PROF. DONG ZHOU (Orcid ID : 0000-0001-7101-4125)

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Dynamic gray matter and intrinsic activity changes after epilepsy surgery

Running title: Dynamic GMV and ALFF changes after TLE surgery

Wei Li[1], Yuchao Jiang[2], Yingjie Qin[1], Baiwan Zhou[3], Du Lei[3], Cheng Luo[2,4], Heng Zhang[5], Qiyong Gong[3], Dong Zhou[1], Dongmei An[1]

[1]Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

[2]The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, Center for Information in Medicine, School of life Science and technology, University of Electronic Science and Technology of China, Chengdu, Sichuan, China.

[3]Huaxi MR Research Center, Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

[4]Research Unit of NeuroInformation, Chinese Academy of Medical Sciences, 2019RU035, Chengdu, P. R. China;

[5]Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Corresponding authors:

Dongmei An, Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan, China. Fax: +86 28 85422550. E-mail: andongmei2010@gmail.com

Dong Zhou, Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan, China. Fax: +86 28 85422550. E-mail: zhoudong66@yahoo.de
Qiyong Gong, Huaxi MR Research Center, Department of Radiology, Center for Medical Imaging, West China Hospital, Sichuan University, Chengdu, Sichuan, China. Fax: +86 28 85423503. E-mail: qiyonggong@hmrrc.org.cn

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Abstract

Objectives: To explore the dynamic changes of gray matter volume and intrinsic brain activity following anterior temporal lobectomy (ATL) in patients with unilateral mesial temporal lobe epilepsy (mTLE) who achieved seizure-free for two years.

Materials & Methods: High-resolution T1-weighted MRI and resting-state functional MRI data were obtained in ten mTLE patients at five serial time points: before surgery, three months, six months, 12 months and 24 months after surgery. The gray matter volume (GMV) and amplitude of low-frequency fluctuations (ALFF) were compared among the five scans to depict the dynamic changes after ATL.

Results: After successful ATL, GMV decreased in several ipsilateral brain regions: ipsilateral insula, thalamus and putamen showed gradual gray matter atrophy from 3 to 24 months, while ipsilateral superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, middle occipital gyrus, inferior occipital gyrus, caudate nucleus, lingual gyrus and fusiform gyrus showed significant GMV decrease at 3 months follow-up, without further changes. Ipsilateral insula showed gradual ALFF decrease from 3 to 24 months after surgery. Ipsilateral superior temporal gyrus showed ALFF decrease at 3 months follow-up, without further changes. Ipsilateral thalamus and cerebellar vermis showed obvious ALFF increase after surgery.

Conclusions: Surgical resection may lead to a short-term reduction of gray matter volume and intrinsic brain activity in neighboring regions, while the progressive gray matter atrophy may be due to possible intrinsic mechanism of mTLE. Dynamic ALFF changes provide evidence that disrupted focal spontaneous activities were reorganized after successful surgery.

Keywords: Mesial temporal lobe epilepsy; Anterior temporal lobectomy; Gray matter volume; Amplitude of low-frequency fluctuations; Longitudinal

Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common type of medically intractable epilepsy in adults [1]. Anterior temporal lobectomy (ATL), a well-established standard surgery for mTLE, leads to a seizure-freedom rate of approximately 60–70% [2]. Accumulating evidence has shown that mTLE is a sophisticated network disorder involving widespread cortical and subcortical brain regions rather than confining to the mesial temporal structures [3-6]. Significant gray matter atrophy (GMA) has been shown in ipsilateral extratemporal structures including ipsilateral thalamus, parietal lobe, cingulate gyrus and regions contralateral to the epileptogenic focus [3,7,8], which was also found to be progressive with the course of epilepsy [9,10], even in patients with a prolonged period of seizure freedom [11]. Furthermore, studies also demonstrated disturbed functional brain networks including networks connected to the mesial temporal structures, the thalamo-cortical circuit, default mode network (DMN) at resting state, and cognitive task related brain networks [12-20].

Surgical procedures, as ATL the most adopted, are assumed to resect the most important component or the core hub of the epileptic network, rendering postsurgical seizure freedom. The brain would be reorganized structurally and functionally after surgery which may be related to postoperative seizure outcome and neuropsychological changes [5,21,22]. Yasuda et al showed increase of gray matter volume and white matter concentration post-operatively in patients who achieved favorable outcome, but few changes in those with poor outcome [5]. González et al also showed the thalamic network dysfunction existing pre-operatively was partially improved after seizures were reduced or eliminated with surgery [23]. On the contrary, it has been shown that the preoperative altered functional connectivity cannot be normalized by ATL even in patients achieved seizure free post-surgically, implying the chronic effect of the disease [24].

We previously explored the dynamic time course of fractional anisotropy of white matters at five serial time points after successful ATL, revealing four distinct patterns reflecting postsurgical structural adaption [25]. In the present study, we aimed to depict the dynamic structural and functional brain network alterations following ATL in mTLE patients who achieved seizure-free at least for 24 months after surgery, by exploring the longitudinal changes of gray matter volume and intrinsic brain activity at five serial time points similar to our prior study [25]: before surgery, three months, six months, 12 months and 24 months after surgery.

Materials & Methods

Participants

Patients were selected from the TLE database in West China Hospital. All patients were diagnosed with mTLE according to the International League Against Epilepsy (ILAE) Classification Schemes of Epileptic Seizures and Epilepsy Syndromes [26] and underwent comprehensive preoperative evaluations at our multidisciplinary team consisted of epileptologists, neurosurgeons and radiologists. The seizure onset zone was delineated by analyzing the clinical history, ictal semiology, interictal and ictal electroencephalogram (EEG), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) if available.

Thirty-two patients with intractable mTLE who underwent ATL were originally included from April 2014 to December 2015. Post-surgical seizure outcome was evaluated according to the ILAE classification [2] every three months after surgery. High-resolution T1-weighted MRI and resting-state functional MRI (rs-fMRI) were scanned at five serial time points: before surgery, three months, six months, 12 months and 24 months after surgery.

The inclusion criteria were as follows: (1) patients with intractable mTLE; (2) structural MRI was normal or with evidence of hippocampal sclerosis (HS) ipsilateral to the seizure onset zone delineated by EEG; (3) no evidence of bilateral hippocampal sclerosis or of a secondary extrahippocampal lesion that may contribute to seizures; (4) reached ILAE class 1 for at least two years; (5) underwent five serial T1-weighted MRI and rs-fMRI scans.

The exclusion criteria included: (1) patients with any other neurological disorder, psychiatric disorder or serious systematic disease; (2) with alcohol or other substance abuse; (3) with other structural lesions except HS (according to ILAE classification [27] confirmed by postoperative histopathological examination; (4) suffered persistent postoperative seizures; (5) lost for follow-up or failed to finish all five scans.

At the end of follow-up, one patient who lost to follow-up, two patients with other structural lesions (hemangioma and focal cortical dysplasia, confirmed by postoperative histopathological examination), five patients with postoperative seizures and 14 patients who failed to complete all five scans were excluded. Finally, only ten patients (five with right mTLE and five left mTLE) were enrolled in the study. Detailed flowchart was showed in Figure 1. All patients underwent ATL by two experienced neurosurgeons using the same approach. In addition, ten age- and sex-matched healthy controls (HC) (four males and six females, age range: 20-42 years) without any neurological or psychiatric disorders were included. They were only scanned at one time point. All participants were native Chinese speakers and right-handed assessed by the Edinburgh Inventory handedness test. All participants were the same as our DTI study [25] except one patient in previous study (subject 1, female, 25 years old, left TLE) was replaced by a new patient (TLE07, male, 21 years old, left TLE) because of some data problem of her preoperative rs-fMRI scan.

This study was approved by West China Hospital ethics committee and informed consent was obtained from all participants.

Image Acquisition

All MRI images were acquired on a 3.0 T MRI system (Tim Trio; Siemens, Erlangen, Germany) with an eight-channel head coil at West China Hospital. Participants were instructed to keep their heads still and rest with their eyes closed without falling asleep. Foam pads were used in the scanning procedures to reduce head motion. High-resolution T1-weighted MRI was acquired using a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: repetition time (TR) = 2300 ms; echo time(TE) = 4.18 ms; flip angle = 9°; field of view (FOV) = 256×256 mm^2; voxel size = 1.0×1.0×1.0 mm^3 . Resting state fMRI data was obtained with echo-planar imaging (EPI) sequence: TR/TE = 2000/30 ms; flip angle = 90°; slice thickness = 3 mm (no slice gap); matrix = 64×64; FOV = 24×24 mm^2; voxel size = 3.75×3.75×5 mm^3; 30 axial slices; and 200 image volumes.

Image Processing

High resolution 3D-T1 images were processed by the voxel-based morphometry analysis in SPM12 (www.fil.ion.ucl.ac.uk/spm). The images of right-sided TLE were side flipped to increase the statistical power and obtain ipsilateral and contralateral datasets [28]. Accordingly, a sub-sample of HC, age- and gender- matched with those right-sided TLE patients, was selected to right-left flipped according to a group-matching algorithm [29]. The T1 images of preoperative TLE and HC were normalized into a symmetric template in MNI space by a non-linear transformation. The symmetric template was obtained by averaging the MNI template and its left-right flipped counterpart [28]. The normalized images were segmented into GM, WM and CSF and re-sampled to 2×2×2 mm^3. The postoperative T1 images were registered to the corresponding preoperative images using rigid transformation, and followed by normalization and segmentation process mentioned above. Finally, the preoperative and postoperative images were smoothed with an isotropic Gaussian kernel (8-mm full-width-half-maximum), after masking out the resection areas. The surgical resection masks were created by manually drawing on the postoperative T1 images co-registered to the preoperative T1 images. The final decision was based on the agreement of the two investigators.

Functional images analysis was performed using SPM12 and DPABI (http://rfmri.org/dpabi). Firstly, functional images of right-sided TLE and matched HC were also right-to-left flipped to obtain ipsilateral and contralateral datasets. The preprocessing steps included removing the first five volumes, slice-timing, spatial realignment, normalization to a symmetric MNI template and re-sampling to 3×3×3 mm^3. Any participants with translational head motion exceeding 1 mm or rotational motion exceeding 1° would be excluded. The 24 motion parameters, WM and CSF signals were regressed out as nuisance covariates. Finally, the smoothing was performed after masking out the resection areas. Postoperative data were preprocessed followed by firstly co-registered to their preoperative images. After preprocessing, individual amplitude of low-frequency fluctuation (ALFF) maps were calculated using DPABI. Fast Fourier transform (FFT) algorithm was used to transform time domain signals to the frequency domain. The mean square root of each power spectrum across the low frequency band (0.01-0.08 Hz) at each voxel was determined as ALFF value [30]. The voxel-wise ALFF was calculated masking out the resection areas and the individual ALFF map was obtained in all patients and controls.

Statistical Analysis

Independent samples t-test was applied to compare the demographic information (gender, age, race and handedness) and imaging parameters (GMV and ALFF) between the patients and controls group. $P < 0.05$ was considered as statistical significance.

An analysis of covariates (ANCOVA) was used to detect regions with significant GMV and ALFF changes among all pre- and post-operative data, with age, gender and intracranial volumes as nuisance covariates. A whole-brain statistical threshold correction was applied using false discovery rate (FDR, $P<0.05$, cluster size > 100 voxels). Post-hoc paired t-test was used to compare the GMV and ALFF differences between any two of the five time points (before surgery, three months, six months, 12 months and 24 months after surgery). $P < 0.005$ was considered statistically significant after Bonferroni correction for multiple comparisons. Furthermore, Bootstrap, repeated sampling for 1000 times during the paired t-test to repeat the comparisons of GMV and ALFF between different timepoints, was used to conduct the reproducibility analysis. $P < 0.01$ was considered as statistical significance. Pearson correlation was used to analyze the relationship between GMV and ALFF at different timepoints in those regions with both GMV and ALFF changes. $P < 0.05$ was considered as statistical significance.

Besides, independent sample t-test was used to compare the GMV and ALFF differences between preoperative data and data from healthy controls in those regions confirmed by ANCOVA. $P < 0.05$ was considered as statistical significance.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Clinical data

Six of the ten patients were female. The median age at surgery was 26.9 years old (range:

19-39). The median duration of epilepsy was 13.7 years (range: 4-26 years). All patients had at least one focal seizure per month before surgery, with or without secondary generalized tonic-clonic seizures (SGTC). All patients underwent unilateral ATL (five/five, L/R) and achieved ILAE class 1 after surgery for at least two years. The median follow-up time was 35 months (range: 25-43 months). Antiepileptic medications within the first two years after surgery remained the same as those prior to surgery for all patients. Hippocampal sclerosis (HS) was confirmed by postoperative histopathological examination in five patients and gliosis only was found in the other five patients. Detailed demographic and clinical information of the patients were summarized in Table 1.

There was no statistically significant difference in age, gender, race and handedness between the patients and healthy controls group ($P > 0.05$).

GMV changes

GMV decreased after surgery in multiple regions of ipsilateral hemisphere, including ipsilateral superior temporal gyrus (STG), middle temporal gyrus (MTG), inferior temporal gyrus (ITG), middle occipital gyrus (MOG), inferior occipital gyrus (IOG), insula, putamen, thalamus, caudate nucleus, lingual gyrus and fusiform gyrus (Figure 2). No obvious GMV increase was found.

Details of comparisons of GMV in these regions between five different time points were showed in Table S1 and S2. These regions showed obvious GMV reductions at postoperative timepoints when comparing with preoperative data ($P < 0.005$). Ipsilateral insula, thalamus and putamen showed gradual GMV decreases from 3 to 24 months after surgery ($P < 0.005$) (Figure 3), while the other regions showed significant GMV decreases at 3 months follow-up ($P < 0.005$), without further changes ($P > 0.005$).

Within these regions with significant GMV changes after surgery, ipsilateral STG, insula and thalamus had already showed GMV reduction before surgery, relative to healthy controls ($P < 0.05$).

ALFF changes

Significant ALFF changes were observed in ipsilateral thalamus, insula, STG, as well as cerebellar vermis (Figure 4).

As showed in Figure 5, ipsilateral insula showed obvious ALFF decrease at 3 months after surgery ($P < 0.005$), with a further decrease between 3 and 24 months follow up ($P < 0.005$). Ipsilateral STG showed significant ALFF decrease at 3 months follow-up ($P < 0.005$), without further changes ($P > 0.005$). While ipsilateral thalamus and cerebellar vermis showed significant ALFF increases after surgery ($P < 0.005$). Details of comparisons of ALFF in these four regions between five different time points were showed in Table S3 and S4.

Within these regions, there were no obvious ALFF changes before surgery when compared with healthy controls ($P > 0.05$).

Correlations between GMV and ALFF

Both GMV and ALFF changed in ipsilateral thalamus, insula and STG. Detailed correlations between GMV and ALFF in these regions were showed in Table S5. GMV and ALFF in ipsilateral thalamus showed obvious negative correlations at three months, six months and 24 months after surgery ($P < 0.05$), while ipsilateral insula and STG didn't show significant correlations between GMV and ALFF at different timepoints ($P > 0.05$).

Discussion

The current study explored the dynamic time course of gray matter volume and intrinsic brain activity before and after ATL at five serial time points in mTLE patients who achieved seizure-free for at least 2 years. Significant GMV reduction was observed in many ipsilateral brain regions after surgery, without obvious increase. Ipsilateral insula, thalamus and putamen showed progressive gray matter atrophy after surgery, while others showed gray matter atrophy at 3 months, without further changes from 3 to 24 months follow-up. Furthermore, we found obvious ALFF changes in ipsilateral brain regions and cerebellar vermis after surgery. Ipsilateral insula showed gradual ALFF decrease after surgery. Ipsilateral STG showed ALFF decrease at 3 months follow-up, without further changes. While ipsilateral thalamus and cerebellar vermis showed obvious ALFF increases after surgery. These findings may extend our understanding of dynamic structural and functional reorganization in epileptic brain following successful surgery for mTLE.

Our findings showed gray matter atrophy post-surgically in the ipsilateral hemisphere, including ipsilateral temporal lobe, occipital lobe as well as some subcortical structures, which was consistent to previous studies [3,5,7,8,31,32]. Furthermore, among those regions with postoperative GMV changes, volume of ipsilateral STG, insula and thalamus was significantly smaller than healthy controls preoperatively. Widespread presurgical gray matter atrophy in mTLE has been consistently reported by the literatures, which may result from acute effect of repetitive seizures or chronic effect of epilepsy itself [5,31,32]. Other studies have also shown postoperative GMV increase within ipsilateral parietal and frontal lobes, and more extensive regions in the contralateral hemisphere, including the temporal, frontal, occipital lobes, as well as basal ganglia and cerebellum, indicating a compensatory mechanism involving the contralateral hemisphere [5,31,33]. However, our study did not find any GMV increase, possibly resulting from our small sample size and ANCOVA comparison between five timepoints. Previous studies evaluating the postoperative GMV changes were often only assessed at one, or two time points at most [5,9,11]. The current study was a serial study with all patients scanned at five serial time points, which may give more detailed information of the dynamic changes.

Regarding the reduction of GMV in ipsilateral brain regions after ATL, surgical manipulation must be one of the most important reasons. Standard ATL directly resects ipsilateral anterior temporal lobe, leading to tissue shrinkage in the remnant of temporal lobe and the neighboring regions, such as ipsilateral fusiform gyrus, lingual gyrus and occipital lobe [31,34]. Direct effect of the surgery often occurs at the early stage after surgery, thus, GMV of ipsilateral temporal lobe and the neighboring structures decreased at 3-month follow-up and remained relatively stable thereafter. However, it is of note that the ipsilateral thalamus, insula and putamen showed progressive reduction of GMV, which cannot be solely explained with the resection. Thalamus has been recognized as one of the most important structures in TLE especially in the propagation of epileptic discharges and thalamic atrophy has been commonly observed in refractory TLE which may be related to persistent seizures pre- and post-surgery [13,35], and even in patients achieved seizure free after effective AEDs or surgery [11,31]. In the present study, not only did we find similar extrahippocampal atrophy after ATL, but we also revealed progressive gray matter atrophy process after successful surgery, which has not been reported to our knowledge. One possibility is the underlying pathologic mechanism of mTLE even in seizure-free periods, similarly to the progression of GMA demonstrated in TLE patients who achieved seizure-free for at least 2 years with AEDs therapy [11]. Furthermore, AEDs were thought to be associated with reduced cortical thickness and brain volume [11,36], the effects of AEDs may be also considered as possible reason for the progressive GMA, since all our patients continued AEDs treatment after surgery.

Amplitude of low-frequency fluctuation (ALFF) measures spontaneous fluctuations of blood oxygen level-dependent (BOLD) signal intensity reflecting local spontaneous brain activity at rest. ALFF has been widely used in fMRI studies of neurological and psychiatric disorders [37-39]. Preoperative studies found ALFF increased in temporal epileptic network, such as mesial temporal structures, the thalamus, some other cortical and subcortical structures, which was thought to be concordant with the BOLD activation induced by ictal and interictal epileptic discharge (IEDs), indicating the epileptic activity generation and propagation [39,40], while ALFF decreased mainly in the DMN, such as precuneus, mesial prefrontal cortex, bilateral angular gyri, and cerebellum, consistent with the BOLD deactivation induced by IEDs [12,16,39]. However, ALFF changes after surgery were rarely studied. One of our previous studies showed diffuse ALFF changes occurred shortly after mTLE surgery (mean 4.5 months), without considering the seizure outcomes [41]. Some other studies revealed postoperative language and memory network remodeling [33,42], as well as postoperative large-scale brain functional connectome reconfiguration in patients achieved favorable outcome following ATL [43]. However, another fMRI study argued that postoperative seizure freedom did not lead to normalization of the altered network connectivity, suggesting those functional network abnormalities may result from the intrinsic etiology of epilepsy rather than the effect of ongoing seizures [24].

In this present study, we found postoperative ALFF changed in ipsilateral thalamus, insula, STG and cerebellar vermis. However, in these regions, we did not observe ALFF changes before surgery when compared to controls, which might be due to our limited number of patients. After successful surgery, ALFF of ipsilateral STG and insula showed similar changing patterns as that of GMV. Ipsilateral STG showed ALFF decrease at 3 months follow-up without further change, while ipsilateral insula showed gradual ALFF decrease from 3 to 24 months. Since previous studies [39,40] have demonstrated increased ALFF in areas taking part of generation and propagation of epileptic activities, including the temporal lobe and insula, our findings of ALFF decreases in these regions might indicate, at least in part, function normalization after seizure control. Besides, we observed significant ALFF increase in ipsilateral thalamus and cerebellar vermis at several timepoints after surgery, without ALFF changes before surgery. Considering the cessation of ictal and interictal epileptic discharges after seizure control, increased ALFF in ipsilateral thalamus may be a potential reflection of functional recovery after successful surgery. Previous studies also showed thalamic network functional connectivity was partially recovered after surgery [23]. Other possibilities included the adaptive process related to the afferent loss caused by resection and a possible chronic intrinsic effect of epilepsy which has been burned in for long time. In addition, postoperative ALFF increase in cerebellar vermis may suggest the reversibility of preoperative function inhibition induced by IEDs. Interestingly, both the thalamus and cerebellum were thought to have complex inhibiting effect on TLE, and deep brain stimulation (DBS) in these regions was proved to be effective for intractable seizures [44-46]. Thus, the ALFF increase in thalamus and cerebellar vermis, as a reflection of focal spontaneous hyperfunction, may be partly involved in post-surgical seizure control.

Regarding the correlations between GMV and ALFF in ipsilateral thalamus, insula and STG, we only found ipsilateral thalamus showed obvious negative correlations between GMV and ALFF at three months, six months and 24 months after surgery, although the changing patterns of GMV and ALFF in ipsilateral insula and ATG seemed similar. It is interesting to note that the thalamus showed progressive volume reduction, while the ALFF showed gradual increase after surgery. Since the thalamus contains many different nuclei with different functions, these changes may infer different structural and functional reorganization in different thalamic nuclei, which needs further exploration focusing on the microstructure of thalamus.

In conclusion, surgical resection may lead to a short-term reduction of gray matter volume and intrinsic brain activity in neighboring regions, while the progressive gray matter atrophy may be due to possible intrinsic mechanism of mTLE. Dynamic ALFF changes provide evidence that disrupted focal spontaneous activities were reorganized after successful surgery.

Limitations

This current study has several limitations. First of all, the sample size was small since we only recruited patients with five follow-up data, which may limit the statistical power. Secondly, images of right-sided TLE patients were right-left flipped, which may interfere with the results taking account of the intrinsic differences between the two hemispheres as well as between left-sided and right-sided ATL. Further studies with larger sample size may allow analyze the changes in each hemisphere independently. Thirdly, we enrolled patients with and without HS, which may affect the results since they may show distinct patterns of structural and functional abnormalities. Further studies would allow independent analysis in HS- and non-HS-TLE patients. Finally, neuropsychological tests were not included for correlation with these changes, which need further studies enrolling larger group of patients to clarify.

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Conflict of interest

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

Authorship contributions

Wei Li collected the clinical and neuroimage data, interpreted the data and drafted the manuscript. Yuchao Jiang and Cheng Luo performed the data analysis and visualization. Yingjie Qin and Baiwan Zhou helped the data collection. Du Lei helped the data analysis and interpretation. Heng Zhang performed the surgery and helped the follow-up of patients. Qiyong Gong, Dong Zhou and Dongmei An conceptualized and designed the study and revised the manuscript.

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Table 1. Clinical characteristics of TLE patients

Subject	Sex	Age at surgery (year)	Course of disease (year)	Seizure type	Seizure frequency (No/mon)	Seizure focus	Pathology (ILAE classification)	Postop seizure outcome (ILAE classification)
TLE01	F	38	26	FS	5	R	gliosis	Class 1
TLE02	M	27	20	FS, SGTC (rare)	1	L	gliosis	Class 1
TLE03	M	20	14	FS, SGTC	2	R	HS type 1	Class 1
TLE04	M	20	4	FS, SGTC	6	L	HS type 1	Class 1
TLE05	F	26	9	FS, SGTC (rare)	60	L	HS type 1	Class 1
TLE06	F	26	6	FS, SGTC	30	L	gliosis	Class 1
TLE07	M	21	20	FS, SGTC (rare)	4	L	gliosis	Class 1
TLE08	F	33	18	FS	3	R	gliosis	Class 1
TLE09	F	19	12	FS	5	R	HS type 2	Class 1
TLE10	F	39	8	FS	13	R	HS type 1	Class 1

Abbreviations: TLE, temporal lobe epilepsy; F, female; M, male; FS, focal seizure; SGTC, secondary generalized tonic-clonic seizure; L, left; R, right; HS, hippocampal sclerosis; ILAE, International League Against Epilepsy.

Figure legends

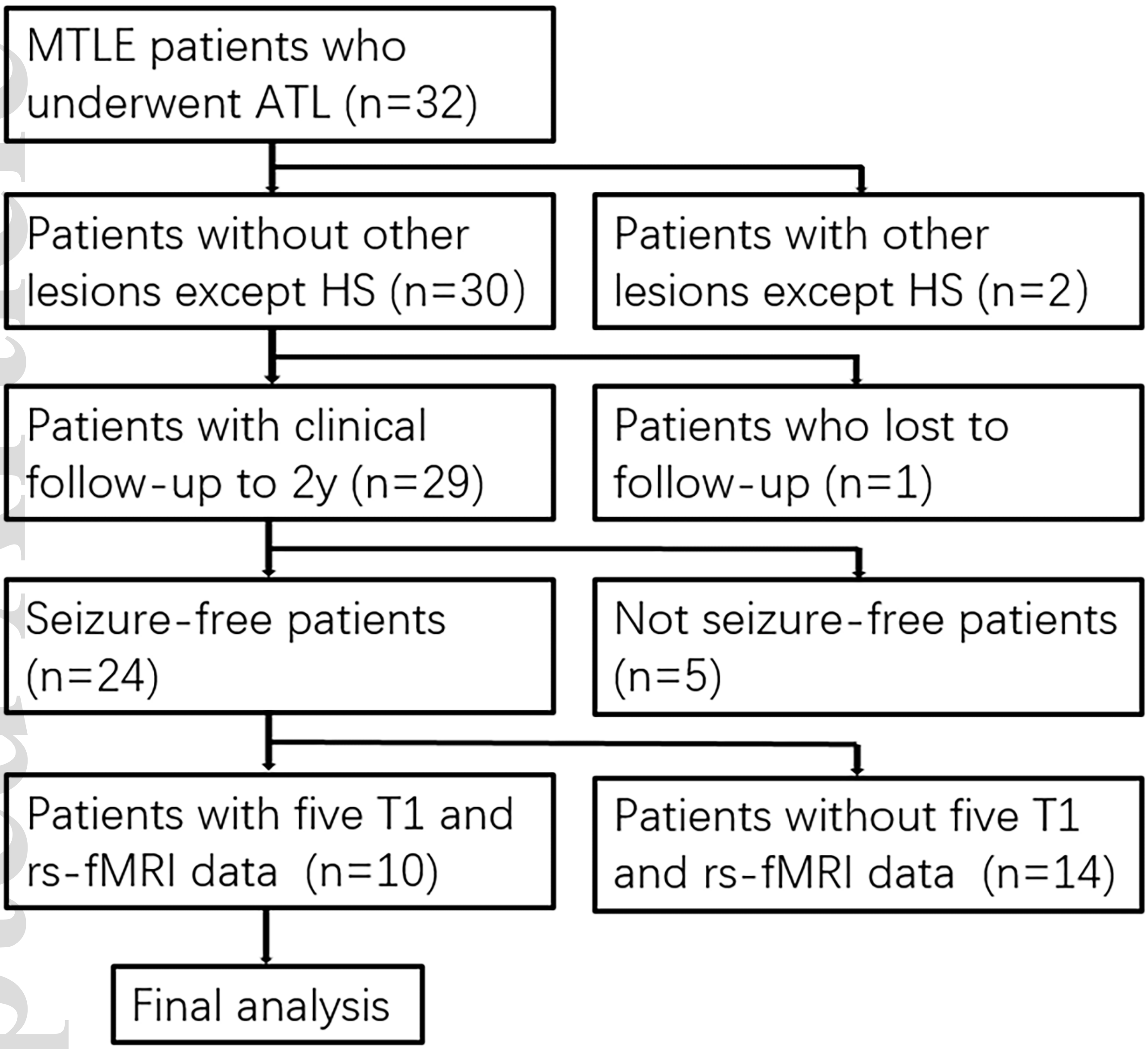
Figure 1: Flowchart showing study protocol and results.

Figure 2: Regions with significant GMV decrease after successful surgery. Abbreviations: Con, contralateral hemisphere; Ips, ipsilateral hemisphere.

Figure 3: Dynamic changing of GMV in ipsilateral insula, thalamus and putamen after surgery. X axis: five time points at scan (1: before surgery; 2: three months after surgery; 3: six months after surgery; 4: 12 months after surgery; 5: 24 months after surgery). Y axis: GMV values. * $P < 0.005$. This figure only showed the change tendency of GMV in three regions at three time points (time point 1 vs 2, and time point 2 vs 5).

Figure 4: Regions with significant ALFF changes after successful ATL. Abbreviations: Con, contralateral hemisphere; Ips, ipsilateral hemisphere.

Figure 5: Dynamic changing process of AFLL in regions with significant changes after surgery. The left side showed ALFF changes at the group level, while the right side showed ALFF changes at the individual level. The X axis represented five time points at scan (1: before surgery; 2: three months after surgery; 3: six months after surgery; 4: 12 months after surgery; 5: 24 months after surgery). The Y axis represented ALFF values. * $P < 0.005$. This figure only depicted the change tendency of ALFF at three time points (time point 1 vs 2, and time point 2 vs 5).



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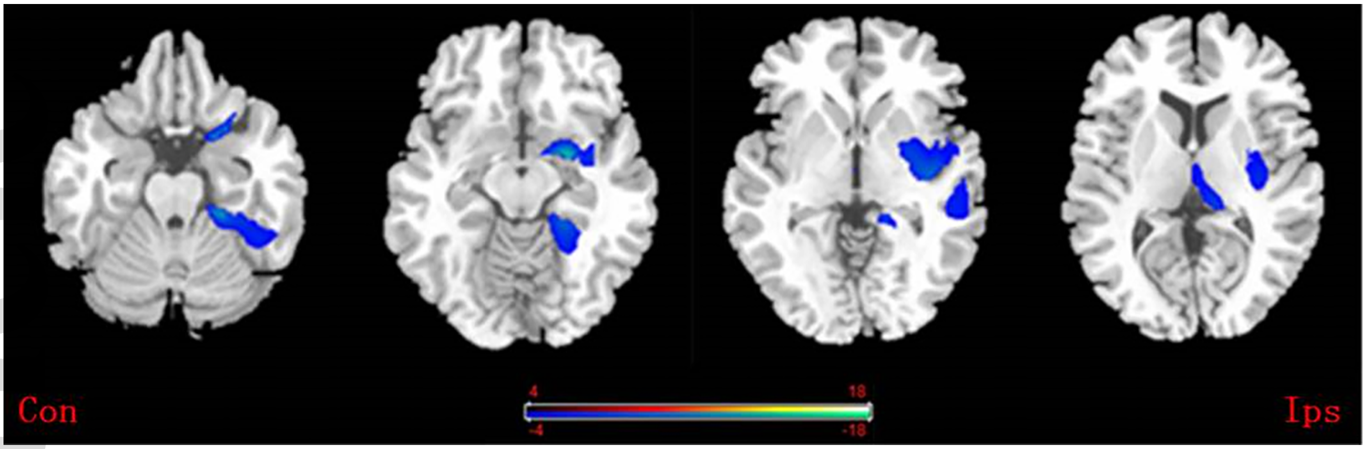

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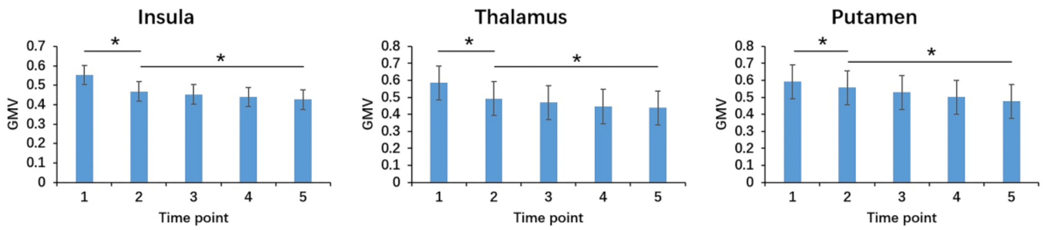

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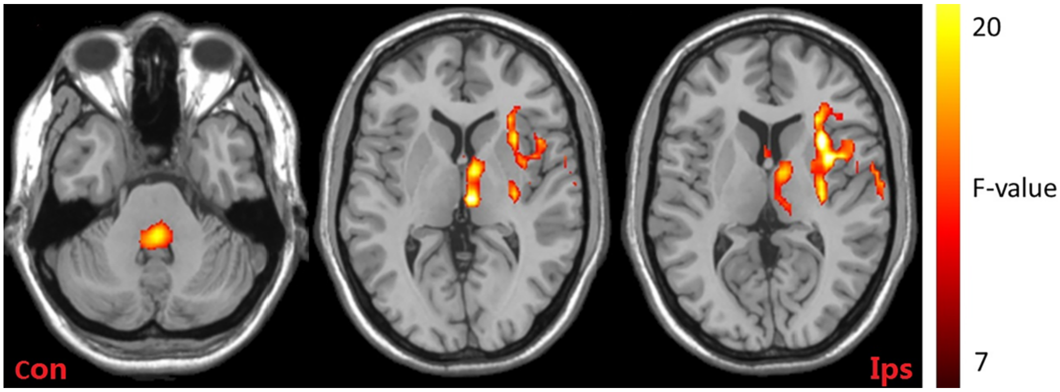

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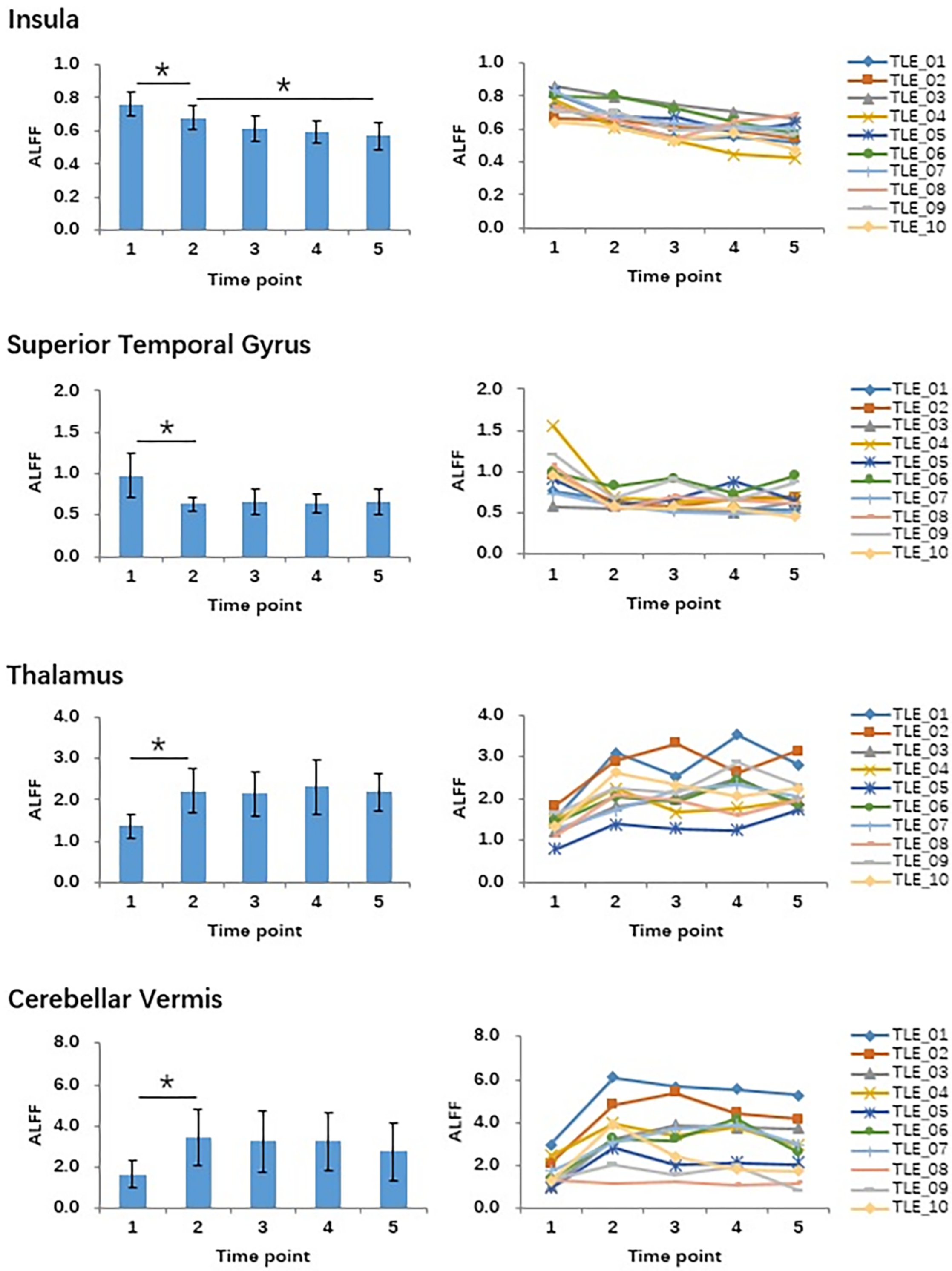

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