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Original contribution

Cortical morphologic changes in recent-onset, drug-naïve idiopathic generalized epilepsy

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ABSTRACT

Purpose: Only a few studies have investigated the brain morphology abnormalities in structural MRI in patients with drug-naïve idiopathic generalized epilepsy (IGE) and mainly focused on brain volume changes. In the present study, we aimed to investigate the changes in three morphologic measurement differences including cortical thickness, cortical volume, and surface area using FreeSurfer in a pediatric cohort of recent-onset, drug-naïve IGE.

Methods: Forty-five recent-onset, drug-naïve patients diagnosed with IGE and 32 demographically matched healthy controls were recruited. All participants underwent structural MRI scans with a 3.0 T MR system. FreeSurfer, an automated cortical surface reconstruction toolbox, was applied to compare the cortical morphology between patients and controls. The brain regions with significant group differences after multiple comparison correction were extracted in common space for each patient, and then correlated with their clinical characteristics (including onset age, duration of epilepsy, and mini-mental state examination (MMSE)) using partial correlation analysis with age, sex and intracranial volume as covariates.

Results: Compared with controls, IGE patients showed decreased cortical thickness in the left rostral middle frontal gyrus, decreased cortical volume in the right cuneus and left superior frontal gyrus that extended to the precentral gyrus, and decreased surface area in the right cuneus and right inferior parietal gyrus. None of these regions showed significant relationships with clinical measurements in the patient group.

Conclusion: Our findings suggest that cortical thickness, cortical volume, and surface area changes occurred in the early stage of IGE. These findings provide structural neuroimaging evidence underlying the pathology of IGE.

1. Introduction

Idiopathic generalized epilepsy (IGE) is characterized by bilaterally diffuse generalized spike-wave discharges (GSWD) or polyspike-wave discharges on electroencephalography (EEG) but IGE patients appear normal on conventional magnetic resonance imaging (MRI). Recurrent generalized seizure types include absence, myoclonic, atonic, tonic, and generalized tonic-clonic seizures (GTCS), which usually occur predominantly upon awakening and are often precipitated by sleep deprivation, alcohol consumption, and stress. According to the latest International League Against Epilepsy (ILAE) classification of the epilepsies [1], IGE mainly encompasses four well-established epilepsy syndromes: Childhood Absence Epilepsy (CAE), Juvenile Myoclonic Epilepsy (JME), Juvenile Absence Epilepsy (JAE), and Generalized Tonic-Clonic Seizures, which differs from the ratified epilepsy classification in 1989 [2].

There is substantial evidence demonstrating that individuals with IGE exhibit anomalies in brain structure [3–10], cognition [11–15], and behavior [16,17], and have poor social outcomes [18,19], including depression, isolation, and underemployment, which can have a severe adverse impact on patient's lives. Although IGE is a well-recognized and common subgroup of epilepsy, the pathogenesis and pathophysiological processes of this illness are not well understood. Investigating the brain morphology may help to explain the underlying pathologic mechanism

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of this disorder.

Many studies have reported anatomical and functional brain abnormalities in patients with IGE compared to healthy controls [20–26]. Most of these studies reported reduced gray matter volume (GMV) in regions including the thalamus [3,4,7,8,26,27], frontal lobe [6,26], cingulate cortex [6,25,28], and hippocampus [23,24], as well as reduced cortical thickness in regions including the precentral, frontal, and temporal lobe [3]. Some studies found increased GMV in regions including the mesial frontal lobe [5], hippocampus [6], middle temporal pole [6], and thalamus [9,10], and increased cortical thickness in regions including the orbitofrontal and mesial frontal gyrus [4]. These inconsistent reports of cortical or subcortical morphologic changes in IGE are potentially due to several factors, such as field strength of the magnetic resonance (MR) scanner, heterogeneity and chronicity of patients, medication effects, and different analytic methods.

Previous studies have confirmed that cortical gray matter volume was influenced by two major determinants, i.e., cortical thickness and surface area. The developmental trajectories of cortical thickness and surface area, both in their pattern and timing, are believed to be different from each other [29] and influenced by various genetic factors [30]. Most previous studies have proved that cortical volume is more associated with surface area than cortical thickness [31,32]. Cortical thickness reflects the density, size, and arrangement of neuroglia, neurons, and nerve fibers [33], and thus, measurement of the cortical thickness could provide important and relatively unique information regarding disease-specific neuroanatomical changes. For instance, regional thinning of the cortex can reflect decreased dendritic arborization or changing myelination at the gray/white matter interface [34] within specific brain systems. However, there is no study that has simultaneously reported the cortical volume, cortical thickness, or surface area changes in IGE patients, and independent measurements of cortical anatomy are important for understanding the specific neuroanatomical changes.

It has been demonstrated that FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), a powerful tool in vivo based on MRI scans, exhibits good test-retest reliability, particularly with different scanners, manufacturers, and field strength [35]. To the best of our knowledge, there is only one study that used FreeSurfer to explore brain morphology anomalies in recent-onset, drug-naïve IGE patients [36]. Such studies of recent-onset, drug-naïve IGE patients are not only important for evaluating the initial brain alterations before being influenced by potential confounders, such as medication effects and disease duration, but they are also critical for providing novel information relevant to the underlying mechanisms. However, the previous study [36] using region of interest (ROI) analysis may distort the results of selective analyses, even when rigorous statistical tests are used during selection [37].

Thus, the primary aim of the present study was to explore the morphological changes of the whole brain in a recent-onset drug-naïve pediatric cohort with IGE. In addition, a partial correlation analysis was used to investigate the changed morphometric parameters in the patient group and their clinical characteristics (including onset age, duration of epilepsy, and mini-mental state examination (MMSE) score).

2. Materials and methods

The present study was approved by the local Ethics Committee and institutional review board. Written informed consent was obtained from all participants and/or their guardians.

2.1. Participants

Sixty first-episode, drug-naïve patients and 37 matched healthy controls were recruited from the Affiliated Hospital of Southwest Medical University in the beginning. Six patients and 2 controls were excluded because of failure to finish either the MRI scanning or the MMSE assessment. Nine patients and 3 controls with head motion artifacts were also excluded. Finally, Forty-five patients (including 2 with childhood absence epilepsy (CAE), 1 with juvenile absence epilepsy (JAE), 11 with JME, 21 with GTCS, and 10 with an unidentifiable subsyndrome; age range: 5–18 years, males:females = 26:19) and 32 matched healthy controls (age range: 5–18 years, males:females = 21:11) were recruited (Table 1). All patients underwent a comprehensive evaluation that confirmed the clinical features of IGE according to the ILAE diagnostic criteria [1]. The duration of time from the first illness manifestation to the time of MR scan ranged from 1 to 24 weeks. The long illness duration up to 24 weeks is due to that some patients lived in remote mountainous areas thus it's inconvenient for them to see a doctor in the city; and that some patients were brought to hospital when their second episode occurred, which often had a long interval to their first episode. The age of onset ranged from 5 to 18 years. Healthy controls were collected through poster advertisements. Criteria for controls included no histories of (i) any initial precipitating event (e.g., simple or complex febrile seizures); (ii) any seizure or seizure-like episode; (iii) neurologic, psychological, developmental, or systemic disease; or (iv) loss of consciousness > 5 min. All children were attending regular school. The two groups showed no significant differences in the age and sex ratios, or in MMSE scores.

Table 1
Demographic information for epilepsy patients and healthy controls.

	IGE (n = 45)	HC (n = 32)	p-Value
Age	11.0 (3.6)	10.7 (3.2)	0.95
Sex (male/female)	26/19	21/11	0.49
MMSE	23.8 (6.2)	26.2 (5.2)	0.09
Age of onset	10.6 (3.2)		
Duration of epilepsy (months)	3.4 (3.8)		

Notes: IGE, idiopathic generalized epilepsy; HC, healthy controls; MMSE, mini-mental state examination; scores in the bracket are the standard deviation (SD).

2.2. MR data acquisition, processing, and statistical analysis

Patients and control subjects were scanned using a 3.0 T MR scanner system (Intera Achieva; Philips Medical Systems, Amsterdam, the Netherlands) equipped with an eight-channel phased-array head coil. Participants were fitted with soft earplugs, positioned comfortably in the coil, and instructed to relax and remain still. Head motion was minimized with foam pads. High-resolution 3-dimensional T1-weighted (3D-T1) images were obtained with a spoiled gradient recalled (SPGR) sequence with the following parameters: 176 axial slices with thickness = 1.7 mm, repetition time (TR) = 18 ms, echo time (TE) = 5 ms, flip angle = 30°, FOV = 220 × 220 cm^2, and data matrix = 256 × 256. The average scanning time was 7 min.

The reconstruction of cortical surfaces was based on 3D SPGR images using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/vision 5.3.0) software. This method uses automated surface reconstruction, transformation, and high-resolution interparticipant alignment procedures to accurately and rapidly measure the morphometric parameters of the entire cortex [38–41]. The detailed procedure for surface reconstruction with FreeSurfer has been previously described and validated elsewhere [35,40–43]. In brief, this processing includes motion correction, removal of nonbrain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter and white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray matter-white matter and gray matter-cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Quality control of the FreeSurfer output was

performed by visual inspection according to the criteria specified in the FreeSurfer user manual (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/). When errors were noted, they were fixed, and if the errors could not be fixed, the images were discarded to prevent further analysis. After the cortical models were constructed, a number of deformable procedures were performed for further data processing and analysis, such as surface inflation, registration to a spherical atlas using individual cortical folding patterns to match cortical geometry across participants, parcellation of the cerebral cortex into units based on gyral and sulcal structures, and creation of a variety of surface-based data structures, including maps of curvature, sulcal depth, and Jacobian metric distortion. To improve the ability to detect population changes, we blurred each participant's morphometric parameter map using a 25-mm full-width at half-maximum surface-based Gaussian kernel.

Three morphometric measurements including cortical thickness, cortical volume, and surface area were compared using a general linear model with age, sex and intracranial volume as covariates. A Monte Carlo method (with 1000 iterations per Monte Carlo simulation) was used for the multiple comparison correction ($p < 0.05$). In order to test whether altered cortical measurements in patients were associated with clinical scores, we performed the following correlation analysis. The regions that showed group differences after multiple comparison correction were extracted in the common space for each individual. The mean morphometric measurements in each region of the patient group were correlated with their clinical characteristics (including onset age, duration of epilepsy, and MMSE) using partial correlation analysis with age and sex as covariates. Furthermore, we performed additional vertex-wise correlation analysis of cortical thickness with clinical measurements. Monte Carlo method was used for the multiple comparison correction, as mentioned above.

3. Results

As shown in Fig. 1 and Table 2, compared with controls, IGE patients showed decreased cortical thickness in the left rostral middle frontal gyrus, decreased cortical volume in the right cuneus and left superior frontal gyrus that extended to the precentral gyrus, and decreased surface area in the right cuneus and right inferior parietal gyrus ($P < 0.05$, after Monte Carlo correction). None of these regions showed significant relationships with clinical measurements in the patient group. In addition, no significant correlation was observed in the vertex-wise correlation analysis.

Table 2
Brain regions with altered morphometric parameters in IGE patients compared to healthy controls.

Morphometric parameter	Region	Size (mm^2)	−log (p)	Talarach coordinate		
				x	y	z
Cortical thickness	L-rostral middle frontal gyrus	1491.74	2.24	−25.7	26.3	33.6
Volume	R-cuneus	1475.64	2.51	4.7	−74.1	21
	L-superior frontal gyrus	1344.19	2.24	−12.8	−11.1	67.7
Pial area	R-cuneus	1453.4	3.10	4.7	−74.1	21
	R-inferior parietal gyrus	889.97	1.43	34	−71.1	28.7

4. Discussion

To the best of our knowledge, the present study is the first to simultaneously measure cortical thickness, cortical volume, and surface area using FreeSurfer in drug-naïve patients with recent-onset IGE. We observed decreased cortical thickness in the left rostral middle frontal gyrus, decreased volume in the right cuneus and left superior frontal gyrus that extends to the precentral gyrus, and decreased surface area in the right cuneus and right inferior parietal gyrus. Although none of these regions showed significant relationships with clinical measurements in the patient group, our findings confirmed the subtle abnormalities of cortical morphology in the early course of IGE.

The most unique finding from our study is the observation of decreased cortical measurements in the early course of untreated patients, which is in accordance with previous studies showing frontal volume

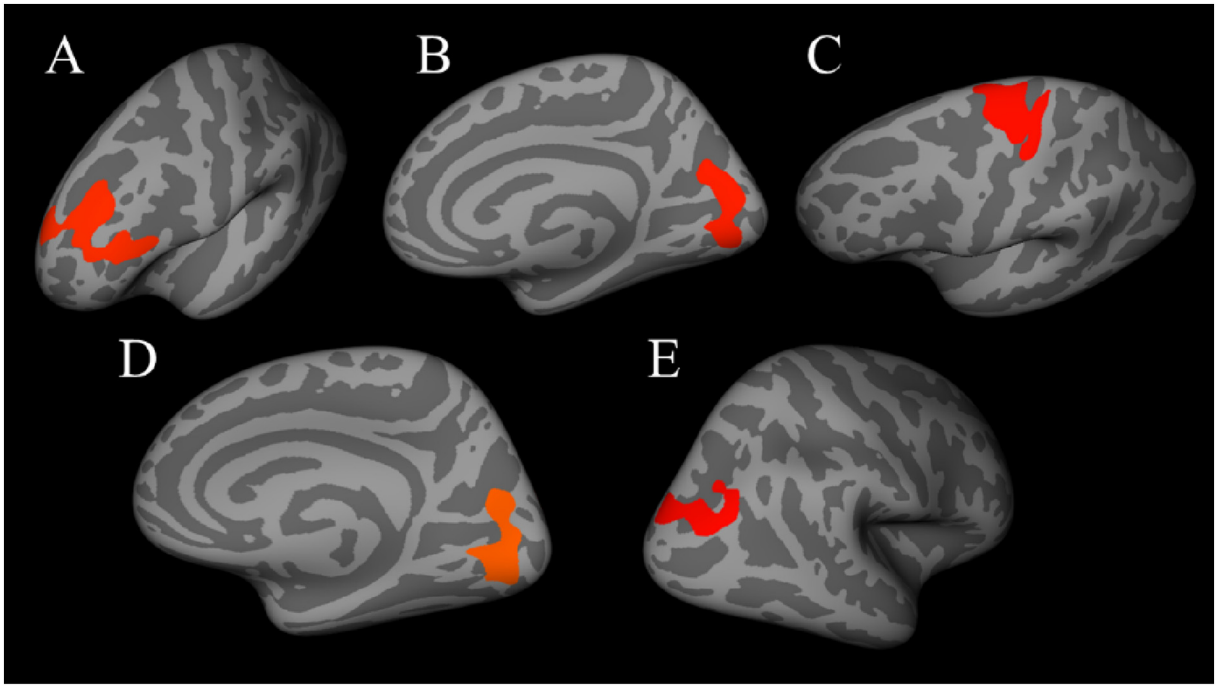

Fig. 1. Brain regions showing significantly decreased cortical thickness in left rostral middle frontal gyrus (A), decreased volume in right cuneus (B) and left superior frontal gyrus which extend to precentral gyrus (C), and decreased surface area in right cuneus (D) and right inferior parietal gyrus (E).

reduction in new-onset IGE patients [44,45]. Similar to our findings, Wang et al. [46], found decreased gray matter (GM) volumes in the subcortical structure (bilateral thalamus) in 20 drug-naïve idiopathic CAE patients using a voxel-based morphometry (VBM) method. Another study by Perani et al. [36] using the ROI method also reported reduced gray matter volume in the bilateral thalamus in 29 drug-naive patients with new-onset genetic generalized epilepsy (GGE) compared to healthy controls. The reports that differed from the current study may have arisen from the heterogeneity of IGE patients, different sample sizes, or analytic method. Moreover, our findings are consistent with those of a previous study reporting decreased gray matter volume in chronic, treated IGE patients [26]. In addition, a longitudinal study revealed that frontal lobe volume loss in new-onset IGE persisted over a 2-year interval [45]. Combining our findings and previous studies, we suggest that the cortical morphology changes are present at or antecedent to epilepsy onset, and continue to the later stage of the disease.

The decreased cortical thickness observed in the present study was primarily found in the prefrontal cortex (left rostral middle frontal gyrus), suggesting that this region has a particularly important role in IGE. Abnormalities of the prefrontal cortex have been widely reported in IGE patients [3,47]. The rostral middle frontal gyrus, which is part of the rostral dorsolateral prefrontal cortex (DLPFC), plays an important role in execution and cognition [48,49]. Ekmekci et al. [50] detected decreased fractional anisotropy (FA) values in the DLPFC in patients with new-onset JME, and the FA values in the DLPFC were negatively correlated with cognitive function abnormalities (the Stroop and trail-B test). A decreased FA value is often seen when the fiber density is reduced or fiber integrity is collapsed, which demonstrates that microstructural abnormalities exist from the very beginning of the disease, and that is similar to our findings.

Decreased volume of the left superior frontal gyrus, which extends to the precentral gyrus, was also found in the current study. The left superior frontal gyrus, located in the mesiofrontal cortices, is part of the 'internal awareness' network and shares many fiber connections with the rostral middle frontal gyrus [51], which also revealed decreased cortical thickness in our study and is part of the 'external awareness' network. The abnormalities in these interconnected cortico-cortical circuits are believed to play critical roles in conscious cognition [52,53]. For instance, CAE patients showed decreased functional MRI activation in the medial frontal cortex compared to controls while performing attentional vigilance tasks [22]. In addition, we found volume reduction in the precentral gyrus, which is responsible for movement, presumably related to limb clonus caused by seizures. The observation of decreased cortical thickness and volume in the frontal gyrus in the present study suggested the presence of microstructural and functional abnormalities in the frontal lobe of IGE patients, which is consistent with results from previous studies [3,4,6,47,54–58].

Both decreased surface area and volume in the right cuneus were found in the present study, which is in accordance with previous reports stating that cortical volume is associated more frequently with surface area rather than cortical thickness [31,32]. The cuneus is a part of the occipital lobe, and previous studies have reported its functional and microstructural abnormalities in patients with GTCS [59]. The occipital lobe is related to visual information processing. Photic stimulation can induce seizures in some IGE patients, and a previous structural study revealed axial and radial diffusivity changes in the occipital regions in IGE and photoparoxysmal response patients (IGE-PPR group) [60]. Similar findings had been reported that reduced GMV in the occipital cortices of those JME patients with photosensitivity, but was not seen in those without photosensitivity [61]. However, we could not judge how many photosensitive IGE patients were included in our study. Further study should be performed to detect whether the decreased surface area and volume in the right cuneus were related to photic stimulation-induced seizures.

In addition, our study found decreased surface area in the right inferior parietal gyrus in IGE patients. The surface area and cortical thickness are influenced by different genetic factors regulating sulcal patterning and the thickness of the cortical mantle itself [30]. For instance, the regional thinning of the cortex can reflect reduced dendritic arborization [62] or changing myelination at the gray/white matter interface [34]. Therefore, it is not surprising to observe predominant or selective alterations in one of the two cortical measures if we consider that IGE is a neurodevelopmental disorder, and the cortical thickness and surface may express different corticogenesis pathways [63]. The parietal lobe is believed to participate in the posterior default-mode network [64,65], which is called the random episodic silent thinking (REST) network and is affected by states of awareness [66]. A previous study revealed that the blood oxygen level-dependent (BOLD) signal increase in the posterior REST network appears to precede the onset of the epileptiform activity, whereas that was not observed in other cortical regions in 11 untreated CAE patients [67], and the BOLD signal decrease had also been reported in the parietal cortex during absence seizures in drug-naïve, newly diagnosed patients [65]. Thus, we hypothesize that the decreased surface area in the right inferior parietal gyrus may represent a structural correlate of impaired consciousness during epilepsy seizures. That is consistent with previous reports describing how the parietal lobe is part of the network of consciousness regulation [68].

Although we found changes in different morphological measurements in multiple brain regions, none of our findings showed any significant relationships with clinical measurements (including onset age, duration of epilepsy, and MMSE) in the patient group. Given that we cannot fully address the circular issue of the ROI analysis [37], interpretation of the non-correlation requires caution.

Several potential limitations of this study should be considered. First, the number of children with epilepsy is modest, and we were unable to conduct a further subgroup analysis. Second, this is a cross-sectional study, and it was better to determine the dynamic brain development by examining changes over time rather than at a single time point. Longitudinal clinical studies may help to illustrate the question of whether the cortical morphology changes that we report close to illness onset reflect altered brain maturation that developed over time.

5. Conclusions

For the first time, we demonstrated that multiple cortical morphologic abnormalities existed at the onset of IGE in drug-naïve patients. We observed significant differences in cortical measurements in the middle frontal gyrus, cuneus, superior frontal gyrus, and inferior parietal gyrus. Combining our results with previous studies, we confirmed that cortical morphology changes are present at or antecedent to epilepsy onset. These changes may be associated with brain neurodevelopmental abnormalities. In the future, we need to enlarge our sample size, and distinguish the IGE subtype to further study the different multiple cortical morphologic changes in the IGE subtype.

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Identifying information from "Materials and Methods"

The present study was approved by the local Ethics Committee and institutional review board. Written informed content and all medical records pertinent to the child's epilepsy and treatment were obtained from the patient or the child's parents or guardian.

Declaration of Competing Interest

No conflicts of interest exist in the submission of this manuscript. I would like to declare on behalf of my co-authors that the work

described was original research that has not been published previously, and is not under consideration for publication elsewhere, in whole or in part. All the authors listed have read the enclosed manuscript and approved it for publication.

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References

[1] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[2] Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389–99.
[3] Bernhardt BC, Rozen DA, Worsley KJ, Evans AC, Bernasconi N, Bernasconi A. Thalamo-cortical network pathology in idiopathic generalized epilepsy: insights from MRI-based morphometric correlation analysis. NeuroImage 2009;46:373–81.
[4] Alhusaini S, Ronan L, Scanlon C, Whelan CD, Doherty CP, Delanty N, et al. Regional increase of cerebral cortex thickness in juvenile myoclonic epilepsy. Epilepsia 2013;54:e138–41.
[5] Woermann FG, Free SL, Koepp MJ, Sisodiya SM, Duncan JS. Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI. Brain 1999;122:2101–8.
[6] Liao W, Zhang Z, Mantini D, Xu Q, Wang Z, Chen G, et al. Relationship between large-scale functional and structural covariance networks in idiopathic generalized epilepsy. Brain Connect 2013;3:240–54.
[7] Saini J, Sinha S, Bagepally BS, Ramchandraiah CT, Thennarasu K, Prasad C, et al. Subcortical structural abnormalities in juvenile myoclonic epilepsy (JME): MR volumetry and vertex based analysis. Seizure 2013;22:230–5.
[8] Kim JB, Suh SI, Seo WK, Oh K, Koh SB, Kim JH. Altered thalamocortical functional connectivity in idiopathic generalized epilepsy. Epilepsia 2014;55:592–600.
[9] Swartz BE, Spitz J, Vu AL, Mandelkern M, Su ML. Heterogeneity of anatomic regions by MR volumetry in juvenile myoclonic epilepsy. Acta Neurol Scand 2016;134:300–8.
[10] Betting LE, Mory SB, Lopes-Cendes I, Li LM, Guerreiro MM, Guerreiro CA, et al. MRI volumetry shows increased anterior thalamic volumes in patients with absence seizures. Epilepsy Behav 2006;8:575–80.
[11] Lin JJ, Dabbs K, Riley JD, Jones JE, Jackson DC, Hsu DA, et al. Neurodevelopment in new-onset juvenile myoclonic epilepsy over the first 2 years. Ann Neurol 2014;76:660–8.
[12] Jackson DC, Dabbs K, Walker NM, Jones JE, Hsu DA, Stafstrom CE, et al. The neuropsychological and academic substrate of new/recent-onset epilepsies. J Pediatr 2013;162:1047–53.
[13] Rathouz PJ, Zhao Q, Jones JE, Jackson DC, Hsu DA, Stafstrom CE, et al. Cognitive development in children with new onset epilepsy. Dev Med Child Neurol 2014;56:635–41.
[14] Taylor J, Kolamunnage-Dona R, Marson AG, Smith PE, Aldenkamp AP, Baker GA, et al. Patients with epilepsy: cognitively compromised before the start of anti-epileptic drug treatment? Epilepsia 2010;51:48–56.
[15] Cheng D, Yan X, Gao Z, Xu K, Chen Q. Attention contributes to arithmetic deficits in new-onset childhood absence epilepsy. Front Psych 2017;8:166–72.
[16] Gelziniene G, Jurkeviciene G, Marmiene V, Adomaitiene V, Endziniene M. Executive functions in adolescents with idiopathic generalized epilepsy. Medicina 2011;47:313–9.
[17] Almane D, Jones JE, Jackson DC, Seidenberg M, Hermann BP. The social competence and behavioral problem substrate of new- and recent-onset childhood epilepsy. Epilepsy Behav 2014;31:91–6.
[18] Camfield P, Camfield C. Idiopathic generalized epilepsy with generalized tonic-clonic seizures (IGE-GTC): a population-based cohort with > 20 year follow up for medical and social outcome. Epilepsy Behav 2010;18:61–3.
[19] Vorderwulbecke BJ, Kowski AB, Kirschbaum A, Merkle H, Senf P, Janz D, et al. Long-term outcome in adolescent-onset generalized genetic epilepsies. Epilepsia 2017;58:1244–50.
[20] Qiao PF, Niu GM. Resting-state fMRI findings in patients with first-episode idiopathic epilepsy before and after treatment. Neurosciences 2017;22:316–9.
[21] Lee JH, Joo EY, Seo DW, Hong SB. Lateralizing cortical excitability in drug naive patients with generalized or focal epilepsy. J Epilepsy Res 2015;5:75–83.
[22] Killory BD, Bai X, Negishi M, Vega C, Spann MN, Vestal M, et al. Impaired attention and network connectivity in childhood absence epilepsy. NeuroImage 2011;56:2209–17.
[23] Zhou SY, Tong L, Song F, Hong XJ, Sun HF, Chang H, et al. Selective medial temporal volume reduction in the hippocampus of patients with idiopathic generalized tonic-clonic seizures. Epilepsy Res 2015;110:39–48.
[24] Tae WS, Hong SB, Joo EY, Han SJ, Cho JW, Seo DW, et al. Structural brain abnormalities in juvenile myoclonic epilepsy patients: volumetry and voxel-based morphometry. Korean J Radiol 2006;7:162–72.
[25] Ke M, Jin B, Liu G, Yang X. Impairments of cingulated cortex in the generalized tonic-clonic seizure epilepsy by combining morphological and functional connectivity magnetic resonance imaging. J Integr Neurosci 2017;16:429–39.
[26] Huang W, Lu G, Zhang Z, Zhong Y, Wang Z, Yuan C, et al. Gray-matter volume reduction in the thalamus and frontal lobe in epileptic patients with generalized tonic-clonic seizures. J Neuroradiol 2011;38:298–303.
[27] Kim JH, Kim JB, Seo WK, Suh SI, Koh SB. Volumetric and shape analysis of thalamus in idiopathic generalized epilepsy. J Neurol 2013;260:1846–54.
[28] O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, et al. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. Neurology 2011;76:34–40.
[29] Wierenga LM, Langen M, Oranje B, Durston S. Unique developmental trajectories of cortical thickness and surface area. NeuroImage 2014;87:120–6.
[30] Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 2009;19:2728–35.
[31] Im K, Lee JM, Lyttelton O, Kim SH, Evans AC, Kim SI. Brain size and cortical structure in the adult human brain. Cereb Cortex 2008;18:2181–91.
[32] Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. NeuroImage 2010;53:1135–46.
[33] Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szeszko PR, et al. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. Cereb Cortex 2005;15:708–19.
[34] Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. J Neurosci 2004;24:8223–31.
[35] Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, et al. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. NeuroImage 2006;32:180–94.
[36] Perani S, Tierney TM, Centeno M, Shamshiri EA, Yaakub SN, O'Muircheartaigh J, et al. Thalamic volume reduction in drug-naive patients with new-onset genetic generalized epilepsy. Epilepsia 2018;59:226–34.
[37] Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 2009;12:535–40.
[38] Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000;97:11050–5.
[39] Jovicich J, Czanner S, Greve D, Haley E, van der Kouwe A, Gollub R, et al. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. Neuroimage 2006;30:436–43.
[40] Fischl B, Liu A, Dale AM. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans Med Imaging 2001;20:70–80.
[41] Segonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, et al. A hybrid approach to the skull stripping problem in MRI. Neuroimage 2004;22:1060–75.
[42] Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex 2004;14:11–22.
[43] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341–55.
[44] Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, et al. Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. Epilepsia 2009;50:1210–9.
[45] Pulsipher DT, Dabbs K, Tuchsherer V, Sheth RD, Koehn MA, Hermann BP, et al. Thalamofrontal neurodevelopment in new-onset pediatric idiopathic generalized epilepsy. Neurology 2011;76:28–33.
[46] Wang G, Dai ZY, Song W, Wang S, Shi H, Pan P, et al. Grey matter anomalies in drug-naive childhood absence epilepsy: a voxel-based morphometry study with MRI at 3.0T. Epilepsy Res 2016;124:63–6.
[47] Tae WS, Kim SH, Joo EY, Han SJ, Kim IY, Kim SI, et al. Cortical thickness abnormality in juvenile myoclonic epilepsy. J Neurol 2008;255:561–6.
[48] Fossati P, Ergis AM, Allilaire JF. Executive functioning in unipolar depression: a review. Encephale 2002;28:97–107.
[49] Wood JN, Grafman J. Human prefrontal cortex: processing and representational perspectives. Nat Rev Neurosci 2003;4:139–47.
[50] Ekmekci B, Bulut HT, Gumustas F, Yildirim A, Kustepe A. The relationship between white matter abnormalities and cognitive functions in new-onset juvenile myoclonic epilepsy. Epilepsy Behav 2016;62:166–70.
[51] Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology 2010;35:192–216.
[52] Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, et al. Two distinct neuronal networks mediate the awareness of environment and of self. J Cogn Neurosci 2011;23:570–8.
[53] Dehaene S, Changeux JP. Experimental and theoretical approaches to conscious processing. Neuron 2011;70:200–27.
[54] Park KM, Kim TH, Han YH, Mun CW, Shin KJ, Ha SY, et al. Brain morphology in juvenile myoclonic epilepsy and absence seizures. Acta Neurol Scand 2016;133:111–8.
[55] Tondelli M, Vaudano AE, Ruggieri A, Meletti S. Cortical and subcortical brain alterations in juvenile absence epilepsy. Neuroimage Clin 2016;12:306–11.
[56] Vollmar C, O'Muircheartaigh J, Barker GJ, Symms MR, Thompson P, Kumari V, et al. Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study. Brain 2011;134:1710–9.
[57] Vollmar C, O'Muircheartaigh J, Symms MR, Barker GJ, Thompson P, Kumari V,

et al. Altered microstructural connectivity in juvenile myoclonic epilepsy: the missing link. Neurology 2012;78:1555–9.
[58] Bai X, Guo J, Killory B, Vestal M, Berman R, Negishi M, et al. Resting functional connectivity between the hemispheres in childhood absence epilepsy. Neurology 2011;76:1960–7.
[59] Ji GJ, Zhang Z, Xu Q, Zang YF, Liao W, Lu G. Generalized tonic-clonic seizures: aberrant interhemispheric functional and anatomical connectivity. Radiology 2014;271:839–47.
[60] Groppa S, Moeller F, Siebner H, Wolff S, Riedel C, Deuschl G, et al. White matter microstructural changes of thalamocortical networks in photosensitivity and idiopathic generalized epilepsy. Epilepsia 2012;53:668–76.
[61] Lin K, Jackowski AP, Carrete Jr. H, de Araujo Filho GM, Silva HH, Guaranha MS, et al. Voxel-based morphometry evaluation of patients with photosensitive juvenile myoclonic epilepsy. Epilepsy Res 2009;86:138–45.
[62] Huttenlocher PR. Morphometric study of human cerebral cortex development. Neuropsychologia 1990;28:517–27.
[63] Jalbrzikowski M, Jonas R, Senturk D, Patel A, Chow C, Green MF, et al. Structural abnormalities in cortical volume, thickness, and surface area in 22q11.2 microdeletion syndrome: relationship with psychotic symptoms. Neuroimage Clin 2013;3:405–15.
[64] Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. Proc Natl Acad Sci U S A 2005;102:15236–40.
[65] Moeller F, Siebner HR, Wolff S, Muhle H, Granert O, Jansen O, et al. Simultaneous EEG-fMRI in drug-naive children with newly diagnosed absence epilepsy. Epilepsia 2008;49:1510–9.
[66] Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001;98:676–82.
[67] Carney PW, Masterton RA, Harvey AS, Scheffer IE, Berkovic SF, Jackson GD. The core network in absence epilepsy. Differences in cortical and thalamic BOLD response. Neurology 2010;75:904–11.
[68] Yamauchi T. Impairment of consciousness during epileptic seizures with special reference to neuronal mechanisms. Epilepsia 1998;39(Suppl. 5):16–20.