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ABSTRACT

BACKGROUND AND PURPOSE: Idiopathic generalized epilepsy (IGE) accounts for approximately 20% of epilepsy cases. Characterized by generalized spike-wave discharge, IGE is increasingly recognized as a network disorder with potential metabolic underpinnings. This study leverages the advantages of simultaneous PET/MRI, which enables the concurrent acquisition of MRI and PET data, to integrate structural connectivity (SC), functional connectivity (FC), and glucose metabolism into a unified framework. This study aims to elucidate the multimodal abnormalities of the neocortex in IGE, to analyze the correlations between these abnormalities and clinical presentations, and to investigate the interactions among different imaging modalities.

MATERIALS AND METHODS: Twenty-one patients with IGE and 34 healthy controls (HCs) were recruited. Simultaneous PET/MRI scans were performed, incorporating DTI, resting-state fMRI, and [^{18}F]FDG-PET. DTI generated a neocortical connectivity blueprint, while resting-state fMRI provided a whole-brain connectivity matrix. [^{18}F]FDG-PET data were processed to obtain standardized uptake value ratios (SUVRs). Multivariate distance matrix regression was used to identify abnormal neocortical regions in SC and FC. Differences in SUVRs were identified by using least absolute shrinkage and selection operator regression. Statistical analyses, including *t* tests, linear models, mediation analysis, and Pearson correlations, were conducted to compare values of each technique between groups and explore relationships with clinical features.

RESULTS: SC abnormalities were primarily found in the limbic (40% of all abnormal neocortical regions) and visual networks (31%), while FC abnormalities were mostly in the default mode network (DMN, 45%). Metabolic abnormalities were predominantly in the frontoparietal (26%) and somatomotor (22%) networks. SC in the limbic was positively correlated with onset age, while seizure frequency was negative correlated with DMN FC and positively correlated with frontoparietal metabolism. Mediation analysis showed that DMN FC mediated the relationship between limbic SC and frontoparietal and somatomotor metabolism.

CONCLUSIONS: A multimodal approach reveals distinct and interrelated abnormalities in IGE, with different modalities reflecting various aspects of the disease, thus enhancing our understanding of its complex mechanisms. This integrative analysis could inform more effective treatments.

ABBREVIATIONS: ACME = average causal mediation effect; BOLD = blood oxygen level–dependent; DMN = default mode network; FC = functional connectivity; FDR = false discovery rate; FPN = frontoparietal network; GSWD = generalized spike-wave discharges; HC = healthy control; IGE = idiopathic generalized epilepsy; LASSO = least absolute shrinkage and selection operator; MDMR = multivariate distance matrix regression; SC = structural connectivity; SMN = somatomotor network; SUVR = standardized uptake value ratio; VN = visual network

Idiopathic generalized epilepsy (IGE) is a common neurologic disorder, comprising approximately 20% of all epilepsy cases.[1] The prevalence of psychiatric and other comorbidities, including sudden unexpected death in epilepsy, is similar to that in focal epilepsy.[2] Generalized epilepsy is a clinical syndrome typically characterized by paroxysmal generalized spike-wave discharges (GSWD), and recent evidence suggests it to be a network disorder.[3-5] Additionally, epilepsy can be considered a metabolic disease,

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SUMMARY

PREVIOUS LITERATURE: Prior studies have recognized IGE as a network and metabolic disorder, with disruptions observed across structural, functional, and metabolic aspects of the brain. Neuroimaging findings indicate that structural alterations are more stable, while functional changes often reflect short-term dynamics. Hypometabolism in specific brain regions, though not visually apparent in patients with IGE, can be detected by using quantitative analyses. These imaging modalities reveal distinct yet interconnected dimensions of IGE, aiding in a comprehensive understanding of the disorder.

KEY FINDINGS: This study found dissociated patterns of abnormalities in IGE across multimodalities: structural connectivity abnormalities were concentrated in the limbic and visual networks, functional connectivity deficits were most prominent in the default mode network, and metabolic reductions were observed in the frontoparietal and somatomotor networks.

KNOWLEDGE ADVANCEMENT: The study advances understanding of IGE by revealing how distinct imaging modalities capture complementary aspects of disease mechanisms. The integration of structural, functional, and metabolic data underscores the importance of a multimodal approach in characterizing IGE and offers insights for developing more targeted and comprehensive treatment strategies.

with primordial mechanisms triggered by compounds such as adenosine being highly relevant to seizures and epileptogenesis.[6] Despite advances in neuroimaging and clinical research, the precise pathophysiologic mechanisms of IGE remain elusive and warrant further investigation.

Neuroimaging offers new insights into the structural, functional, and metabolic aspects of the brain that may contribute to the pathophysiology of IGE.[7] Although the term generalized implies that all brain neurons are synchronously and homogeneously affected in IGE, electrical neuroimaging, and molecular studies indicate the involvement of specific cortical networks while sparing others.[8] In patients with IGE, structural imaging studies reveal atrophy, and functional imaging studies show abnormal nodes in frontocentral cortical areas. Reduced connectivity in the default mode network (DMN) may be related to drug resistance in IGE.[9] DMN connectivity negatively correlates with seizure duration.[10,11] On PET, patients with epilepsy usually show hypometabolism in specific brain regions.[12] However, in patients with IGE, regions of hypometabolism are usually typically not visually apparent, but quantitative analyses at the vertex level can identify metabolic abnormalities. These different modalities reflect various facets of IGE, with distinct anatomic, functional, and metabolic dissociations observed. Previous studies suggest that fMRI captures physiologic alterations related to acute episodes, while structural changes reflect more stable and long-standing modifications in the brain.[13]

Integrating these diverse imaging modalities into a unified analytical framework can enhance our understanding of the complex mechanisms of IGE. This comprehensive approach allows for a detailed examination of disease-related changes across different imaging modalities and facilitates the exploration of interrelationships among these modalities. This study focuses on the neocortex, utilizing structural blueprint techniques to pinpoint regions with disrupted connectivity to major white matter fiber tracts in patients with IGE. Utilizing multivariate distance matrix regression (MDMR) and least absolute shrinkage and selection operator (LASSO) regression, we can identify IGE-imaging correlations at the individual vertex level without relying on prior hypotheses. Additionally, we aim to identify areas with abnormal whole-brain functional connectivity (FC) and glucose metabolism and to examine the relationships between these abnormalities and clinical features from the perspective of large-scale brain networks.

To achieve these goals, we utilize simultaneous PET/MRI to acquire MRI and PET data concurrently, integrating DTI, blood oxygen level–dependent (BOLD) fMRI, and [^{18}F]FDG-PET data. This study aims to elucidate the distinctive structural, functional, and metabolic abnormalities in the neocortex of patients with IGE, analyze the correlations between these abnormalities and clinical presentations, and investigate the interactions among different imaging modalities. We seek to provide a more holistic view of the pathophysiologic underpinnings of IGE and advance our understanding of how structural, functional, and metabolic alterations interrelate in this disorder.

MATERIALS AND METHODS

Participants

Twenty-one patients with IGE (mean age, 27.67 ± 11.15 years, 8 men) were recruited between December 2021 and October 2023 according to International League Against Epilepsy classification.[14] All patients were further classified into subtypes: 5 patients had childhood absence epilepsy, 10 patients had juvenile myoclonic epilepsy, and 6 patients had epilepsy with generalized tonic-clonic seizures alone.[15] A total of 61.9% (13/21) of patients had received monotherapy, and the others had received multiple drugs. All patients in this study still experienced epileptic seizures, but 16 of the 21 drug-treated patients responded well to antiepileptic drugs, showing significantly decreased seizure frequency. None had brain lesions, developmental disabilities, or other neurologic disorders. Thirty-four sex- and age-matched healthy controls (HCs) (mean age, 31.12 ± 6.35 years, 16 men) were recruited, without neurologic or psychiatric disorders based on a health screening measure. Ethics approval was obtained from the ethics committee of Xuanwu Hospital, and written informed consent was provided by each participant. Detailed demographic and clinical information are provided in the Table.

MRI Acquisition and Preprocessing

Interictal [^{18}F]FDG-PET and MRI data were simultaneously obtained by using a hybrid TOF-PET/MRI scanner (Signa, GE Healthcare). MRI sequences included 3D T1 BRAVO (GE Healthcare), BOLD, and DTI. DTI data preprocessing generated a neocortical connectivity blueprint between the neocortex and major white matter fiber tracts. A whole-brain connectivity matrix was calculated based on the BOLD images. PET images were preprocessed to obtain a standardized uptake value ratio (SUVR) map. The preprocessing results for these modalities were projected into the fsaverage5 space for subsequent statistical analyses and comparisons. Details about PET/MRI acquisition and data postprocessing are provided in the Supplemental Data.

IGE-Related Abnormal Neocortical Regions Identification

For DTI and BOLD, a connectome-wide association study used MDMR.[16] The correlation coefficients for each vertex in the structural connectivity (SC) map were compared with the values of corresponding vertices in maps generated from every other participant. This resulted in a Pearson correlation coefficient r that measures the spatial correlation of maps between patients. The similarity of SC maps between participants was computed by using the distance metric $\sqrt{2(1-r)}$. MDMR then tested the relationship between intersubject differences on a grouping variable and intersubject distances, resulting in a pseudo-F statistic for each vertex that demonstrated how intergroup differences were reflected in SC at that vertex. This process was repeated for every single vertex, resulting in a whole neocortical map of IGE reflected in SC at each vertex. A 5000-permutation test of the pseudo-F values yields the corresponding P values. Multiple comparisons were corrected by using the false discovery rate (FDR) at a significance level of $P < .05$. Covariates in this analysis included sex and age. The FC maps underwent the same MDMR analysis as described above.

To identify neocortical regions with differences in PET SUVR maps between patients with IGE and HCs, we used a LASSO regression model. LASSO regression is an L1-norm regularization technique that introduces a shrinkage penalty term (λ) to prevent model overfitting, compelling some predictor coefficients to shrink to zero.[17] The tuning parameter (λ) was optimized through a repeated 5-fold cross-validation method and subsequently applied to predict the remaining subjects within the cycles. We selected the smallest mean-squared error to determine the coefficients of the SUVRs. SUVRs with nonzero coefficients were considered important features and were retained (Fig 1). Additionally, we also

The demographics and clinical characteristics of patients with IGE and healthy controls

	Patients (n=21)	Controls (n=34)	P Value
Age	27.67 ± 11.15	31.12 ± 6.35	.21[a]
Sex (male/female)	8/13	16/18	.52[b]
Education (years)	12.07 ± 3.30	13.35 ± 3.18	.16[a]
Age of onset (years)	15.90 ± 10.02		
Duration of illness (years)	12.57 ± 9.27		
Seizure frequency (times/week)	1.75 ± 1.10		
Subtypes (CAE/JME/GTCA)	5/10/6		
AED (response/nonresponse)	13/8		
Therapy (single/multiple)	16/5		

[a] P value by 2-sample t test.
[b] P value by 2-tailed χ^2 test.
Note:—Data are presented as means (standard deviation).
AED indicates antiepileptic drug; CAE = childhood absence epilepsy; GTCA = epilepsy with generalized tonic-clonic seizures alone; JME = juvenile myoclonic epilepsy.

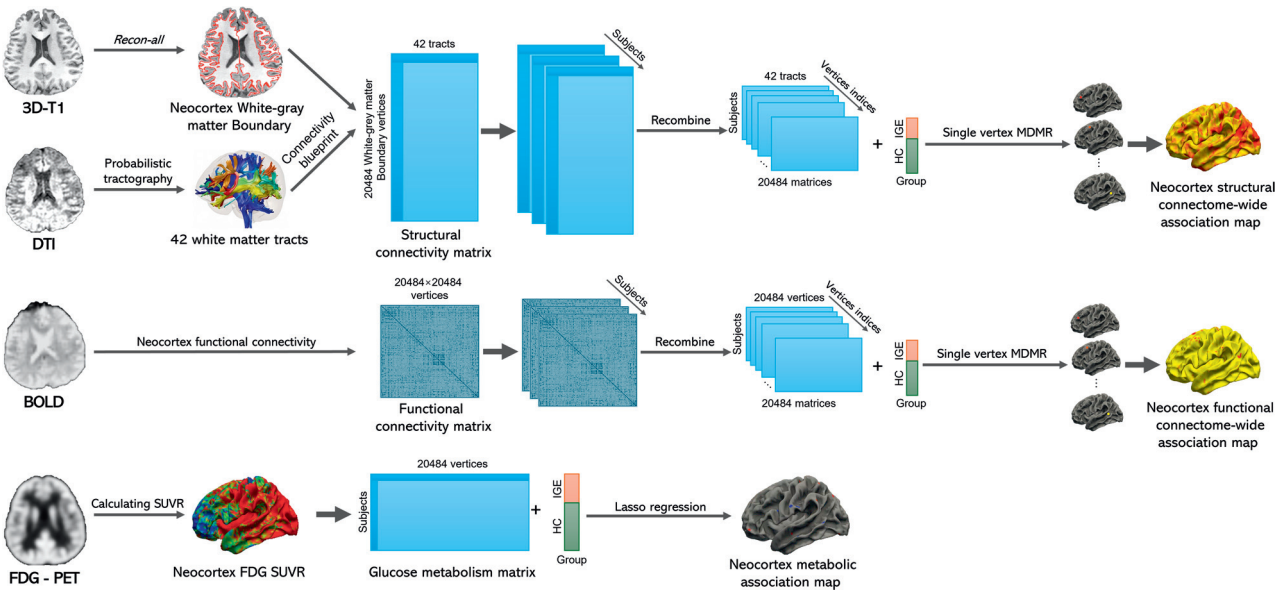

FIG 1. Flowchart of this study. The neocortex white-gray matter boundaries from 3D-T1 images were extracted as masks after the Recon-all process. These masks were combined with probabilistic tractography to calculate SC blueprints. BOLD MRI was used to calculate whole-neocortex FC for each vertex. [^{18}F]FDG-PET was used to calculate the neocortical SUVRs. MDMR was performed on each vertex's SC and FC to obtain pseudo-F values and P values. Repeated execution of MDMR produced a neocortical structural and functional connectome-wide association map. LASSO regression was used to for SUVRs.

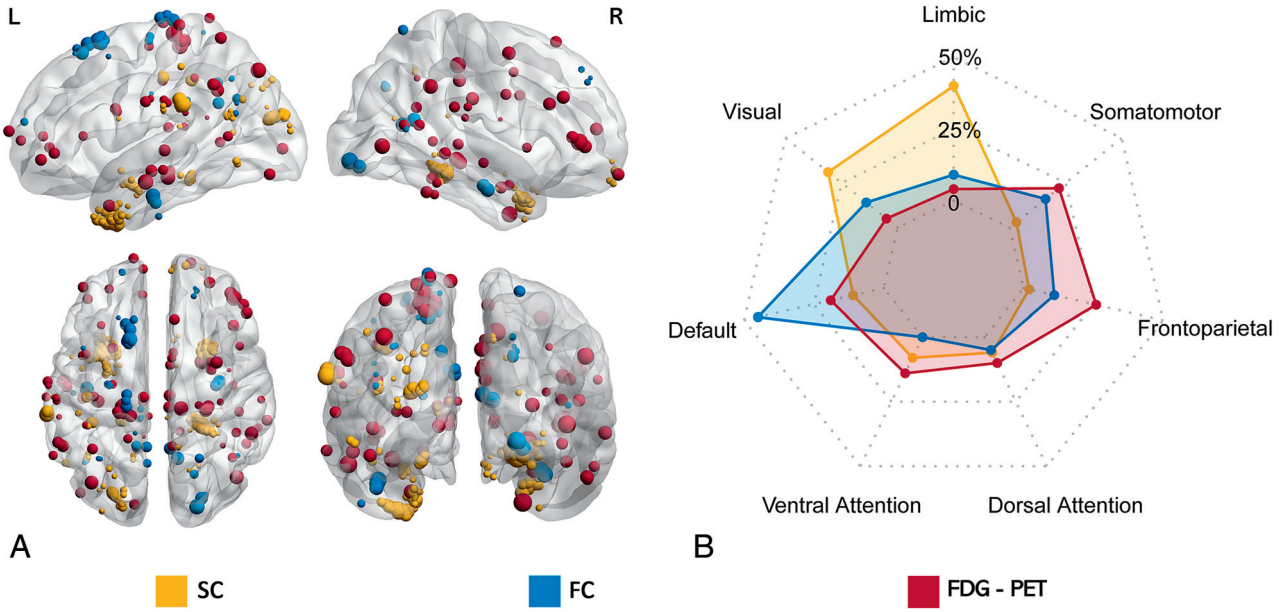

FIG 2. Distribution of abnormal brain regions for each technique in patients with IGE (*A*) and functional network affiliation of the regions (*B*). Larger spherical volumes represent larger pseudo-*F* values in (*A*).

used LASSO regression modeling to identify abnormalities of neocortical thickness in patients with IGE.

Statistical Analysis

The proportion of structurally connected, functionally connected, and metabolically abnormal brain regions in each network, and their mean values, were calculated according to the 7 functional networks.[18] Mean values were compared between the patients with IGE and HCs by using linear models with sex and age as covariates and adjusting for FDR. For features with abnormalities in each technique, an analysis of covariance was performed to determine whether they differed in IGE subtypes, and the linear model was performed to determine whether they differed in antiepileptic drug response and medication type. The features were used as the dependent variable, while the independent variable was the patient's subtypes or clinical presentations, with age and sex as covariates. In cases of significant differences, post hoc analyses using the least significant difference method were conducted to pinpoint the specific groups that exhibited significant distinctions.

Pearson correlations were performed between each functional network mean for each technique and age of onset, and seizure frequency. We focus on networks in which the distribution of significant vertices in each technique accounted for more than 50% of the total distribution across other networks (ie, the distribution accounts for more than 21%) for the mediation analysis. This can help focus the analysis on the most prominent and relevant networks, reduce noise, and increase the likelihood of identifying meaningful relationships among the variables of interest. Mediation analysis was conducted by using the "mediation" package in *R*. Notably, SC was used as an independent variable in this study because previous research has indicated that fMRI typically reflects short-term changes in brain activity, while structural imaging focuses on long-term structural alterations in the brain.[13] Because the relationship between FC and FDG metabolism is not well defined, we therefore analyzed FC and FDG as mediator and outcome variables, respectively.

Demographic and clinical data were compared between the 2 groups by using the χ^2 test for sex distribution and the 2-sample *t* test for age, education, age of onset, duration of illness, and seizure frequency. All statistical analyses were conducted by using *R* (Version 4.2.1), with significance set at $P < .05$. This study methodology follows the guidelines outlined in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis Checklist.[19]

RESULTS

Distribution of Each Technique and Correlation with Clinical Features

SC. For SC, the neocortical regions with abnormalities in patients with IGE were primarily in the limbic (40% of the total) and the visual network (VN, 31%), with the frontoparietal network (FPN, 2%), and somatomotor network (SMN, 3%) being the least affected (Fig 2, Supplemental Data). The SC of limbic (Δmean, −0.001; 95% CI, −0.002 to −0.001) and VN (Δmean, −0.001; 95% CI, −0.002 to −0.0005) were significantly lower in patients with IGE than in HCs (Fig 3*A*). Additionally, the neocortical thickness with abnormalities in patients with IGE were primarily in the limbic network (46%, Supplemental Data), which were significantly thinner in patients (Δmean, −0.170 mm; 95% CI, −0.103 to −0.237).

We found that SC in the limbic network of patients with IGE was positively correlated with onset age ($r = 0.45$, $P = .04$), with SC becoming weaker at younger onset ages (Fig 3*D*). However, cortical thickness of the limbic network was not significantly correlated with either onset age or seizure frequency.

FC. For FC, the abnormal neocortical regions were mostly located in the DMN (45%, Fig 2, Supplemental Data). For the FC of the

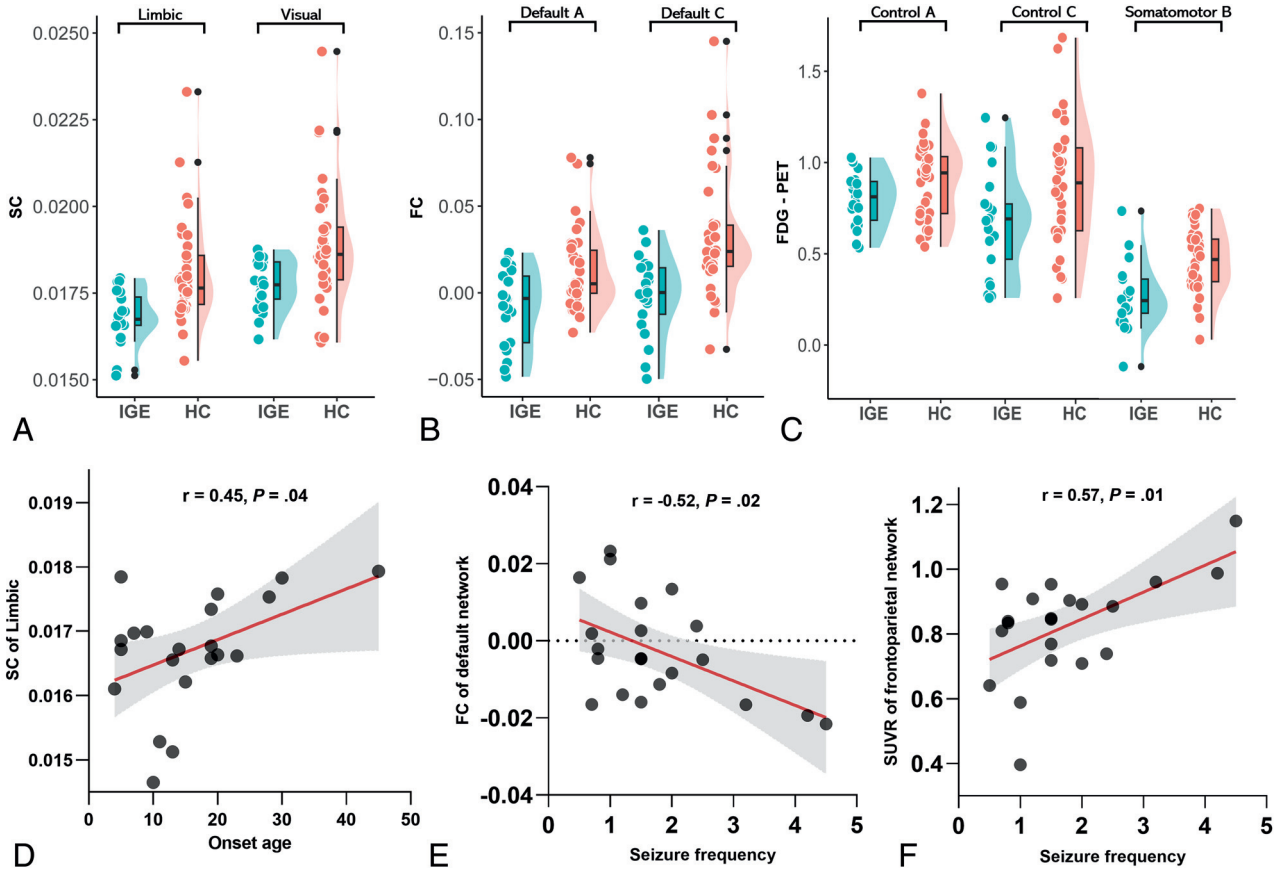

FIG 3. Mean values of SC and FC, as well as SUVR, in patients with IGE and HCs, and their correlation with clinical characteristics.

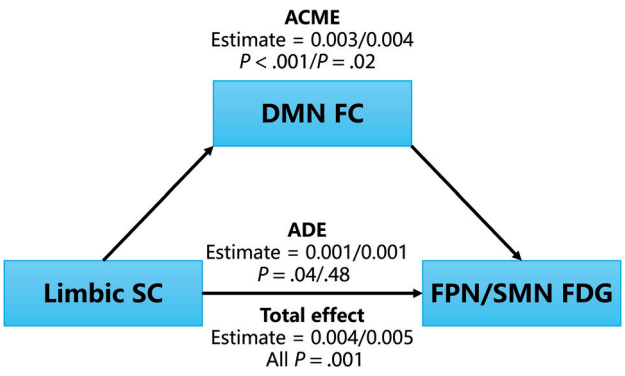

FIG 4. Mediation analysis between the SC of the limbic network, FC of the DMN, and FDG metabolism in the FPN and SMN networks. For the estimate and *P* values, the value before the "/" represents the FPN FDG as outcome variable, while the number after the "/" indicates the SMN FDG as outcome variable. ADE indicates average direct effect.

DMN, patients with IGE showed significantly reduced connectivity in the default A (Δmean, −0.021; 95% CI, −0.034 to −0.008) and default C (Δmean, −0.034; 95% CI, −0.051 to −0.016) networks (Fig 3*B*). FC of the DMN was negatively correlated with the seizure frequency ($r = -0.52$, $P = .02$, Fig 3*E*).

FDG-PET. The brain regions with metabolic abnormalities in patients with IGE were mainly in the FPN (26%) and SMN (22%), with the limbic (4%) and visual (5%) networks being the least affected (Fig 2, Supplemental Data). We found that FDG metabolism in several subregions of the FPN and SMN in patients with IGE was significantly lower than in HCs, including control A (Δmean, −0.097; 95% CI, −0.192 to −0.002), control C (Δmean, −0.217; 95% CI, −0.396 to −0.038), and somatomotor B (Δmean, −0.199; 95% CI, −0.297 to −0.101) networks (Fig 3*C*). FDG metabolism in the FPN was positively correlated with seizure frequency ($r = 0.57$, $P = .01$, Fig 3*F*).

Please see Supplemental Data for details on the differences in vertices within the large-scale networks of the 3 models in IGE and HCs, as well as the correlations between clinical features and the vertices of SC, FC, and FDG-PET in the large-scale networks of IGE. Supplemental Data show the results of the subgroup comparisons.

Mediation Analysis

We observed that FC in the DMN mediates the relationship between SC in the limbic network and glucose metabolism in the FPN (average causal mediation effect [ACME] = 0.003, $P < .001$) and SMN (ACME = 0.004, $P = .02$, Fig 4). In contrast, glucose metabolism in the FPN and SMN did not have significant mediating effects between SC in the limbic network and FC in the DMN. Additionally, mediation analyses based on the SC of the VN were not associated with any significant mediation effects. The average causal mediation effect showed the detailed results of the above mediation analyses.

DISCUSSION

Our study observed a dissociated pattern of abnormal neocortical regions for SC, FC, and glucose metabolism in patients with IGE. The primary SC abnormalities in patients with IGE were found in the limbic network and VN, while whole-brain FC abnormalities were concentrated in the DMN. Abnormalities in glucose metabolism were distributed in the FPN and SMN. Additionally, SC of the limbic network was positively correlated with age at onset, whereas the FC of the DMN and glucose metabolism of the FPN were associated with seizure frequency. Moreover, the FC of the DMN mediated the relationship between SC of the limbic network and glucose metabolism of the FPN and SMN in patients with IGE.

Seizure initiation and spread seizures are closely related to intracerebral circuits, such as the Papez circuit,[3] which has a high degree of anatomic overlap with the limbic network, suggesting a significant role in IGE pathogenesis.[20] Neuromodulation of these circuits has been shown to alleviate epileptic symptoms, indicating its importance in the IGE.[21] This study also found that SC in the llimbic network was disorder and positively correlated with the age at onset of IGE, suggesting that earlier onset is associated with weaker SC. During early brain development, critical periods exist when neural circuits are particularly plastic and vulnerable to disruptions. IGE may interfere with the normal development and maturation of the limbic network.[22,23] Early onset of epilepsy could disrupt the formation of white matter tracts and synaptic connections, leading to lower SC.[22] Additionally, cumulative damage from prolonged seizures, chronic neuroinflammation due to recurrent seizures, excitotoxicity, and metabolic stress, all of which can damage neural connections,[24] reduce structural integrity, and result in lower connectivity.[25] Consequently, SC reflects cumulative brain damage and long-term alterations in IGE. SC of the VN was also decreased, with VN and limbic changes often converging in patients with IGE,[26] which may be due to their spatial proximity and reflect the similar disease dynamics of IGE. Despite some research linking VN dysfunction with photosensitivity or disrupted visual perception in epilepsy, clinical evidence was lacking in this study.[27,28]

The deactivation of the DMN and activation of the thalamus are consistently reported as responsible for generation and propagation epileptic activities.[29] The weak whole-brain connectivity of the DMN found in this study supports this view. Epileptic activity, particularly generalized seizures, can disrupt normal brain network functioning. The DMN, crucial for maintaining a resting state and involved in high-level cognitive processes like self-referential thinking and memory, may be particularly susceptible to these disruptions, which leads to reduced FC efficiency and coherence within the DMN. The current conceptualization of DMN anatomy resembles the unitary model of the limbic system, which, through the coordination of its subregions, subserves the elaboration of emotion, memories, and behavior.[30,31] This finding of mediation analysis underscores the pivotal role of the DMN in integrating structural and metabolic abnormalities in IGE.

Epileptic activity can induce hypometabolism in brain regions involved in seizure propagation and generalization.[32] The FPN and SMN might be particularly affected by this hypometabolic state due to their involvement in cognitive and motor functions often disrupted in IGE. Simultaneous electroencephalogram-fMRI studies have shown hypersynchronization of SMN often occurs in later ictal and postictal periods, suggesting its passive involvement in GSWD.[33] Patients with IGE exhibit mild or severe cognitive or motor disorders, whether they have absence seizures, myoclonic, or generalized seizures. Thus, these 2 network abnormalities may cause or be affected by seizures. One interpretation of hypometabolism is that chronic epilepsy is associated with neuroinflammation and neuronal damage, affecting metabolic activity.[34,35] Microglial activation and cytokine release associated with chronic seizures can contribute to this metabolic impairment. Additionally, in response to recurrent seizures, the brain might undergo compensatory mechanisms and network reorganization, involving a shift in metabolic activity to other regions or networks to maintain overall brain function.[36] This compensatory reallocation of resources might result in reduced metabolic activity in the FPN and SMN as the brain attempts to mitigate epilepsy's impact.

FC in the DMN and glucose metabolism in the FPN were correlated with seizure frequency, indicating that these modalities might reflect the symptom and more dynamic and reversible aspects of the disease. These seizures impair synaptic plasticity, neurotransmitter balance, and SC, all of which are essential for maintaining functional and metabolic activity.[6,37] Additionally, compensatory mechanisms attempting to mitigate seizure effects may further alter FC and metabolic processes.[38,39] Each technique captures different aspects of brain, and the lack of correlation could reflect the complexity of brain network interactions, where changes in 1 domain (eg, SC) do not always correspond directly to changes in another (eg, metabolism) at the same regions. However, different modalities and brain regions can relate to each other. This complex interplay highlights the importance of considering multiple modalities to fully understand the pathophysiology of IGE. While no randomized controlled trials have established the efficacy of neuromodulation in IGE, open-label studies suggest potential benefits.[1,40] Common neuromodulation approaches target several key brain regions, including the thalamus, limbic system, and specific cortical areas.[41-43] However, the effectiveness of these targets is inconsistent across patients. Our study highlights abnormal brain regions, including the DMN and FPN, which could serve as novel neuromodulation targets. Modulating the excitability, activity, and energy demand of them may reduce seizure frequency in IGE. Moreover, the SC in the limbic system could serve as a valuable marker for evaluating the effectiveness of the treatments.

Our study also has some limitations. First, the long-term use of antiepileptic drugs can influence brain metabolism, and the drug selection and medication dosage were not controlled in this study. The side effects of these medications could compound the structural, functional, or metabolic disturbances caused by the disease itself, leading to further neuroimaging changes. Although challenging, future studies could mitigate this concern by selecting drug-naïve patients. Second, the sample size of our study is small, so the results need to be interpreted with caution. Though there was no statistically significant difference between the ages of patients and HCs, the mean age of HCs was slightly older. Therefore, the results of this study merit replication in future

studies with larger sample sizes. Additionally, a limitation of our mediation analysis is that it is based on assumptions derived from previous research, which primarily considers the progression the disease over time as the causal framework, rather than focusing on the causal relationships between the physiologic changes reflected by different imaging modalities. As a result, our analysis is exploratory in nature, and while it provides valuable insights, the interpretation and application of the findings should be approached with caution, pending further studies to validate these relationships.

CONCLUSIONS

Our study underscores the complexity of disease-related changes in IGE. While SC, FC, and glucose metabolism each reveal distinct abnormalities, the dissociation and limited correlation between these modalities suggests that they may reflect different aspects of the disorder, possibly operating independently or at different stages of disease progression. By integrating multiple neuroimaging modalities, we can advance our understanding of IGE and pave the way for more comprehensive and effective treatments.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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