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ORIGINAL COMMUNICATION

Trajectories of brain remodeling in temporal lobe epilepsy

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Abstract

Temporal lobe epilepsy has been usually associated with progressive brain atrophy due to neuronal cell loss. However, recent animal models demonstrated a dual effect of epileptic seizures with initial enhancement of hippocampal neurogenesis followed by abnormal astrocyte proliferation and neurogenesis depletion in the chronic stage. Our aim was to test for the hypothesized bidirectional pattern of epilepsy-associated brain remodeling in the context of the presence and absence of mesial temporal lobe sclerosis. We acquired MRIs from a large cohort of mesial temporal lobe epilepsy patients with or without hippocampus sclerosis on radiological examination. The statistical analysis tested explicitly for common and differential brain patterns between the two patients' cohorts and healthy controls within the computational anatomy framework of voxel-based morphometry. The main effect of disease was associated with continuous hippocampus volume loss ipsilateral to the seizure onset zone in both temporal lobe epilepsy cohorts. The post hoc simple effects tests demonstrated bilateral hippocampus volume increase in the early epilepsy stages in patients without hippocampus sclerosis. Early age of onset and longer disease duration correlated with volume decrease in the ipsilateral hippocampus. Our findings of seizure-induced hippocampal remodeling are associated with specific patterns of mesial temporal lobe atrophy that are modulated by individual clinical phenotype features. Directionality of hippocampus volume changes strongly depends on the chronicity of disease. Specific anatomy differences represent a snapshot within a progressive continuum of seizure-induced structural remodeling.

Keywords Temporal lobe epilepsy · Magnetic resonance imaging · Computational anatomy · Voxel-based morphometry · Brain plasticity · Hippocampus · Medial temporal lobe

Abbreviations

AO	Age of disease onset
FS	Frequency of seizures
FWE	Family-wise error correction
MRI–	MRI negative temporal lobe epilepsy
MTS	Mesial temporal lobe sclerosis
ROI	Region-of-interest
SPM	Statistical parametric mapping
TD	Time duration of disease
TIV	Total intracranial volume
TLE	Medial temporal lobe epilepsy
VBM	Voxel-based morphometry

Elisabeth Roggenhofer and Emiliano Santarnecchi shared the first authorship.

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Introduction

There is mounting evidence about disease-related remodeling of specific brain structures and associated networks in medial temporal lobe epilepsy (TLE). The in vivo investigation of brain anatomy using MRI in TLE consistently showed atrophy patterns affecting not only medial temporal lobe structures, but also thalamus and fronto-limbic cortical areas [10, 28]. Given the high diagnostic value of the MRI assessment in patients with mesial temporal lobe sclerosis (MTS), the assumption of coexisting focal and wide-spread pathology holds true, particularly in drug-resistant TLE. This notion is supported by the fact that resective surgery improves not only seizure frequency, but partially also cognitive function associated topologically with remote cortical areas [8, 20]. From the viewpoint of TLE clinical phenotype, cross-sectional studies confirmed the progression of cognitive decline beyond memory deficits with concomitant altered ipsilateral hippocampal activation [44] in the course of the disease [3]. Much less is known about the factors and processes underlying the remodeling of brain structure in TLE patients. The presumption here is that genetic susceptibility [7, 27], inflammatory and neurodevelopmental factors [6, 48] as well as history of complex and prolonged febrile convulsions [34] are associated with the occurrence of epilepsy and MTS rather than its chronicity and progression.

Hippocampus volume loss ipsilateral to the seizure onset is a typical finding in TLE, reported in cross-sectional [13] and longitudinal brain-imaging studies [12]. Currently, the presence or absence of hippocampus sclerosis on MRI in TLE patients motivates the widely presumed dichotomization in separate nosological entities associated with distinct trigger factors and progression [16, 32, 38]. Previous neuroimaging studies in TLE reported controversial results ranging from continuous hippocampal volume loss [12] to preserved hippocampal volume during disease progression [16, 38]. To increase the complexity of this issue, a recent study reported profound differences in network properties between patients with and without MTS when using resting measures of brain oxygen consumption and graph theoretical approach [15, 51].

However, considering neuronal circuits as potential target for structural brain remodeling, there is recent evidence about differential impact of seizures on the brain, characterized not only by progressive neuronal cell loss, but also by resilience to impairment as a function of time and inter-seizure intervals [33, 47]. Recent animal models demonstrated a dual effect of epileptic seizures with initial enhancement of hippocampal neurogenesis including mossy fiber sprouting, alterations in dendritic branching, spine density and shape, followed by abnormal astrocyte proliferation and neurogenesis depletion in the chronic stage [30, 46]. The temporal evolution from an activating to a degenerative state might have an impact on structural plasticity of TLE patients. In human TLE studies, longitudinal studies have been controversial regarding a disease-specific [12] or seizure-dependent [14] hippocampal atrophy whereas some studies did not show these effects [23, 35].

Based on animal studies, the hypothesis is that an enhancement of hippocampal volume during early disease stages is followed by a hippocampal volume decrease in late stages. This bidirectional process within the course of the disease was never addressed in human TLE studies to our knowledge. Theoretical work and experiments on activity-dependent and seizure-induced plasticity provided a window to predict the differential impact of chronic seizures on clinical and cognitive outcome in individuals with TLE [21, 33]. Another controversy concerns the role of recurrent seizures on disease progression and associated focal and network changes [16, 23]. Along these lines, the question about causal relationship between seizure severity and hippocampal integrity remains unanswered.

The main goals of our study are to prove the hypothesized bi-directionality of brain structure remodeling and to investigate the impact of clinical phenotype on brain anatomy in the context of the presence and absence of MTS. More specifically, we wanted to test the potential differential effect of duration of the disease (TD) on brain anatomy. We hypothesize that increases of hippocampal volume emerge in the early phase of TLE. MTS and prolonged TD are associated with reduction of hippocampus volume ipsilateral to the epileptogenic seizure onset zone. To this aim, we use a well-balanced mix between established and novel approaches in the Statistical Parametric Mapping (SPM) framework of computer-based assessment of brain anatomy. We analyze whole-brain images with voxel-based morphometry (VBM) to detect patterns related to TLE progression and to subsequently test for focused hippocampus changes associated with seizure-induced structural remodeling.

Materials and methods

Participants

We acquired cross-sectional data from 128 patients with TLE (69 females and 59 males, mean age ± standard deviation of 38.17 ± 10.81 years, age range between 19 and 63 years) and from 120 sex- and age-matched healthy volunteers (63 females and 57 males, mean age of 36.01 ± 9.89 years, age range between 17 and 60 years; Table 1) at the center for epilepsy surgery of the University of Siena. No group differences were found between healthy controls and patients

Table 1 Demographic and clinical information of study participants

	No	Gender (no.)		Age (years)	Drug resistance (no.)		Seizure frequency (no.)			TIV (l)	*p* value
		f	*m*		*D+*	*D−*	Freq.	Mod.			
TLE	128	69	59	38 ± 11	52	76	30	76	22	1.40 ± 0.17*	0.01 (TLE vs C)
lTLE	72	45	27	39 ± 11	36	36	17	41	14	1.38 ± 0.15*	0.002 (lTLE vs C)
rTLE	56	24	32	38 ± 11	40	16	13	35	8	1.43 ± 0.19	
MTS	57	34	23	40 ± 10	7	50	10	40	7	1.36 ± 0.18*	0.002 (MTS vs C)
MRI-	71	35	36	37 ± 11	45	26	20	36	15	1.43 ± 0.16	
C	120	63	57	36 ± 10	–	–	–	–	–	1.45 ± 0.14*	0.01 (TLE vs C)
Total	248	132	116	37 ± 10						1.42 ± 0.16	

Statistical significance for TIV group differences between TLE (sub)group and C or between MTS and MRI− TLE of $p < 0.05$ marked by * and given as values in last column

TLE temporal lobe epilepsy, *lTLE* left lateralized, *rTLE* right lateralized, *MTS* mesial temporal lobe sclerosis, *MRI−* MRI negative, without macroscopic MRI brain changes, *C* healthy control volunteers, *TIV* total intracranial volume, *f* female, *m* male, *D+* drug-responsive, *D−* drug-resistant

with TLE with respect to education levels. The protocol was approved by the local Ethical Review Committee. Informed consent was obtained from each participant. All procedures were performed in accordance with national and international guidelines.

The diagnosis of TLE followed the well-established criteria of the International League Against Epilepsy [9, 19] including: (1) clinical aspects of seizures such as semiology, onset and history, (2) standard and/or sleep electroencephalography with or without hyperventilation and intermittent photic stimulation additional to long-term video-EEG monitoring, and (3) neuro-radiological assessment. The evaluation of the lateralization of the epileptogenic seizure onset zone, i.e., what hemisphere was affected, depended on seizure semiology, evidence of unilateral epileptic activity in serial routine or long-term video-EEG monitoring and MRI findings. Patients without strong evidence for lateralization of the epileptogenic seizure onset zone, bilateral, lateral temporal or extra-temporal focus or with macroscopically evident brain pathology outside the medial temporal lobe were excluded from subsequent analysis. Additional exclusion criteria included history of psychogenic non-epileptic seizures, autoimmune etiologies of epilepsy, history of alcohol or drug abuse, history of brain trauma, evidence of ischemic and hemorrhagic brain lesions or tumors.

Among the 128 patients, 56 had right lateralized TLE and 72 left lateralized TLE. The neuro-radiological assessment confirmed the absence of macroscopic anatomical abnormalities in a total of 71 MRI negative patients (MRI−), whereas the remaining 57 patients were diagnosed with MTS (for details on group distribution, see Table 1) according to neuro-radiological criteria. Inclusion and exclusion criteria are specified in Table s1. The MTS diagnostic criteria included reduced hippocampal volume, increased medial temporal lobe T2 signal and abnormal morphology like loss of internal architecture (interdigitations of hippocampus) and the stratum radiata, a thin layer of white matter which separates the dentate nucleus and Ammon horn. In the MTS group with mesial temporal lobe sclerosis, there were 30 patients with a left lateralized focus and 27 patients with a right lateralized one. The MRI− group contained 42 patients with left-sided focus and 29 patients with right-sided one. Individual treatment responses were classified based on the revised criteria of the International League Against Epilepsy [31]. When stratifying by seizure frequency within the preceding 12 months before MRI acquisition, we identified three subgroups: (1) frequent seizures (≥4 seizures/month), (2) moderate seizures (1–3 seizures/month), and (3) rare seizures (1–11 seizures/year). Seizures occurring in cluster on the same day were counted as a single episode. Patients with 4 or more seizures occurring in 1 week within a month (i.e., catamenial epilepsy) were classified as "moderate" (for details on group distribution, see Table 1). Disease duration was defined as the time interval between the first secondarily generalized seizure and the date of MRI acquisition.

MRI acquisition and processing

We acquired T1-weighted MRIs on a 1.5 Tesla Philips INTERA system (Philips Medical Systems, Best, The Netherlands) using a 3D magnetization prepared rapid gradient echo protocol (MP-RAGE) yielding 150 contiguous slices (TE = 4.6 ms, TR = 30 ms, flip angle = 30°, FOV = 250 mm, matrix 256 × 256, voxel size 1 mm^3 isotropic).

Image preprocessing was performed using the SPM12 software package (Statistical Parametric Mapping software, https://www.fil.ion.ucl.ac.uk/spm/software/spm12) running under Matlab 7.13 (Mathworks Inc., Sherborn, MA). The algorithm followed the default settings including automated tissue classification in the "unified segmentation" framework

[5] using a novel set of brain tissue priors showing increased accuracy for subcortical structures [36]. Following this step, grey and white matter probability maps were spatially registered to a standardized Montreal Neurological Institute space using the diffeomorphic algorithm based on exponentiated lie algebra—DARTEL [4]. The resulting grey matter probability maps were scaled with the corresponding Jacobian determinants to preserve the initial total amount of signal intensity followed by spatial smoothing using an isotropic Gaussian kernel of 8 mm full-width-at-half-maximum.

Statistical analysis

For statistical analysis, we used a VBM ANOVA design including the healthy participants and four subgroups of TLE patients. The TLE subgroups were defined based on laterality of the epileptogenic seizure onset zone—left TLE vs. right TLE and presence or absence of radiological evidence of a structural epileptogenic sclerosis—MTS vs. MRI−. We included age, gender and total intracranial volume (TIV) as additional regressors to control for effects of these variables on brain anatomy. We used a separate design matrix with four TLE subgroups for correlation analysis with disease duration. To differentiate subgroup-related patterns of structural plasticity and to disentangle spatially overlapping bidirectional effects, we performed post hoc tests (Fig. 2).

First, between-group differences were calculated using two-sample *t* tests including comparisons between single or multiple TLE subgroups and healthy controls (Figs. 1, 2, Tables 1, 2). Contrast estimates of VBM clusters of Fig. 1 identifying volume differences were plotted for global maxima within hippocampus bilaterally (Figs. 1b, 2). We report significant results at statistical threshold of $p < 0.05$ after family-wise error correction (FWE) for multiple comparisons and as trends when below $p < 0.001$, uncorrected for multiple comparisons. For projection of statistical results to hippocampal surfaces, we used rendered masks of the Automated Anatomical Labeling (Fig. 2) [50].

For further analysis of hippocampal volumetric profiles, we used a region-of-interest (ROI) approach (Fig. 3). Local volume estimates were extracted using an atlas-based parcellation (version 2.0, provided by Neuromorphometrics, Inc. https://neuromorphometrics.com, derived from "MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling") and were computed as ratio of hippocampal volume estimates divided by TIV (Fig. 3). Ipsilateral ($p < 0.005$) ROI volumes in TLE patients were significantly different from healthy controls for left and right TLE separately. Given the fact that there were no significant differences between left/right lateralized ipsilateral or contralateral regional volumes ratios, we aggregated the hippocampal volumetric profiles relative to lateralization of the epileptogenic seizure onset zone: (1) left-sided ROIs of left lateralized TLE were combined with right ROIs in right lateralized TLE as ROI ipsilateral to the epileptogenic seizure onset zone; (2) right-sided ROIs of left lateralized TLE were combined with left ROIs in right lateralized TLE as ROI contralateral to the epileptogenic seizure onset zone. We calculated a general linear model as ANOVA to detect differences between TLE lateralities and subtypes and their interaction dependent on the ipsi- and contralateral hippocampal ROI volumes

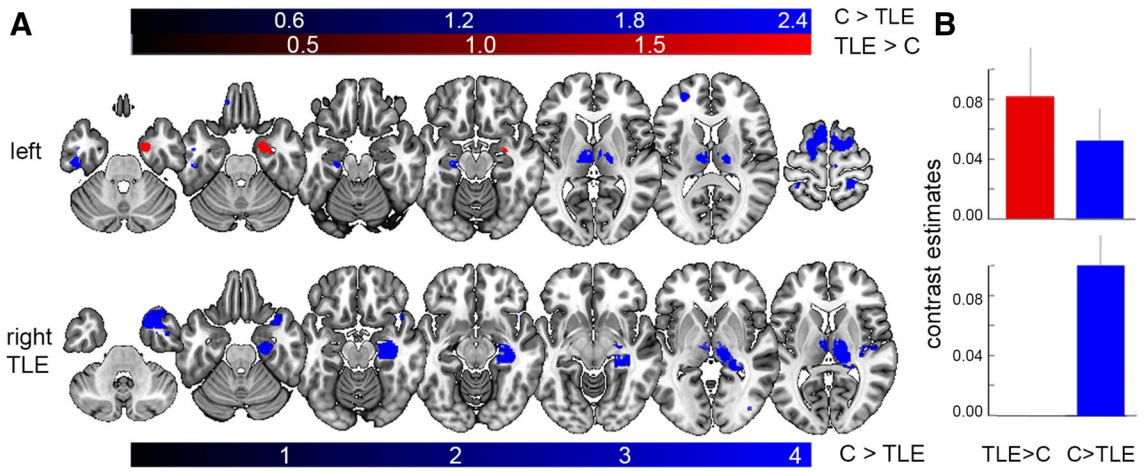

Fig. 1 Structural brain remodeling in temporal lobe epilepsy. **a** Statistical parametric maps—SPMs, of between-groups *t* tests in left lateralized TLE (top) and right lateralized TLE (bottom) in comparison to C, based on VBM whole-brain analysis. Red color—increases in grey matter volume, blue color—decreases of grey matter volume. SPMs displayed on axial T1-weighted image in standard MNI space. For visualization purposes, SPMs thresholded at $p < 0.001$, uncorrected for multiple comparisons, displaying trends. **b** Group differences of hippocampus volume—contrast estimates and 90% confidence interval are plotted for local maxima within ipsi- [for C > TLE] and contralateral hippocampal regions [for TLE > C]. *TLE* temporal lobe epilepsy, *C* healthy controls

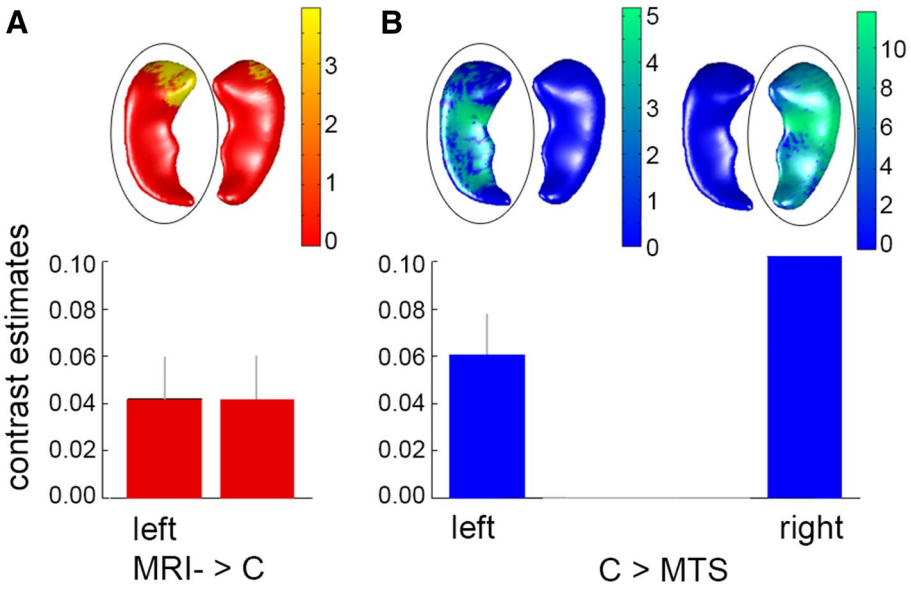

Fig. 2 Structural remodeling of hippocampus. Top: statistical parametric maps of between-groups *t* tests, comparing left and right lateralized TLE to C, based on VBM whole-brain analysis, projected on hippocampus surface, differentiating between **a** MRI− and **b** MTS patients. Side of epileptogenic seizure onset zone assigned by circle around ipsilateral hippocampus. Bottom: bar plots of contrast estimates for group differences with 90% confidence interval. **a** Volume increases for left MRI− TLE. **b** Volume decreases for left and right MTS TLE. *TLE* temporal lobe epilepsy, *MRI−* MRI negative, *MTS* mesial temporal lobe sclerosis, *C* healthy controls

Table 2 Clinical information of TLE patients

	AO (years)	*p* value	TD (years)	*p* value
TLE	19.2 ± 14.3		19.0 ± 13.7	
lTLE	20.4 ± 15.5		18.2 ± 13.3	
rTLE	17.7 ± 12.8		20.0 ± 13.5	
MTS	15.6 ± 13.2*	0.01 (MTS vs MRI−)	24.2 ± 13.3*	< 0.01 (MTS vs MRI−)
MRI-	22.1 ± 14.5*	0.01 (MTS vs MRI−)	14.8 ± 11.7*	< 0.01 (MTS vs MRI−)

Statistical significance for TLE subgroup differences between MTS and MRI− TLE of $p < 0.05$ are marked by * and given as *p* value in next column

TLE temporal lobe epilepsy, *lTLE* left lateralized, *rTLE* right lateralized, *MTS* mesial temporal lobe sclerosis, *MRI−* MRI negative, without macroscopic MRI brain changes, *AO* age of disease onset, *TD* time duration of disease

as dependent variables, controlling for age and gender. We tested for correlations between TD and the hippocampal volume ratios.

Results

Main effects of disease, based on VBM analysis

On VBM whole-brain analysis, the comparison between TLE patients and healthy controls showed a spatially continuous pattern of decreased grey matter volume extending over the medial temporal lobes ipsilateral to the epileptogenic seizure onset zone, thalamus, parahippocampal gyrus, orbitofrontal cortex, cingulum and insula (Fig. 1, Table 3). We note that SPM maps were thresholded at $p < 0.001$ for visualization purposes, uncorrected for multiple comparisons.

Independent of seizure onset zone laterality, there was a significant volume decrease of the ipsilateral hippocampus. The atrophy pattern corresponded to a network common for both right and left hemispheric TLE and extended further to the ipsilateral inferior temporal gyrus, dorso-medial prefrontal and parietal regions. We observed bilateral involvement of dorso-medial prefrontal and parietal cortices solely in left TLE, whereas patients with right TLE showed decreased volume of antero-lateral temporal regions.

In left lateralized TLE, we demonstrate increased volume of right hippocampus, amygdala, entorhinal and parahippocampal cortex when compared to healthy controls (Fig. 1, Table 3).

We observed between-group differences in TIV with higher effect size in MTS, followed by MRI− TLE in comparison to healthy controls (Table 1). The voxel-based analysis showed bilateral increase of hippocampus volume solely in left MRI− TLE with more prominent effects within the ipsilateral hippocampus head (Figs. 2a and s1A). We further report contiguous volume increases in the amygdala and entorhinal cortex bilaterally as well as in the left parahippocampal gyrus (Fig. s1A-B). In MTS patients, we report volume reduction only for the ipsilateral hippocampus

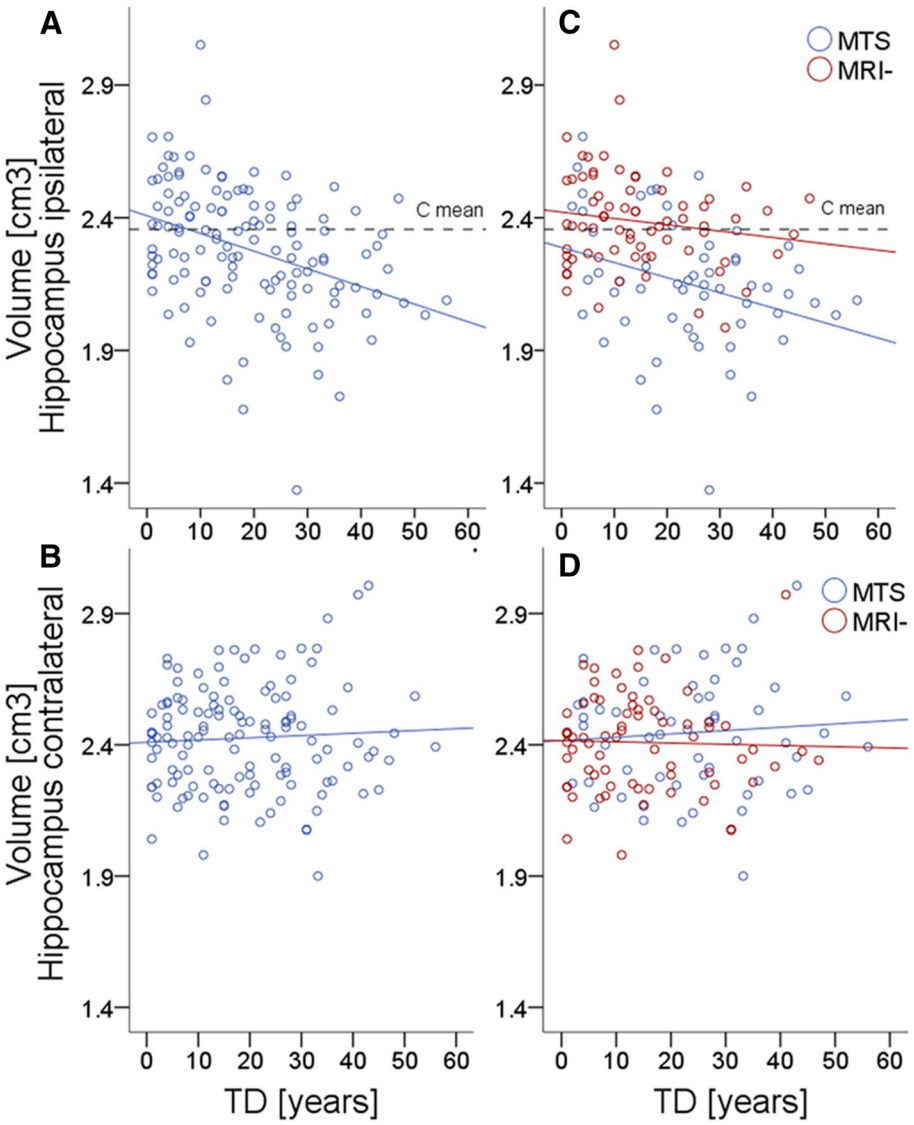

Fig. 3 Correlation between hippocampus volume and disease duration. ROI hippocampal volume was computed as ratio of hippocampal volume estimates, divided by TIV. Linear volume decreases ipsilateral to epileptogenic focus (**a**), but not contralateral (**b**): initial higher volume compared to C (black dashed horizontal line—C mean) followed by progressive decrease. **c**, **d** Correlation analyses across MRI− and MTS subgroups of TLE patients. *TLE* temporal lobe epilepsy, *TD* disease duration, *MRI−* MRI negative, *MTS* mesial temporal lobe sclerosis, *C* healthy controls

(Figs. 2b and s1B-C). The pattern of atrophy extends over the hippocampus body and tail, and is more accentuated in right MTS compared with left MTS (Fig. 2b).

Disease duration (TD) based on ROI analysis

Both our whole-brain (data not shown) and ROI analyses showed a moderate negative correlation between TD and the volume of the ipsilateral hippocampus (Fig. 3 for left TLE and left hippocampus ROI; $p < 0.005$, Pearson correlation coefficient $r = -0.40$, for right TLE and right hippocampus ROI: $p < 0.005$, $r = -0.44$). We observed bidirectional temporal effects with initial volume increase in ipsilateral hippocampus followed by volume reduction in the course of the disease. The hippocampus contralateral to epileptogenic seizure onset zone did not correlate with TD and showed preponderant preserved volume estimates (Fig. 3b).

When contrasting MRI− and MTS patients, we confirm the significant negative correlation between TD and ipsilateral hippocampus volume in MTS ($p < 0.05$, for left MTS TLE, $r = -0.36$) and a trend for a similar effect in MRI− (Fig. 3c, d, for MRI− TLE, $r = -0.22$).

Discussion

Our study demonstrates the unique spatial and temporal pattern of brain structure remodeling in TLE that integrates previous controversies in the literature into a unified disease model. The observed initial increase of hippocampus volume is consistent with seizure-induced enhancement of neurogenesis that is subsequently replaced by marked volume reduction in due course of disease, interpreted as depletion of the neural stem cells pool. Given the controversies

Table 3 Main effects of disease

Contrast	Brain region	Hemisphere	MNI coordinates (mm)			Cluster size	*Z* scores
	Cluster max	L/R	*x*	*y*	*z*	(# voxels)	
C > lTLE	Thalamus proper	L	− 3	− 11	8	579	4.74
	Superior frontal gyrus	L	− 17	− 6	72	2611	4.30
	Inferior temporal gyrus	L	− 48	− 14	− 32	403	4.05
	Middle temporal gyrus	L	− 56	− 38	− 8	141	4.02
	Hippocampus	L	− 23	− 23	− 17	130	3.92
	Thalamus proper	R	18	− 17	9	277	3.87
	Middle frontal gyrus	L	− 29	48	12	170	3.81
	Precuneus	L	0	− 57	57	499	3.76
	Superior parietal lobule	R	24	− 42	69	252	3.68
	Supramarginal gyrus	L	− 48	− 33	39	274	3.57
	Precentral gyrus	L	− 30	− 6	48	183	3.40
lTLE > C	Hippocampus	R	23	− 5	− 29	284	3.84
C > rTLE	Hippocampus	R	33	− 21	− 11	3270	7.64
	Temporal pole	R	29	11	− 30	2269	5.28
	Thalamus proper	L	− 2	− 11	3	285	4.69
	Suppl. motor cortex	R	5	− 12	71	238	3.48
	Posterior insula	R	33	− 23	8	144	3.47
	Precuneus	R	5	− 60	62	134	3.44

Comparison between grey matter volume in TLE cohorts and C. Parameters refer to local maxima for each cluster at statistical threshold of $p < 0.001$, uncorrected for multiple comparisons (see Fig. 1)

TLE temporal lobe epilepsy, *lTLE* left lateralized TLE, *rTLE* right lateralized TLE, *C* healthy controls

in the literature, we provide unique evidence for the common effects of epilepsy on brain structure in TLE with and without hippocampus sclerosis. Our findings highlight the ipsilateral hippocampus as main target of bidirectional and spatially differential remodeling by disease phenotype characteristics.

Our main finding is the bidirectional character of hippocampus volume changes depending on the disease stage of TLE that is common for patients with MTS and without MRI-visible hippocampus sclerosis on MRI exam. Although cross-sectional, our study allowed drawing inferences about temporal remodeling of brain anatomy given the relatively high number of participants with adequate representation of different stages of disease. The relative increase of hippocampus volume in the early phase of epilepsy which we detected in left MRI− TLE bilateral with a predominance ipsilateral to the seizure focus (Fig. 2a and s1A) and indirectly as a negative correlation between ipsilateral hippocampal volume and disease duration (Fig. 3a, c) could represent the seizure-related boost of neurogenesis in the dentate gyrus accompanied by mossy fiber sprouting, neuronal hypertrophy and persistence of hilar basal dendrites [17, 45]. Conversely, the hippocampus volume reduction in the chronic disease stage mirrors the process of stem cell pool depletion with continuous production of reactive astrocytes and neuronal loss [46]. Given that our findings are based on a semi-quantitative MRI technique that relies on contrast intensities representing mixed effects of cellular and extracellular tissue components, we can only speculate about the exact nature of underlying neurobiological processes [22, 41]. The assumption here is that the observed volume decrease reflects the combination of neuronal loss and synaptic reorganization [2], most likely secondary to seizures.

Within the hippocampus, we were able to differentiate between volume increases localized within the head of the hippocampus, opposed to atrophy affecting predominantly the hippocampal body and tail. The spatial sensitivity of our results is confirmed by previous histo-pathological findings showing marked neuronal cell loss localized within the CA1 and CA4 segment of the hippocampal body [49]. However, we also acknowledge the potential impact of inter-individual variability consistent with differential seizure-induced vulnerability of the hippocampus along its longitudinal axis with the ventral region being more seizure-prone and susceptible to neuronal damage compared with the dorsal hippocampus [25]. Our findings extend the reported findings on the effects of epilepsy on brain structure by demonstrating specific changes in MRI− patients. Conversely to published results showing either atrophy predominantly of the ipsilateral subiculum and CA1 [37] or absence of changes [16, 32, 38], we observe hippocampus volume increases in this TLE subgroup. The discrepant results could be interpreted as lack of statistical power in the previous studies or increased sensitivity of the applied computational methods

for seizure-associated brain volume increases in the hippocampus [18].

Laterality of the seizure onset influences the spatial pattern of structural remodeling. We demonstrate a relative ipsilateral hippocampal volume increase in left MRI− TLE compared to healthy controls and less volume decrease in left TLE compared to right TLE (see Figs. 1b, 2b). These findings are supported by previous reports of patients with left TLE that showed more wide spread and diffuse abnormalities including cortical volume loss [29, 42] and changes in white matter fibre tracts [1] extending to contralateral regions.

The asymmetry in topology patterns could be a consequence of hemisphere-specific rates of brain fibre tract maturation. Quantitative and diffusion imaging corroborated that maturation occurs earlier and evolves quicker in the left than in the right hemisphere [39] whereas local efficiencies are significantly decreased until early adulthood [52]. In the context of quicker left hemispheric development, less integrated connection and less efficient communication, the left hemisphere tends to be more susceptible to initial events like febrile convulsions and early onset seizures [29]. Analogously, hippocampal sclerosis is observed more often in left rather than right hemisphere after febrile convulsions [26]. Furthermore, left hemispheric white matter connectivity in individuals with left-sided language dominance exhibits a more wide-spread pattern and comprises more complex hippocampal connections [40] whereas age-related maturation of white matter is delayed in children with new-onset epilepsy [24]. This can provide a network fundament for a more diffuse seizure propagation after a left lateralized onset, underlying network deterioration. We extend previous findings on main effects of epilepsy on brain anatomy by demonstrating the unique modulatory effect of disease duration. Whole-brain correlation analysis with disease duration showed that after an initial increase, the hippocampal volume ipsilateral to the seizure onset zone continuously declines during disease progression. The supposition here is that a febrile convulsive status epilepticus and prolonged and complex febrile childhood seizures [34] can affect the hippocampal integrity as precipitating injury with the consequence of increased probability to develop hippocampal sclerosis, reoccurring seizures and subsequently TLE [43]. Our interpretation of initial MTL volume increases is confirmed by previous findings of bilateral amygdala and hippocampus hypertrophy related to short disease durations in TLE [11]. Given that this hippocampal hypertrophy pattern is associated with low probability of postoperative seizure freedom [11], we note the importance of computer-based detection of hippocampus volume increase as potential predictor for clinical outcome after surgery.

We make note of potential study limitations that could impact our results and interpretations. The cross-sectional nature of the study limits our inferences to merely correlational findings rather than causality. The localization of seizure origin was defined by routine clinical, EEG and MRI diagnostic criteria and was confirmed by depth-electrode EEG recordings in a subset of patients. We excluded patients without unequivocal evidence for lateralization. The unconsidered impact of antiepileptic drug treatment or medication in general could modify atrophy patterns and/or rates. Current results correspond to the methodological approach of VBM and can be corroborated with complementary tools such as surface-based morphometry in future.

Conclusion

Previous classifications of TLE subtypes were interpreted in the context of differential underlying etiology. We interpret our results as evidence for seizure-induced boost of neurogenesis followed by progressive atrophy of ipsilateral hippocampus consistent with hippocampal sclerosis. This unified disease model has implications for the clinical evaluation and outcome prediction in TLE in future. Differentiating the spatial and temporal pattern of brain structure remodeling on the individual patient's level could help to evaluate the current state within a disease progression on a morphometric level. Hippocampus integrity as main target of bidirectional and spatially differential remodeling by disease progression may provide a complementary future neuroimaging marker for postoperative outcome prediction.

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Author contributions ER, ES, RW, MS and BD were involved in conception of the project. ER and BD were involved in design of the study. ES and GV were involved in acquisition of data. ER and SM performed imaging preprocessing. ER analyzed the data. ER, FK and BD interpreted the data. ER and BD prepared the manuscript. All the authors reviewed, edited the manuscript and were involved in subsequent revisions.

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Compliance with ethical standards

Conflicts of interest Nothing to report.

References

1. Ahmadi ME, Hagler DJ Jr, McDonald CR, Tecoma ES, Iragui VJ, Dale AM, Halgren E (2009) Side matters: diffusion tensor imaging tractography in left and right temporal lobe epilepsy. AJNR 30:1740–1747
2. Alonso-Nanclares L, Kastanauskaite A, Rodriguez JR, Gonzalez-Soriano J, Defelipe J (2011) A stereological study of synapse number in the epileptic human hippocampus. Front Neuroanat 5:8
3. Amlerova J, Laczo J, Vlcek K, Javurkova A, Andel R, Marusic P (2013) Risk factors for spatial memory impairment in patients with temporal lobe epilepsy. Epilepsy Behav 26:57–60
4. Ashburner J (2007) A fast diffeomorphic image registration algorithm. NeuroImage 38:95–113
5. Ashburner J, Friston KJ (2005) Unified segmentation. NeuroImage 26:839–851
6. Baulac M, De Grissac N, Hasboun D, Oppenheim C, Adam C, Arzimanoglou A, Semah F, Lehericy S, Clemenceau S, Berger B (1998) Hippocampal developmental changes in patients with partial epilepsy: magnetic resonance imaging and clinical aspects. Ann Neurol 44:223–233
7. Baulac S, Gourfinkel-An I, Nabbout R, Huberfeld G, Serratosa J, Leguern E, Baulac M (2004) Fever, genes, and epilepsy. Lancet Neurol 3:421–430
8. Bell B, Lin JJ, Seidenberg M, Hermann B (2011) The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol 7:154–164
9. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer IE (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 51:676–685
10. Bernasconi N, Duchesne S, Janke A, Lerch J, Collins DL, Bernasconi A (2004) Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. NeuroImage 23:717–723
11. Bernhardt BC, Hong SJ, Bernasconi A, Bernasconi N (2015) Magnetic resonance imaging pattern learning in temporal lobe epilepsy: classification and prognostics. Ann Neurol 77:436–446
12. Bernhardt BC, Kim H, Bernasconi N (2013) Patterns of subregional mesiotemporal disease progression in temporal lobe epilepsy. Neurology 81:1840–1847
13. Bonilha L, Rorden C, Castellano G, Pereira F, Rio PA, Cendes F, Li LM (2004) Voxel-based morphometry reveals gray matter network atrophy in refractory medial temporal lobe epilepsy. Arch Neurol 61:1379–1384
14. Briellmann RS, Berkovic SF, Syngeniotis A, King MA, Jackson GD (2002) Seizure-associated hippocampal volume loss: a longitudinal magnetic resonance study of temporal lobe epilepsy. Ann Neurol 51:641–644
15. Caciagli L, Bernhardt BC, Hong SJ, Bernasconi A, Bernasconi N (2014) Functional network alterations and their structural substrate in drug-resistant epilepsy. Front Neurosci 8:411
16. Coan AC, Campos BM, Yasuda CL, Kubota BY, Bergo FP, Guerreiro CA, Cendes F (2014) Frequent seizures are associated with a network of gray matter atrophy in temporal lobe epilepsy with or without hippocampal sclerosis. PLoS ONE 9:e85843
17. Coras R, Siebzehnrubl FA, Pauli E, Huttner HB, Njunting M, Kobow K, Villmann C, Hahnen E, Neuhuber W, Weigel D, Buchfelder M, Stefan H, Beck H, Steindler DA, Blumcke I (2010) Low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction in humans. Brain 133:3359–3372
18. Dukart J, Sambataro F, Bertolino A (2015) Accurate prediction of conversion to Alzheimer's disease using imaging, genetic, and neuropsychological biomarkers. JAD 49:1143–1159
19. Engel J Jr (2006) ILAE classification of epilepsy syndromes. Epilepsy Res 70(Suppl 1):S5–10
20. Evans SJ, Elliott G, Reynders H, Isaac CL (2014) Can temporal lobe epilepsy surgery ameliorate accelerated long-term forgetting? Neuropsychologia 53:64–74
21. Goldberg EM, Coulter DA (2013) Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. Nat Rev Neurosci 14:337–349
22. Goubran M, Hammond RR, de Ribaupierre S, Burneo JG, Mirsattari S, Steven DA, Parrent AG, Peters TM, Khan AR (2015) Magnetic resonance imaging and histology correlation in the neocortex in temporal lobe epilepsy. Ann Neurol 77:237–250
23. Holtkamp M, Schuchmann S, Gottschalk S, Meierkord H (2004) Recurrent seizures do not cause hippocampal damage. J Neurol 251:458–463
24. Hutchinson E, Pulsipher D, Dabbs K, y Gutierrez AM, Sheth R, Jones J, Seidenberg M, Meyerand E, Hermann B (2010) Children with new-onset epilepsy exhibit diffusion abnormalities in cerebral white matter in the absence of volumetric differences. Epilepsy Res 88:208–214
25. Isaeva E, Romanov A, Holmes GL, Isaev D (2015) Status epilepticus results in region-specific alterations in seizure susceptibility along the hippocampal longitudinal axis. Epilepsy Res 110:166–170
26. Janszky J, Woermann FG, Barsi P, Schulz R, Halasz P, Ebner A (2003) Right hippocampal sclerosis is more common than left after febrile seizures. Neurology 60:1209–1210
27. Kasperaviciute D, Catarino CB, Matarin M, Leu C, Novy J, Tostevin A, Leal B, Hessel EV, Hallmann K, Hildebrand MS, Dahl HH, Ryten M, Trabzuni D, Ramasamy A, Alhusaini S, Doherty CP, Dorn T, Hansen J, Kramer G, Steinhoff BJ, Zumsteg D, Duncan S, Kalviainen RK, Eriksson KJ, Kantanen AM, Pandolfo M, Gruber-Sedlmayr U, Schlachter K, Reinthaler EM, Stogmann E, Zimprich F, Theatre E, Smith C, O'Brien TJ, Meng Tan K, Petrovski S, Robbiano A, Paravidino R, Zara F, Striano P, Sperling MR, Buono RJ, Hakonarson H, Chaves J, Costa PP, Silva BM, da Silva AM, de Graan PN, Koeleman BP, Becker A, Schoch S, von Lehe M, Reif PS, Rosenow F, Becker F, Weber Y, Lerche H, Rossler K, Buchfelder M, Hamer HM, Kobow K, Coras R, Blumcke I, Scheffer IE, Berkovic SF, Weale ME, Consortium UKBE, Delanty N, Depondt C, Cavalleri GL, Kunz WS, Sisodiya SM (2013) Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. Brain 136:3140–3150
28. Keller SS, Roberts N (2008) Voxel-based morphometry of temporal lobe epilepsy: an introduction and review of the literature. Epilepsia 49:741–757
29. Kemmotsu N, Girard HM, Bernhardt BC, Bonilha L, Lin JJ, Tecoma ES, Iragui VJ, Hagler DJ Jr, Halgren E, McDonald CR (2011) MRI analysis in temporal lobe epilepsy: cortical thinning and white matter disruptions are related to side of seizure onset. Epilepsia 52:2257–2266
30. Kuruba R, Hattiangady B, Shetty AK (2009) Hippocampal neurogenesis and neural stem cells in temporal lobe epilepsy. Epilepsy Behav 14(Suppl 1):65–73
31. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51:1069–1077

32. Labate A, Cerasa A, Gambardella A, Aguglia U, Quattrone A (2008) Hippocampal and thalamic atrophy in mild temporal lobe epilepsy: a VBM study. Neurology 71:1094–1101
33. Leite JP, Neder L, Arisi GM, Carlotti CG Jr, Assirati JA, Moreira JE (2005) Plasticity, synaptic strength, and epilepsy: what can we learn from ultrastructural data? Epilepsia 46(Suppl 5):134–141
34. Lewis DV, Shinnar S, Hesdorffer DC, Bagiella E, Bello JA, Chan S, Xu Y, MacFall J, Gomes WA, Moshe SL, Mathern GW, Pellock JM, Nordli DR Jr, Frank LM, Provenzale J, Shinnar RC, Epstein LG, Masur D, Litherland C, Sun S, Team FS (2014) Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. Ann Neurol 75:178–185
35. Liu RS, Lemieux L, Bell GS, Sisodiya SM, Bartlett PA, Shorvon SD, Sander JW, Duncan JS (2005) Cerebral damage in epilepsy: a population-based longitudinal quantitative MRI study. Epilepsia 46:1482–1494
36. Lorio S, Fresard S, Adaszewski S, Kherif F, Chowdhury R, Frackowiak RS, Ashburner J, Helms G, Weiskopf N, Lutti A, Draganski B (2016) New tissue priors for improved automated classification of subcortical brain structures on MRI. NeuroImage 130:157–166
37. Maccotta L, Moseley ED, Benzinger TL, Hogan RE (2015) Beyond the CA1 subfield: local hippocampal shape changes in MRI-negative temporal lobe epilepsy. Epilepsia 56:780–788
38. Mueller SG, Laxer KD, Cashdollar N, Buckley S, Paul C, Weiner MW (2006) Voxel-based optimized morphometry (VBM) of gray and white matter in temporal lobe epilepsy (TLE) with and without mesial temporal sclerosis. Epilepsia 47:900–907
39. O'Muircheartaigh J, Dean DC 3rd, Dirks H, Waskiewicz N, Lehman K, Jerskey BA, Deoni SC (2013) Interactions between white matter asymmetry and language during neurodevelopment. J Neurosci 33:16170–16177
40. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Koepp MJ, Duncan JS (2007) Abnormalities of language networks in temporal lobe epilepsy. NeuroImage 36:209–221
41. Reeves C, Tachrount M, Thomas D, Michalak Z, Liu J, Ellis M, Diehl B, Miserocchi A, McEvoy AW, Eriksson S, Yousry T, Thom M (2015) Combined ex vivo 9.4T MRI and quantitative histopathological study in normal and pathological neocortical resections in focal epilepsy. Brain Pathol 26:319–333
42. Riederer F, Lanzenberger R, Kaya M, Prayer D, Serles W, Baumgartner C (2008) Network atrophy in temporal lobe epilepsy: a voxel-based morphometry study. Neurology 71:419–425
43. Shinnar S (2003) Febrile seizures and mesial temporal sclerosis. Epilepsy Curr Am Epilepsy Soc 3:115–118
44. Sidhu MK, Stretton J, Winston GP, Symms M, Thompson PJ, Koepp MJ, Duncan JS (2015) Factors affecting reorganisation of memory encoding networks in temporal lobe epilepsy. Epilepsy Res 110:1–9
45. Sierra A, Grohn O, Pitkanen A (2015) Imaging microstructural damage and plasticity in the hippocampus during epileptogenesis. Neuroscience 309:162–172
46. Sierra A, Martin-Suarez S, Valcarcel-Martin R, Pascual-Brazo J, Aelvoet SA, Abiega O, Deudero JJ, Brewster AL, Bernales I, Anderson AE, Baekelandt V, Maletic-Savatic M, Encinas JM (2015) Neuronal hyperactivity accelerates depletion of neural stem cells and impairs hippocampal neurogenesis. Cell Stem Cell 16:488–503
47. Sutula TP (2004) Mechanisms of epilepsy progression: current theories and perspectives from neuroplasticity in adulthood and development. Epilepsy Res 60:161–171
48. Thom M (2014) Review: hippocampal sclerosis in epilepsy: a neuropathology review. Neuropathol Appl Neurobiol 40:520–543
49. Thom M, Liagkouras I, Martinian L, Liu J, Catarino CB, Sisodiya SM (2012) Variability of sclerosis along the longitudinal hippocampal axis in epilepsy: a post mortem study. Epilepsy Res 102:45–59
50. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15:273–289
51. Vaughan DN, Rayner G, Tailby C, Jackson GD (2016) MRI-negative temporal lobe epilepsy: a network disorder of neocortical connectivity. Neurology 87:1934–1942
52. Zhong P, Yan Z (2016) Distinct physiological effects of dopamine D4 receptors on prefrontal cortical pyramidal neurons and fast-spiking interneurons. Cereb Cortex 26:180–191