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Imaging and SEEG Functional Networks to Guide Epilepsy Surgery

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Introduction

Epilepsy is a common neurological disorder affecting approximately 1% of the global population.[1] Approximately 40% of patients don't respond to medical treatment alone. Patients with drug resistant epilepsy (DRE) can be treated surgically through resection, ablation, or neuromodulation and between 65–70% of patients can achieve seizure freedom.[2,3] Surgical treatment of epilepsy is predicated on the successful localization of the area thought to be generating seizures, the seizure onset zone (SOZ).[4,5] However, localization is a complex process that can differ across institutions and does not always result in a clear surgical plan.[6] In fact, nearly 50% of those evaluated for epilepsy surgery

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are not candidates for surgery and the principle reason is the lack of a hypothesis for SOZ localization (Figure 1).[7] Despite this difference, surgical cases have been stable. Therefore, it has been proposed that the complexity of epilepsy being evaluated for surgery has increased in recent years.[7]

Shifts in patient complexity have occurred before. From the early to late 20th century, the surgical treatment of epilepsy vastly expanded as physicians were able to better localize the SOZ. Originally, epilepsy surgery was limited to only Jacksonian focal epilepsy syndromes. The clinical features combined with intraoperative stimulation to localize the "spasming center" were the only localizing methodologies available.[8–10] The addition of electroencephalography (EEG) along with more advanced intraoperative stimulation spurred the expansion of epilepsy surgery to temporal lobectomies.[11] Localization was improved further by intracranial EEG (iEEG) and neuroimaging such as magnetic resonance imaging (MRI).[12–14] While challenging, the prior paradigm shift led to one of the most effective operations in the field of neurosurgery.[9,10] Just as historical approaches to epilepsy surgery shifted their paradigm from the "spasming center" to the SOZ, the modern epilepsy surgery paradigm has shifted from the SOZ to the seizure network.

The "network revolution" in epilepsy has shifted the paradigm of epilepsy surgery towards localization strategies that quantify the network and treatment plans that disrupt the network (Figure 2A).[15–18] The seizure network can be disrupted by resection, ablation, neuromodulation, or a combination of modalities (Figure 2B–D). However, the network must first be discovered, quantified, then treated. Representing the brain as a network relies on examining the connectivity, or relation of signals between areas of the brain. Structural connectivity (SC) represents white matter connections between regions. Functional connectivity (FC) represents neural communication between areas in the brain, with high FC representing a strong connection and low FC representing a weak connection. These measures are often derived from diffusion weighted imaging (DWI), functional magnetic resonance imaging (fMRI), and iEEG. Discovery of the seizure network may be completed noninvasively through neuroimaging techniques such as DWI and fMRI. DWI and fMRI have shown promise in the lateralization of the epileptic network as well as the prediction of seizure freedom after surgery. Localization of the network can be completed with iEEG. The addition of connectivity-based studies may be a missing link in identifying and treating the seizure network in patients previously not considered epilepsy surgery candidates.

Functional Magnetic Resonance Imaging (fMRI)

FMRI is a non-invasive imaging technique that is being increasingly utilized in the pre-surgical workup for epilepsy for lateralization and localization of language and memory.[19,20] However, network studies with fMRI may benefit epilepsy surgery through lateralization of the seizure network and prediction of seizure freedom.

Lateralization

Lateralization of the epileptic network is one of the key predictors of seizure freedom.[5,21,22] While conventional methods can lateralize seizure networks in most patients, more complex patients are difficult to lateralize and may benefit from fMRI augmented lateralization.[23]

FC abnormalities in mesial temporal networks have been relatively successful in lateralizing epilepsy.[24] However, the exact connections vary between studies. Narasimhan et al used FC between mesial temporal structures and the default mode network to lateralize mesial temporal lobe epilepsy (mTLE) patients.[25] Morgan et al sought to improve lateralization by splitting their cohort of temporal lobe epilepsy (TLE) patients into those who seizure free after surgery vs not seizure free after surgery. The authors found that FC from the hippocampi to the ventral lateral nucleus of the right thalamus was the best differentiator for left TLE vs right TLE.[26]

Given these slight disparities in lateralization hypotheses, machine learning methods have been utilized to improve epilepsy lateralization, but results have been mixed. A machine learning study by Gholipour et al used fMRI data from a multicenter cohort to lateralize TLE but achieved an accuracy below that of FC methods alone.[27] Deep learning models may improve this accuracy, but they must remain interpretable. Only recently have studies began using these methods with Luckett et al publishing innovative work utilizing a convolutional neural network.[28] A unique strength of this study was the interrogation of what anatomical areas the model used to classify left and right TLE, overcoming the “black box” nature of deep learning (Figure 3). Like prior FC studies, the authors found that resting state networks including the default mode network, medial temporal network, and dorsal attention network were all the strongest predictors of left vs right TLE (Figure 3). The overall accuracy was substantially greater than other methods, but the generalizability is unknown.

Outcome Prediction

Prediction of patients who will respond well to epilepsy surgery may aid in surgical decision making and provide insights into why some patients have less favorable outcomes. Although clinical variables have been used previously, FC may allow for a more accurate outcome prediction model. He et al demonstrated that hubness of the thalamus was increased in patients who weren’t seizure free after surgery, perhaps representing more widespread epilepsy.[29] Guo et al used dynamic FC and found that the states that seizure free and not seizure free patients spent most of their time in were different.[30] Additionally, Negishi et al found that patients who were seizure free had connectivity abnormalities localized to one lobe than those who were not seizure free, which may represent a more localized epilepsy.[31]

DWI

DWI is a method by which white matter tracts can be estimated. Tractography is typically performed in the pre-operative assessment for epilepsy surgery and has historically been used for stratifying risk.[32] The risk of a visual field deficit, memory deficits, and naming deficits can all be predicted though localization of well-known white matter tracts.[33–38] Prior work has demonstrated that structural connectivity is different in patients with epilepsy vs healthy controls and represents an opportunity to lateralize the seizure network and predict outcome in epilepsy.[39,40]

Lateralization

Lateralization of the seizure network with DWI is most helpful in ambiguous, non-lesional cases. It is possible to use common white matter tracts for this purpose, but these approaches are most accurate with lesional cases of TLE.[41] The addition of machine learning and deep learning techniques on diffusion measures has improved lateralization.[42] The combination of the structural connectome and machine learning was shown to lateralize TLE accurately, agnostic to lesional and non-lesional cases.[43] Furthermore, the connections used by the network to lateralize were consistent with other studies of left vs right TLE, increasing interpretability of the network.

Outcome Prediction

It can be useful for surgical decision making to know the chances of achieving seizure freedom after epilepsy surgery. Prediction of seizure freedom can aid in the decision process to proceed with epilepsy surgery, modify the surgical plan, or avoid surgery for those that are not candidates. Several scoring systems have been proposed based on clinical variables, however, a connectome-based approach may achieve more accurate outcome predictions.[44,45] Structural connectivity has been particularly accurate in the prediction of seizure freedom after surgery. Increased ipsilateral structural connectivity abnormalities, especially those related to the ipsilateral mesial structures, are most often used.[46–48] One study examined seizure recurrence and found that more widespread SC abnormalities were associated with seizure recurrence (Figure 4).[47] However, these studies were limited to anterior temporal lobectomies and were limited to TLE.

Machine learning approaches have also been used for seizure outcome prediction.[49,50] However, it can be difficult to interpret what machine learning approaches use to stratify patients. One such example of this is a study by Johnson et al where the authors reduced the features down to the connections that best stratified patients who were and were not seizure free.[50]

Intracranial EEG

Neurostimulation

One of the first techniques for identifying the SOZ for resection in epilepsy was through intraoperative stimulation.[10] Stimulation has also been employed for localization of eloquent cortex, both intraoperatively and pre-operatively.[51,52] In the early 21st century, single pulse electrical stimulation (SPES) has been increasingly used after implantation of iEEG for the identification of epileptogenic tissue.[53] A prospective study by Valentin et al demonstrated the effectiveness of SPES to identify epileptogenic tissue. They reported that when abnormal responses (delays and repetitive spiking) were present in the resected area, 96% of patients achieved an Engel I or II favorable seizure outcome.[54,55] The results of this study were promising for patients who had abnormal responses to SPES, however, nearly 40% of patients had no abnormal responses. Can we make use of this technique in more patients using a network-based approach?

Network stimulation studies with SPES allow for directional information to be inferred, as a stimulus is delivered and responses are computed from all other contacts.[56,57] Two major thoughts have predominated in this field: (1) SOZs influence the entire network more so than other regions and (2) SOZs are more highly connected to itself.

The idea of SOZs influencing the network more so than other regions has been proposed and studied by several in the field, with SPES studies providing evidence.[58,59] Furthermore, these findings become even stronger when only contacts that were labeled as an SOZ and resected in patients with an Engel I outcome are analyzed.[60] In addition to influencing the network, SOZs have been shown to demonstrate increased within SOZ connections.[60,61] The finding of “hypercoupling” of SOZs may represent the seizure network and is most present in patients who were seizure free after surgery.[62]

Although the connectivity metrics used by prior studies have performed relatively well, many were originally developed for use in iEEG grids. This allowed for the assumption of directionality of neurons. This can represent a limitation as more centers are using stereotactic EEG (SEEG) which have varying directionality of pyramidal neurons. In order to overcome this limitation, one study used a deep learning model to analyze SPES responses, resulting in improvements in the accuracy of SOZ localization.[43]

Resting state networks

While ictal data acquired from iEEG is the gold standard for localization of the seizure network, interictal data has the potential to improve localization, especially in cases in which ictal localization fails. Interictal network approaches to iEEG have been utilized since the early 2000s. Initially, several studies reported that SOZs had increased connectivity to other SOZs.[63–68] With the addition of directional connectivity measures, Narasimhan et al noted that SOZs had higher inward connectivity from all other regions in the brain in 2020.[69] This finding was also observed by Jiang et al.[70] More recent studies have noted that in addition to the increase in inward connectivity, there is a decreased outward connectivity from seizure networks, leading to the idea that seizure networks are suppressed at baseline.[71,72] One such study proposed the Interictal Suppression Hypothesis (ISH), which postulated that SOZs had higher inward connectivity and lower outward connectivity during the resting state, suggesting that SOZs are suppressed at rest to prevent seizures (Figure 5).[72] Other group have described a similar “Sources and Sinks” phenomenon, suggesting that inward inhibition of the SOZ may aid presurgical localization.[71] While these network-based approaches appear valuable, they have yet to be prospectively evaluated.

Multimodal

The combination of structural and functional connectivity has been shown to improve the accuracy of outcome prediction.[72–74] One such approach is to combine SC and FC to develop a connectivity profile of seizure free patients. Such a fingerprint can then be compared to a patient's connectome to predict seizure freedom with an accuracy of 100% in one study (Figure 6).[73,74]

Others have had success expanding the combination of structural and functional connectivity to combine iEEG and DWI. Due to the difference in sampling between iEEG and neuroimaging methods, this can be a technical challenge. To overcome this, Johnson et al developed an algorithm for subsampling whole-brain tractography with iEEG near-field dynamic localization (SWiNDL), thus allowing for the computation of structural connectivity in the same areas sampled by iEEG.[72] By combining the Interictal Suppression Hypothesis findings of increased inward FC and decreased outward FC along with SC, the authors found that they were able to better differentiate SOZs, PZs, and NIZs (Figure 7).

Discussion

Despite an increase in surgical evaluations, there has not been an increase in surgical treatments.[7] The reason most cited for patients not being surgical candidates is lack of a localization hypothesis. Why are we increasingly unable to understand the seizure network in patients when we have access to more technology than before?[4,6] Some suggest increasingly complex patients are being evaluated for epilepsy surgery.[7] Roadblocks such as these have been present in epilepsy surgery before and they were overcame with a paradigm shift, moving from "the spasming point" to the SOZ that if removed would result in seizure freedom. Now, the paradigm has shifted from a SOZ to a seizure network that can be treated with resection, ablation, neuromodulation, or a combination.[5,15,75–77]

There are limitations to network evaluations of epilepsy, and it is paramount to remember that network studies are a tool to augment clinical decision making. DWI and fMRI network studies are useful for lateralization and outcome prediction, but accurate localization of the seizure network with MRI connectivity alone has been more challenging. Network studies with iEEG have demonstrated promise in localizing and identifying the seizure network. However, a strong hypothesis must be developed due to the sparse sampling intrinsic to iEEG. A further limitation is the variability of processing methods between groups, creating challenges in generalizability. Thus, even with published methods and similar data acquisition between centers, connectomics can be difficult to implement. A further challenge is the paucity of prospective studies evaluating network measures for epilepsy surgery. However, the few studies published changed decision making in 58% of cases and increased epilepsy surgery candidacy by 26%.[78]

Currently the largest gap in epilepsy surgery is the lack of translation from the lab to the clinic. Despite the need for new ways to treat more complex epilepsy patients, the promising results from network studies, and several proposed implementation paths such as the one depicted in Figure 8, few have utilized network approaches to augment presurgical evaluations.[77] Therefore, the next steps in this process require prospective evaluation of localization methodologies along with academic-commercial partnerships to bring the research from theoretical to practical. One could envision a network evaluation software package that is simple to use, repeatable, and clinically useful. Such an approach may allow for localization of a patient's seizure network and identification of key areas for multimodal treatment.

Summary

The paradigm of epilepsy surgery has shifted to that of a network disorder.[15–18,75–77] This shift in the paradigm of epilepsy surgery may allow for the localization of seizure networks that were previously unable to be localized and the treatment of epilepsies which were previously thought not to be surgical candidates. Connectivity can be evaluated with fMRI, DWI, and iEEG. FMRI and DWI connectivity studies have demonstrated the most success in lateralization of the seizure network and outcome prediction, whereas iEEG connectivity patterns have shown value in localizing the seizure network. Multimodal connectivity analyses, such as those combining structural and functional connectivity, have demonstrated the most success. However, translating connectomics from the lab to the clinic has been challenging. There is a need for improvement in localization and treatment of epilepsy. The field has taken a half measure in discussion and research of these methods, but there is a need for action in the form of prospective evaluations of connectomics and partnerships between industry and academia to bring connectomics to all centers.

Clinical Care Points

- Epilepsy should be conceptualized as a network disorder with the goal of treatment being to disrupt the seizure network.
- Connectomics can aid in localizing and quantifying the seizure network and these measures can be computed using existing data from the presurgical evaluation pipeline.

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Key Points:

- Despite improvements in technology, many patients evaluated for epilepsy surgery are not deemed to be candidates, often due to an incomplete hypothesis.
- Connectomics can be implemented into epilepsy surgery evaluations.
- Connectomics may help expand surgical options for patients who were previously not candidates.
- Prospective evaluations of connectomics methods and partnerships between academia and industry are necessary to bring connectomics to the clinic.

Synopsis:

Epilepsy surgery is a potentially curative treatment for drug resistant epilepsy that has remained underutilized both due to inadequate referrals and incomplete localization hypotheses. The complexity of patients evaluated for epilepsy surgery has increased, thus new approaches are necessary to treat these patients. The paradigm of epilepsy surgery has evolved to match this challenge, now considering the entire seizure network with the goal of disrupting it through resection, ablation, neuromodulation, or a combination. The network paradigm has the potential to aid in identification of the seizure network as well as treatment selection.

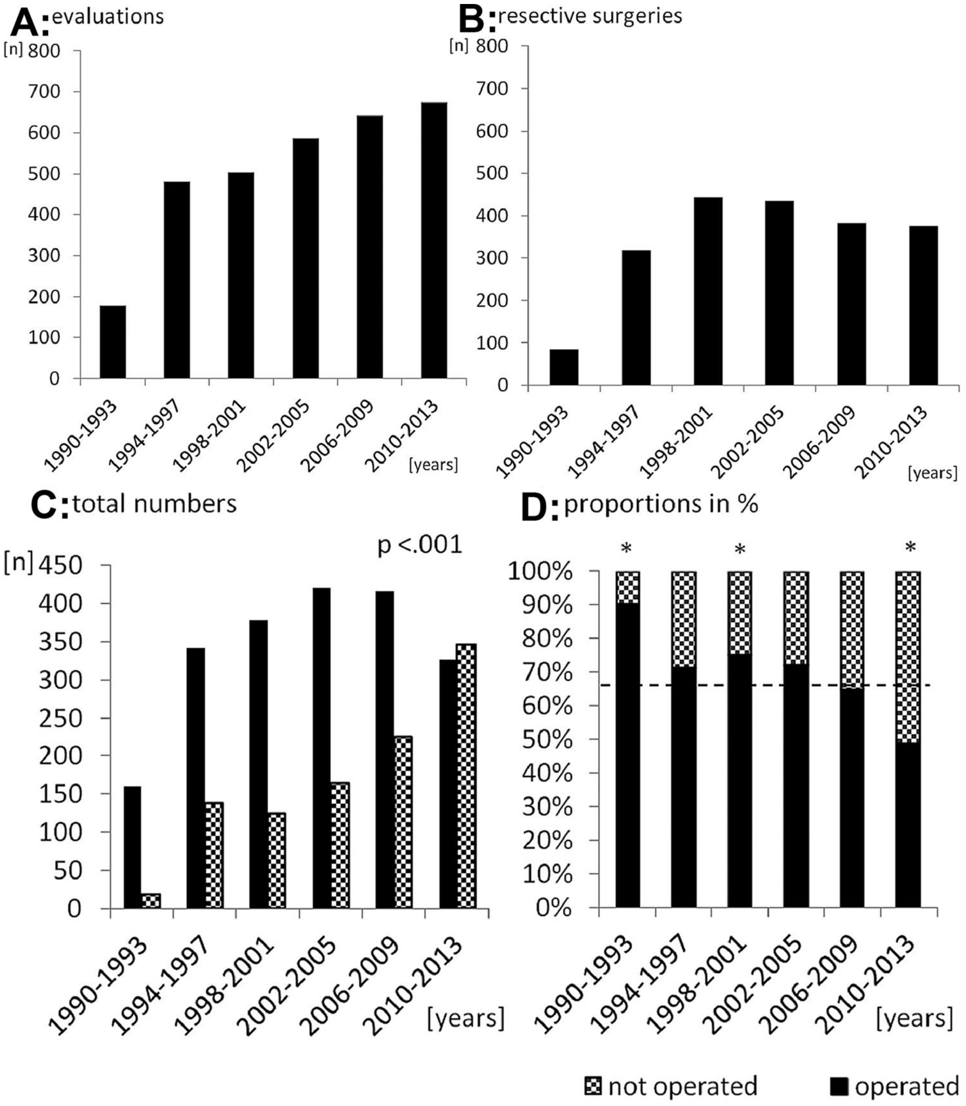

Figure 1: Epilepsy surgery evaluations are increasing, but resection trends are stable, and the most cited reason is the lack of a hypothesis.

Panel A shows the number of presurgical evaluations across different timepoints. Panel B shows the number of resective surgeries during the same timepoints. Panel C shows the percentage of rejected cases by patient/parent or neurologist. Panel D shows the breakdown of reason for rejection, with the most common being risks and no hypothesis. Adapted from Cloppenborg et al[7]; with permission.

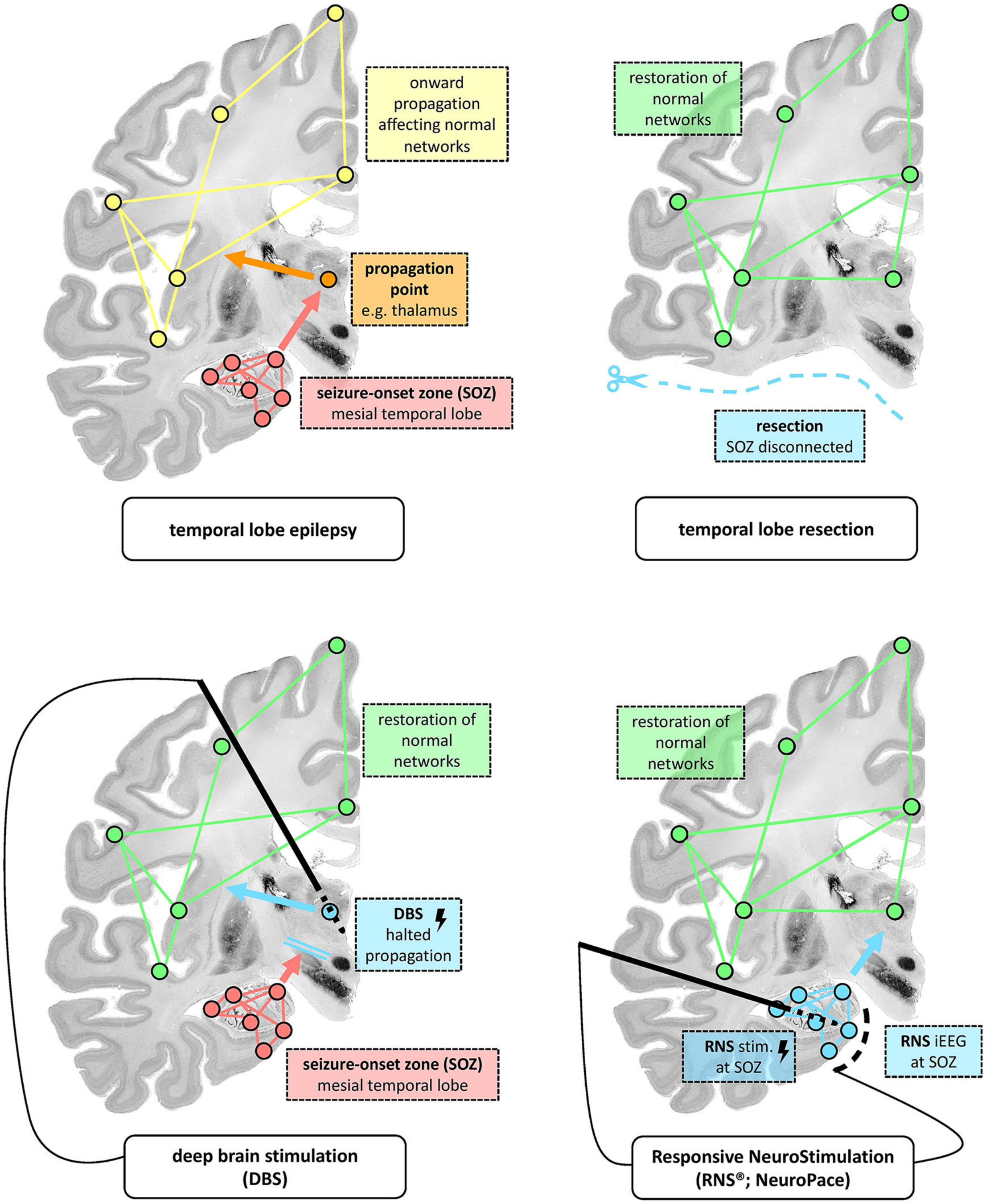

Figure 2: Conceptual depiction of how various treatment modalities may disrupt the seizure network in epilepsy.

Panel A depicts normal networks, propagation networks, and the seizure network. Panel B demonstrates how resection is thought to disrupt the seizure network. Panel C demonstrates how DBS is thought to disrupt the seizure network. Panel D demonstrates how RNS is through to disrupt the seizure network. Adapted from Piper et al[15]; with permission.

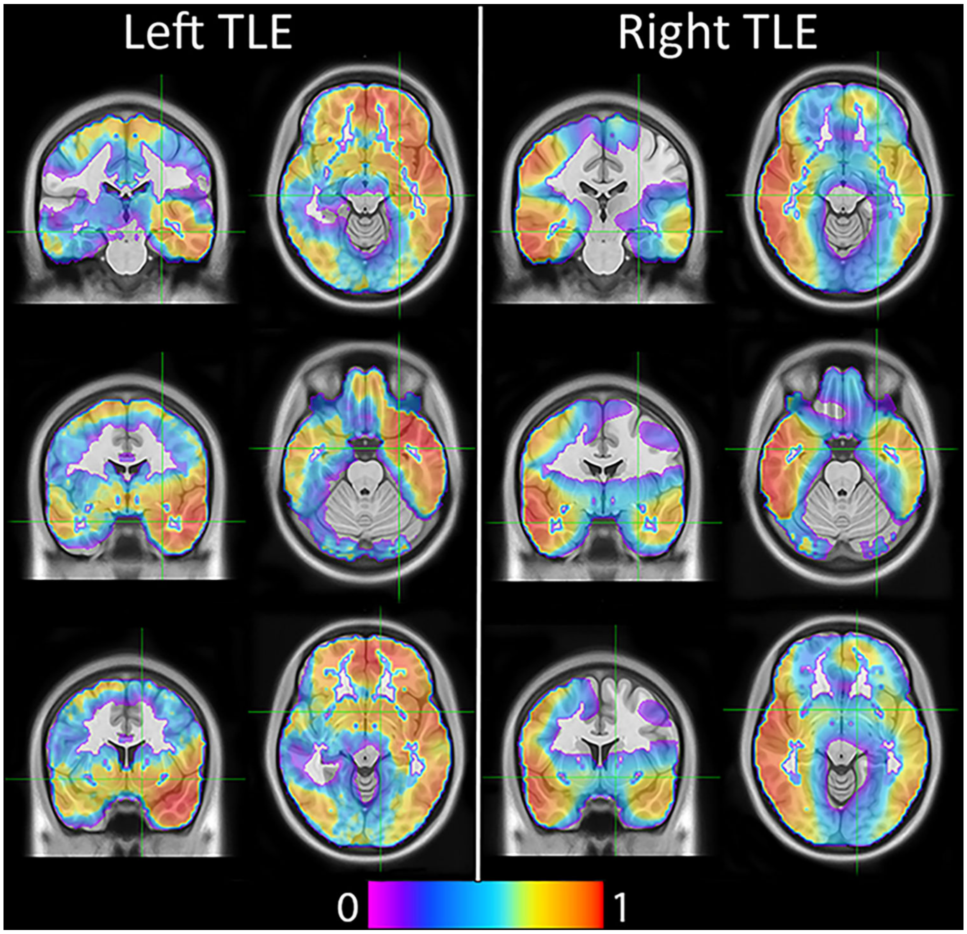

Figure 3: Deep learning approaches to lateralize TLE can be used both as tools for epilepsy surgery and hypothesis generation.

The displayed heatmap represents the spatial location of features used in a deep learning model. As can be seen, the right hemisphere is more important for classification of right TLE, and the left hemisphere is more important for classification of left TLE. From Luckett et al[28]; with permission

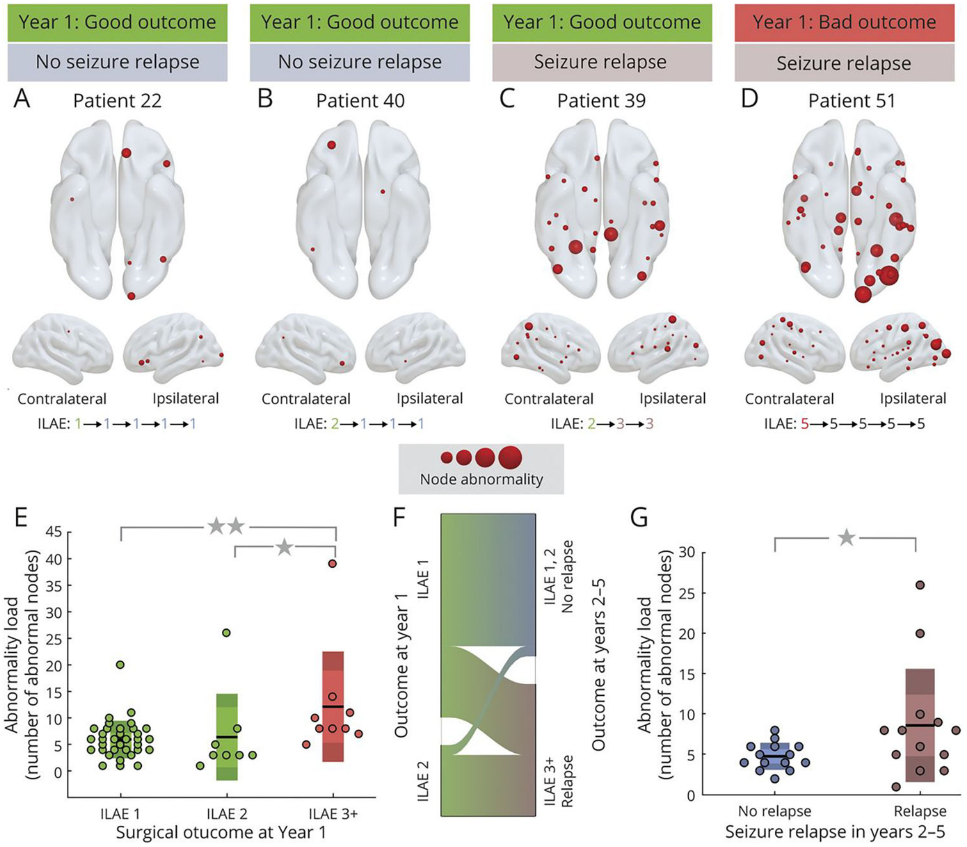

Figure 4: More widespread structural abnormalities were present in patients with a poor outcome after epilepsy surgery.

An example of these widespread abnormalities can be seen in panel D. Examples of more localized abnormalities can be seen in panels A and B. From Sinha et al[47]; with permission.

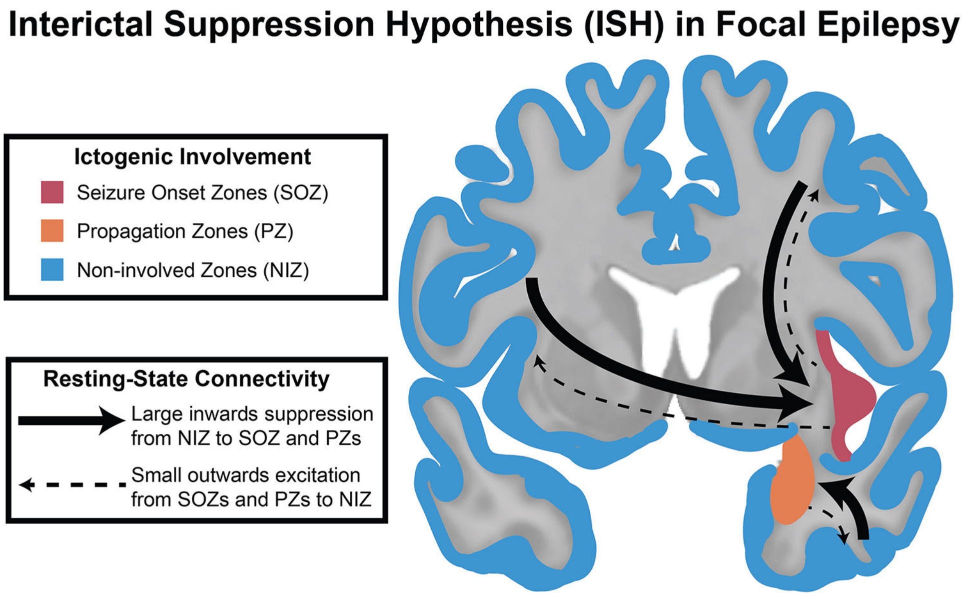

Figure 5: The Interictal Suppression Hypothesis (ISH) is a novel conceptualization that may localize the seizure network.

The ISH proposes that at baseline, the seizure network is suppressed by regions not involved in the seizure network. The non-involved zones can be seen in blue, the propagation zones can be seen in orange, and the seizure onset zones can be seen in red. From Johnson et al[72]; with permission.

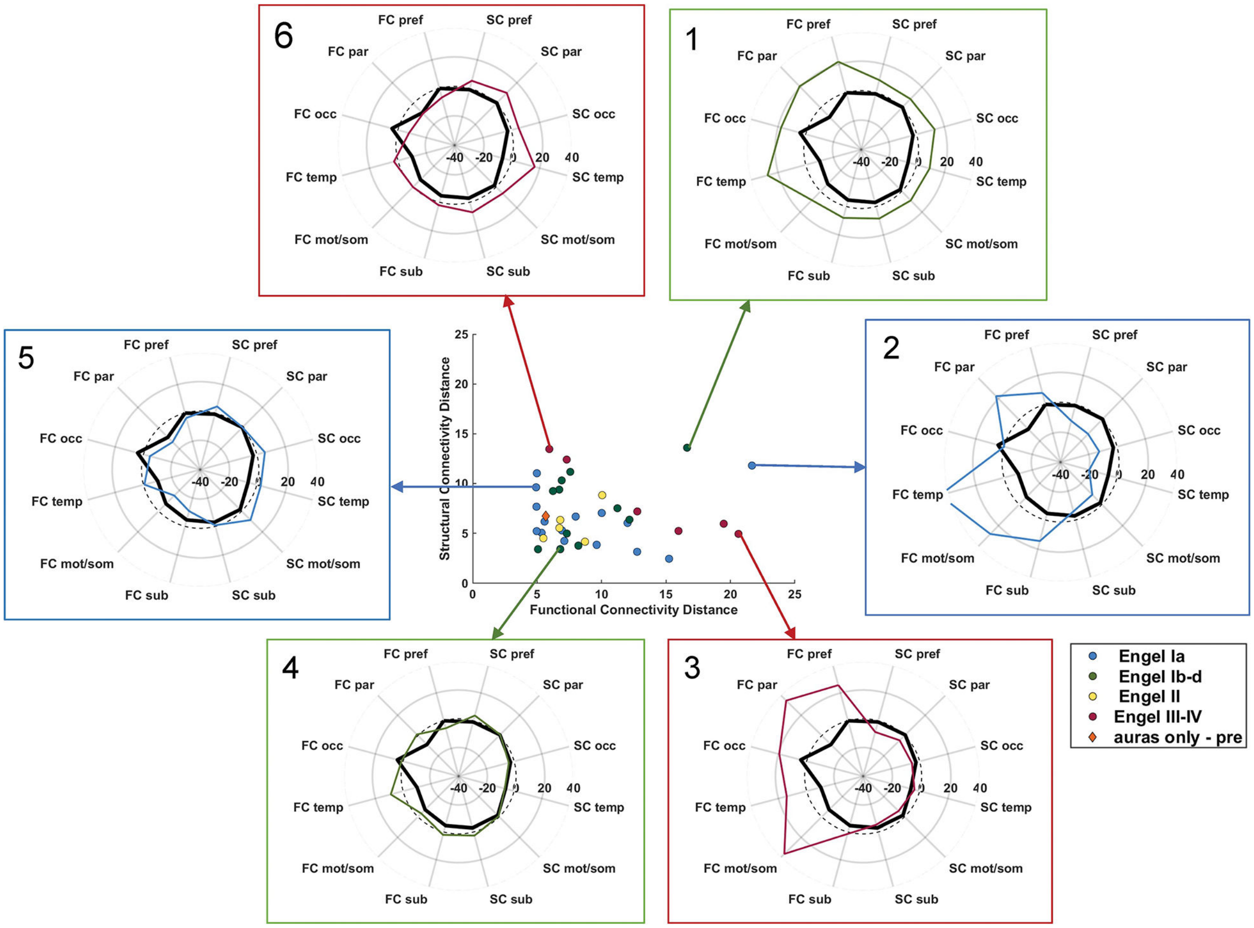

Figure 6: Structural and functional connectivity profiles can be used to accurately predict outcomes from epilepsy surgery.

Both functional and structural connectivity were used to develop a “network fingerprint” of patients who were seizure free. Connectivity profiles of 6 example patients with their corresponding outcome data are depicted. Adapted from Morgan et al[74]; with permission. FC = functional connectome distance; SC = structural connectome distance; pref = prefrontal lobe; par = parietal lobe; occ = occipital lobe; temp = temporal lobe; mot/som = motor and sensory/motor lobe; sub = subcortical structures (all ipsilateral to seizure focus); dashed line = zero denoting age-matched control.

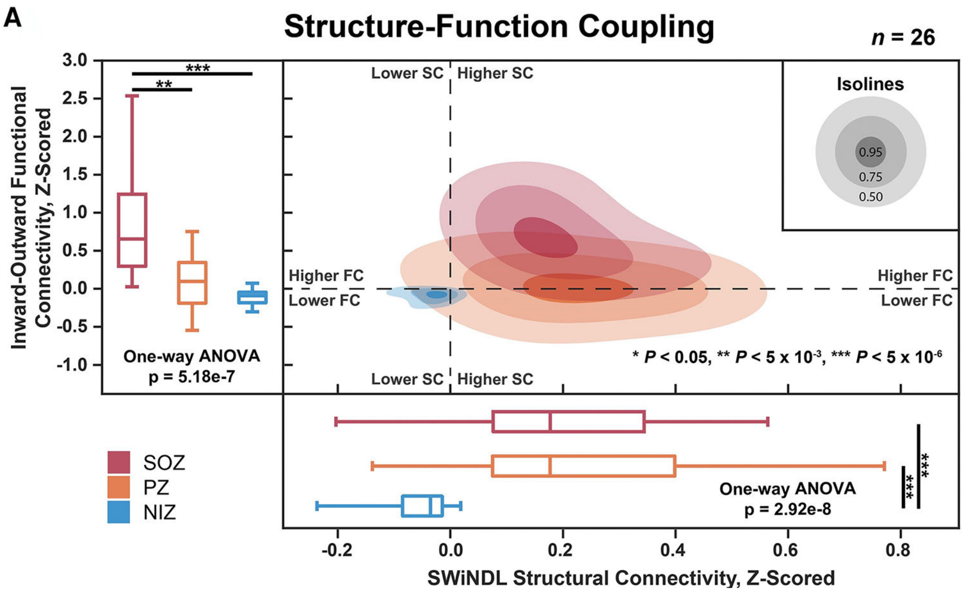

Figure 7: The combination of the Interictal Suppression Hypothesis functional connectivity and structural connectivity can more accurately differentiate the seizure network than functional or structural connectivity alone.

SOZs are depicted in red, PZs are depicted in orange, and NIZs are depicted in blue. Structural connectivity is on the x-axis and inward-outward connectivity is on the y-axis. Adapted from Johnson et al[72]; with permission.

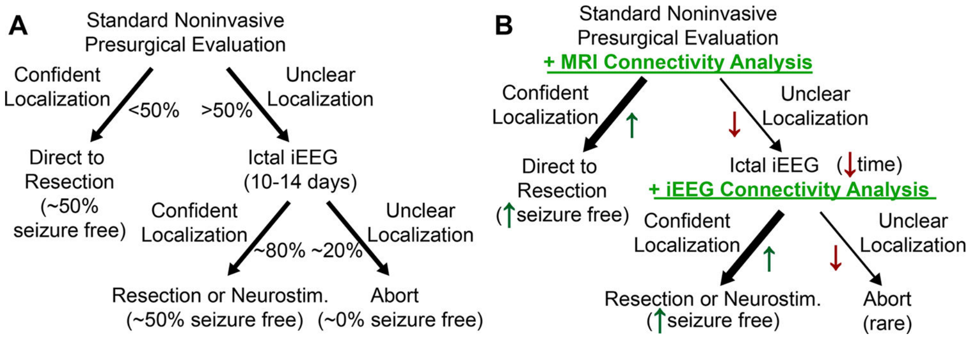

Figure 8: How the addition of network studies could impact the presurgical evaluation for epilepsy surgery.

The typical presurgical evaluation is depicted in panel A. The proposed network augmented evaluation is depicted in panel B. From Johnson et al[77]; with permission.