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Connectome the Dots for Presurgical Predictions

Kyle P. Lillis, PhD[1]

Presurgical Temporal Lobe Epilepsy Connectome Fingerprint for Seizure Outcome Prediction

Morgan VL, Sainburg LE, Johnson GW, Janson A, Levine KK, Rogers BP, Chang C, Englot DJ. *Brain Comm*. 2022;4(3):fcac128. doi:10.1093/braincomms/fcac128

Temporal lobe epilepsy presents a unique situation where confident clinical localization of the seizure focus does not always result in a seizure-free or favourable outcome after mesial temporal surgery. In this work, magnetic resonance imaging derived functional and structural whole-brain connectivity was used to compute a network fingerprint that captures the connectivity profile characteristics that are common across a group of nine of these patients with seizure-free outcome. The connectivity profile was then computed for 38 left-out patients with the hypothesis that similarity to the fingerprint indicates seizure-free surgical outcome. Patient profile distance to the fingerprint was compared with 1-year seizure outcome and standard clinical parameters. Distance to the fingerprint was higher for patients with Engel III-IV 1-year outcome compared with those with Engel Ia, Ib-d, and II outcome (Kruskal-Wallis, $P < 0.01$; Wilcoxon rank-sum $p_{corr} < 0.05$ Bonferroni-corrected). Receiver operator characteristic analysis revealed 100% sensitivity and 90% specificity in identifying patients with Engel III-IV outcome based on distance to the fingerprint in the left-out patients. Furthermore, distance to the fingerprint was not related to any individual clinical parameter including age at scan, duration of disease, total seizure frequency, presence of mesial temporal sclerosis, lateralizing ictal, interictal scalp electroencephalography, invasive stereo-encephalography, or positron emission tomography. And two published algorithms utilizing multiple clinical measures for predicting seizure outcome were not related to distance to the fingerprint, nor predictive of seizure outcome in this cohort. The functional and structural connectome fingerprint provides quantitative, clinically interpretable and significant information not captured by standard clinical assessments alone or in combinations. This automated and simple method may improve patient-specific prediction of seizure outcome in patients with a clinically identified focus in the mesial temporal lobe.

Commentary

Intractable epilepsy, a condition in which multiple anti-seizure medications fail to prevent seizures, represents approximately a third of all patients with epilepsy.[1] Currently, the next course of treatment for people with this diagnosis may include surgical resection, laser ablation, or implantation of an electrical stimulator. For intractable temporal lobe epilepsy (TLE), the most common treatment is resection of the temporal lobe or a portion thereof. However, a temporal lobectomy is highly invasive and offers a moderate success rate, with seizure freedom in $\sim 55\%$ to 75% of patients 2 years after surgery.[2] In the large proportion of cases where surgery fails, the patient is left with refractory epilepsy *and* the risks and side effects associated with brain surgery. While substantial progress is being made in the refinement of surgical procedures for the treatment of TLE, a complementary means to improving success rates of temporal lobe resections could be to improve the prediction of surgical outcome. This would reduce surgical failure by reducing the number of resections performed on patients who are unlikely to become seizure free. The current set of biomarkers with predictive value for surgical outcome is relatively limited. In one large cohort, Borger et al[3] found that the only demographics/characteristics predictive of poor surgical outcome were the presurgical placement of depth electrodes and the absence of lesions in presurgical magnetic resonance imaging (MRI). However, a patient-independent, minimally invasive, quantitative predictor of surgical outcome remains lacking.

In the highlighted study, Morgan et al build on the growing premise that epilepsy is a network disorder[4] and that, broadly

[1] Massachusetts General Hospital, Charlestown, MA, USA

speaking, surgical resections are designed to remove a focus or network node that is key to ictogenesis. It is likely that the brain's interdependent networks of genes, synaptic connections, blood vessels, metabolic pathways, and more, all interact to make up an epileptic network. However, almost none of the aforementioned networks can be directly clinically measured in a way that informs surgical planning. For example, in networks defined at the level of synaptic connectivity, nodes are defined as neurons, with edges occurring between synaptically connected neurons weighted by the strength and number of synapses. But, there are currently no clinical imaging modalities capable of resolving synaptic connectivity per se. There are, however, 2 MRI modalities that ostensibly provide a gross measure of connectivity: diffusion weighted imaging (DWI), which takes advantage of the nonrandom diffusion of water molecules to measure anatomical *structural connectivity* (SC) such as white matter tracts; and resting state functional MRI (fMRI), which infers *functional connectivity* (FC) based on correlated signals in the blood-oxygen level dependent (BOLD) signal. Both SC and FC abnormalities have been reported in patients with TLE.[5,6]

Morgan et al[7] exploit these technologies to establish a means for predicting surgical outcome based on comparison of presurgical MRI-based connectomes describing SC and FC. These connectomes consist of nodes, which are volumetric brain regions, and edges with weights that represent the strength of the structural or functional connection between two nodes as measured by DWI and fMRI respectively. First, to establish the "fingerprint" to which all other patients would be compared, an average connectome from a *model* group of patients, which had at least a 3-year Engel Ia seizure outcome, was computed. This group represents the population of patients with a successful surgical outcome. Next, a *testing* group, which included both Engel Ia and Engel III seizure outcomes, was used to optimize the fingerprint comparison algorithm such that distance between the Engel III outcome and the fingerprint was maximized, while minimizing the distance between Ia patients and the fingerprint. Finally, a *left-out* group was used to evaluate the fingerprint and comparison algorithm performance in a completely independent dataset. To improve generalizability of the approach, all 3 groups purposely included TLE patients with heterogeneous epilepsy lateralization and surgery type. Ultimately, the optimization step determined that an efficient approach for comparing test subjects to the fingerprint involved computing distance using 14 nodes of interest, with ipsilateral distances weighted twice as heavy as contralateral.

One potential clinical application of the findings of Morgan et al would involve estimating the likelihood of surgical success by comparing the patient's MRI to an established fingerprint and determining the best course of action, partially based on that estimate. For example, if a patient's connectome suggests that temporal lobe resection surgery would result in an Engel Class III outcome, one would need to decide—Is the surgery worth it? One could compare the predicted outcome to the a priori estimated success rate of responsive neurostimulation or vagus nerve stimulation, which rarely result in seizure freedom, but have approximately 40% to 60% seizure reduction and are comparatively noninvasive.[8] With ideal predictors, one could quantify the probability of postsurgical seizure freedom *and* the probability of "success" (e.g., >50% seizure reduction) with other treatments such as neurostimulation. However, currently available technologies (e.g., MRI) for making clinical predictions are not ideal. The MRI-based fingerprint approach described here was able to predict a binary outcome (seizure freedom) using a combination of functional and anatomical connectivity measures, though neither FC nor SC measures alone was able to predict outcome, suggesting that there was narrowly enough information content for the predictions made in the highlighted study. Before incorporating such statistics into clinical heuristics, this study would need to be expanded in a large multisite study to determine whether fingerprints and analysis techniques are robust and consistent enough for general application.

It remains unclear what the MRI-based connectome means in terms of its mechanistic relationship to epileptogenicity, but the paper highlighted here suggests that it contains information about the likelihood of success of temporal lobe resective surgery. It thus has the potential to make usable predictions about the outcomes of various treatments at a relatively low risk to the patient. If the findings of this study are confirmed, and as connectome measurements improve, the connectome fingerprint comparison approach may be applicable to multiple anti-seizure therapies and may become a clinical tool that aids clinicians in determining the best course of treatment for patients with refractory epilepsy.

ORCID iD

Kyle P. Lillis https://orcid.org/0000-0003-0219-8113

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