Gray Matter Structural Compromise Is Equally Distributed in Left and Right Temporal Lobe Epilepsy

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Abstract: In drug-resistant temporal lobe epilepsy (TLE), MRI studies have shown consistent mesiotemporal and neocortical structural alterations when comparing patients to healthy controls. It remains, however, relatively unclear whether the side of seizure focus differentially impacts the degree of structural damage. This work performed a comprehensive surface-based analysis of mesiotemporal and neocortical morphology on preoperative 1.5 T MRI in 25/35 LTLE/RTLE patients that achieved seizure freedom after surgery (i.e., Engel-I outcome; 7 ± 2 years follow-up), an imaging-independent confirmation of focus lateralization. Compared to 46 age- and sex-matched controls, both TLE groups displayed marked ipsilateral atrophy in mesiotemporal regions, while cortical thinning was bilateral. Direct contrasts between LTLE and RTLE did not reveal significant differences. Bootstrap simulations indicated low reproducibility of observing a between-cohort difference; power analysis revealed that more than 110 patients would be necessary to detect subtle differences. No difference between LTLE and RTLE was confirmed when using voxel-based morphometry, an independent proxy of gray matter volume. Similar results were obtained analyzing a separate 3 T dataset (15/15 LTLE/RTLE patients; Engel-I after 4 ± 2 years follow-up; 42 controls). Our results strongly support equivalent gray matter compromise in left and right TLE. The morphological profile of seizure-free patients, presenting with ipsilateral mesiotemporal and bilateral cortical atrophy, motivates the development of neuromarkers of outcome that consider both mesiotemporal and neocortical structures. *Hum Brain Mapp* 37:515–524, 2016. © 2015 Wiley Periodicals, Inc.

Key words: magnetic resonance imaging; temporal lobe epilepsy; cortical thickness; voxel-based morphometry; epilepsy surgery

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INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common drug-resistant epilepsy. In patients with a unilateral seizure focus, surgery is the most effective treatment [Wiebe et al., 2001]. MRI has played a pivotal role in mapping structural alterations in TLE. Relative to controls, both left and right TLE (LTLE and RTLE) patients show variable degrees of mesiotemporal atrophy [Hogan et al., 2004] and neocortical thinning predominantly in lateral temporal and frontocentral regions [Bernasconi et al., 2003; Bernhardt et al., 2013; Lin et al., 2007; McDonald et al., 2008]. Only few studies have so far sought to evaluate the impact of the side of the seizure focus on overall structural connectivity by comparing LTLE patients to those with RTLE; moreover, mesiotemporal lobe structures and the neocortex have not been analyzed conjointly in the same cohorts. Findings have been mixed with some studies reporting more marked atrophy in LTLE than RTLE [Coan et al., 2009; Keller et al., 2012; Kemmotsu et al., 2011; Santana et al., 2010], while others observed the reverse [Pail et al., 2010] or no differences [Dabbs et al., 2012]. In four reports, direct morphological comparisons compared hemispheric differences, neglecting the side of the seizure focus [Coan et al., 2009; Dabbs et al., 2012; Kemmotsu et al., 2011; Santana et al., 2010]. On the other hand, the assessment in which hemispheres were flipped (i.e., comparing the left hemisphere of LTLE to the right hemisphere of RTLE) did not account for interhemispheric asymmetries [Keller et al., 2012]. Furthermore, focus lateralization in all previous assessments was based on electroclinical and imaging markers and not the strict, MRI-independent reference standard based on seizure freedom after surgery [Gaillard et al., 2011].

To objectively assess the impact of focus lateralization on brain structure in TLE, we studied a large sample of patients examined on a 1.5 T scanner. Selecting only those with long-term seizure freedom guaranteed a rigorous definition of unilateral TLE. Our multimethod neuroimaging approach entailed mesiotemporal surface-shape analysis, cortical thickness mapping, and voxel-based morphometry. In all analyses, symmetrical templates were employed to ensure hemispheric correspondence. Moreover, hemisphere-specific measures were z-normalized relative to corresponding measures in healthy controls to account for normal interhemispheric asymmetry, prior to sorting data relative to the side of the focus. To evaluate whether cohorts differ, we employed a comprehensive analytical battery including statistical comparisons, power analysis, and bootstrap simulations. Reproducibility and generalizability of findings were further verified at a different spatial scale, and through the evaluation of an independent dataset comprising TLE and control cohorts scanned at 3 T.

MATERIALS AND METHODS

Subjects

We studied 119 patients with TLE investigated at the Montreal Neurological Institute and 88 healthy controls.

Patients were retrospectively included only if they had undergone successful surgery for the treatment of drug-resistant unilateral TLE (see below); all underwent a selective amygdalohippocampectomy, the standard procedure in our center.

Preoperative diagnosis and lateralization of the seizure focus were determined by a comprehensive evaluation including detailed history, neurological examination, review of medical records, scalp video-EEG recordings, and MRI assessment in all patients. No patient had a mass lesion (malformations of cortical development, tumors, or vascular anomalies), traumatic brain injury, or a history of encephalitis.

Patient and control cohorts were separated into two datasets based on the preoperative MRI hardware. The first dataset consisted of 92 patients (41 males; 36 ± 10 years; 16–55 years) and 46 age- and sex-matched healthy individuals (22 males; 33 ± 12 years; 20–66 years) evaluated between 1998 and 2006 on a 1.5 T scanner. Based on postsurgical seizure outcome classification [Engel et al., 1993] at 7 ± 2 years, 60 (65%) patients had Engel Class I.

The second dataset included 39 TLE patients (16 males; 31 ± 9 years; 17–52 years), and 42 age- and sex-matched healthy individuals (22 males; 30 ± 7 years; 20–53 years), evaluated between 2008 and 2014 on a 3 T MRI. At a postsurgical interval of 4 ± 2 years, 30 (77%) had Class I outcome.

We divided patients with Engel Class I outcome into LTLE (1.5 T: $n = 25$; 3 T: $n = 15$) and RTLE (1.5 T: $n = 35$; 3 T: $n = 15$) based on the side of surgery. These cohorts, together with their respective controls, were subsequently included in the morphometric analysis. Hippocampal specimens were available in the majority of patients (1.5 T: $n = 47$; 3 T: $n = 30$) and confirmed hippocampal cell loss and/or isolated gliosis in all [Blümcke et al., 2013].

In both datasets, LTLE and RTLE patients did not show statistical differences in age, gender, age at seizure onset, duration of epilepsy, history of febrile convulsions, incidence of hippocampal sclerosis, and hippocampal atrophy detected on MRI ($p > 0.1$). Please see Table I for demographic and clinical details.

The Ethics Committee of the Montreal Neurological Institute and Hospital approved the study and written informed consent was obtained from all participants.

MRI Acquisition and Processing

T1-weighted MRI data at 1.5 T were obtained on a Philips Gyroscan (Philips Medical Systems, Eindhoven, Netherlands) using a 3D Fast-Field-Echo sequence (repetition time [TR] = 18 ms; echo time [TE] = 10 ms; flip angle = 30° ; matrix = 256×256 ; field-of-view [FOV] = 256×256 mm²; 176 sagittal slices with 1 mm thickness). T1-weighted data at 3 T were acquired on a Siemens TimTrio (Siemens Healthcare, Erlangen, Germany) using a 3D MPRAGE sequence (TR = 2300 ms; TE = 2.98 ms; TI = 900 ms; flip

TABLE I. Demographic and clinical information

	Age	Men	Onset	Duration	HA (MRI)	HS/gliosis	FC
1.5 T							
LTLE ($n = 25$)	35 ± 10 (16–52)	15	15 ± 11 (1–41)	20 ± 12 (1–38)	20 (80%)	14/7	12
RTLE ($n = 35$)	37 ± 10 (19–55)	14	15 ± 12 (1–49)	23 ± 12 (1–45)	25 (71%)	21/5	15
Controls ($n = 46$)	33 ± 12 (20–66)	22	N/A	N/A	N/A	N/A	N/A
3 T							
LTLE ($n = 15$)	31 ± 10 (18–44)	6	18 ± 11 (4–41)	13 ± 8 (3–31)	11 (73%)	10/5	4
RTLE ($n = 15$)	31 ± 10 (20–52)	5	12 ± 10 (1–35)	19 ± 13 (3–39)	11 (73%)	10/5	8
Controls ($n = 42$)	30 ± 7 (20–53)	22	N/A	N/A	N/A	N/A	N/A

Age, onset, and duration are presented in mean ± SD (year range); HA: number (percentage) of patients with hippocampal atrophy ipsilateral to the seizure focus defined by MRI volumetry; Pathology: number of patients with hippocampal sclerosis or isolated gliosis among available specimens; FC: number of patients with a history of febrile convulsions; no group differences were observed in any variable.

angle = 9°; matrix = 256 × 256; FOV = 256 × 256 mm²; 176 sagittal slices with 1 mm thickness). Image preprocessing was uniform across both datasets and included automated correction for intensity nonuniformity, intensity standardization, and linear registration to a stereotaxic space based on the hemisphere-symmetric MNI-ICBM152 template [Fonov et al., 2009]. The use of a symmetric template allows for direct comparison between corresponding regions in the left and right hemisphere; it further ensures an unbiased analysis when sorting hemispheres into ipsi- and contralateral with respect to the focus.

Surface-Based Morphometry

Mesiotemporal subregional volumes

For participants studied at 1.5 T, a single rater (NB) blinded to subjects' category (patient/control), manually segmented the hippocampus, amygdala, and entorhinal cortex using our published guidelines [Bernasconi et al., 1999, 2003]. For the 3 T cohorts, mesiotemporal structures were automatically segmented using a surface-based multitemplate algorithm that has previously shown excellent segmentation accuracy in healthy individuals and TLE patients [Kim et al., 2012].

Manual mesiotemporal labels were converted to surface meshes and parameterized using spherical harmonics with a point distribution model (SPHARM-PDM). For each structure, SPHARM-PDM surfaces of an individual were rigidly aligned to a template constructed from the mean surface of controls and patients with respect to the centroid and the longitudinal axis of the first-order ellipsoid. We calculated displacement vectors between each subject's surface and the template across 1,002 surface points (henceforth, *vertices* [Styner et al., 2006]). The signed surface normal components of these vectors quantify inward/outward deformations. To compute volume changes, we applied the heat equation to interpolate vertex-wise displacement vectors within the volume enclosed by SPHARM-PDM surfaces [Kim et al., 2008]. The Jacobian

determinant J of the resulting vector field was projected back onto the surface, quantifying growth ($J-1 > 0$) or shrinkage ($J-1 < 0$) in surface-normal direction.

Cortical thickness measurements

We applied the Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) algorithm to generate cortical surface models and measure cortical thickness across 81,924 vertices [Kim et al., 2005]. After automatically classifying an image into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), a surface mesh was iteratively warped to fit the WM–GM boundary. This boundary was expanded along a Laplacian map to model the GM/CSF surface. Surface-based registration improved anatomic vertex-correspondence across subjects. Importantly, the surface template was also chosen to be hemisphere-symmetric based on the MNI152 dataset [Lytelton et al., 2007]. Thickness data were blurred using a surface-based diffusion kernel of 20 mm full-width at half-maximum (FWHM).

Statistical Analysis

Analyses were performed using SurfStat (<http://www.math.mcgill.ca/keith/surfstat/>) for Matlab (R2012b, The Mathworks, Natick, MA) [Worsley et al., 2009].

Group comparisons

Our main analysis was performed on the 1.5 T dataset. We first compared mesiotemporal volumes and cortical thickness between each patient cohort (LTLE and RTLE) and controls. To directly compare LTLE and RTLE, patients were analyzed relative to the epileptogenic hemisphere (i.e., ipsi- and contralateral to the focus). In all analyses, to eliminate potential confounds related to asymmetry, we normalized features (thickness and local volume) at each vertex using a z -transformation with respect to the corresponding distribution in controls (i.e.,

each patient's right/left feature was expressed as z-score with respect to right/left values in controls). Findings were corrected using random field theory [Worsley et al., 1999], controlling the family-wise error (FWE) to be below $p_{\text{FWE}} < 0.05$. In an exploratory analysis, we also applied uncorrected thresholds ($p < 0.01$, extent of 20 vertices).

Bootstrap reproducibility

Bootstrap comparison aims at approximating the consistency of between-cohort differences [Bernhardt et al., 2010]. Each TLE cohort was randomly resampled with 1000 replacements. We performed vertex-wise *t*-tests between resampled LTLE and RTLE cohorts, corrected at $p_{\text{FWE}} < 0.05$, and mapped the vertex-wise probability of observing a significant between-cohort difference across all 1000 iterations.

Power analysis

At each vertex, we calculated the effect size of difference between LTLE and RTLE using *Cohen's d* (the absolute mean difference divided by the pooled standard deviation). We estimated the required sample size to detect the observed group difference based on the resultant *Cohen's d* set at a moderate power of $1 - \beta = 0.9$ and uncorrected $\alpha = 0.01$, as implemented in R (3.1.1; <http://www.r-project.org/>).

Robustness Evaluations

We used the following approaches to further verify the reproducibility of findings:

- To assess the possible influence of the spatial scale (influencing the number of comparisons) on statistical sensitivity, we repeated group- and power-analyses after parcellating mesiotemporal and neocortical surfaces [Bernhardt et al., 2015b; Tzourio-Mazoyer et al., 2002].
- We quantified gray matter morphology through optimized voxel-based morphometry, in keeping with previous studies that applied this framework [Coan et al., 2009; Santana et al., 2010]. The analysis, based on SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) and VBM8 (<http://dbm.neuro.uni-jena.de/vbm/download/>), employed high-dimensional DARTEL registration to a symmetrical brain template; normalized gray matter estimates were blurred using a Gaussian kernel of 10 mm FWHM. As for the main surface-based analysis, gray matter estimates in patients were normalized with respect to the corresponding distribution in controls and sorted relative to the epileptogenic hemisphere (i.e., ipsi- and contralateral to the focus). Likewise, findings were corrected at $p_{\text{FWE}} < 0.05$.
- We repeated the surface- and voxel-wise comparisons between LTLE and RTLE based on the independent 3 T dataset.

RESULTS

Comparisons to Controls

Compared to controls, both TLE groups showed similar patterns of mesiotemporal lobe changes characterized by predominantly ipsilateral atrophy in the hippocampus ($p_{\text{FWE}} < 0.001$; average *Cohen's d* in LTLE/RTLE = $-1.4/-1.1$) and amygdala (uncorrected $p < 0.01$; *Cohen's d* LTLE/RTLE = $-0.69/-0.59$); while entorhinal cortex atrophy was bilateral ($p_{\text{FWE}} < 0.001$), effects were more marked ipsilaterally (*Cohen's d* LTLE/RTLE = $-0.83/-0.87$; Fig. 1). LTLE and RTLE also showed a comparable pattern of cortical thinning affecting large portions of temporoparietal, central, and frontal cortices ($p_{\text{FWE}} < 0.05$; *Cohen's d* LTLE/RTLE = $-0.75/-0.73$). In LTLE, atrophy appeared more extensive in lateral frontotemporal regions, while in RTLE, anomalies were more widespread in medial fronto-central cortices.

Direct Patient Comparisons

Directly comparing LTLE to RTLE did not reveal significant differences in mesiotemporal volumes (Fig. 2A). At uncorrected thresholds ($p = 0.01$, 20 vertices), only single clusters in the ipsilateral hippocampus in LTLE (corresponding to CA1) and in the ipsilateral caudal entorhinal cortex in RTLE showed tendencies for atrophy. We did not observe any differences in cortical thickness between patient groups. At uncorrected thresholds ($p = 0.01$, 20 vertices), LTLE patients displayed small and scattered clusters of reduced thickness in ipsilateral occipital, angular, and contralateral frontal regions; conversely, trends for reduced thickness in RTLE were seen in ipsilateral orbitofrontal as well as contralateral medial central and occipital regions. Given that patient cohorts were comparable in age, sex, duration of epilepsy, history of febrile convulsions, prevalence of hippocampal atrophy, and global mean thickness ($p > 0.1$), it is unlikely that these variables contributed to the observed marginal effects. Indeed, repeating the group comparisons using models that additionally controlled for these variables did not modify results.

Bootstrap Reproducibility

Among 1000 simulated comparisons, only the ipsilateral entorhinal cortex showed a low likelihood (25–54%) of smaller volume in RTLE compared to LTLE, while we observed a below-chance likelihood (25–47%) of a between-cohort difference in scattered lateral temporal, medial occipitotemporal, and lateral frontal neocortices (Fig. 2B).

Power Analysis

Average absolute vertex-wise effect size of differences between LTLE and RTLE were low in both the mesiotemporal lobe (*Cohen's d* = 0.25 ± 0.19) and neocortex (*Cohen's*

Figure 1.

Mapping mesiotemporal and neocortical morphology in **(A)** left TLE (LTLE) and **(B)** right TLE (RTLE) patients with Engel-I outcome relative to controls. Significant clusters after correction for multiple comparisons are outlined in black; uncorrected findings at $p < 0.01$ are shown in semitransparent. The hippocampus, entorhinal cortex, and amygdala are shown from a superior, inferomedial, and posterior view, respectively. A = anterior; M = medial. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$d = 0.22 \pm 0.17$) (Fig. 3). High effects (Cohen's $d > 0.7$) were observed only in small clusters, similar to those detected in uncorrected group comparisons. Power analysis in these regions revealed that >110 patients in total (55 per group; 1:1 allocation ratio) would have been necessary to detect a significant LTLE vs RTLE difference, even at marginal error and power criteria (uncorrected $\alpha = 0.01$, $1 - \beta = 0.9$, one-tailed t -test).

Robustness Evaluations

Multiscale analysis

Based on a mesiotemporal and cortical parcellation, we assessed the consistency of our findings at a lower spatial scale (Fig. 4A). None of the mesiotemporal and cortical parcels showed a statistically significant difference between LTLE and RTLE patients, even at uncorrected

thresholds ($p > 0.05$). In the parcel-based power analysis, the highest, but still moderate, effect size was detected in the ipsilateral medial occipital cortex (Cohen's d of 0.48). To detect significant between-group differences, even higher total sample sizes than in the case of the vertex-wise analysis would have been necessary (uncorrected $\alpha = 0.05$, $1 - \beta = 0.9$, one-tailed t -test; Fig. 4B).

VBM analysis

As for the surface-based findings, we did not detect significant differences in gray matter estimates between LTLE and RTLE cohorts.

Analysis of independent dataset

Comparing the LTLE and RTLE cohorts to controls based on the 3 T dataset revealed similar, yet slightly less

A. GROUP COMPARISON

B. BOOTSTRAP REPRODUCIBILITY

Figure 2.

Direct comparison of mesiotemporal and neocortical morphology between left and right TLE. **(A)** Comparing groups at a vertex-level, no finding survived multiple comparison correction. Uncorrected trends ($p < 0.01$, extent > 20 vertices) are shown. Blue/red indicates less/more gray matter in LTLE compared to

RTLE. **(B)** Bootstrap reproducibility analysis showed a low likelihood of finding an LTLE versus RTLE difference. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

extensive findings as the main analysis at 1.5 T (Supporting Information, Fig. 1). Importantly, directly contrasting LTLE and RTLE cohorts in the independent 3 T dataset confirmed null findings observed at 1.5 T for mesiotemporal surface shape mapping, cortical thickness, and voxel-based morphology (Supporting Information, Fig. 2).

DISCUSSION

Based on strictly defined and well-matched unilateral patient cohorts, this study evaluated the impact of the side of seizure focus on brain morphology in TLE. Compared to controls, LTLE and RTLE cohorts presented with similar patterns of mainly ipsilateral hippocampal and entorhinal cortex volume loss, while neocortical thinning affected multiple midline regions as well as lateral temporal and frontal cortices bilaterally. Importantly, direct patient cohort comparisons, performed both in a vertex- and parcel-wise fashion,

did not indicate any significant differences between LTLE and RTLE. Separate evaluation of voxel-based morphometry as an independent proxy for gray matter morphology, as well as analysis of an additional dataset containing patient and control cohorts scanned at higher field strength confirmed results. Collectively, our multimethod approach demonstrates that TLE markedly impacts mesiotemporal morphology ipsilateral to the seizure focus; neocortical atrophy, on the other hand, follows a bilateral pattern and extent that is relatively independent of the side of seizure focus.

Methodological aspects might have contributed to the difference between our null findings and previous work suggesting a between-cohort divergence [Coan et al., 2009; Dabbs et al., 2012; Kemmotsu et al., 2011; Pail et al., 2010; Santana et al., 2010]. First, our patients were selected based on long-term seizure freedom, contrary to all previous studies where diagnosis and lateralization were based on electroclinical and visual MRI evidence alone; in these investigations, patient operation rate and surgical outcome

A. EFFECT SIZE

B. SAMPLE SIZE

Figure 3.

Vertex-wise power analysis. **(A)** Maps of effect size of a difference between LTLE and RTLE and **(B)** the required total sample size to detect statistical differences at a moderate power of $1 - \beta = 0.9$ and uncorrected $\alpha = 0.01$ (1:1 allocation rate). Gray

shade indicates that a total of more than 300 patients (150 per group) would have been necessary to detect a difference. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

were not reported [Coan et al., 2009; Dabbs et al., 2012; Kemmotsu et al., 2011; Pail et al., 2010; Santana et al., 2010]. Second, we explicitly controlled for normal interhemispheric morphological variations, both through the use of hemisphere-symmetric templates and by standardizing structural measurements in patients relative to healthy controls' data, prior to sorting hemispheres into ipsi-/contralateral. Conversely, none of the previous studies accounted for the normal asymmetry prior to hemisphere flipping [Keller et al., 2012], if there was flipping at all [Coan et al., 2009; Dabbs et al., 2012; Kemmotsu et al., 2011; Santana et al., 2010]. Third, our approach represents the most comprehensive statistical assessment to date as it comprises group-level surface mapping, reproducibility assessment, and power analysis to evaluate the impact of seizure focus laterality on brain morphology. Reproducibility assessment using a bootstrap approach indicated that the likelihood of observing a between-cohort difference would be low in a simulated population. As shown

by power analysis, a total of more than 110 patients would be necessary to detect meaningful vertex-wise differences between LTLE and RTLE. Complemented by the null findings in an independent dataset, we are relatively confident that strictly lateralized cohorts with LTLE and RTLE do not show sizable differences in gray matter morphology.

Our patients were recruited from surgical cohorts who underwent a selective amygdalohippocampectomy [Tanriverdi et al., 2008; Wieser, 1991; Yaşargil et al., 2010]. While restricting our analysis to patients who achieved seizure freedom after a long follow-up of 7 ± 2 years supported the focus lateralization, this specificity might have possibly excluded a small subgroup of patients not rendered seizure free by the selective approach, e.g., those with generators in temporolimbic cortices outside the hippocampal formation [Ryvlin, 2003].

Selecting a homogeneous population with long-term seizure-freedom ruled out potential effects of a more severe disease. Nevertheless, we observed a divergence with

A. PARCELLATION

B. POWER ANALYSIS

Figure 4.

Morphological comparisons at lower spatial scale. **(A)** Mesio-temporal structures are parcellated into 24 regions (i.e., 12 per hemisphere) according to histological atlases (Amunts et al., 2005; Duvernoy and F, 2005; Insausti et al., 1995). The neocortex is subdivided into 78 regions (i.e., 39 per hemisphere) using the AAL algorithm (Tzourio-Mazoyer et al., 2002). **(B)** Parcel-based power analysis. Line plots show the required total number

of subjects to detect statistical differences between LTLE and RTLE across individual parcels (color-coded according to surface renderings in A), and on average (black lines) as a function of uncorrected α (0.05, 0.01, 0.005, and 0.001), set at a power of $1 - \beta = 0.9$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

regards to changes between the mesiotemporal lobe and neocortex. The mainly unilateral character of mesiotemporal anomalies reemphasizes findings from our recent data-driven classification of TLE [Bernhardt et al., 2015a], in which unsupervised clustering operating on subregional volumes identified a patient class presenting with strictly ipsilateral atrophy and a 90% likelihood of achieving seizure freedom after surgery. Conversely, other patient sub-

classes presented with marked bilateral compromise across all mesiotemporal regions and lower chances of seizure freedom [Bernhardt et al., 2015a]. At the level of the neocortex, our findings in Engel-I patients indicate that bilateral anomalies does not necessarily equate seizure relapse after surgery. In light of ample neuroimaging data suggesting progressive brain damage in patients with drug-resistant TLE [Bernhardt et al., 2009; Briellmann et al., 2002; Coan

et al., 2009], bilateral cortical anomalies may be secondary to a combination of seizure-induced excitotoxicity [Meldrum, 1993] and white matter disconnection [Bonilha et al., 2010]. These findings motivate the use of combined mesiotemporal and neocortical markers in developing prognostic neuro-markers of seizure outcome. Notably, although some forms of bilateral cortical damage may be compatible with postsurgical seizure freedom, its cognitive and social consequences need to be clarified [Dabbs et al., 2009; Gutierrez-Galve et al., 2012].

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