cere4–5.R: Cerebelum 4–5; Cere6: Cerebelum 6; DRE: Drug resistant epilepsy; DSE: Drug sensitive epilepsy; HC: Healthy control. *** indicates $p < 0.005$, **** indicates $p < 0.001$.

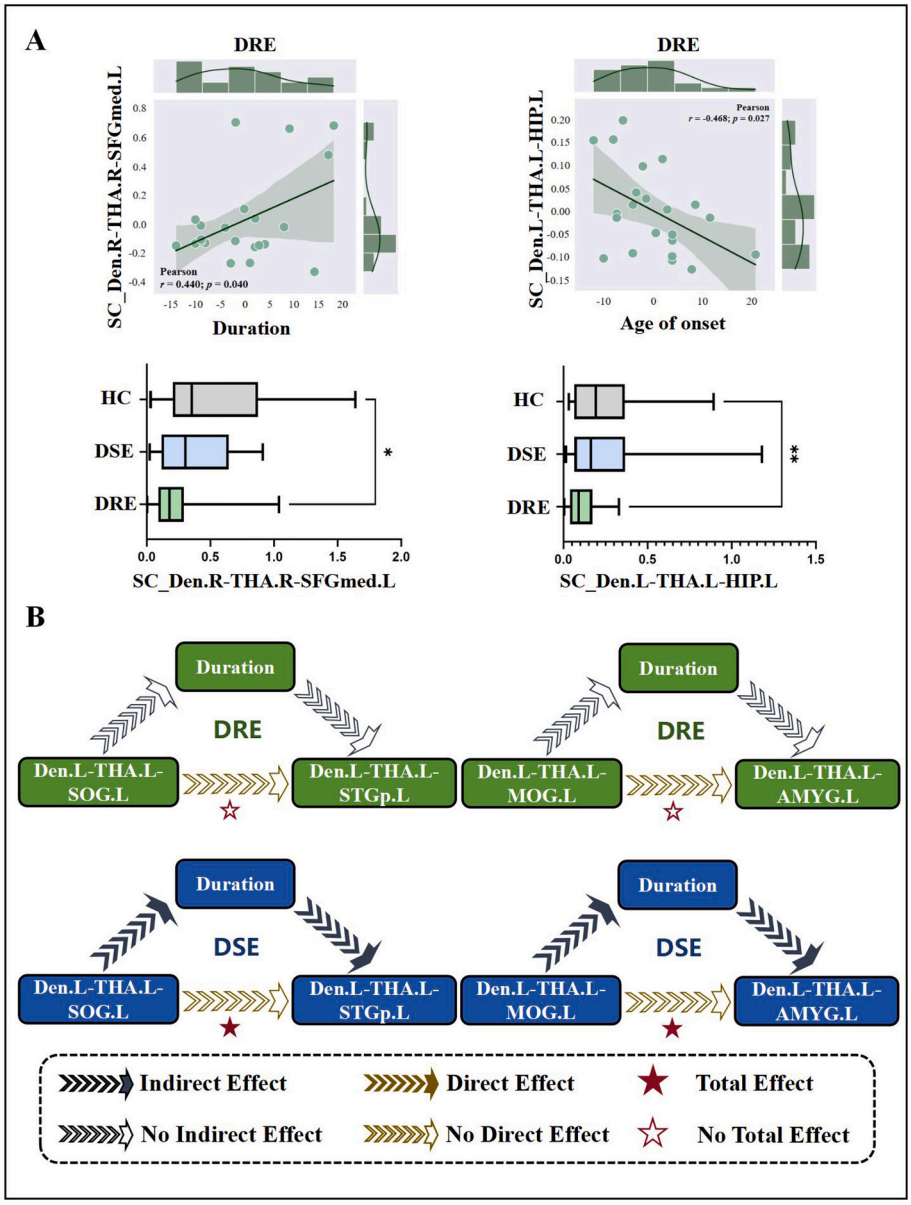

Fig. 5. Correlation analysis and mediation model analysis of duration and cerebellar-cerebral SC. (A) shows correlation analysis between SC and age at onset, and SC and duration of disease in DRE after controlling for variables (gender, seizure type). (B) shows the mediation model for DRE (no mediation effect) and the mediation model for DSE (total mediation effect). The independent and dependent variables are SC and the median variables is duration. * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.005$. R: Right; L: Left; Den: Dentate nuclei; OLF: Olfactory; SFGmed: Medial superior frontal gyrus; HIP: Hippocampus; SOG: Superior occipital gyrus; STGp: Superior temporal pole; MOG: Middle occipital gyrus; AMYG: Amygdala; DRE: Drug resistant epilepsy; DSE: Drug sensitive epilepsy; HC: Healthy control.

Our focus was on the differences in moderation models between DRE and DSE. In these analyses, the cerebellum in DSE appears to attenuate interactions between subcortical and cortical regions. Biological experiments identifying epilepsy-associated afferent and efferent cerebellar projections reveal that inhibitory connectivity of the cerebellar cortex to the DCN, which drives excitatory projections from the DCN to the thalamus, can trigger seizures (Kros et al., 2015). This evidence certainly supports our findings. In the context of drug resistance in epilepsy, the cerebellum is implicated in promoting hyperconnectivity between subcortical and cortical regions. There are recent studies in the field of epilepsy that report increased functional connectivity within the epileptogenic zone in patients with drug resistant epilepsy and an information flow from onset epileptogenic areas to areas of spread (Matarrese et al., 2023; Corona et al., 2023). The output of the cerebellum is modulated to suppress seizures, possibly by controlling this information flow. Furthermore, excitation-inhibition imbalance is considered a shared pathological mechanism for epilepsy and early Alzheimer's disease (Okechukwu et al., 2026). Frequent epileptic seizures or interictal epileptiform discharges can lead to the loss of normal physiological coordination of the interactions between the brain networks required for cognitive functions (Gelinas and Khodagholy, 2025). The cerebellum promotes hyperconnectivity between the subcortical and cortical regions in DRE, which may promote cortical excitability and result in cognitive impairment. Since no formal neuropsychological assessment was included in this study, the potential contribution of cognitive factors cannot be completely excluded from our results of drug resistance and should be addressed in future studies.

Our findings present more convergent results. Using task-fMRI, the function of cerebellar subregions was determined, with areas 5 and 6 activated during a sensorimotor task, while area 6 also participated in

executive functions, visuospatial tasks, and emotional processing (Stoodley and Schmahmann, 2009). The vermis, particularly involved in motor processes of the head and neck, and vermis areas 6 and 7, receive visual and auditory afferents (Schmahmann, 2019). An EEG study indicated that coupling in the hippocampal-cortical network of DRE was associated with short-term memory linked to auditory information (Borderie et al., 2024). Reduced connectivity in the bilateral hippocampus and frontal lobes in TLE is implicated in memory network reorganization and correlates with longer disease duration and higher seizure frequency (Fleury et al., 2022). A positive modulation effect of cerebellum area 6 on the hippocampus and superior frontal gyrus may be involved in memory deficits and memory network reorganization. Two of the three cortical areas included in our moderation analysis were related to vision; notably, the middle occipital gyrus displayed completely opposite modulatory effects in DRE and DSE. Research has shown reduced FC between the thalamus and occipital lobe in patients with both focal and generalized seizures (He et al., 2015). Abnormal-appearing hypertrophic astrocytes were found in the occipital lobe in brain tissue of postmortem cases of Alper's syndrome, which presents with refractory seizures (Smith et al., 2023). There is also evidence of structural and functional decoupling of the visual network (VN) between modules in TLE (Zhou et al., 2024), underscoring the significance of the occipital lobe in epilepsy. It has been found that FC between the VN and the basal ganglia network is reduced in DRE (Li et al., 2022). This aligns with our findings that DRE has lower connectivity than DSE in thalamic and occipital regions. However, in our results, the cerebellum reinforced this functional interaction, and this reinforcement, which also involved the caudate and pallidum, was not beneficial. Visual stimuli can induce clinical reflex myoclonus (Dubbioso et al., 2023). The temporo-parieto-occipital disconnection is often chosen for DRE surgery in children, fre quently resulting in excellent outcomes (Limpo et al., 2023; Liu et al., 2024). Whether maintaining a lower connectivity state of the occipital lobe and subcortical nuclei represents a well-controlled manifestation of epilepsy warrants further investigation. We suspect that in DRE, the cerebellum negatively impacts the processing of visually and spatially relevant information, involving more subcortical nuclei compared to DSE.

The influence of the cerebellum and duration on the connectivity between the thalamus and middle occipital gyrus was evident from the results of the moderation model in both DRE and DSE. Further investigation into the relationship between connectivity and duration revealed a positive correlation between partial SC and duration in both DRE and DSE. This appears contradictory to the observed decline in SC. Interestingly, a full mediation effect of duration was observed in DSE, which was absent in DRE. This suggests that the increase in SC over time may represent a compensatory change in epilepsy, which diminishes in DRE as duration increases. Given that the thalamus was designated as a pathway point in the fiber tracking, the absence of significant differences in thalamic SC was anticipated. Nonetheless, the critical role of the thalamus in SC results cannot be overlooked. A study examining the moderation effect of duration on the striato-thalamo and thalamo-cerebellar networks in epilepsy identified a negative impact on the covariance between the cerebellum and cortex (Xu et al., 2021), aligning with our findings in DSE. We documented cerebello-occipital cortex and cerebello-temporal cortex/amygdala detachment in SC within the DRE group. Analysis of disease progression patterns revealed that patients with refractory TLE, who had no cortical atrophy but enlarged amygdala, faced the poorest surgical outcomes (Jiang et al., 2024b). However, these findings alone cannot conclusively explain the role of the amygdala in the mechanisms of epileptic drug resistance and disease progression. Notably, the results were recurrent in the occipital cortex. In both mediation and moderation models, the cerebellum and duration were implicated in the connectivity dynamics between the subcortical nuclei and the visual cortex, displaying distinct patterns in DRE and DSE. The thalamus and the middle occipital gyrus, as key nodes, may be influenced by the cerebellum and duration, thereby participating in the development of drug resistance mechanisms.

4.3. Limitations

In terms of limitations, firstly, the small sample size may have affected the results, necessitating further validation with larger datasets. Secondly, the seizure type and duration were not matched between the two patient groups, which could have influenced the findings, although the effect of duration was considered. Thirdly, the effects of different ASMs and drug doses on the brain networks of epilepsy do exist. Our work did not take into account the potential influence of different ASMs in the results, but this is also limited by the large number of ASMs involved. We need to conduct more rigorous experimental designs in the future. Fourth, while patients with structural brain lesions were excluded and seizure type was controlled for in correlation analyses, further subgroup analyses are necessary to refine our understanding. Fifth, the exclusion of results related to the cerebellar cortex in the SC analysis, due to the lack of recognition of probabilistic fiber tracking starting from this region, represents a limitation in exploring cerebellar-cerebral connectivity fully. Lastly, the modulation model did not address the influence of the cerebral cortex on subcortical nuclei. Findings from the mediation analysis suggest that visual cortical regions may impact subcortical and limbic regions, although this effect was not evident in DRE.

5. Conclusion

This study identified characteristic cerebellar-subcortical/cortical connectivity patterns in DRE, including a decoupling of connectivity between the cerebellum and subcortical nuclei. The cerebellum and duration appear to promote hyperconnectivity of functional activity between subcortical and cortical regions, potentially serving as a critical pivot for the development of drug resistance in epilepsy. The thalamus and middle occipital gyrus may be key regions involved in these mechanisms.

Author contribution

Ting Liu, Junxia Chen, and Sisi Jiang designed the study. Binji Liang, Yufan Zhou, Bao Lu, Huixia Lin, and Fei Li were responsible for data collection and preparation. Ting Liu, Junxia Chen, Sisi Jiang, Qiang Guo, María Luisa Bringas Vega, Cheng Luo, and Qifu Li analyzed and interpreted the data. Ting Liu and Junxia Chen drafted the manuscript. All authors critically reviewed and revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

CRediT authorship contribution statement

Ting Liu: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Junxia Chen:** Writing – review & editing, Methodology, Conceptualization. **Sisi Jiang:** Writing – review & editing, Funding acquisition, Conceptualization. **Binji Liang:** Writing – review & editing, Data curation. **Yufan Zhou:** Writing – review & editing, Methodology. **Bao Lu:** Writing – review & editing, Methodology. **Fei Li:** Writing – review & editing. **Huixia Lin:** Writing – review & editing. **Dezhong Yao:** Writing – review & editing, Funding acquisition. **María Luisa Bringas Vega:** Formal analysis. **Qiang Guo:** Writing – review & editing. **Cheng Luo:** Writing – review & editing, Funding acquisition. **Qifu Li:** Writing – review & editing, Funding acquisition.

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Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2026.107406.

Data availability

The data supporting the findings of this study are available from the corresponding authors upon reasonable request. They are not publicly available due to privacy and ethical restrictions.

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