Association Between Anatomical Location of Surgically Induced Lesions and Postoperative Seizure Outcome in Temporal Lobe Epilepsy

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Running head: Surgical-outcome mapping in temporal lobe epilepsy

Association between anatomical location of surgically-induced lesions and postoperative seizure outcome in temporal lobe epilepsy

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Abstract

Objective: To determine the association between surgical lesions of distinct grey and white structures and connections with favorable post-operative seizure outcomes.

Methods: Patients with drug-resistant temporal lobe epilepsy (TLE) from three epilepsy centers were included. We employed a voxel-based and connectome-based mapping approach to determine the association between favorable outcomes and surgery-induced temporal lesions. Analyses were conducted controlling for multiple confounders, including total surgical resection/ablation volume, hippocampal volumes, side of surgery, and site where the patient was treated.

Results: The cohort included 113 patients with TLE [54 women; 86 right-handed; 16.5 (SD = 11.9) age at seizure onset, 54.9% left] who were 61.1% free of disabling seizures (Engel class 1) at follow-up. Postoperative seizure freedom in TLE was associated with 1) surgical lesions that targeted the hippocampus as well as the amygdala-piriform cortex complex and entorhinal cortices; 2) disconnection of temporal, frontal, and limbic regions through loss of white matter tracts within the uncinate fasciculus, anterior commissure, and fornix; and 3) functional disconnection of the frontal (superior and middle frontal gyri, orbitofrontal region) and temporal (superior and middle pole) lobes.

Conclusions: Better postoperative seizure freedom are associated with surgical lesions of specific structures and connections throughout the temporal lobes. These findings shed light on the key components of epileptogenic networks in TLE and constitute a promising source of new evidence for future improvements in surgical interventions.

Classification of Evidence: This study provides Class II evidence that for patients with temporal lobe epilepsy, postoperative seizure freedom is associated with surgical lesions of specific temporal lobe structures and connections**.**

Introduction

Surgery for temporal lobe epilepsy (TLE) can be curative [1, 2]. Nonetheless, 30 to 40% of patients with TLE continue to experience seizures with loss of awareness after surgery [1, 3, 4]. Unfortunately, seizures with loss of awareness are directly associated with a lower quality of life [5]. The reasons for suboptimal surgical outcomes are complex and many studies have investigated pre-surgical clinical factors that may be associated with seizure freedom. Consistently, good outcomes are most frequent among patients with unilateral hippocampal sclerosis on MRI [6-8]. Other factors associated with favorable outcomes include shorter duration of epilepsy, younger age at surgery [9], history of febrile seizures [10], unilateral [8, 11] and infrequent [12] interictal epileptiform discharges. Nonetheless, even when combined, these predictive factors only partially explain postoperative outcomes, and many patients who are expected to achieve optimal results continue to have seizures after surgery.

Beyond clinical variables, the location and extent of the anatomical resection have been deemed to be a crucial determinant of outcome, with hippocampal removal being necessary for seizure freedom [13-16]. Nonetheless, recent studies have challenged this notion [17, 18] and other medial temporal structures may be similarly important for outcomes, such as the entorhinal [19, 20] and piriform [21] cortices, which can independently generate and/or sustain seizures in TLE [22]. Furthermore, many recent whole-brain neuroimaging studies have indicated that the structural and functional connectivity of the medial temporal lobe can also support seizures in TLE [23-31].

Voxel-based lesion-mapping neuroimaging methods have been extensively employed and refined to assess the quantitative relationship between brain injury and clinical variables outside of epilepsy [32, 33]. When a lesion to a specific brain region is statistically associated with a clinical variable, it constitutes a rigorous demonstration that the region is *critical* for that function [32]. In

this context, a lesion-based approach is optimally suited to elucidate the relationship between finer anatomical landmarks in TLE resections and outcomes. Moreover, our group has expanded conventional lesion-based approaches to include structural connectivity lesion mapping [34], which can greatly elucidate the anatomy of medial temporal network disconnections and their importance towards seizure freedom.

Based on the evidence supporting the role of the medial temporal cortical structures in seizure onset in TLE [19-21], we hypothesized that resection of the entorhinal and amygdala-piriform regions would be associated with further favorable postoperative outcomes. We further hypothesized that medial temporal structural and functional *disconnections* are also independently associated with better surgical outcomes. In this study, we employed a multi-modal quantitative lesion-clinical approach to test these hypotheses leveraging a large dataset from multiple epilepsy centers and a combination of voxel-based outcome-resection mapping combined with structural- and functional- connectivity outcome-lesion mapping.

Methods

Standard Protocol Approval and Patient Consent

Data gathering followed Institutional Review Board (IRB) approval at each site. The majority of patients had been enrolled prospectively through informed consent for the use of anonymized neuroimaging and clinical data. In addition, the IRB at the Medical University of South Carolina approved the use of retrospective analysis of anonymized multicentric data.

Patients

We included data from 113 patients with TLE from three different epilepsy centers: Medical University of South Carolina (MUSC, n = 10), Emory University (Emory, n = 59), and Bonn University (Bonn, n = 44). Patients were included at each site following local Institutional Review Board protocols. Patients were diagnosed with unilateral TLE following the criteria proposed by the ILAE [35]. Only patients that had normal MRI or findings suggestive of underlying medial temporal sclerosis were included in the study, i.e. we did not include patients that had other lesions (e.g. tumors, cavernoma, etc.). All patients were refractory to pharmacological treatment, prompting pre-surgical evaluation at their site, and were referred to epilepsy surgery based on expert consensus. The choice between the type of procedure (open resection or laser ablation) depended on a combination of factors including the availability of laser ablation at the time and place of the surgery referral, suiting the size of the procedure to the putative or demonstrated early ictal network, and patient preference. A subset of patients from this study was studied as part of prior multisite studies from our group[26].

Surgical outcome

Seizure control outcomes were quantified at least one year after the procedure by an epileptologist based on the Engel outcome scale[36] where Engel = 1 indicates freedom of disabling seizures (i.e., without loss of consciousness), Engel = 2 indicates significant improvement in seizures with persistence of rare disabling seizures, Engel = 3 indicates worthwhile improvement, and Engel = 4 indicates no changes. If patients underwent more than one procedure (e.g. resection following ablation), only data related to the first surgical procedure were included in this study. For the majority of patients, imaging included for the purposes of

this analysis was obtained within a two-month window of the clinical assessment of seizure outcomes.

Neuroimaging acquisition and processing

T1-weighted isotropic volumetric images were acquired at each site with the following parameters:

- **MUSC**: Siemens Skyra 3T scanner, isotropic voxel size 1 mm, 12-channel head coil, TR = 2050-2250 ms, TE = 2.5-3 ms, FOV = 256- 320 mm, flip angle 10°;
- **Emory**: Siemens Skyra 3T scanner, isotropic voxel size 0.8 mm, 12-channel head coil, TR = 2300 ms, TE = 2.75 ms, TI = 1100 ms, flip angle 8°.
- **Bonn**: Siemens Magnetom Trio 3T scanner, 8-channel head coil, isotropic voxel size of 1 mm, TR = 1300 ms, TE = 3.97 ms, TI = 650 ms, flip angle 10°

Individual voxels were rearranged by flipping sides so that voxels represented ipsilateral vs. contralateral (to the side of surgery) areas rather than a left vs. right dichotomy. For example, for a patient with left-sided TLE, voxels on the left hemisphere became ipsilateral, whereas voxels in the right hemisphere were considered contralateral. We arbitrarily chose to represent ipsilateral findings on the left side of the brain.

We employed three different and complementary approaches to define the relationship between surgical cavity and clinical outcomes: voxel-based lesion-outcome mapping, which is based on conventional voxel-based lesion-symptom mapping from classical cognitive neuroscience studies [32], as well as structural connectivity lesion-outcome mapping, and functional connectivity lesion-outcome mapping. All analyses were performed based on post-

operative high-resolution volumetric T1-weighted imaging acquired at least 12 months after surgery to ensure complete or near-complete resolution of edema and gliosis. Structural and functional connectivity analyses were calculated from the T1-defined surgical cavity using high-volume normative databases of brain connectivity, from which projected connectivity loss from the resection was calculated. These steps are summarized below:

A) Definition of the surgical cavity and spatial normalization. Manual tracing of the surgical cavity on all post-operative T1-weighted scans was performed by a blinded rater trained on neuroanatomy with emphasis on medial temporal lobe anatomy [37] using the open source software MRIcroGL (https://www.nitrc.org/projects/mricrogl). All surgical delineations were reviewed by the first author (EG). We employed an enantiomorphic approach described by Nachev et al. [38] implemented into the software SPM [39] by the NiiStat toolbox developed by Chris Rorden. (https://www.nitrc.org/projects/niistat/) to normalize brain images and surgical masks into standard space (see details below)

B) Assessment of structural connectivity. We measured structural connectivity as the predicted structural network damage from the surgical cavity on a normative structural white matter *connectogram* derived from the diffusion MRI Human Connectome Project template - HCP842 with 1mm resolution [40], a map of diffusion tensor imaging pathways in MNI152 space consistent across a large number of healthy adult individuals. For each TLE patient, we assessed which connectogram fibers would have been affected by the surgical cavity by evaluating the overlap between voxels in the surgical cavity in stereotaxic space and each fiber in the connectogram. The result was a map of lesioned fibers (a “disconnectogram”) per individual, from which a tract density image was created, where each voxel in MNI152 space represented a continuous integer denoting the number of fibers affected by the surgical resection at that voxel.

C) Assessment of functional connectivity. Similarly, we measured functional connectivity based on the predicted functional network affected by the surgical cavity using a large normative meta-analytical functional MRI database. Specifically, using the surgical cavity in MNI space as the region of interest (ROI), we used Neurosynth's meta-analytical data and code to calculate the ROI's coactivation. Neurosynth is a seed-based approach which generates a whole brain map of areas with reported coactivation with a given ROI across the a large database including 14,371 functional MRI studies at the time of this study [41]. We employed an FDR corrected threshold of $p < 0.01$, resulting in a voxel-wise whole brain map per patient where each voxel indicated the potential loss of connectivity from the surgical cavity represented as a Z score float variable. This step was performed using Neurosynth's coactivation function and in-house developed Python and Matlab scripts for image co-registration.

Steps A, B, and C are shown for one representative patient in **eFigure 1.**

Pre-surgical hippocampal atrophy as a covariate measure.

Presurgical hippocampal atrophy is an important confounder in TLE. For example, patients with less prominent degree of pre-operative hippocampal atrophy would require more hippocampal tissue resected. As such, an association between higher hippocampal volume resection and outcomes would not be truly related to the resection *per se*, but merely to the presence or absence of hippocampal atrophy. To account for this important confounder, we used voxel-based morphometry (VBM) to measure pre-surgical hippocampal volumes/concentration, which were used as control variables in the statistical analyses described above. VBM was computed using the software package SPM with iterative normalization and segmentation using the modulated normalization option [42]. The resulting probabilistic gray matter map was

segmented into regions of interest based on the Automatic Anatomical Labeling (AAL) atlas [43] and the hippocampal volumes ipsilateral and contralateral to the side of resection were derived.

Statistical analyses

This study seeks to investigate the association of postoperative seizure outcomes with surgical lesions of specific temporal lobe structures and connections (Class II evidence). In order to achieve this, the following analyses were conducted:

Lesion and disconnection

A) Voxel-based outcome-resection mapping. Each surgical resection mask is a binary map, where a voxel is coded as 1 if lesioned or 0 if intact. We performed a voxel-based general linear model with surgical outcome as the ranked dependent variable, and with independent variables including the presence or absence of lesion, the total surgical resection volume, the hippocampal volumes, the side of surgery, and the site where the patient was treated (the latter two encoded as dummy variables). The *beta* and *p* values indicating the relationship between resection and outcomes were computed for each voxel.

B) Structural connectivity outcome-lesion mapping. Different from voxel-based outcome lesion mapping, the individual structural disconnectogram is a continuous voxel-based map, i.e., each voxel is not a binary mask but rather encodes a continuous value related to the number of affected fibers. For this reason, we employed voxel-wise partial rank-based correlations (Spearman) to assess the relationship between surgical outcome as a ranked variable and number of fibers affected per voxel, controlling for the total surgical resection volume, the hippocampal

volumes, the side of surgery, and site where the patient was treated. The voxel-wise *R* and *p* values were computed.

C) Functional connectivity outcome-lesion mapping. Similar to structural disconnectograms, functional maps also represented continuous voxel-wise values, in this case, Z score co-activation values. We therefore employed a comparable approach: voxel-wise partial rank-based correlations (Spearman) measuring the relationship between surgical outcome as a ranked variable and voxel-wise co-activation Z score, again controlling for the total surgical resection volume, the hippocampal volumes, the side of surgery, and site where the patient was treated. The voxel-wise *R* and *p* values were computed.

Image processing pipeline- surgical resection and related disconnections.

We employed an enantiomorphic approach described by Nachev et al. [38] implemented into the software SPM [39] by the NiiStat toolbox developed by Chris Rorden (https://www.nitrc.org/projects/niistat/) to spatially normalize the individual surgical cavities to the MNI152 stereotaxic standard space. This approach applies segmentation/normalization routines from SPM to estimate a non-linear normalization matrix for the post-operative image in native space with the surgical cavity being replaced by the homologous contralateral non-lesioned tissue. The normalization matrix is then applied to the original post-op image resulting in a T1-weighted scan in standard space without the tissue deformation that would have ensued by non-linear normalization estimation using the cavity. The same normalization matrix was applied to the surgical mask in native space, yielding a surgical mask in stereotaxic space, which is comparable across individuals by being in the same space.

Strategies to avoid statistical type I and II errors

A common limitation of massive univariate voxel-based approaches is the high probability of type I (false negative) and type II (false positive) errors. This pitfall is greatly compounded when multiple correction variables are included in the voxel-wise models, i.e., where the statistical analysis for each voxel includes multiple control variables to determine the more subtle association between one variable (resection or disconnection at that voxel) with outcomes while controlling for many other variables. This process is repeated for a very large number of voxels, and further multiple comparison corrections become disproportionately stringent and greatly increases the chances of Type I errors. In this study, we opted to maintain the use of multiple controlling variables per voxel (i.e., resection volume, hippocampi volumes, site, and side of surgery) since these are fundamentally important to determine the true relationship between resection and outcomes while accounting for clinically relevant confounders. Nonetheless, the penalty of such an approach is the massive reduction in statistical power. To balance this bias and prevent type II errors, we adopted a voxel-wise cluster correction for multiple comparisons where only voxels with $p < 0.05$ located in clusters with at least 16 mm^3 were considered significant. Moreover, we also prevented type II errors by performing analyses using three different imaging modalities and assessing the anatomical concordance between the results as important corroboration of true positive findings.

Data availability

Anonymized data inclusion lesion masks and behavioral outcomes is available from the authors upon written request.

Results

Cohort characteristics and surgical outcomes

The cohort's demographic and clinical profile is summarized in **Table 1**. Of the 113 patients included, 61 (54%) were female and 98 (86%) were right-handed. Age at seizure onset was 16.5 (SD = 11.9). Side of surgery was left in 54.9% of cases. A total of 62 (54.9%) patients underwent resection and 51 (45.1%) underwent stereotactic laser ablation at an average age of 38.8 (SD = 12.9). At least 12 months post-operatively, 69 (61.1%) patients were free of disabling seizures (Engel class 1). Of those who experienced post-operative seizures, 19 (16.8%) were Engel class 2, 20 (17.7%) were Engel class 3, and 5 (4.4%) were Engel class 4. There were no significant differences across sites except for the proportion of each surgical approach ($\chi^2 = 69.5$, df = 2, $p < .001$), with Emory performing mostly laser ablations (81.3% of their cohort) and Bonn performing exclusively resections. Of note, neither the site ($\chi^2 = 6.5$, df = 6, $p = .37$) nor the type of surgery was significantly associated with differences in outcomes ($\chi^2 = 1.85$, df = 3, $p = .60$).

Neuroimaging results

The overlay of all surgical cavities in stereotaxic space is shown in **Figure 1**. Lesions were flipped to be represented as ipsilateral to the area of TLE onset, represented on the figure over the left side according to radiological convention. **eFigure 2** demonstrates the association between pre-operative grey matter volume and area of resection, demonstrating that there are larger resections associated with more prominent presurgical atrophy particularly in the hippocampus but less so in the surrounding tissue.

A) Voxel-based outcome-resection mapping revealed two clusters associated with better outcomes (**Figure 2** and **Table 2**). More specifically, resection of voxels in the hippocampus and the amygdala-piriform cortex complex (cluster 1) as well as in the parahippocampal gyrus (entorhinal cortex) extending into the rhinal sulcus (cluster 2) were associated with better outcomes, controlling for the total volume of resection/ablation, side of surgery, treatment center and pre-surgical hippocampal volumes.

B) Structural connectivity outcome-lesion mapping demonstrated a single cluster where structural disconnections were associated with better outcomes (**Figure 3** and **Table 2**). Disconnection of fibers in the uncinate fasciculus, anterior commissure, and fornix (cluster 1) were associated with better outcomes. This association was also observed after controlling for the total volume of resection/ablation, side of surgery, treatment center, and pre-surgical hippocampal volumes.

C) Functional connectivity outcome-lesion mapping revealed four clusters where functional disconnection was associated with better outcomes (**Figure 4** and **Table 2**). Functional disconnection of the contralateral superior frontal gyrus and contralateral middle frontal gyrus (cluster 1), bilateral gyri rectus (cluster 2), ipsilateral middle and superior gyri of the temporal pole (cluster 3), and the ipsilateral middle orbitofrontal cortex (cluster 4) were all associated with better outcomes, controlling for the total volume of resection/ablation, side of surgery, treatment center and pre-surgical hippocampal volumes.

D) Concordant anatomical pattern between connectivity modalities. Structural and functional connectivity outcome-lesion mapping are based on different brain tissues, i.e., white and gray matter, respectively. For this reason, it is expected that there is incomplete overlap

between their statistical maps. It is nonetheless possible to evaluate the concordance between the results by qualitatively inspecting the projection of disconnected fibers towards disconnected cortex. This is demonstrated in **Figure 5,** where a clear pattern reveals the correspondence between disconnected anterior temporal fibers (corresponding to cluster 1 from structural connectivity outcome lesion mapping) with temporal pole and inferior frontal functional disconnection (clusters 2 and 3 from functional connectivity outcome lesion mapping). Functional disconnection of the orbitofrontal cortex was not associated with significantly disconnected structural fibers; nonetheless, there is a clear and unique projected structural pathway towards the orbitofrontal cortex that might be significance in larger cohorts with increased power.

Discussion

This study employed a multi-modal lesion-mapping approach to evaluate the relationship between surgical outcomes in TLE and resection/ablation location or its ensuing disconnection from the brain network. Controlling for pre-surgical medial temporal lobe atrophy, we observed that better outcomes were associated with resections involving the hippocampal formation and the entorhinal-rhinal and amygdala-piriform cortices, as well as temporal pole and temporal-frontal structural and functional disconnections. The results reconcile previous seemingly inconsistent findings from the literature and can provide insight into factors related to surgical outcomes. They also underscore the value and caveats of voxel-based approaches for this type of investigation. These are discussed in further detail below.

Hippocampal and/or medial temporal resection

Many studies have underscored the importance of complete hippocampal resection for seizure freedom [13-15, 44]. Nonetheless, there are anecdotal reports of optimal outcomes with incomplete resection [44, 45] and a recent elegant study challenged the importance of hippocampal resection in non-lesional cases by demonstrating overall favorable outcomes in patients with hippocampal-sparing surgery [17]. Our analysis shows that there is indeed a tendency to perform more extensive resections/ablations when the hippocampal volume is more atrophied preoperatively (as seen in eFigure 1). Hence, we sought to understand the anatomy that supports seizure outcomes beyond hippocampal resection. This stems from the observation of patients that continue to have seizures despite surgical lesioning of the hippocampus as well as intracranial EEG studies demonstrating that the entorhinal and perirhinal cortices are likely involved in seizure onset in a proportion of patients [46-48]. Our results indicate that resection of the anterior hippocampus-amygdala-piriform region or the entorhinal/perirhinal regions is associated with better outcomes, thus reconciling these observations. We did not specifically test whether the resection of the rhinal or amygdala-piriform cortices are the crucial determinant for patients with hippocampal sparing surgery, which may be a focus of a future study. Nonetheless, our findings suggest that resection of these regions is associated with better outcomes. Further studies are needed to determine if resection/ablation of these regions can yield surgical freedom independently of each other or whether their combined removal is associated with better outcomes. It should be noted that we did not observe a relationship between hippocampal body resection and better outcomes, but this was likely an artifact related to the use of hippocampal volumes as a control covariate, i.e., patients with less atrophied hippocampus would have large hippocampal body resections. Our findings also corroborate converging evidence from prior independent studies showing the favorable outcomes seen with surgical lesioning of the

entorhinal [19, 49] and piriform [21] cortices independent of lesion volume, controlling for potential confounders such as total surgical resection volume, hippocampal volumes, side of surgery, and site performing the surgery.

Disconnection as a prognostic factor

Gray matter disconnection is an important factor in various conditions in neurology [50, e51] such as stroke e.g.[e52, 53], dementia [e.g. e54] and traumatic brain injury [e.g. e55]. Yet ,disconnection in epilepsy remains underappreciated as a potential factor associated with clinical phentoypes, including surgical outcomes. Essentially, cortical disconnection stipulates that seemingly intact gray matter has impaired function despite structural preservation directly as a result of reduced white matter connections[e51]. For example, we have recently demonstrated that cortical disconnection of the left cingulum, bilateral amygdala, and left thalamus was associated with worse memory performance even after controlling for medial temporal volume loss, confirming the functional consequences of disconnection beyond the degree of grey matter loss.[e56] Our present findings demonstrate that disconnection may also play a key role in seizure outcomes following epilepsy surgery. Specifically, disconnecting the anterior temporal lobes from the medial and lateral orbitofrontal cortex (by disrupting the uncinate fasciculus), the anterior and ventral temporal lobes including the amygdala from their contralateral homologs (by disrupting the anterior commissure), and the medial temporal structures from the remainder of the limbic system (by disrupting the fornix) were independently associated with better outcome. These findings support prior evidence from correlational analyses showing distinct changes in diffusion scalar maps associated with seizure freedom vs. refractoriness after surgery [e57-59] as well as previous observations that a larger resection of uncinate fibers is associated with better ouctomes [e60], in line with authors advocating for disconnecteion surgery for TLE[e61, 62].

Our results also indicate that functional disconnection of regions in the frontal (superior and middle frontal gyri, orbitofrontal region) and temporal (superior and middle pole) lobes are likely crucial for postoperative seizure freedom. Concordant anatomical patterns between

connectivity modalities suggest these functionally disconnected regions could be related to the structural disconnections identified above.

Voxel-based lesion approaches

Voxel lesion-symptom mapping was introduced by Bates and collaborators[32] to statistically assess which brain regions are not just *associated* but are rather *essential* for a given function or behavior. Few in-vivo methods confirm the essential regions, since other imaging modalities, e.g., fMRI, cannot dissociate between areas that are involved or are required for a function. Since then, lesion-mapping has been widely used to determine the crucial anatomy of higher cognitive functions [e63, 64, 65] and has been refined to take into account caveats related to spatial normalization of brains with lesions [e66] with implementation of statistical approaches to avoid statistical errors [e67]. Lesion variability is one of the most desirable characteristics for datasets in lesion-symptom mapping studies [e68] since inter-individual differences in resection sites and outcomes provide statistical power to define voxel-based differences. The combination of temporal lobe open resections with laser ablation from multiple sites was purposefully chosen for this study for this reason. Importantly, lesion-symptom mapping approaches allow for a systematic and objective stastistical approach to confirm anecdotal observations from lesion case series.

Limitations

Cluster correction of voxel-based lesion analyses is a well-established method to control for multiple comparisons [e69, 70, 71], however, massive univariate analyses carry the risk of type I errors and these should be taken in context. Second, we note that the co-occurrence of

parahippocampal and hippocampal lesions in traditional approaches (i.e., non-hippocampal sparing) limits the ability to dissociate the differential role of each structure in outcomes, a well established phenomenon in lesion-symptom mapping studies [e68]. Third, we note that the regions of interest in the AAL atlas employed may be too large for a fine-grained characterization of subtle anatomical variability. For example, the AAL "amygdala" ROI actually extendes to the piriform cortex, reason why we have chosen to refer to this as the amygdala-piriform complex. Similarly, the AAL "fusiform" ROI has more prominent involvement of the entorhinal and perirhinal regions. Thus, it will be critical for future studies following this approach to apply atlases with a focus on mesial temporal subfields[37]. Fourth, we recognize that we employed indirect measures of disconnection, instead of *de facto* disconnections obtained from individual diffusion and functional MRI. The advantage of the indirect approach lies in the larger number of individuals from a connectome template, yielding a realistic approximation of white matter anatomy and functional synchronicity [e72], but it does not take into account individual-specific changes related to chronic white matter disease [23]. Along the same lines, it is important to recognize that left- and right-sided TLE may have subtle differences in the pattern of aberrant structures and pathways; in addition, their surgical lesions may differ (e.g. right-sided lesions tend to be more extensive). Larger cohorts may allow enough power to explore independent lesion-symptom mapping for each side independently. Finally, seizures can relapse after more than one year post-surgery. We employed the one-year cut-off routinely used in outcome analysis of epilepsy surgery [e73], but this study did not assess longer-term outcomes, which should be of interest for future studies in this field.

Conclusions

We found that postoperative seizure freedom in TLE is associated with 1) surgical lesions that target the hippocampus as well as the amygdala-piriform cortex complex and entorhinal cortex; 2) disconnection of temporal, frontal, and limbic regions through loss of white matter tracts within the uncinate fasciculus, anterior commissure, and fornix; and 3) functional disconnection of the frontal (superior and middle frontal gyri, orbitofrontal region) and temporal (superior and middle pole) lobes may be associated with better postoperative seizure freedom. These findings shed light on the key components of epileptogenic networks in TLE and constitute a promising source of new evidence for future improvements in surgical interventions. Seizure freedom is an undoubtedly important outcome of epilepsy surgery. However, destructive or resective procedures need to be balanced with minimally invasive and highly targeted approaches to diminish morbidty, including visual field defects as well as language and memory impairments. Future that focus on the trade-off between these detrimental consequences of surgery and seizure outcomes will be critical for personalized medicine in epilepsy.

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Conflicts of interest

The authors report no conflicts of interest related to this manuscript.

Figures Legends

Figure 1. Lesion overlap across participants. For statistical analysis, left- and right-sided TLE were condensed into a single group by flipping their voxels into ipsilateral or contralateral. Lesions are represented here for both groups as ipsilateral arbitrarily on the left-side (radiological convention).

Figure 2. Summary results from **voxel-based** outcome-resection mapping. The results are corrected for multiple comparisons using a cluster-based threshold of $p < 0.05$. The ipsilateral (*Ipsi*) and contralateral (*Contra*) sides are identified on the first axial slice for orientation. For each modality, significant cluster details are in Table 1. Colorbars represent p-values at each voxel.

Figure 3. Summary results from **structural connectivity** outcome-lesion mapping. The results are corrected for multiple comparisons using a cluster-based threshold of $p < 0.05$. The ipsilateral (*Ipsi*) and contralateral (*Contra*) sides are identified on the first axial slice for orientation. For each modality, significant cluster details are in Table 1. Colorbars represent p-values at each voxel.

Figure 4. Summary results from **functional connectivity** outcome-lesion mapping. The results are corrected for multiple comparisons using a cluster-based threshold of $p < 0.05$. The ipsilateral (*Ipsi*) and contralateral (*Contra*) sides are identified on the first axial slice for orientation. For each modality, significant cluster details are in Table 1. Colorbars represent p-values at each voxel.

Figure 5. Overlay between statistical p-value maps from structural and functional connectivity outcome-lesion mapping ($p < 0.5$). The crosshairs indicate the locations with significant

structural or functional disconnection associated with outcomes. Note the correspondence between fiber projections (blue) and cortical disconnections (red).

eFigure 1. Sample maps for a representative patient. **Panel A** shows the surgical cavity delineated in yellow; this is a binary mask, where resected/ablated voxels are labeled as 1 and spared voxels are labeled as 0. **Panel B** shows the structural disconnectogram representing the tract density image from the fibers affected by the lesions is shown; this is a continuous map where each voxel indicates the number of affected fibers traversing through that voxel, as depicted by the colorbar. **Panel C** shows the functional connectivity map of voxels that are functionally connected to those within the surgical cavity; this is a continuous map where each voxel indicates the Z score strength of connectivity, also denoted in the colorbar.

eFigure 2. Association between pre-operative grey matter volume and size of the surgical cavity. The color bar represents p-values. Findings show that there is a tendency for larger resection/ablation when there is higher degree of atrophy particularly in the hippocampal body but not necessarily the surrounding structures. Hence, the present study sought to investigate lesions to which structures support seizure outcomes beyond hippocampal resection/ablation.

Tables

Table 1. Summary of demographic and clinical profile. Values represent mean (SD) unless otherwise specified.

	All *n* = 113	**Emory** *n* = 59	**Bonn** *n* = 44	**MUSC** *n* = 10
Age at onset	16.7 (11.9)	15.5 (11.5)	15.9 (11.6)	25.0 (13.4)
Age at surgery				
Gender (M : F)	52 : 61	24 : 35	21 : 23	7: 3
TLE side (L : R)	62 : 51	27 : 32	30 : 14	5 : 5
% resection	54.5%	18.6%	100%	70%
% Seizure Free	62.5%	60%	68%	60%

Table 2. The anatomical locations and peak stereotaxic coordinates related to each lesion-symptom model. All clusters for each modality are visually demonstrated in Figure 2.

	Cluster	***Size (voxels)***	***Peak XYZ***	***Peak Structure***	***Structures involved***
Voxel-based outcome resection mapping (Atlas: AAL)	1	11	-21.9 -3.1 -23.8	Amygdala	Hippocampus, Amygdala-Piriform complex, Parahippocampal gyrus (Entorhinal Cortex)
	2	12	-33 -14.2 -31.9	Fusiform*	Fusiform gyrus (entorhinal-perirhinal region)*
Structural connectivity outcome lesion mapping (Atlas: Natbrain)	1	19	-33.0 16.1 -31.2	Uncinate Fasciculus	Uncinate Fasciculus, Anterior Commissure, Fornix
Functional connectivity outcome lesion mapping (Atlas: AAL)	1	131	20.1 59.6 27.8	Middle Frontal Gyrus (contralateral)	Superior Frontal Gyrus (contralateral), Middle Frontal Gyrus (contralateral)
	2	35	-2.0 24.2 -27.5	Gyrus Rectus (ipsilateral)	Gyrus Rectus (ipsi and contralateral)
	3	456	-24.1 16.1 -34.2	Middle aspect of the Temporal Pole (ipsilateral)	Middle aspect of the Temporal Pole (ipsilateral), Superior aspect of the Temporal Pole (ipsilateral)
	4	22	-24.1 64.0 -7.6	Middle Orbitofrontal Cortex (ipsilateral)	Middle Orbitofrontal Cortex (ipsilateral), Middle Orbitofrontal Cortex (ipsilateral)

**The ROI "fusiform gyrus" from the AAL atlas encompasses the entorhinal and perirhinal regions[37]*

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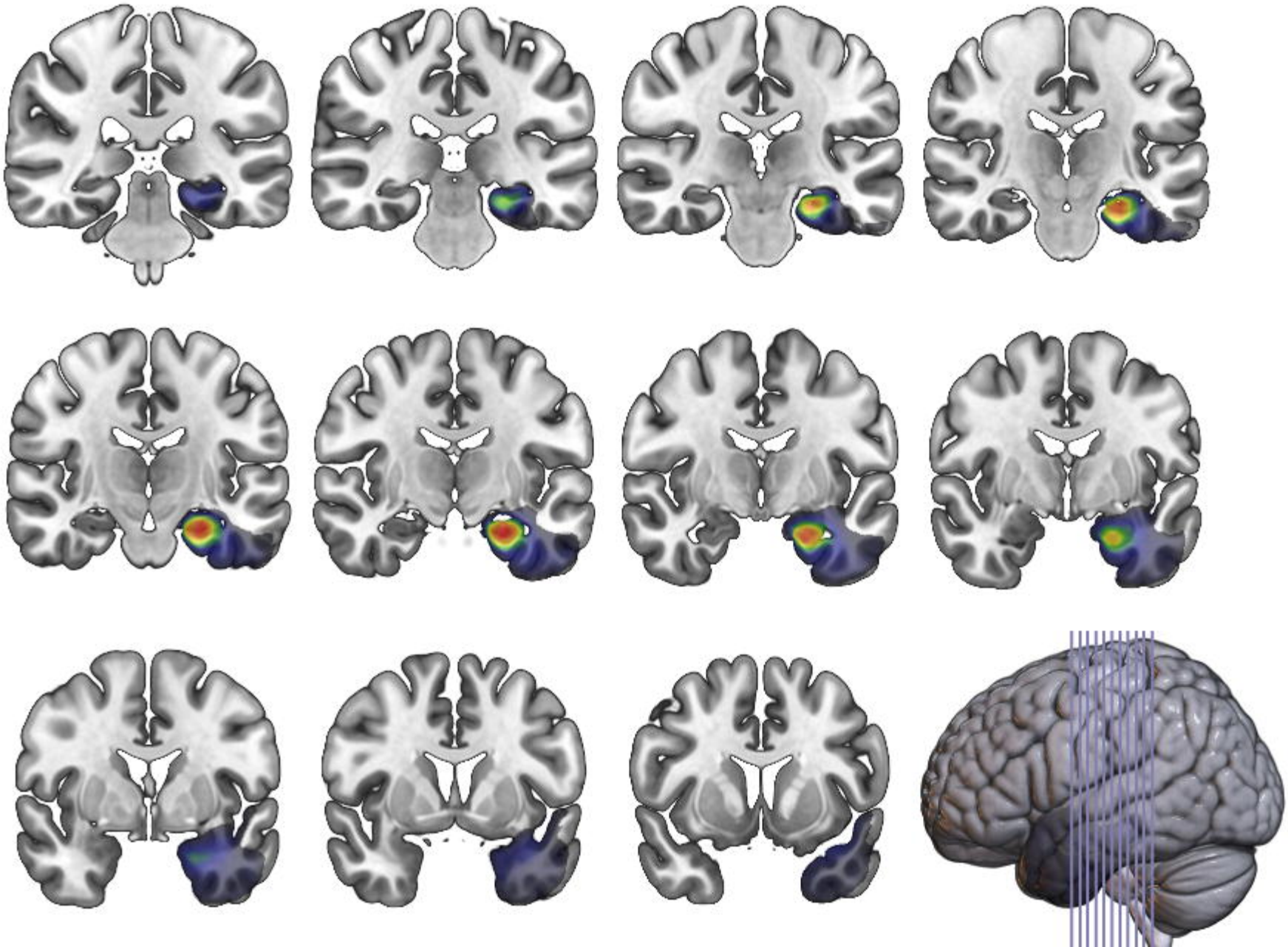
Please refer to Supplementary References for additional references e51-e73

Appendix 1

Name	Locations	Contribution
Ezequiel Gleichgerrcht, MD, PhD	Medical University of South Carolina, Charleston, SC	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Daniel L. Drane, PhD	Emory University, Atlanta, GA	Major role in the acquisition of data, drafted the manuscript for intellectual content
Simon S. Keller, PhD	University of Liverpool, Liverpool, UK	Major role in the acquisition of data, drafted the manuscript for intellectual content
Kathryn A. Davis, MD, MS	University of Pennsylvania, Philadelphia, PA	Revised the manuscript for intellectual content
Robert E. Gross, MD, PhD	Emory University, Atlanta, GA	Major role in the acquisition of data, drafted the manuscript for intellectual content
Jon T. Willie, MD, PhD	Washington University in St. Louis, St. Louis, MO	Revised the manuscript for intellectual content
Nigel P. Pedersen, MBBS	Emory University, Atlanta, GA	Revised the manuscript for intellectual content
Christophe de Bezenac, PhD	University of Liverpool, Liverpool, UK	Revised the manuscript for intellectual content
Jens Jensen, PhD	Medical University of South Carolina, Charleston, SC	Interpreted the data, revised the manuscript for intellectual content
Ruben Kuzniecky, MD	Hofstra University / Northwell, NY	Interpreted the data, revised the manuscript for intellectual content
Leonardo Bonilha, MD, PhD	Medical University of South Carolina, Charleston, SC	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content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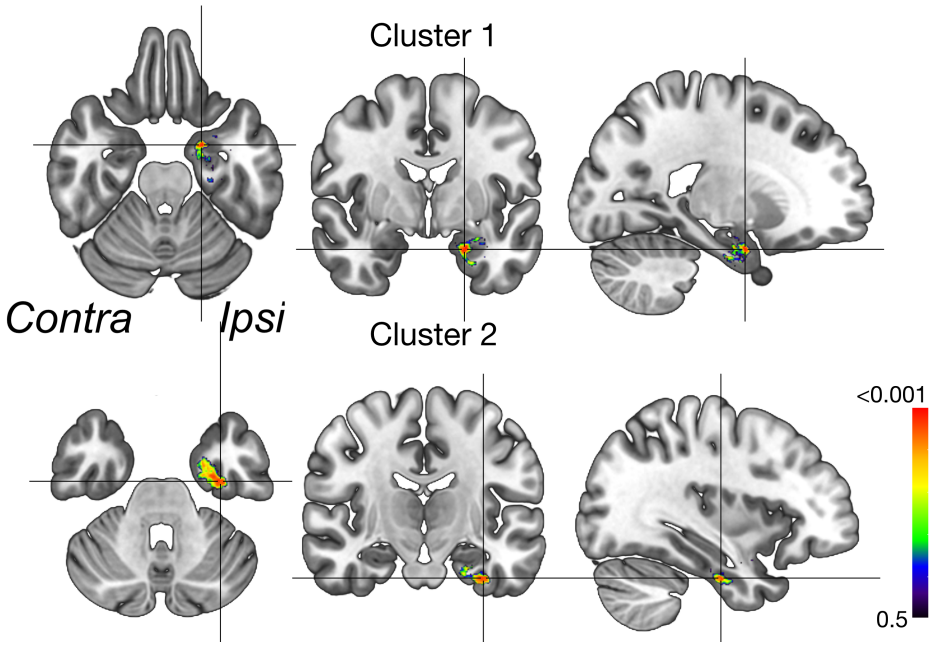
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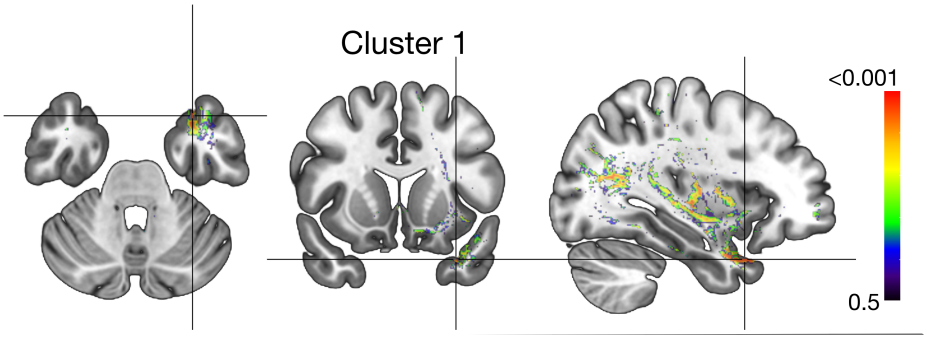
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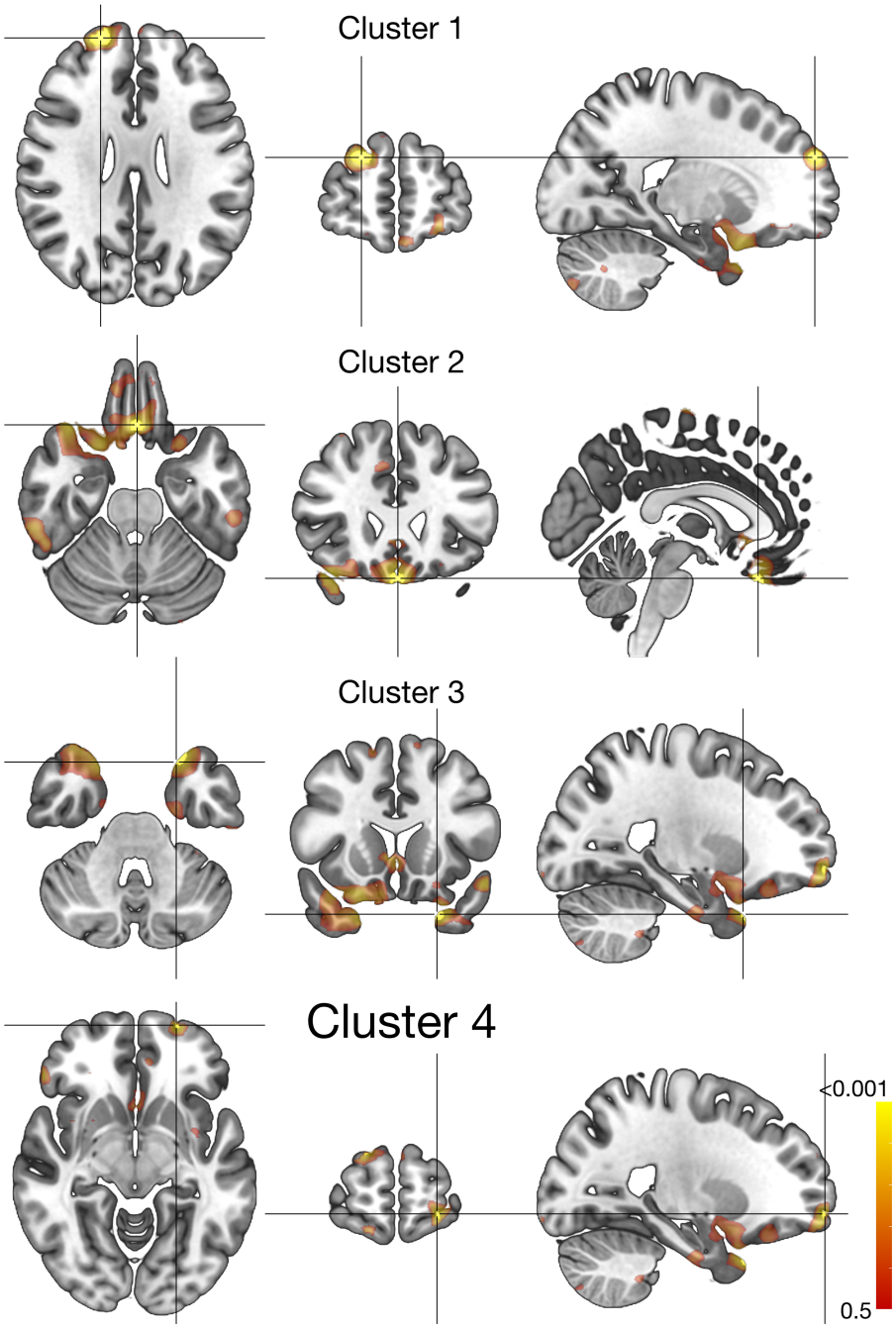
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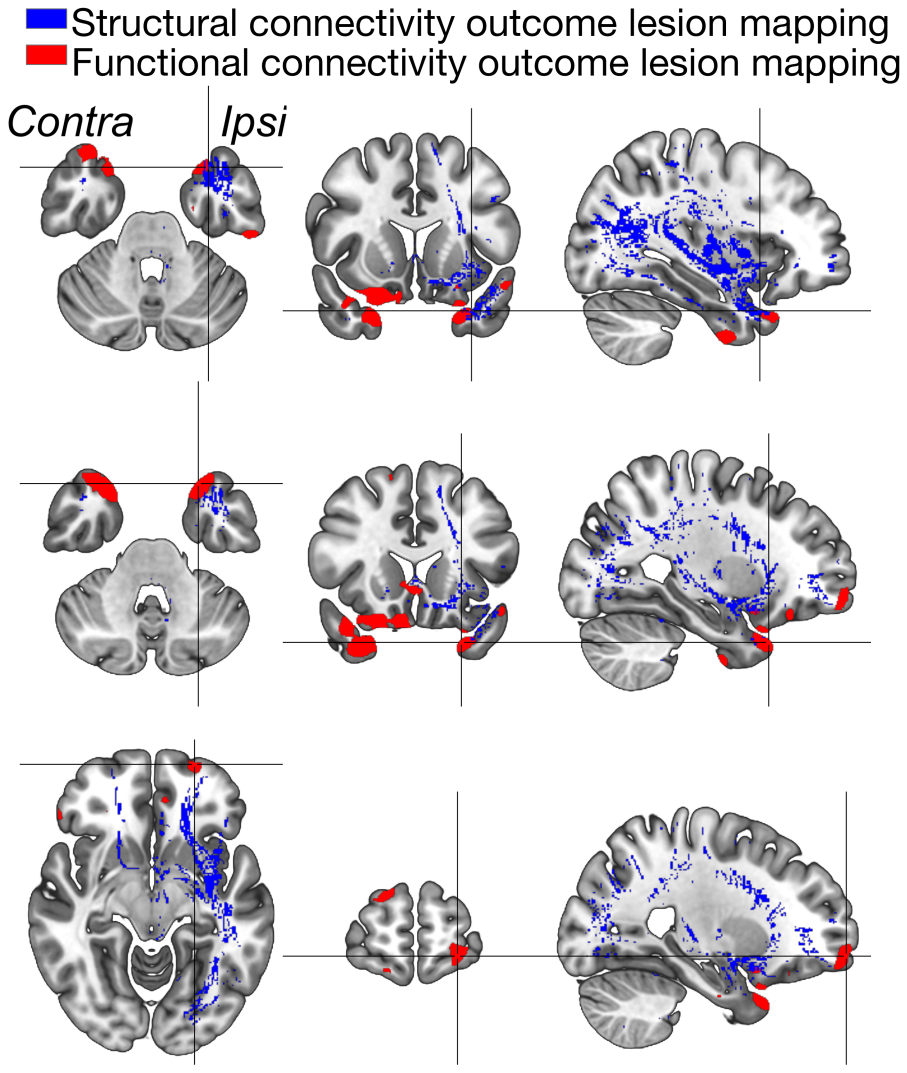
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