Relationship between visuoperceptual functions and parietal structural abnormalities in temporal lobe epilepsy

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Abstract

Purpose: Progressive gray matter volume reductions beyond the epileptogenic area has been described in temporal lobe epilepsy. There is less evidence regarding correlations between gray and white matter volume changes and multi-domain cognitive performance in this setting. We aimed to investigate correlations between volume changes in parietal structures and visuospatial performance in temporal lobe epilepsy patients.

Methods: we performed a cross-sectional study comparing global and regional brain volume data from 34 temporal lobe epilepsy patients and 30 healthy controls. 3D T1-weighted sequences were obtained on a 3.0 T magnet, and data were analyzed using age and sex-adjusted linear regression models. Global and regional brain volumes and cortical thickness in patients were correlated with standardized visual memory, visuoperceptual, visuospatial, and visuoconstructive parameters obtained in a per-protocol neuropsychological assessment.

Results: temporal lobe epilepsy patients had smaller volume fractions of the deep gray matter structures, putamen and nucleus accumbens, and larger cerebrospinal fluid volume fraction than controls. Patients had worse scores in visual memory, attention, processing speed, and executive functions. Correlations were found between: 1) visual memory and precuneus and inferior parietal cortical thickness; 2) visuoperceptual performance and precuneus and supramarginal white matter volumes; 3) visuospatial skills and precuneus, postcentral, and inferior and superior parietal white matter volumes; 4) visuoconstructive performance and inferior parietal white matter volume.

Conclusion: Brain volume loss is widespread in temporal lobe epilepsy. Volumetric reductions in parietal lobe structures were associated with visuoperceptual cognitive performance.

Introduction

Temporal lobe epilepsy (TLE), one the most common forms of focal epilepsy in adults(Téllez-Zenteno and Hernández-Ronquillo 2012), is associated with volume loss in the temporal regions, particularly the hippocampus(L Bonilha et al. 2003)(Blümcke et al. 2013). Recent studies highlight the progressive volume loss associated with hippocampal sclerosis, which seems to correlate with epilepsy duration (Lopez et al. 2022).

Quantitative magnetic resonance imaging (MRI) provide objective, reproducible biomarkers of brain atrophy(Caciagli et al. 2017; Fischl and Dale 2000). Automated MRI segmentation tools yield quantitative measures of global and regional brain volumes and cortical thickness(Caciagli et al. 2017; Jber et al. 2021). Analyses with these tools have shown that brain volume loss in TLE affects also extra-temporal regions beyond the seizure-onset focus (Leonardo Bonilha and Keller 2015)(Whelan et al. 2018), which seems to be a progressive phenomenon(Galovic et al. 2019). It is uncertain whether the volume loss is directly associated with the severity of epilepsy(Coan et al. 2009)(Boris C Bernhardt et al. 2010). In

addition, widespread abnormalities in white matter (WM) integrity seem to correlate with disease duration(Liu et al. 2015)(Tsuda et al. 2018)(Chang et al. 2019).

Cognitive decline has also been well described in long-term TLE. Memory is classically affected(Helmstaedter and Kockelmann 2006), although impairment of other domains(Hermann et al. 2006)(Allone et al. 2017). Visuospatial and visuoperceptual functions have received less attention in TLE. Some authors have reported impaired perceptual ability in these patients(Grant et al. 2005), whereas others describe normal visuospatial performance(Grant et al. 2008). Recent evidence has shown that visuospatial memory impairment in TLE appears in parallel to preserved non-memory visuospatial functions(Tallarita et al. 2019). Whether cognitive performance in these particular domains reflects extra-temporal structural abnormalities remains to be determined.

The cognitive abnormalities and neuroimaging findings in TLE suggest that the structural brain damage extends beyond the seizure onset zone and causes diffuse brain dysfunction. It is important to elucidate the structural abnormalities leading to cognitive decline in TLE patients to better understand the mechanisms of epileptogenesis and underlying brain damage. With this study, we aimed to evaluate changes in regional brain volumes, focusing on the parietal structures, and explore their correlation with visuoperceptual impairment in adult patients with TLE.

Methods

Study design and participants

This is a cross-sectional study conducted in a dedicated epilepsy unit, comparing neuroimaging from adult TLE patients assessed in the outpatient clinic between 2016 and 2018 and age-/sex-matched healthy controls. The protocol was approved by the local Ethics Committee [PR(AG)391/2017], and all patients provided signed informed consent. TLE patients with a 3.0T-MRI study, who had undergone per-protocol neuropsychological assessment within ≤ 12 months after neuroimaging, were selected from our outpatient database. The TLE diagnosis and lateralization were based on a combination of seizure semiology suggesting a temporal onset, consistent MRI findings, and temporal lobe interictal/ictal epileptiform activity on video-electroencephalographic recordings. Seizure and epilepsy diagnoses were classified according to the latest International League Against Epilepsy (ILAE) classification(Scheffer et al. 2017). Demographic and clinical data were collected and drug resistance criteria was established according to the 2010 ILAE task force(Kwan et al. 2010). Patients with an unconfirmed diagnosis, unknown seizure onset, structural abnormalities with visible extension to the parietal lobe, or suboptimal MRI scans were excluded from the study, as were patients unable to complete the neuropsychological assessment and those with severe sensory impairment or an intelligence quotient ≤ 70.

MRI analysis

MRI data were acquired using a 12-channel phased-array head coil on a 3.0 T magnet (MAGNETOM Trio, Siemens AG). The MRI protocol included the following sequences: transverse 2D T2-fluid-attenuated

inversion recovery (FLAIR) (repetition time = 9000ms, echo time = 87ms, inversion time = 2500ms, voxel size = 0.49×0.49×3.0mm) and sagittal 3D T1-weighted magnetization prepared–rapid gradient echo (MP-RAGE) (TR = 2300ms, TE = 3000ms, voxel size = 1.0×1.0×1.2mm). The MRI data were re-assessed by an experienced neuroradiologist (SS) for the study. All analyses were performed using FreeSurfer (version 6.1) on the 3D T1-weighted MP-RAGE images to calculate global and regional brain volume fractions and cortical thickness. MRI data were analyzed following established pipelines(FreeSurfer Analysis Pipeline Overview). Image voxels were classified as WM or non-WM based on image intensity and neighbor constraints. An initial surface was generated for each hemisphere by tiling the outside of the WM mass. This initial WM surface was then refined to follow the intensity gradients between the WM and gray matter (GM). The WM surface was then nudged to follow the intensity gradients between the GM and cerebrospinal fluid (CSF) to obtain the pial surface. The distance between the WM and pial surfaces gives the thickness of the cortex at each location. Subcortical GM (sGM) volumes and the global GM, WM, and CSF volumes were also calculated as part of the established pipeline. Lobar WM volumes were calculated as the sum of region-specific WM volumes for each lobe. In each patient, estimated volume fractions were multiplied by 100 and divided by the corresponding estimated total intracranial volume to obtain the GM, sGM, WM, and CSF volume fractions. Imaging data from TLE patients were compared with data from healthy controls in our laboratory database.

Cognitive assessment

All patients were evaluated by a trained neuropsychologist and completed a full cognitive assessment protocol in the epilepsy unit. Attention was evaluated using the Mental Control subtest from the Wechsler Memory Scale (WMS-III), the Digit Span Forward test from the Wechsler Adult Intelligence Scale (WAIS-III), and the Trail Making Test (TMT), part B. Verbal memory was assessed with the Rey Auditory Verbal Learning Test, using the total trial score as a verbal learning measure and the trial#6 and trial#7 scores as short- and long-term recall measures, respectively. Flexibility and inhibition, working memory, and phonetic fluency (executive functions) were further evaluated with the color-word score from the Stroop Color and Word Test, the Digit Span Backward test from WAIS-III, and the FAS phonemic fluency task, respectively. The word score from the Stroop Color and Word Test, Symbol Digit Modalities Test (oral version), and TMT part A were used to assess processing speed. Visual memory was assessed by immediate recall (ROCF-IR) and 30-minute delayed recall (ROCF-DR) in the Rey-Osterrieth Complex Figure test. Visuoperceptual, visuospatial, and visuoconstructive skills were evaluated using the Hooper Visual Organization Test (VOT), the Judgment of Line Orientation test (JLO), the Block Design subtest from WAIS-III (WAIS III-BD), and the ROCF immediate copy (ROCF-IC). Finally, language abilities were assessed using the Boston Naming Test and the Semantic Fluency Test. Attention, executive and visuoperceptual functions, processing speed, and verbal memory scores were analyzed as the average value obtained from the sum of values on the specific tests. Visuoperceptual, visuospatial, and visuoconstructive skills were also analyzed individually as separate specific functions. All test scores were converted into T-scores based on a Spanish population of healthy controls by normalizing scores with a mean value of 50 and a standard deviation of 10. Lower scores indicate poorer cognitive performance. T-scores of 40 or higher were considered to indicate normal performance in the various tests.

Statistical analysis

Descriptive and frequency statistics were obtained and compared using the SPSS Statistics 22.0 software package. As quantitative data were normally distributed (checked with QQ plot), parametric tests were performed for all comparisons involving continuous variables. The paired-sample *t* test was used to assess differences in volume fractions between the left and the right hemisphere. The asymmetry index (AI) was calculated as a percentage ratio; that is, the difference in volume values between the left and right hemisphere over the sum of these (AI= [left-right]*100/[left + right]). A positive AI indicates larger volume in the left hemisphere, whereas a negative index indicates larger volume in the right hemisphere. Patient results were compared with those of healthy controls using Pearson's chi-square test for categorical variables and the *t* test for continuous variables. Correlations between continuous variables were assessed with Pearson's correlation coefficient. Age- and sex-adjusted linear regression models were used to compare patient characteristics and cognitive performance with the estimated brain volume fractions. B coefficients were used to calculate relative volume differences with respect to the reference group.

Bonferroni was applied to manage multiple comparison correction using the Dubey/Armitage-Parmar (D/AP) method(AJ et al. 1997). Thus, to achieve statistical significance at a level of 0.05, it was necessary to obtain a p-value of < 0.0091 when comparing global brain volumes between TLE patients and healthy controls, and < 0.0027 when comparing brain volume/cortical thickness with cognitive assessment. Given the exploratory nature of the study, we also reported results with a p-value of < 0.05 as findings of potential interest.

Results

Thirty-eight patients were initially selected from the outpatient database. After reassessment, four patients were excluded because of an imprecise TLE diagnosis or incomplete neuropsychological assessment due to sensory impairment. Thirty-four TLE patients (mean ± SD age 39.7 ± 14.4 years; range 19–68 years; 55.9% women) were ultimately recruited. The patients' imaging data were compared with data from 30 healthy controls comparable for age (mean age 40.5 ± 16.8 years; range 18–69) and sex (51.6% women). The patients' demographic and clinical data are summarized in Table 1.

Table 1
Demographic and clinical characteristics of patients with temporal lobe epilepsy.

Variable		
Age, mean ± SD, years	39.7 ± 14.4	
Sex, % (n)	Female	55.9 (19)
	Male	44.1 (15)
Age at onset, mean ± SD, years	24.8 ± 15.1	
Age at onset by age group, % (n)	Neonatal – nursing age	5.9 (2)
	Infancy	11.8 (4)
	Adolescence	26.5 (9)
	Adulthood ≤ 45 years	44.1 (15)
	Adulthood > 45 years	11.8 (4)
Epilepsy duration, median (range), years	6 (0–53)	
Etiology, % (n)	Unknown	26.5 (9)
	Hippocampal sclerosis	29.4 (10)
	Cortical dysplasia	11.8 (4)
	Vascular	8.8 (3)
	Post-traumatic	2.9 (1)
	Tumor	2.9 (1)
	Other	17.6 (6)
Lateralization, % (n)	Left	35.3 (12)
	Right	47.1 (16)
	Undefined	8.8 (3)
	Bilateral	8.8 (3)
Seizures evolving to GTC, % (n)	52.9 (18)	
Impaired awareness seizures, % (n)	88.3 (30)	
Drug-resistant epilepsy, % (n)	55.9 (19)	
Number of ASDs, % (n)	1	20.6 (7)

ASDs, antiseizure drugs; GTC, generalized tonic-clonic; SD, standard deviation.

Variable		
	2	29.4 (10)
	3	35.3 (12)
	4	14.7 (5)
Cognitive function T-scores, mean ± SD	Attention	39.2 ± 8.1
	Verbal memory	41.0 ± 9.8
	Visual memory	37.5 ± 16.0
	Processing speed	39.2 ± 10.3
	Visual perceptual	42.4 ± 10.1
	Executive	39.0 ± 9.3
	Language	46.6 ± 10.1
ASDs, antiseizure drugs; GTC, generalized tonic-clonic; SD, standard deviation.		

In the cognitive function assessment, TLE patients had mean T-scores < 40 (below normal performance) in attention, visual memory, processing speed, and executive functioning (Table 1). In specific visual processing and perceptual skills, TLE patients had low T-scores in both the ROCF-IR and ROCF-DR (Fig. 1).

TLE patients compared with healthy controls

TLE patients had a smaller GM (-3.6%, p = 0.015) and a larger CSF (+ 10.7%, p = 0.006) volume fraction compared to controls. Regarding the regional volumes, smaller fractions were found in the frontal lobe WM (-4.8%, p = 0.027) and the sGM (-6.4%, p = 0.003), where several subcortical nuclei were affected (Fig. 2). There were no significant differences in cortical thickness or AI between TLE patients and controls.

As to the specific parietal volumes, the posterior cingulate WM tended to be smaller in TLE patients (-4.6%; p = 0.067). No other differences were found in the specific parietal WM volumes or cortical thickness between TLE patients and controls.

Correlations between global volumes and cognitive performance

A correlation was found between attention and cortical thickness of the right frontal region (r=-0.326, p = 0.014). There were no correlations between any of the other cognitive domains and cortical thickness in the other regions explored. Smaller WM volume fraction correlated with poorer performance in attention (r = 0.470, p = 0.005), processing speed (r = 0.409, p = 0.008), visuoperceptual skills (r = 0.434, p = 0.004),

and executive functions (r = 0.534, p = 0.002). An inverse correlation was found between the CSF volume fraction and attention (r=-0.378, p = 0.034), processing speed (r=-0.466, p = 0.014), visuoperceptual skills (r=-0.453, p = 0.013), and executive functions (r=-0.388, p = 0.012).

Correlation between parietal cortical thickness and visuoperceptual functioning (Fig. 3)

No significant correlations were found between cortical thickness and visuoperceptual, performance in the overall group of TLE patients. On separate analysis of these correlations according to the hemispheric seizure onset zone, an inverse correlation was found in right-TLE patients between visual memory (ROCF-IR) and right superior parietal cortical thickness (r= -0.463, p = 0.044), and between visuospatial performance and right posterior cingulate (r= -0.522, p = 0.037) and post-central gyrus (r= -0.566, p = 0.036) cortical thickness. In addition, a direct correlation was found between visuoconstructive functions (ROCF-IC) and left precuneus cortical thickness (r = 0.625, p = 0.045).

In left-TLE patients, visual memory correlated with right precuneus cortical thickness in both the ROCF-IR (r = 0.689, p = 0.010) and ROCF-DR tests (r = 0.529, p = 0.044). ROCF-IR scores also correlated with right inferior parietal cortical thickness (r = 0.717, p = 0.029). In addition, poorer performance in visuoperceptual skills was associated with right precuneus cortical thinning (r = 0.411, p = 0.009). No significant correlations were found between visuoperceptual functions and cortical thickness in the left hemisphere in these patients.

Correlation between parietal WM volumes and visuoperceptual functioning (Fig. 4)

Regarding the regional WM volumes, several correlations were found in the overall TLE patient group: poorer performance in visuospatial functioning correlated with right inferior (r = 0.491; p = 0.002) and superior parietal (r = 0.449; p = 0.009), left (r = 0.417; p = 0.021) and right (r = 0.470; p = 0.003) precuneus, and left post central (r = 0.343; p = 0.030) WM volume reductions. In addition, poorer visuoconstructive functioning correlated with left inferior parietal WM volume decrease (r = 0.455; p = 0.008).

In right-TLE patients, a correlation was found between poorer visuoperceptual functioning and right precuneus (r = 0.521; p = 0.040) and left supramarginal (r = 0.725; p = 0.013) WM volume loss. Poorer visuoconstructive performance correlated with right posterior cingulum (WAIS III-BD: r = 0.361; p = 0.036) and left inferior parietal (ROCF-IC: r = 0.613; p = 0.008) volume reductions. In addition, poorer performance in visuospatial skills correlated with reduced right inferior (r = 0.624; p = 0.022) and superior (r = 0.606; p = 0.033) parietal WM volume.

In left-TLE patients, an inverse correlation was found between visuoconstructive functioning and left postcentral WM volume (r= -0.216; p = 0.047). No significant correlations were found between visuoperceptive functioning and WM volume status in the right hemisphere in these patients.

Correlation with epilepsy features

Longer epilepsy duration correlated with smaller right supramarginal WM volume (r= -0.330; p = 0.031). Patients with focal seizures evolving to bilateral tonic-clonic status showed a tendency to have larger left precuneus (0.61 ± 0.07 vs 0.55 ± 0.10; p = 0.054) and right posterior cingulum (0.29 ± 0.03 vs 0.27 ± 0.03; p = 0.079) WM volumes. No significant correlations were found for either brain volume or cognitive performance with respect to drug resistance, seizure type, or epilepsy duration.

Discussion

In this study, we systematically investigated regional brain volume abnormalities occurring in TLE patients, and the relationship between parietal lobe volumes and visuoperceptual cognitive performance. Our results show significant volume decreases in several brain structures involving both GM and WM regions in this population, as well as close correlations between parietal lobe volume status and visuoperceptual functioning, which have not been strictly established in TLE.

These data provide further evidence that TLE is associated with brain damage beyond the temporal lobe(Jber et al. 2021; Keller and Roberts 2008). The structural changes may indicate a neural network dysfunction that is reflected in cognitive functioning classically understood to be extra-temporal(Neal et al. 2019).

The percentage of drug-resistant patients enrolled was slightly higher than has been reported in the literature(Currie et al. 1971)(Téllez-Zenteno and Hernández-Ronquillo 2012). All participants were assessed using a high-quality, standardized MRI protocol that is commonly performed in epilepsy patients, facilitating reproducibility and interpretation of the results.

As expected, TLE patients showed lower scores in several cognitive domains, including executive functioning, attention, and processing speed, as well as visual memory(Allone et al. 2017). This supports the well-established non-verbal memory impairment known to be present in these patients(Helmstaedter and Kockelmann 2006)(Sheldon et al. 2020). Mean T-scores in visuoperceptual, visuospatial, and visuoconstructive skills were in line with previous evidence indicating normal performance in these cognitive domains(Grant et al. 2008). However, T-scores in the patients included showed a wide distribution, which allowed us to establish more reliable correlations between these cognitive domains and parietal volumes.

Our results are consistent with previously reported volume differences in GM and WM structures and CSF in TLE patients. Although a progressive reduction in cortical thickness has been described in TLE(Galovic et al. 2019)(B. C. Bernhardt et al. 2009), we found no large differences in this parameter between patients and the control group. Patterns of cortical thickness loss seem to vary depending on the type of epilepsy and its lateralization(Galovic et al. 2019); hence, it could be more difficult to detect cortical thinning in smaller and more heterogeneous groups of patients. As to the sGM structures, our results are consistent with previous evidence showing hippocampal atrophy in TLE patients(Riederer et al. 2020). The findings also provide further evidence of demonstrable atrophy in extratemporal regions, such as the putamen(Kim et al. 2016). There is currently very little evidence of accumbens volume loss in TLE

patients(Wang et al. 2017) as was seen here, although there is some data from animal models(Fu et al. 2018).

Several correlations were found between the global and regional WM volume loss and poorer cognitive performance, particularly executive functioning. In contrast, cortical thickness showed weaker and even inverse correlations with cognitive function. Evidence in Alzheimer's disease has suggested that cortical atrophy in itself may be a poorer predictor of global cognitive decline than other biomarkers(Hedderich et al. 2020). Disrupted WM integrity has also been widely described in epilepsy patients(Tsuda et al. 2018), and our results sustain the idea that this neural network disturbance underlies the global cognitive dysfunction observed in TLE (Chang et al. 2019).

Also as expected, a larger percentage of correlations between parietal WM volume loss and poorer visuoperceptual functioning were found in patients with right-onset TLE. Thus, WM status in this region seems to be more highly implicated in these cognitive functions(De Schotten et al. 2011). Previous functional neuroimaging studies have shown that the superior and inferior parietal cortex are involved in visuospatial skills (Seydell-Greenwald et al. 2017), but specific correlations have not been assessed to date in TLE patients.

In line with previous studies, the right posterior cingulate correlated with visuospatial and visuoconstructive skills(Leech and Sharp 2014). We also found that the precuneal region correlated with visuoperceptual, visuospatial, and visuoconstructive skills. Interestingly, structural and metabolic abnormalities in this region have been associated with poorer performance in constructional praxis skills in patients with early Alzheimer's disease (Hedderich et al. 2020). Our results provide support that the cingulum and precuneus are both implicated in the visuoperceptual network of these patients. Furthermore, these correlations could represent an interindividual diversity in the established damage in parietal regions, which could underlie the contrasting findings for visuoperceptual impairment in previous analyses(Grant et al. 2005)(Grant et al. 2008).

Our study has limitations. The relatively small sample size and the cross-sectional design may have prevented us from elucidating certain findings in further detail. In addition, our sample included TLE of several etiologies and a high percentage of patients were receiving two or more ASDs, which might have influenced the structural and cognitive correlations described. Further studies including larger samples of non-lesional and strictly unilateral epilepsies would be useful to confirm these results.

Conclusions

Widespread GM loss affecting several brain regions is common in TLE and is reflected by an increase in CSF volume. In this setting, WM volume differences in parietal lobe structures could be an indicator of visuoperceptual cognitive performance. These results suggest that TLE is not focal, but instead a more complex neurological disorder causing structural changes related to the epileptogenic network and cognitive dysfunction beyond verbal memory and language.

Declarations

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AUTHOR CONTRIBUTIONS

Author contributions included conception and study design (EF, SS, DP and MT), data collection or acquisition (EF, SS, DP, ES, LA and CT), statistical analysis (EF and MQ), interpretation of results (EF, MQ, SS and DP), drafting the manuscript work or revising it critically for important intellectual content (EF, SS, DP, MT, AR, MT) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (all authors).

DECLARATIONS

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Conflicts of interest

E. Fonseca declares research funding and honoraria from UCB Pharma, Esteve laboratorios, Eisai Inc, GW Pharmaceuticals, Angelini Pharma and Sanofi Genzyme. E. Santamarina declares research funding and speaking fees from UCB Pharma, BIAL Pharmaceutical, EISAI Inc. and Esteve laboratorios. L. Abraira declares research funding and speaking fees from UCB Pharma, BIAL Pharmaceutical, EISAI Inc., Sanofi Genzyme and Esteve laboratorios. I. Seijo declares research funding from UCB Pharma, Neuraxpharm and GW pharmaceuticals. M. Toledo declares research funding and speaking fees from UCB Pharma, BIAL Pharmaceutical, EISAI Inc., GW Pharmaceuticals, Arvelle Therapeutics, Angelini Pharma and Esteve laboratorios. S. Sarria, D. Pareto, M. Turon, M. Quintana, C. Tortajada and A. Rovira have no conflicts of interest to declare.

Ethics approval

We confirm that we have read the journal's position on issues concerning ethical publication and that this report is consistent with those guidelines. The study protocol was approved by the Vall d'Hebron Research Institute Ethics Committee [PR(AG)391/2017], following the Ethics of the World Medical Association for experiments involving humans. The study conforms with the STROBE guidelines for observational studies.

Consent to participate

All patients provided signed written informed consent prior to inclusion in the study.

Consent for publication

Not applicable.

Availability of data and material

Anonymized data that support the findings of this study are available from the authors on reasonable request.

Code availability

Not applicable.

References

1. AJ, S., MF, H., & SD, D. (1997). Some Comments on Frequently Used Multiple Endpoint Adjustment Methods in Clinical Trials. *Statistics in medicine*, *16*(22). https://doi.org/10.1002/(SICI)1097-0258(19971130)16:22<2529::AID-SIM692>3.0.CO;2-J
2. Allone, C., Lo Buono, V., Corallo, F., Pisani, L. R., Pollicino, P., Bramanti, P., & Marino, S. (2017). Neuroimaging and cognitive functions in temporal lobe epilepsy: A review of the literature. *Journal of the neurological sciences*, *381*, 7–15. https://doi.org/10.1016/j.jns.2017.08.007
3. Bernhardt, B. C., Worsley, K. J., Kim, H., Evans, A. C., Bernasconi, A., & Bernasconi, N. (2009). Longitudinal and cross-sectional analysis of atrophy in pharmacoresistant temporal lobe epilepsy. *Neurology*, *72*(20), 1747–1754. https://doi.org/10.1212/01.wnl.0000345969.57574.f5
4. Bernhardt, Boris C, Bernasconi, N., Concha, L., & Bernasconi, A. (2010). Cortical thickness analysis in temporal lobe epilepsy: reproducibility and relation to outcome. *Neurology*, *74*(22), 1776–84. https://doi.org/10.1212/WNL.0b013e3181e0f80a
5. Blümcke, I., Thom, M., Aronica, E., Armstrong, D. D., Bartolomei, F., Bernasconi, A., et al. (2013). International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: A Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia*, *54*(7), 1315–1329. https://doi.org/10.1111/epi.12220
6. Bonilha, L, Kobayashi, E., Rorden, C., Cendes, F., & Li, L. M. (2003). Medial temporal lobe atrophy in patients with refractory temporal lobe epilepsy. *Journal of neurology, neurosurgery, and psychiatry*, *74*(12), 1627–30. https://doi.org/10.1136/jnnp.74.12.1627
7. Bonilha, Leonardo, & Keller, S. S. (2015). Quantitative MRI in refractory temporal lobe epilepsy: relationship with surgical outcomes. *Quantitative imaging in medicine and surgery*, *5*(2), 204–24. https://doi.org/10.3978/j.issn.2223-4292.2015.01.01
8. Caciagli, L., Bernasconi, A., Wiebe, S., Koepp, M. J., Bernasconi, N., & Bernhardt, B. C. (2017). A meta-analysis on progressive atrophy in intractable temporal lobe epilepsy: Time is brain? *Neurology*,

89(5), 506–516. https://doi.org/10.1212/WNL.0000000000004176

9. Chang, Y. A., Marshall, A., Bahrami, N., Mathur, K., Javadi, S. S., Reyes, A., et al. (2019). Differential sensitivity of structural, diffusion, and resting-state functional <scp>MRI</scp> for detecting brain alterations and verbal memory impairment in temporal lobe epilepsy. *Epilepsia*, *60*(5), 935–947. https://doi.org/10.1111/epi.14736
10. Coan, A. C., Appenzeller, S., Bonilha, L., Li, L. M., & Cendes, F. (2009). Seizure frequency and lateralization affect progression of atrophy in temporal lobe epilepsy. *Neurology*, *73*(11), 834–42. https://doi.org/10.1212/WNL.0b013e3181b783dd
11. Currie, S., Heathfield, K. W. G., Henson, R. A., & Scott, D. F. (1971). Clinical course and prognosis of temporal lobe epilepsy: A survey of 666 patients. *Brain*, *94*(1), 173–190. https://doi.org/10.1093/brain/94.1.173
12. De Schotten, M. T., Dell'Acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G. M., & Catani, M. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience*, *14*(10), 1245–1246. https://doi.org/10.1038/nn.2905
13. Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11050. https://doi.org/10.1073/PNAS.200033797
14. FreeSurferAnalysisPipelineOverview - Free Surfer Wiki. (n.d.). http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview. Accessed 4 March 2020
15. Fu, J., Liu, Y., Yang, K., Long, H., Wang, K., & Qi, S. (2018). Effect of accumbens nucleus shell lesioning on bitemporal lobe epilepsy in rat model. *Folia Neuropathologica*, *56*(4), 346–353. https://doi.org/10.5114/fn.2018.80868
16. Galovic, M., van Dooren, V. Q. H., Postma, T., Vos, S. B., Caciagli, L., Borzì, G., et al. (2019). Progressive Cortical Thinning in Patients With Focal Epilepsy. *JAMA Neurology*. https://doi.org/10.1001/jamaneurol.2019.1708
17. Grant, A. C., Donnelly, K. M., Chubb, C., Barr, W. B., Kuzniecky, R., & Devinsky, O. (2008). Temporal lobe epilepsy does not impair visual perception. *Epilepsia*, *49*(4), 710–713. https://doi.org/10.1111/j.1528-1167.2007.01483.x
18. Grant, A. C., Henry, T. R., Fernandez, R., Hill, M. A., & Sathian, K. (2005). Somatosensory processing is impaired in temporal lobe epilepsy. *Epilepsia*, *46*(4), 534–539. https://doi.org/10.1111/j.0013-9580.2005.54604.x
19. Hedderich, D. M., Drost, R., Goldhardt, O., Ortner, M., Müller-Sarnowski, F., Diehl-Schmid, J., et al. (2020). Regional Cerebral Associations Between Psychometric Tests and Imaging Biomarkers in Alzheimer’s Disease. *Article*, *11*, 1. https://doi.org/10.3389/fpsyt.2020.00793
20. Helmstaedter, C., & Kockelmann, E. (2006). Cognitive outcomes in patients with chronic temporal lobe epilepsy. *Epilepsia*, *47*(SUPPL. 2), 96–98. https://doi.org/10.1111/j.1528-1167.2006.00702.x

21. Hermann, B. P., Seidenberg, M., Dow, C., Jones, J., Rutecki, P., Bhattacharya, A., & Bell, B. (2006). Cognitive prognosis in chronic temporal lobe epilepsy. *Annals of Neurology*, *60*(1), 80–87. https://doi.org/10.1002/ana.20872
22. Jber, M., Habibabadi, J. M., Sharifpour, R., Marzbani, H., Hassanpour, M., Seyfi, M., et al. (2021). Temporal and extratemporal atrophic manifestation of temporal lobe epilepsy using voxel-based morphometry and corticometry: clinical application in lateralization of epileptogenic zone. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *42*(8), 3305–3325. https://doi.org/10.1007/S10072-020-05003-2
23. Keller, S. S., & Roberts, N. (2008). Voxel-based morphometry of temporal lobe epilepsy: An introduction and review of the literature. *Epilepsia*, *49*(5), 741–757. https://doi.org/10.1111/j.1528-1167.2007.01485.x
24. Kim, J. S., Koo, D. L., Joo, E. Y., Kim, S. T., Seo, D. W., & Hong, S. B. (2016). Asymmetric Gray Matter Volume Changes Associated with Epilepsy Duration and Seizure Frequency in Temporal-Lobe-Epilepsy Patients with Favorable Surgical Outcome. *Journal of Clinical Neurology*, *12*(3), 323. https://doi.org/10.3988/jcn.2016.12.3.323
25. Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Allen Hauser, W., Mathern, G., et al. (2010). Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*, *51*(6), 1069–77. https://doi.org/10.1111/j.1528-1167.2009.02397.x
26. Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain*. Oxford University Press. https://doi.org/10.1093/brain/awt162
27. Liu, Z., Xu, Y., An, J., Wang, J., Yin, X., Huang, R., et al. (2015). Altered Brain White Matter Integrity in Temporal Lobe Epilepsy: A TBSS Study. *Journal of Neuroimaging*, *25*(3), 460–464. https://doi.org/10.1111/jon.12154
28. Lopez, S. M., Aksman, L. M., Oxtoby, N. P., Vos, S. B., Rao, J., Kaestner, E., et al. (2022). Event-based modelling in temporal lobe epilepsy demonstrates progressive atrophy from cross-sectional data. *Epilepsia*. https://doi.org/10.1111/EPI.17316
29. Neal, E. G., Di, L., Reale-Caldwell, A. R., Maciver, S., Schoenberg, M. R., & Vale, F. L. (2019). Network connectivity separate from the hypothesized irritative zone correlates with impaired cognition and higher rates of seizure recurrence. *Epilepsy and Behavior*, *101*. https://doi.org/10.1016/j.yebeh.2019.106585
30. Riederer, F., Seiger, R., Lanzenberger, R., Pataraia, E., Kasprian, G., Michels, L., et al. (2020). Voxel-based morphometry-from hype to hope. A study on hippocampal atrophy in mesial temporal lobe epilepsy. *American Journal of Neuroradiology*, *41*(6), 987–993. https://doi.org/10.3174/ajnr.A6545
31. Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., et al. (2017). ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*, *58*(4), 512–521. https://doi.org/10.1111/epi.13709

32. Seydell-Greenwald, A., Ferrara, K., Chambers, C. E., Newport, E. L., & Landau, B. (2017). Bilateral parietal activations for complex visual-spatial functions: Evidence from a visual-spatial construction task. *Neuropsychologia*, *106*, 194–206. https://doi.org/10.1016/j.neuropsychologia.2017.10.005
33. Sheldon, S., Heydari, N., Cole, J., & Hamberger, M. J. (2020). Intraindividual relative deficits in visual memory to lateralize seizure onset in temporal lobe epilepsy. *Epilepsy and Behavior*, *111*. https://doi.org/10.1016/j.yebeh.2020.107370
34. Tallarita, G. M., Parente, A., & Giovagnoli, A. R. (2019). The visuospatial pattern of temporal lobe epilepsy. *Epilepsy and Behavior*, *101*. https://doi.org/10.1016/j.yebeh.2019.106582
35. Téllez-Zenteno, J. F., & Hernández-Ronquillo, L. (2012). A Review of the Epidemiology of Temporal Lobe Epilepsy. *Epilepsy Research and Treatment*, *2012*, 1–5. https://doi.org/10.1155/2012/630853
36. Tsuda, K., Tsuji, T., Ishida, T., Takahashi, S., Yamada, S., Ohoshi, Y., et al. (2018). Widespread abnormalities in white matter integrity and their relationship with duration of illness in temporal lobe epilepsy. *Epilepsia Open*, *3*(2), 247–254. https://doi.org/10.1002/epi4.12222
37. Wang, H., Huang, Y., Coman, D., Munbodh, R., Dhaher, R., Zaveri, H. P., et al. (2017). Network evolution in mesial temporal lobe epilepsy revealed by diffusion tensor imaging. *Epilepsia*, *58*(5), 824–834. https://doi.org/10.1111/epi.13731
38. Whelan, C. D., Altmann, A., Botía, J. A., Jahanshad, N., Hibar, D. P., Absil, J., et al. (2018). Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study. *Brain*, *141*(2), 391–408. https://doi.org/10.1093/brain/awx341

Figures

Figure 1

Cognitive performance for visual domains in patients with temporal lobe epilepsy. Box-plots illustrate average T-scores for each cognitive domain in all patients. The dashed line indicates a T-score of 40. Mean T-scores for visual memory measured by the ROCF-IR and ROCF-DR tests were <40. Mean T-scores for visuoperceptual, visuospatial and visuoconstructive functions were >40. *VOT, Hooper visual organization test; JLO, Judgment of Line Orientation test; ROCF-DR, delayed recall of the Rey-Osterrieth Complex Figure; ROCF-IC, immediate copy of the Rey-Osterrieth Complex Figure; ROCF-IR, immediate recall of the Rey-Osterrieth Complex Figure; WAIS III-BD, block design subtest of the Wechsler Adult Intelligence Scale III.*

Figure 2

Comparison of volume fractions between TLE patients and healthy controls. Global volume fractions (GM, WM, and CSF) are shown at the top of the graph. Regional volume fractions (GM and specific subcortical nuclei, followed by lobar and specific WM) are shown below. WM-specific volumes are represented as frontal, parietal, occipital, temporal, and cingulum volumes. Relative differences are shown as 95% confidence intervals with respect to the average volume of each structure in the control group. TLE patients had smaller GM, subcortical GM, putamen, hippocampal, accumbens, and frontal WM volumes, as well as a larger total CSF volume. *Statistically significant differences. *CC, corpus callosum; GM, gray matter; WM, white matter.*

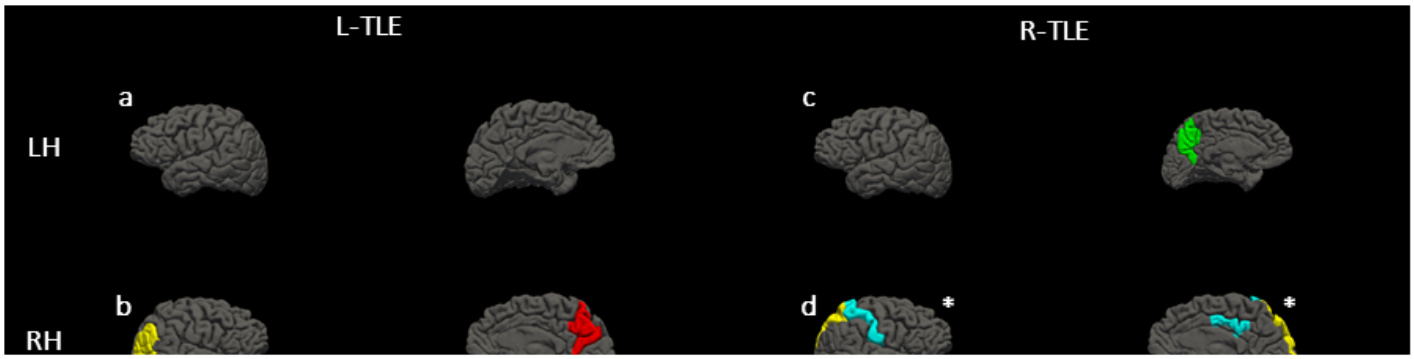

Figure 3

Representation of correlations between cortical thickness and visuoperceptual functioning in TLE patients. Results in L-TLE and R-TLE patients are shown at the left and right side of the figure, respectively. Cortical thickness of LH and RH structures are represented at the top and bottom rows, respectively. *Inverse correlations. (a, b) No correlations were found between LH cortical thickness and visuoperceptual functioning. Correlations between right inferior parietal and precuneus cortical thickness and visual memory and visuoperceptual skills. (c) Correlation between left precuneus cortical thickness and visuoconstructive skills. (d) Correlations between post-central gyrus, cingulate and superior parietal cortical thickness and visuospatial skills and visual memory. The figure shows a larger number of correlations between visuoperceptual function and cortical thickness in RH structures, including inverse correlations in the R-TLE group. *LH, left hemisphere; L-TLE, left-onset temporal lobe epilepsy; RH, right hemisphere; R-TLE, right-onset temporal lobe epilepsy.*

Figure 4

Representation of correlations between WM volume and visuoperceptual functioning in TLE patients. Correlations in L-TLE and R-TLE patients are shown at the left and right side of the figure, respectively. Cortical thickness of structures in the LH and RH are represented at the top and bottom rows, respectively. *Inverse correlations. The figure shows a larger number of correlations between visuoperceptual functioning and WM volume in the R-TLE group, particularly in visual spatial, perceptual and constructive skills. *VOT, Hooper visual organization test; JLO, Judgement of line orientation test; LH, left hemisphere; L-TLE, left-onset temporal lobe epilepsy; RH, right hemisphere; ROCF-DR, delayed recall of the Rey-Osterrieth complex figure; ROCF-IC, immediate copy of the Rey-Osterrieth complex figure; ROCF-IR, immediate recall of the Rey-Osterrieth complex figure; R-TLE, right-onset temporal lobe epilepsy; WAIS III-BD, block design subtest of the Weschler adult intelligence scale III.*

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