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Is Node Disconnection the Key for Improving LITT Outcome?

David King-Stephens, MD

Effects of Laser Interstitial Thermal Therapy for Mesial Temporal Lobe Epilepsy on the Structural Connectome and its Relationship to Seizure Freedom

Ko AL, Tong APS, Mossa-Basha M, et al. *Epilepsia*. 2021. doi:10.1111/epi.17059.

Objective: Laser interstitial thermal therapy (LITT) is a minimally invasive surgery for mesial temporal lobe epilepsy (mTLE), but the effects of individual patient anatomy and location of ablation volumes affect seizure outcomes. The purpose of this study is to see if features of individual patient structural connectomes predict surgical outcomes after LITT for mTLE. Methods: This is a retrospective analysis of seizure outcomes of LITT for mTLE in 24 patients. We use preoperative diffusion tensor imaging (DTI) to simulate changes in structural connectivity after laser ablation. A two-step machine-learning algorithm is applied to predict seizure outcomes from the change in connectomic features after surgery. Results: Although node-based network features such as clustering coefficient and betweenness centrality have some predictive value, changes in connection strength between mesial temporal regions predict seizure outcomes significantly better. Changes in connection strength between the entorhinal cortex (EC), and the insula, hippocampus, and amygdala, as well as between the temporal pole and hippocampus, predict Engel Class I outcomes with an accuracy of 88%. Analysis of the ablation location, as well as simulated, alternative ablations, reveals that a more medial, anterior, and inferior ablation volume is associated with a greater effect on these connections, and potentially on seizure outcomes. Significance: Our results indicate (1) that seizure outcomes can be retrospectively predicted with excellent accuracy using changes in structural connectivity and (2) that favorable connectomic changes are associated with an ablation volume involving relatively mesial, anterior, and inferior locations. These results may provide a framework whereby individual preoperative structural connectomes can be used to optimize ablation volumes and improve outcomes in LITT for mTLE.

Commentary

The surgical treatment of drug-resistant focal-onset seizures rely on the concept that localization-related epilepsy is a disorder of large neural networks and that interruption of these will result in control or abolishment of seizures. Anterior temporal lobectomy (ATL) with resection of the amygdala and hippocampus remains the gold-standard treatment of drug-resistant mesial temporal lobe epilepsy (mTLE). When performed on the dominant hemisphere, the risk of verbal memory decline is significant.[1] To reduce the risk of neuropsychological injury, targeted therapies such as laser interstitial thermal therapy (LITT) have emerged. LITT relies on a straight laser catheter to ablate a target. Due to curvature of the hippocampus and variations in temporal lobe anatomy, a compromise on ablation coverage will be required if a single trajectory is to be performed. When compared to ATL of the dominant hemisphere, LITT has equivalent seizure-freedom rates[2] but superior neurocognitive outcomes.[3] Ablation volume does correlate with seizure control[4] but depending on the trajectory, it can impact the risk of complications such as on visual function.[5]

Multimodal imaging studies demonstrate brain network reorganization in TLE, with structural changes associated with network reconfigurations that result in highly integrated nodes that contribute to ictal onset and propagation.[6] Abnormally high connectivity between nodes may facilitate seizure propagation,[7] and increased network connectedness is inversely related to seizure freedom after surgery.[8] Given the presence of atypical network hubs in epilepsy, can further analysis of brain network topology (i.e., the connectome) guide LITT trajectory planning to optimize efficacy?

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In the current study, Ko et al[9] utilize preoperative diffusion-weighted imaging (DWI) to characterize changes in network connectivity after LITT to determine if these predict seizure outcome. This is a single-center retrospective analysis of 26 patients who underwent LITT as their first surgical intervention for mTLE and had a least 1 year of follow-up. A preoperative structural connectome was constructed using 32-direction DWI acquisitions followed by a simulation of the effects of ablation volume on the postoperative connectome. Surgical effect on network measures (global efficiency, clustering coefficient, and connection strength between 2 nodes) was calculated as a percentage change from preoperative connectomes. Ablation included portions of the amygdala, hippocampus, parahippocampus, and entorhinal cortex, but percent ablation of these regions did not correlate with seizure outcome. In 16 patients, the ablation was performed on the dominant temporal lobe; 9 became seizure free. Median total ablation volume, duration of epilepsy, laterality of interictal discharges, or the presence of mesial temporal sclerosis did not predict outcome. In contrast, greater reduction in connection strength between the entorhinal cortex and the insula, hippocampus and amygdala predicted seizure freedom with a sensitivity of 91% and specificity of 87%, and this was mirrored by the direction of ablation in the antero-inferior axis. These findings suggest that changes in connectivity metrics can predict seizure outcome after LITT and describe a favorable ablation zone not only as an anatomic region but in terms of connectivity metrics than can be individualize.

Strengths of the study include the use of imaging techniques that can be feasibly obtained in routine practice and of straightforward machine-learning approaches. Weaknesses include the retrospective design, small sample size, and most importantly, the postoperative changes in connectivity were derived from a mask that was applied to the preoperative tractogram, rather than one acquired from postoperative MRI data, thereby making assumptions that might be inaccurate (as connections could have been simply displaced by the surgical cavity). Additionally, counting streamlines to measure connectivity strength is likely suboptimal and inaccurate since it can be influenced by length, curvature, degree of branching, and width of white matter bundles.

These results mirror the findings of a study using different imaging methodologies. Wu et al[10] report on a multicenter cohort of 234 patients who underwent LITT with a minimum follow-up of 1 year. In order to compare the specific location of the ablation across patients, pre- and postoperative scans for each subject underwent non-linear registration to a common reference space derived from 7-Tesla MRI. The extent of ablation of the amygdala and hippocampus was calculated for each subject in common atlas space. Once normalized, the manually segmented ablation cavity was superimposed over anatomical structures, allowing for calculation of the percentage of the structures ablated. Ablations that included more anterior, medial, and inferior temporal lobe structures (parahippocampal gyrus and rhinal cortices) were more likely to be associated with favorable outcomes. Additionally, radiographic evidence of hippocampal sclerosis was not associated with seizure outcome.

Two complementary studies support the importance of surgical resections of specific structures and connections throughout the temporal lobe on treatment outcome. Sinha et al[11] report on a group of 51 patients who underwent ATL with 1 year of follow-up, comparing a presurgical network and surgically spared network based on pre-resection structural, diffusion, and post-resection structural MRI data. The surgically spared network contained only the network edges whose streamlines did not pass through/into the resection cavity. Node abnormalities were computed by counting the number of abnormal links to each node. Patients who became seizure free had fewer abnormal nodes. Patients with poor outcome not only had higher number of abnormal nodes but their locations were more widespread in the surgically spared networks. Gleichgerrect et al[12] report on multicenter cohort of 113 patients who underwent ATL, and had at least 1 year of follow-up. Using structural and functional connectivity measures, derived from predicted network damage from the surgical cavity on a normative white matter connectogram and meta-analytical functional MRI databases, respectively, and controlling for the presence or absence of hippocampal atrophy, found that resection of the anterior hippocampus-amygdala-piriform cortex complex and entorhinal cortex and disconnection of the temporal and frontal regions were associated with better outcomes.

Moving forward, prospective studies employing multimodal techniques will be required to validate these findings and determine if these are generalizable. Important questions that need to be investigated include the nature of node abnormalities: Are they indicative of structural abnormalities induced by seizures? Do they serve as amplifiers of ictal activity? how they relate to other clinical features; their relationship to functional areas; and do these apply to extra-temporal epilepsies? The work of Ko et al[9] suggests that functional connectivity is as important as structural connectivity when planning the ablative treatment of drug-resistant mTLE. Improved algorithms, some based on an increased number of directions of DWI acquisitions, might lead to optimized tractography and connectivity analyses that improve the surgical treatment of drug-resistant epilepsies.

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References

1. Stroup E, Langfitt J, Berg M, McDermott M, Pilcher W, Comp P. Predicting verbal memory decline following anterior temporal lobectomy. *Neurology*. 2003;60(8):1266-1273.
2. Kerezoudis P, Parisi V, Richard Marsh W, et al. Surgical outcomes of laser interstitial thermal therapy for temporal lobe epilepsy: systematic review and meta-analysis. *World Neurosurg*. 2020;143: 527-536. e3.
3. Drane DL, Loring DW, Voets NL, et al. Better object recognition and naming outcome with MRI-guided stereotactic laser

amygdalohippocampectomy for temporal lobe epilepsy. *Epilepsia*. 2015;56(1):101-113.
4. Jermakowicz WJ, Kanner AM, Sur S, et al. Laser thermal ablation for mesiotemporal epilepsy: analysis of ablation volumes and trajectories. *Epilepsia*. 2017;58(5):801-810.
5. Donos C, Rollo P, Tombridge K, Johnson JA, Tandon N. Visual field deficits following laser ablation of the hippocampus. *Neurology*. 2020;94(12):e1303-e1313.
6. Khambhati AN, Davis KA, Oommen BS, et al. Dynamic network drivers of seizure generation, propagation and termination in human neocortical epilepsy. *PLoS computational biology*. 2015; 1211(12):e1004608.
7. Gleichgerrcht E, Keller SS, Drane DL, et al. Temporal lobe epilepsy surgical outcomes can be inferred based on structural connectome hubs: a machine learning study. *Ann Neurol*. 2020; 88(5):970-8337.
8. Bernhardt BC, Chen Z, He Y, Evans AC, Bernasconi N. Graph-theoretical analysis reveals disrupted small-world organization of cortical thickness correlation networks in temporal lobe epilepsy. *Cerebral Cortex*. 2011;21(9):2147-2157.
9. Ko AL, Tong APS, Mossa-Basha M, et al. Effects of laser interstitial thermal therapy for mesial temporal lobe epilepsy on the structural connectome and its relationship to seizure freedom. *Epilepsia*. 2021;63(1):176-189. doi:10.1111/epi.17059.
10. Wu C, Jermakowicz WJ, Chakravorti S, et al. Effects of surgical targeting in laser interstitial thermal therapy for mesial temporal lobe epilepsy: a multicenter study of 234 patients. *Epilepsia*. 2019; 60(6):1171-1183.
11. Sinha N, Wang Y, Moreira da Silva N, et al. Structural brain network abnormalities and the probability of seizure recurrence after epilepsy surgery. *Neurology*. 2021;96: e758-e771.
12. Gleichgerrect E, Drane DL, Keller SS, et al. Association between anatomical location of surgically induced lesions and postoperative seizure outcome in temporal lobe epilepsy. *Neurology*. 2022; 98:e141-e151.