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ORIGINAL ARTICLE

The relationship between neuromagnetic networks and cognitive impairment in self-limited epilepsy with centrotemporal spikes

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Abstract

Objective: This was an exploratory study designed to examine the alterations in neuromagnetic networks within brain regions involved in cognitive functions in children with self-limited epilepsy with centrotemporal spikes (SeLECTS). Additionally, it sought to explore the relationship between these neural network differences and cognitive impairment.

Methods: Magnetoencephalography (MEG) data were collected from 63 drug-naïve children diagnosed with SeLECTS and 30 healthy controls (HC). Functional connectivity (FC) across 26 cognitive-related brain regions, as defined by Desikan-Killiany, was assessed using corrected amplitude envelope correlation (AEC-c) analysis. The cognitive function of the children was evaluated using the fourth edition of the Wechsler Intelligence Scale for Children (WISC-IV). Spearman's correlation analysis was then performed to assess the relationship between AEC-c values and WISC-IV indices.

Results: Children with SeLECTS showed reduced FC in the delta band between the left rostral middle frontal (rMFG.L) and the left rostral anterior cingulate (rACC.L), as well as in the gamma2 band between the left superior frontal (SFG.L) and the rACC on both sides, compared to HC ($p < 0.05$). On the other hand, several FC networks were enhanced, including those between the left rMFG and the right rACC, the left rMFG and the left caudal middle frontal (CMF.L), and between the right caudal middle frontal (CMF.R) and the right supramarginal (SMG.R), specifically in the gamma1 band ($p < 0.05$). A correlation analysis revealed a positive association between the AEC-c values between the left rMFG and the right rACC and the Verbal Comprehension Index (VCI) scores ($R = 0.4228$, $p < 0.05$).

Significance: The findings of this study revealed that children with SeLECTS exhibited significant differences in the FC networks in brain regions associated

Jing Lu and Peilin Jiang contributed equally to this work.

with cognition, especially within the delta and gamma frequency bands, when compared to HC. We also found that these differences in FC networks are significantly correlated with verbal comprehension ability, which may contribute to the understanding of the mechanisms underlying the weaknesses in cognitive function in children with SeLECTS. Furthermore, our findings may provide hypotheses for future work dedicated to further exploring the mechanisms associated with brain network alterations in cognitive impairment in children with SeLECTS.

Plain Language Summary: Based on magnetoencephalography technology (MEG), this study found that there were significant differences in cognitive-related neuromagnetic networks in children with SeLECTS compared with HC, which were significantly correlated with relevant indicators in the Wechsler Scale. This finding suggested that differences in the neuromagnetic network may serve as imaging markers to predict changes in cognitive function in children with SeLECTS.

KEYWORDS

cognition, functional connectivity, magnetoencephalography, muti-frequency, self-limited epilepsy with centrotemporal spikes

1 | INTRODUCTION

Self-limited epilepsy with centrotemporal spikes (SeLECTS) is a frequently observed form of idiopathic focal epilepsy syndromes among children, making up about 8%–25% of all epilepsy cases observed in childhood.[1,2] Common signs of this epilepsy condition typically involve facial spasms and rigidity, a sensation of tingling or numbness in the throat and facial area, a halt in speech, and excessive saliva production.[3–5] Traditionally, SeLECTS has been considered to have a benign course, however, with the improvement of neuron electrophysiology and neuropsychological examination, the benign concept of SeLECTS is questioned.[6] Increasing evidence now points to significant neuropsychological impairments associated with SeLECTS, including cognitive impairments, attention issues, learning disabilities, emotional disturbances, language impairments, and behavioral problems.[7–11] Structural neuroimaging studies have reported alterations in gray matter volume, particularly in regions associated with seizure onset and cognitive functions.[12] Functional connectivity studies have revealed disrupted network interactions in children with SeLECTS, particularly within cognitively relevant networks.[13] Additionally, cognitive assessments in children with SeLECTS have demonstrated impairments in attention, executive function, and memory.[14] Although these studies have shown that children with SeLECTS exhibit diffuse brain differences that may be associated with epileptiform activity, both in terms of structure and function, which disrupt brain development and may contribute to cognitive impairments because children have stronger neuroplasticity and less specialized neural networks,[7,15] which gives rise to a more fluid effect of pathological developments,[16–18] the specific mechanism of cognitive impairment in SeLECTS is unclear. However, it is increasingly recognized that complex neural networks can broadly represent cognitive functions, especially high-level multidetermined intellectual abilities.[19]

The brain is a highly complex network composed of distinct regions.[20,21] According to the network theory of epilepsy, seizures are considered disturbances within

Key points

- Children with SeLECTS showed significant cognitive impairment compared with healthy controls (HC). The study aimed to explore the relationship of neuromagnetic network changes and cognitive impairment in children with SeLECTS.
- Neuromagnetic network differences serve as the network basis and mechanisms of cognitive impairment in children with SeLECTS.

these neural networks,[22,23] resulting in cognitive impairments. Among the networks involved, the default mode network (DMN), central executive network (CEN), and salience network (SN) have been closely linked to cognitive dysfunction,[24] forming the "triple network model."[25] DMN is frequently linked to social cognition, episodic and autobiographical memory, language and semantic memory.[26,27] Abnormalities within the CEN typically impair attention, working memory, and executive function.[28] SN serves as a "central controller," playing a pivotal role in processing behaviorally relevant external stimuli.[29] In the presence of external stimuli, the SN inhibits DMN activity while activating the CEN to facilitate attention and executive function. Dysfunction within the SN may result in an imbalance in the coordination between the DMN and CEN, thereby impairing cognitive performance.[30] These neurocognitive networks are anchored in key regions which can be good starting points to explore cognitive function. Childhood represents a critical stage of brain development, but the repeated epileptic seizures and the prolonged presence of epilepsy may impact both the structural and functional maturation of the brain.[31,32] Therefore, it is crucial to investigate the pathophysiological mechanisms that contribute to cognitive impairments in children diagnosed with SeLECTS. The Wechsler Intelligence Scale (WISC), a widely used cognitive assessment tool, provides valuable insight into the cognitive abilities of children.[33] By measuring cognitive functions such as verbal comprehension, working memory, processing speed, and perceptual reasoning, the WISC can help quantify the impact of network dysfunction on specific cognitive domains. This tool can thus be employed to assess the relationship between disruptions in the cognitive network and cognitive performance in children with SeLECTS.

In children with SeLECTS, brain networks exhibit frequency-dependent properties, which have been demonstrated in numerous studies utilizing functional magnetic resonance imaging (fMRI) and electroencephalography (EEG).[34–36] It is well-established that fMRI does not provide direct measurements of neural activity and has relatively low temporal resolution.[37] On the other hand, magnetoencephalography (MEG) directly records neuronal activity, offering advantages over EEG by minimizing signal distortions.[38] Moreover, MEG provides high spatial resolution at the millimeter level and exceptional temporal resolution in the millisecond range, making it a valuable tool for investigating epileptic activity.[39,40] Using MEG, our research team conducted a preliminary study that identified alterations in spectral power within brain regions related to cognitive function in children with SeLECTS, offering insights into the mechanisms behind cognitive impairment in untreated children at early stages of the disorder.[41]

In light of this, the current study focused on 26 brain regions, selected as key nodes within DMN, CEN, and SN, based on the Desikan-Killiany atlas. These regions of interest (ROIs) include the caudal anterior cingulate (CAC), caudal middle frontal (CMF), inferior parietal (IP), insula (INS), middle temporal (MTG), para-hippocampal (PHG), posterior cingulate (PCG), precuneus (PCUN), rostral anterior cingulate (rACC), rostral middle frontal (rMFG), superior frontal (SFG), superior temporal (STG), and supramarginal (SMG) regions bilaterally (Figure S1). Additionally, MEG was utilized to explore the characteristics of the neural network between these ROIs in SeLECTS children in different frequency bands, and The Wechsler Intelligence Scale for Children, fourth edition, was used to assess the intelligence quotient (IQ) of participants, focusing on the relationship between differences in the neural network and cognitive function.

2 | METHODS

2.1 | Participants

We enrolled 63 drug-naïve children diagnosed with SeLECTS from Nanjing Brain Hospital and Nanjing Children's Hospital, alongside 30 age-matched healthy controls (HC). The patients were matched in terms of education, family background, and their parents' education and income. Detailed clinical information of the patients is provided in Table 1. Approval for the protocol was granted by the Institutional Review Boards of Nanjing Medical University, Nanjing Brain Hospital, and Nanjing Children's Hospital. Before the study commenced, the research objectives and methodology were thoroughly explained to both the children diagnosed with SeLECTS and their parents. Informed consent was then obtained from all participants. To ensure the accuracy of the data, no patients experienced a seizure within 72 h prior to or 24 h following the imaging scan.

Children with SeLECTS were considered for inclusion in the study if they satisfied the 2017 classification guidelines outlined by the International League Against Epilepsy (ILAE) and exhibited routine clinical EEG findings characterized by slow, biphasic, and high-voltage spikes in the centrotemporal region. Additionally, eligible participants must have fulfilled the requirements of not yet taking antiepileptic seizure medication prior to enrollment and demonstrate normal intellectual and physical development. Children with metal implants, a history of severe neurological or psychiatric conditions, or other clinically significant illnesses were excluded. Further exclusion criteria included the inability to comply with or comprehend the study protocol and contraindications for MRI or MEG procedures. The study adhered strictly to the

TABLE 1 Clinical patient's data.

Patients	Sex (F/M)	Age (years)	Duration of epilepsy (months)	Location of epileptic spikes (L, R, B)	Patients	Sex (F/M)	Age (years)	Duration of epilepsy (months)	Location of epileptic spikes (L, R, B)
1	M	10	3	B	33	M	11	6	R
2	F	9	1	B	34	F	7	11	B
3	F	10	8	B	35	M	11	9	R
4	M	8	1	L	36	F	11	16	L
5	F	6	1	B	37	M	11	18	R
6	M	8	1	B	38	F	10	13	L
7	M	6	1	B	39	F	10	1	R
8	F	7	3	B	40	F	7	6	B
9	M	7	6	B	41	M	9	10	R
10	F	8	1	B	42	F	9	12	L
11	M	7	2	B	43	F	9	<1	L
12	M	9	1	B	44	F	9	3	R
13	F	10	1	B	45	M	6	<1	L
14	M	6	2	B	46	M	8	3	L
15	F	6	3	B	47	M	13	—	B
16	M	9	1	L	48	F	9	3	L
17	F	10	1	L	49	M	11	—	R
18	M	7	2	L	50	M	10	30	L
19	F	9	1	L	51	F	9	14	L
20	F	8	2	R	52	F	9	<1	B
21	F	7	7	R	53	M	7	9	L
22	F	10	8	L	54	M	7	1	R
23	M	11	3	L	55	F	10	2	B
24	F	11	3	L	56	F	11	2	L
25	F	8	23	R	57	M	9	1	L
26	M	9	10	L	58	M	6	—	B
27	F	8	1	R	59	M	10	12	R
28	M	10	6	L	60	F	12	—	B
29	F	8	3	B	61	F	6	3	L
30	M	7	5	L	62	F	7	—	R
31	F	8	1	L	63	M	8	1	L
32	M	7	20	B					

Abbreviations: —, missing data; B, both sides; F, female; L, left; M, male; R, right.

ethical standards set forth in the Declaration of Helsinki for research involving human subjects.

2.2 | MEG recordings

The CTF275 whole-head magnetoencephalography (MEG) system (VSM MedTech Systems, Inc., Coquitlam, British Columbia, Canada) was used to capture MEG signals within the magnetically shielded chamber at Nanjing Brain Hospital's MEG facility. A tri-coil setup was employed to ensure proper alignment of the subject's head relative to the MEG sensor array. Participants were instructed to remain awake and alert during the data acquisition session, while maintaining a relaxed state with their eyes gently closed and refraining from cognitive activities. A minimum of six data segments, with a sampling frequency of 6000 Hz, each spanning 2 min, were collected for each participant. Head localization was verified at the beginning and end of each recording epoch. Data segments affected by head movements exceeding 5 mm were discarded, and repeat recordings were performed if necessary. To mitigate the potential artifacts from epileptic seizures on the MEG data, recordings were scheduled at least 3 days after the most recent seizure occurrence.

2.3 | MRI scan

A 3.0 T MRI system (Siemens, Germany) was utilized to acquire MRI-T1 data, with parameters set as follows: 176 sagittal slices, each 1 mm thick; repetition time (TR) of 1900 ms; echo time (TE) of 2.48 ms; matrix size of 512 × 512; and a field of view measuring 250 × 250 mm^2. The localization coils were aligned with the MEG coils to facilitate accurate fusion of MEG and MRI data.

2.4 | Data preprocessing

Only artifact-free MEG recordings were retained for subsequent analysis. The preprocessing steps included: (a) A thorough visual examination was conducted to identify data segments contaminated by artifacts stemming from head movements or environmental interference, which were subsequently excluded from the analysis; (b) Following filtering, the MEG data from patients within the 1–70 Hz range, free from both noise and artifacts, facilitate the clear detection of high-amplitude spikes in SeLECTS features; (c) Corrections for instrument, sensor, and ambient noise were required to avoid the effects of ambient and sensor noise. Therefore, a 2-min empty room recording was performed prior to the acquisition of MEG data and was used to calculate the noise covariance for offline source analysis; and (d) To minimize the impact of spikes on network connectivity analysis, 30-second data segments free from spikes were selected for analysis, ensuring homogeneity with the control group. The following steps were undertaken to select interictal MEG data: (1) a segment of MEG data without spike-and-wave discharges (SWDs) was identified; (2) the segment duration exceeded 30 seconds; (3) no SWDs were present within a 30-second window before or after the selected segment; and (4) the interictal waveform within the segment was designated as interictal data. The process for selecting interictal data is illustrated in Figure 1. A corresponding 30-second segment of artifact-free MEG data was selected from healthy children as a control. All MEG data were processed using Brainstorm software (https://neuroimage.usc.edu/brainstorm/).

2.5 | Minimum norm estimate analysis

Depth-weighted Minimum Norm Estimation (MNE) was used to estimate cortical activations from MEG data, providing a distributed source model. This process involves two main steps: first, forward modeling, where each cortical vertex is represented as a current dipole, with a total of 15 000 vertices. The overlapping spheres method is employed to construct this model. The second step, source modeling or solving the inverse problem, estimates the distribution of current sources.

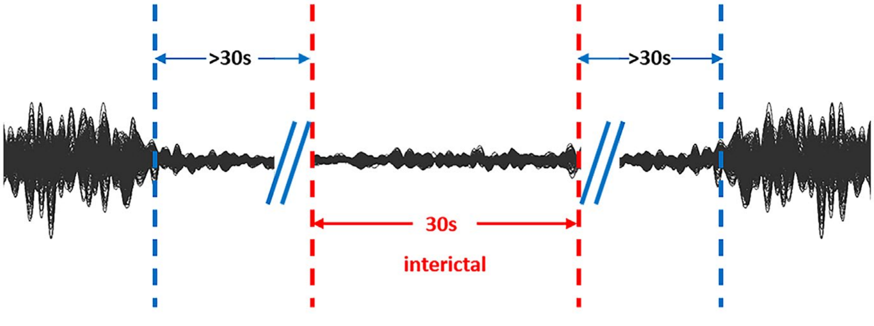

FIGURE 1 Interictal data selection in children with SeLECTS. (Example data from Patient 1. The data was imported into Brainstorm software, resampled to 150 Hz, and processed with a high-pass filter at 1 Hz and a low-pass filter at 40 Hz to enhance the visualization of onset and interictal periods).

The inverse operator calculation is performed with the following constraints: The orientation of the source is set perpendicular to the cortical surface. To address the variation in sensitivity to depth and orientation, a depth weighting algorithm is employed. Additionally, a regularization parameter ($\lambda^2 = 0.33$) is applied to mitigate numerical instability, reduce noise sensitivity, and promote a spatially smooth solution. This regularization value is inversely related to the Signal-to-Noise Ratio (SNR) of the MEG recording. Both the forward modeling using the overlapping spheres method and the inverse problem solution using depth-weighted MNE are implemented in Brainstorm software.

2.6 | The Wechsler intelligence scale for children, fourth edition

Following previous studies,[41,42] we used the Chinese version of the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) to assess the intelligence quotient (IQ) of participants in a quiet, bright room at the Nanjing Brain Hospital immediately after completing the MEG and MRI examination. The WISC-IV is a norm-referenced tool specifically constructed to gauge intellectual abilities.[43] It includes 10 core subtests and 4 supplementary subtests, yielding 4 index scores and 1 full-scale IQ (FSIQ), which ranges from 40 to 160. The Verbal Comprehension Index (VCI) encompasses subtests in vocabulary, similarities, and comprehension, along with an additional common sense subtest. The Perceptual Reasoning Index (PRI) covers block design, picture concepts, and matrix reasoning subtests supplemented by a spatial planning subtest. The Working Memory Index (WMI) assesses performances through digit span and letter-number sequencing tasks, with an additional arithmetic subtest. The Processing Speed Index (PSI) consists of coding and symbol search tasks, as well as an additional cancellation subtest. It is important to note that the scale assessments of our enrolled study participants were completed by experienced clinical psychologists. The reliability of the FSIQ, the four indices, and their constituent subtests has been demonstrated.[44]

2.7 | Functional connectivity analysis

The estimation of oscillatory FC between 26 specific brain regions was performed using the corrected amplitude envelope correlation (AEC-c) analysis approach. This technique has been widely employed in FC network studies and is known for its high reliability.[45,46] The amplitude envelope is obtained by band-pass filtering the cortical source signals in different frequency bands and then taking the absolute value of the Hilbert transform result, which can reflect the change of amplitude over time. The AEC-c metric is derived by comparing the correlation of the amplitude envelopes of the oscillatory activities of the two specific brain regions (ROIs). The larger the value of AEC-c the greater the synchronization of amplitude envelope fluctuations between the two brain regions. To minimize potential pseudo-connections caused by volume conduction and field diffusion, signal pairs were orthogonalized following a standard procedure before calculating the envelopes.[47] AEC-c values were computed for all ROIS across all participants, resulting in a complete 26×26 adjacency matrix.

We chose to analyze the oscillatory connectivity (i.e., AEC-c) between the 26 selected brain regions at six different frequency bands, which included delta (2–4 Hz), theta (5–7 Hz), alpha (8–12 Hz), beta (15–29 Hz), gamma 1 (30–59 Hz), and gamma 2 (60–90 Hz).

2.8 | Statistical analyses

Descriptive statistics for demographic variables and epilepsy-related variables were calculated. The independent-sample t-test was applied to compare the clinical and demographic data between the two groups. The Shapiro–Wilk test was used to assess data normality. FC was measured by the AEC-c values which ranged from −1 to 1. FC networks (AEC-c values) were compared using NBS CONNECTOME software, and False Discovery Rate (FDR) correction was applied for multiple comparisons (available at URL http://www.nitrc.org/projects/nbs/). Since the AEC-c values tested by the Shapiro–Wilk test did not conform to normal distribution, Spearman correlation analysis was performed to assess the relationship between intelligence test scores and AEC-c values, which represent abnormal neural network parameters. A significance level of $p < 0.05$ was used. All statistical analyses, except for the FC network, were conducted using SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Participants

The demographic characteristics of the study participants revealed a sex ratio of 30 males to 33 females, with a median age at onset of 8.67 ± 1.71 years, as outlined in Table 1. For the HC, the average age was 8.97 ± 2.14 years, and the sex distribution was balanced at 15 males to 15 females. No significant differences were observed between the two groups in terms of age or gender. All children in both groups were attending school in accordance with the age requirements set by Chinese educational policies, without any record of extended leave or dropout. The education of all individuals involved was conducted within the formal public school system, with no notable discrepancies in the length of formal educational attainment.

3.2 | Functional connectivity

Upon comparison, our findings revealed that children with SeLECTS exhibited significant alterations in FC networks at specific frequency bands. In the delta band, FC between the left rMFG and the left rACC was reduced ($p<0.05$). In the gamma2 band, a decrease in FC was observed between the left SFG and the rACC on both sides ($p<0.05$). In contrast, certain FC networks were increased. In the gamma1 band, enhanced FC was observed between the left rMFG and the right rACC, as well as between the left rMFG and the left CMF, and between the right CMF and the right SMG ($p<0.05$) (Figure 2).

3.3 | WISC-IV scores

Children with SeLECTS demonstrated notably inferior performances in the VCI, PRI, WMI, and FSIQ metrics in comparison to the HC group, with statistical significance at $p<0.001$. The discrepancies are quantified as mean and standard deviation in Table 2 and graphically illustrated in Figure 3.

3.4 | Clinical correlation

In the gamma1 band, a positive correlation was observed between the VCI scores and the AEC-c values for the connection between the left rMFG region and the right rACC ($R=0.4228$, $p<0.05$) (Figure 4).

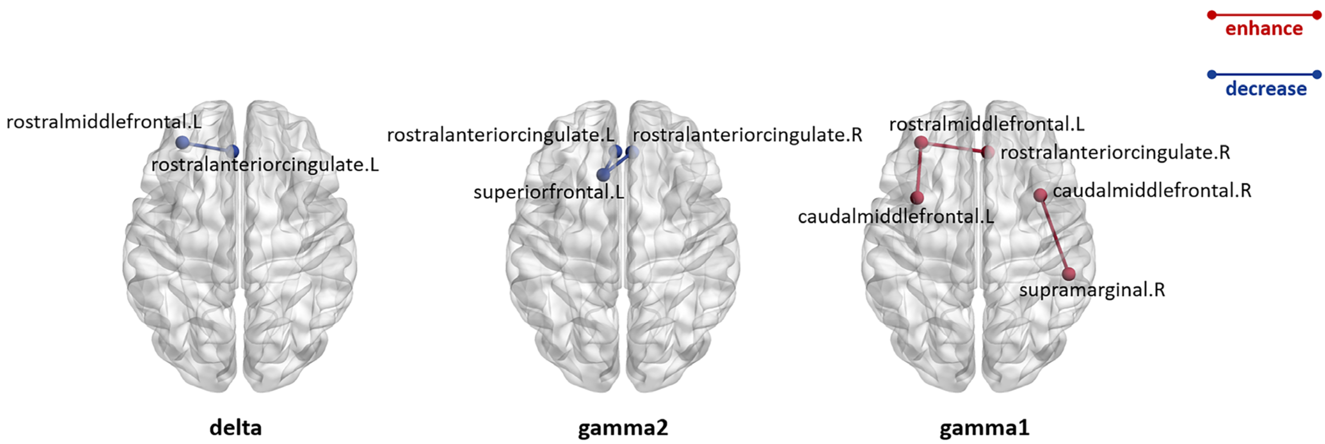

FIGURE 2 Children with SeLECTS demonstrated significant differences in FC networks within certain brain regions when compared with healthy controls. Specifically, the FC networks between the left rMFG and the left rACC ($P_{correction}<0.05$) in the delta band, as well as between the left SFG and the rACC in both sides ($P_{correction}<0.05$) in the gamma2 band, were all decreased, as indicated by the blue lines. Conversely, in the gamma1 band, the FC networks between the left rMFG and the right rACC ($P_{correction}<0.05$), and between the left rMFG and the left CMF ($P_{correction}<0.05$) as well as between the right CMF and the right SMG ($P_{correction}<0.05$) were all enhanced, as represented by the red lines (The AEC-c value is shown in Supplementary S2).

TABLE 2 Comparison of WISC-IV scores between the SeLECTS group and the HC group ($\overline{X}\pm S$).

Groups	VCI	PRI	WMI	PSI	FSIQ
SeLECTS ($n=63$)	92.52 ± 14.71	100.46 ± 15.29	92.76 ± 12.57	99.27 ± 15.10	95.25 ± 13.15
Controls ($n=30$)	110.17 ± 16.60	113.43 ± 13.13	106.03 ± 19.69	103.03 ± 19.69	110.17 ± 13.51
t	−5.2	−4.0	−3.9	−1.2	−5.2
p value	<0.001	<0.001	<0.001	0.224	<0.0001

Abbreviations: FSIQ, Full-Scale Intelligence Quotient; HC: health controls; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; SeLECTS: self-limited epilepsy with centrotemporal spikes; VCI, Verbal Comprehension Index; WISC-IV, Wechsler Intelligence Scale for Children, the fourth edition; WMI, Working Memory Index.

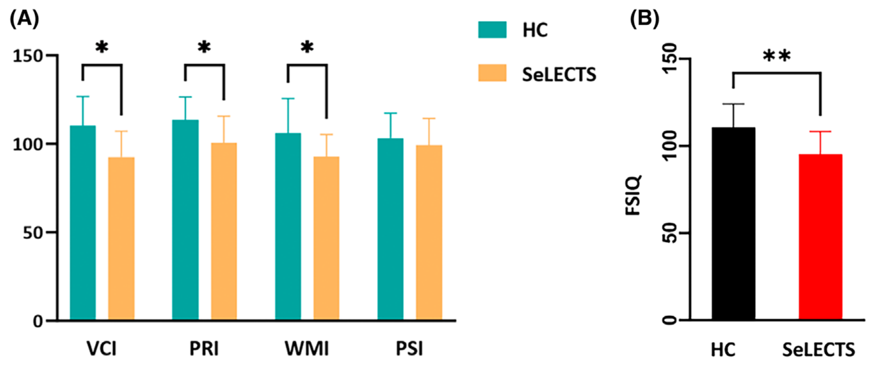

FIGURE 3 WISC IV subtest scaled scores (A), and full scale IQ, index scores (B) comparisons between SeLECTS and HC. FSIQ, full-scale intelligence quotient; HC: Health controls; PRI, perceptual reasoning index; PSI, processing speed index; SeLECTS: Self-limited Epilepsy with Centrotemporal Spikes; VCI, verbal comprehension index; WMI, working memory index; *$p < 0.001$, **$p < 0.0001$.

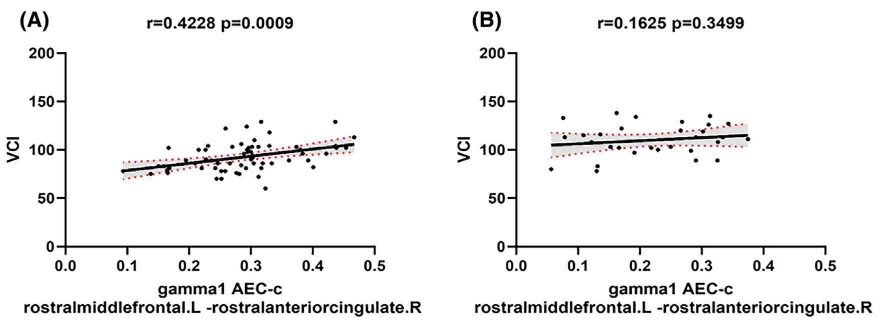

FIGURE 4 (A) The FC network between the left rMFG and the right rACC of the children with SeLECTS was positively associated with VCI scores in the gamma1 band ($R = 0.4228$, $p < 0.05$). (B) The FC network between the left rMFG and the right rACC in the HC group showed no significant correlation with the VCI scores in the gamma 1 band ($R = 0.1625$, $p > 0.05$).

4 | DISCUSSION

Our study identified significant differences in cognitive function between children with SeLECTS and HC. Children with SeLECTS scored lower on the Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Full-Scale IQ (FSIQ). To identify imaging biomarkers related to early cognitive impairment in SeLECTS, we selected 26 cognition-related brain regions based on existing literature. Comparing the SeLECTS group with HC, we found that children with SeLECTS exhibited reduced FC in the delta and gamma2 frequency bands and increased FC in the gamma1 frequency band, and these differences are mainly located in the left hemisphere. Furthermore, correlation analysis revealed a significant positive correlation between the AEC-c value of the left rMFG and right rACC in the gamma1 band and the VCI score. These intriguing findings are discussed further.

4.1 | FC networks

In the delta band, we observed reduced FC between the left rMFG and the left rACC gyrus in SeLECTS children. Delta oscillations are typically associated with deep sleep, but they also play a significant role in various cognitive functions during wakefulness, especially in clinical populations such as children with epilepsy.[48] These waves are thought to originate in the medial frontal cortex and spread to the anterior cingulate and orbitofrontal regions and are typically linked with deep relaxation, memory consolidation, and attentional shifts.[48,49] Although the specific mechanisms are still unclear, the importance of delta activity for memory processing is gradually being recognized, and many researchers believe that delta oscillations are closely related to attention processes.[50] Our finding may suggest that SeLECTS children have weaknesses in the neural mechanisms underlying cognitive fundamentals, such as memory consolidation and attention maintenance. The left rMFG and the left rACC, both key nodes of the DMN and the CEN, are involved in the generation and propagation of delta oscillations. Previous research has highlighted their roles in cognitive function. For example, Tang's study on afferent inputs to the rACC cortex demonstrated its function as a hub integrating frontal cortex inputs across different functional modes, underscoring its critical role in the integration of cognition.[51] Additionally, a resting-state fMRI study by Koyama found that the left middle frontal gyrus is associated with literacy, suggesting its involvement in cognitive processes related to educational tasks.[52] The reduction in the FC network in the delta band may reflect a decrease in coordination between these regions and also a decrease in cross-network coordination, thereby affecting the children's cognitive processing. On the other hand, the decreased FC may reflect a developmental delay in the prefrontal-limbic loop, which in turn affects higher order cognitive functions, although this needs to be further verified in conjunction with structural MRI.

In the gamma2 band, a reduction in FC was observed between the left SFG and the bilateral rACC gyri. Research into the function of the left SFG in humans has shown its significant role in higher cognitive functions, particularly working memory, with individuals having lesions in this area exhibiting poorer performance on working memory tasks.[53] Both the left SFG and the rACC are located within the prefrontal cortex, and existing evidence suggests that these regions are crucial for regulating cognitive control.[54,55] Consequently, the weakening of the connection between these areas may negatively affect cognitive flexibility in children. In contrast, the gamma1 band revealed increased FC in SeLECTS children between several regions: the left rMFG and the right rACC gyrus, the left rMFG and the left CMF, as well as the right CMF and the right SMG. These regions are primarily located within the frontal and parietal lobes. A study on the neural basis of intellectual giftedness in adolescents found that superior intelligence is linked to enhanced functionality of the fronto-parietal network.[56] The gamma band is associated with high-level cognitive processing,[57,58] such as attentional focus, executive functions, working memory, and cognitive control.

The differences in the delta and gamma bands may reflect abnormal regulation of brain function in SeLECTS children. The decrease in the delta band may be associated with impaired basic cognitive functions, while the enhancement and reduction in the gamma bands may respectively represent compensatory mechanisms and functional impairments in the brain. This reduction may indicate difficulties in SeLECTS children when performing tasks that require these cognitive functions, and the enhancement may be a compensatory mechanism aimed at improving the cognitive efficiency and the ability to handle complex tasks in SeLECTS children, as well as reflect the brain's adaptability and plasticity in the face of cognitive challenges.[58,59] This band-specific variability may be driven by the unique neurodevelopmental pathways of SeLECTS children.

Overall, our study identified significant differences in the FC networks of cognitively relevant brain regions within the delta and gamma frequency bands in children with SeLECT, which were more pronounced in the left hemisphere, with the frontal lobe showing the most prominent alterations. The left hemisphere plays a dominant role in language processing, sequential analysis, and logical reasoning, while the frontal lobes are crucial for higher cognitive control. Abnormal lateralization of the left hemisphere may further exacerbate the cumulative damage to the language-dominant hemisphere in this disorder. The results of this study provide new insights into the differences in FC networks at the delta and gamma frequency bands in children with SeLECTS. These findings not only reveal abnormalities in FC networks within cognitive-related brain regions in children with SeLECTS, but also offer evidence for the neurobiological mechanisms underlying cognitive dysfunction. To further explore the relationship between these altered FC networks and cognitive functions, we conducted a correlation analysis between the strength of these differential functional connections and the scores of five different indicators in the Wechsler Scale, and we will discuss the findings of this section in detail in Section 4.3. Future research can further explore the interactions between these frequency bands and brain regions, as well as how they influence the cognitive development of children with SeLECTS.

4.2 | Neuropsychological assessment

A human brain developmental atlas created by analyzing 123 984 MRI data from 101 457 persons of various ages revealed that early childhood was a vital time of brain development marked by strong neuroplasticity,[60] which means cognitive function at this stage was extremely vulnerable to epilepsy. Our study compared the intellectual profile of children with SeLECTS to HC using the WISC-IV. Compared to HC, we observed no difference in PSI. Otherwise, a significant difference was found for four out of five indices: FSIQ, VCI, PRI, and WMI.

The reduction in FSIQ reflects poorer performance on a wide range of cognitive tasks in children with SeLECTS, consistent with previous studies indicating that SeLECTS may affect multiple cognitive networks in the brain. The reduction in VCI may be related to FC abnormalities in the language network in children with SeLECTS, which is consistent with the reduced activity in brain regions reported in the literature related to language impairment.[61,62] Reductions in WMI may be related to FC disruptions in prefrontal and parietal regions related to working memory, which play a key role in maintaining and manipulating information. Decreased PRI may be associated with weaknesses in executive function and information processing speed, possibly due to delayed nerve conduction caused by SeLECTS.

Notably, the PSI did not show significant differences between children with SeLECTS and healthy controls. This finding may have several explanations. First, the PSI mainly assesses non-verbal reasoning abilities, including spatial abilities and visual organization abilities, which may be less affected by SeLECTS. For example, one study found that non-verbal reasoning abilities may remain relatively stable even when faced with challenges in other cognitive domains.[63,64] Second, children with SeLECTS may retain some cognitive functions in nonverbal reasoning tasks, or these tasks may not involve the cognitive domains in which children are primarily impaired. In addition, some researchers believe cognition is organized into domain-specific systems,[65] so we speculate the lack of differences in PSI may be related to the domain-specific nature of cognitive impairment in children with SeLECTS; that is, some cognitive domains may be more susceptible to the disease than other domains. The findings of this study highlight the specific effects of SeLECTS on cognitive function in children and provide important clues to understanding its neurobiological basis. In addition, studies combining behavioral and neuroimaging techniques will help reveal the underlying mechanisms of cognitive differences in children with SeLECTS.

4.3 | Correlation analysis between WISC-4 scores and AEC-c values

The results of the correlation analysis indicate that in the gamma1 band, there is a significant positive linear correlation between the strength of FC (AEC-c value) between the left rMFG and the right rACC and the VCI.

VCI is an indicator of language comprehension and expression ability, and its correlation with the FC between the left rMFG and the right rACC suggests that these brain regions may play a significant role in the neural network for language processing. This finding is interesting and, together with the abnormal left hemisphere lateralization of the FC network that we discussed in Section 4.1, reflects the fact that children with SeLECTS have impaired verbal function, and the degree to which language comprehension ability is preserved or impaired in children with SeLECTS is related to the strength of the FC network in these areas. There is no such significant correlation in HC. Additionally, the gamma1 band is typically associated with high-level cognitive processes such as attention, working memory, and language processing. Therefore, the strong FC between the left rMFG and the right rACC in the gamma1 band may be related to the optimization of these cognitive functions, which could be a compensatory mechanism. Compensatory neural reorganization represents one possible potential mechanism.[66] Gamma oscillations are frequently associated with rapid information integration within local neural circuits, particularly during cognitive processes such as language processing. Children with SeLECTS may maintain language function through enhanced gamma synchronization. Another possible potential mechanism is the adaptive reorganization of the language network.[67] Abnormal discharges in children with SeLECTS may disrupt the default network, which could drive the language network to achieve more efficient local processing via high-frequency oscillations. A study of structural connectivity changes in the white matter tracts of children with SeLECTS and their relationship to language function found that the children had reduced fractional anisotropy, mainly in the left hemisphere, which is associated with lower language performance, consistent with our result.[68] Our finding suggests that the strength of the FC network between these two brain regions in the gamma1 band may be a predictor of impaired speech ability. This finding resonates with previous studies that have indicated that abnormal FC networks in the prefrontal and anterior cingulate regions are associated with cognitive dysfunction.[54,69,70] Finally, this result emphasizes that specific brain region FC abnormalities in children with SeLECTS may be related to specific cognitive deficits. This provides a new perspective for understanding the cognitive impairments in children with SeLECTS and may offer targets for future intervention strategies.

In summary, our research results not only reveal differences in FC in cognitive-related brain regions in children with SeLECTS but also indicate that these differences are correlated with specific cognitive function indicators. Future research can further explore the causal relationship between these brain region functional connections and cognitive functions and develop interventions targeted at these connections.

5 | LIMITATIONS

One of the limitations of this study is that the WISC-IV testing system fails to assess specific skills such as academic abilities, language, and phonological awareness. As a result, it cannot be regarded as an accurate assessment of every specific aspect of a patient's neurocognitive profile. Secondly, the number of SeLECTS patients exceeded the number of HC in this study; however, efforts were made to ensure that both groups were comparable in key demographic characteristics and other potential influencing factors, and in future studies, we plan to increase the sample size, further expand the number of controls, and stratify patients based on cognitive levels to identify additional cognition-related indicators. Third, this study did not take into account the laterality of spikes, which will be further refined in future experiments. Fourth, for children with SeLECTS in this study, routine clinical data were collected, including seizure frequency, seizure duration, and onset date. However, we observed that many parents were unable to provide accurate and reliable information. Consequently, the correlation between network parameters and clinical data was not explored or discussed. In future work, we will focus on raising families' awareness of the importance of recording disease-related information to enhance follow-up quality and obtain more comprehensive and accurate clinical data. Fifth, this study is a multi-frequency band investigation. Although no inter-band corrections were performed, which increases the cumulative risk of Type I errors from the observer's perspective, meaningful differences in FC networks were identified across multiple bands, providing a basis for generating a priori hypotheses for future studies on FC networks in SeLECTS.

6 | CONCLUSION

Utilizing multi-frequency MEG technology, we have identified frequency-dependent alterations in FC networks of brain regions associated with cognitive functions in children with SeLECTS, which may underlie the pathological basis of cognitive impairment in children with SeLECTS. We also found that these differences in FC networks were significantly correlated with variations in verbal comprehension ability, which may contribute to the understanding of the mechanisms underlying the weaknesses in cognitive function in children with SeLECTS. Furthermore, our findings may provide hypotheses for future work dedicated to further exploring the mechanisms associated with brain network alterations in cognitive impairment in children with SeLECTS.

AUTHOR CONTRIBUTIONS

Jing Lu and Peilin Jiang designed the study. Jing Lu, Peilin Jiang, Minghao Li, Yinjie Zhu, Ke Hu, and Xinyi Zhou acquired the raw data. Jing Lu, Yingfan Wang, Minghao Li, and Yinjie Zhu analyzed the data. Jing Lu, Peilin Jiang, and Yingfan Wang wrote the manuscript. Xiaoshan Wang revised the manuscript. All authors read and approved the final submitted manuscript. All authors are responsible for the accuracy and integrity of the work.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The studies involving human participants were reviewed and approved by the Medical Ethics Committee of The Affiliated Brain Hospital of Nanjing Medical University and the Affiliated Children's Hospital of Nanjing Medical University in China (Ethical Review Number: 2022-KY038-01).

PATIENT CONSENT STATEMENT

Written informed consent to participate in this study was provided by the participants or their legal guardians.

CLINICAL TRIAL REGISTRATION

This study is registered at the Chinese Clinical Trial Registry under the registration number ChiCTR2400087738.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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