Epilepsy Currents
2024, Vol. 24(1) 28-30

DOI: 10.1177/15357597231216917
journals.sagepub.com/home/epi
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Seizing the Brain Networks in Lesional Focal Epilepsies

Mapping Lesion-Related Epilepsy to a Human Brain Network

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Importance: It remains unclear why lesions in some locations cause epilepsy while others do not. Identifying the brain regions or networks associated with epilepsy by mapping these lesions could inform prognosis and guide interventions. Objective: To assess whether lesion locations associated with epilepsy map to specific brain regions and networks. Design, Setting, and Participants: This case-control study used lesion location and lesion network mapping to identify the brain regions and networks associated with epilepsy in a discovery data set of patients with poststroke epilepsy and control patients with stroke. Patients with stroke lesions and epilepsy (n = 76) or no epilepsy (n = 625) were included. Generalizability to other lesion types was assessed using 4 independent cohorts as validation data sets. The total number of patients across all datasets (both discovery and validation datasets) were 347 with epilepsy and 1126 without. Therapeutic relevance was assessed using deep brain stimulation sites that improve seizure control. Data were analyzed from September 2018 through December 2022. All shared patient data were analyzed and included; no patients were excluded. Main Outcomes and Measures: Epilepsy or no epilepsy. Results: Lesion locations from 76 patients with poststroke epilepsy (39 [51%] male; mean [SD] age, 61.0 [14.6] years; mean [SD] follow-up, 6.7 [2.0] years) and 625 control patients with stroke (366 [59%] male; mean [SD] age, 62.0 [14.1] years; follow-up range, 3-12 months) were included in the discovery data set. Lesions associated with epilepsy occurred in multiple heterogenous locations spanning different lobes and vascular territories. However, these same lesion locations were part of a specific brain network defined by functional connectivity to the basal ganglia and cerebellum. Findings were validated in 4 independent cohorts including 772 patients with brain lesions (271 [35%] with epilepsy; 515 [67%] male; median [IQR] age, 60 [50-70] years; follow-up range, 3-35 years). Lesion connectivity to this brain network was associated with increased risk of epilepsy after stroke (odds ratio [OR], 2.82; 95%CI, 2.02-4.10; $P < .001$) and across different lesion types (OR, 2.85; 95%CI, 2.23-3.69; $P < .001$). Deep brain stimulation site connectivity to this same network was associated with improved seizure control (r, 0.63; $P < .001$) in 30 patients with drug-resistant epilepsy (21 [70%] male; median [IQR] age, 39 [32-46] years; median [IQR] follow-up, 24 [16-30] months). Conclusions and Relevance: The findings in this study indicate that lesion-related epilepsy mapped to a human brain network, which could help identify patients at risk of epilepsy after a brain lesion and guide brain stimulation therapies.

Commentary

The role of functional anatomical networks in generating seizures was first discussed by Gloor in 1968.[1] Since then, research advances have significantly revolutionized our understanding of human ictogenesis and brain networks. Both functional and structural networks are often altered in focal epilepsies[2] and such network alterations have been quantified in various studies.[2] Eventually, the concept of epilepsy as a network disease was formally introduced in the 2010 seizure classification.[3] Over the past decade, the notion that epileptogenicity in both lesional and nonlesional focal epilepsies is distributed across an epileptic network has become more widely accepted.[4]

In this case–control study,[5] Schaper et al build upon the existing understanding of epilepsy networks and attempt to answer an exciting question using advanced lesion location and lesion network mapping techniques: Does lesion-related epilepsy across various etiologies and locations map to specific

brain networks? The authors compared patients with post-stroke epilepsy in the discovery dataset to controls who had strokes but did not develop epilepsy. External validation to assess the generalizability of results to other lesion types, including hematomas, trauma, tumors, and tubers, was examined in 4 independent datasets.[5]

Lesion size, lobar location, vascular territory, and cortical involvement have often been identified as risk factors for post-stroke epilepsy.[6] SeLECT score, an internationally validated multivariate prediction model, showed that severity of stroke based on higher NIHSS scores, larger lesions, cortical involvement, early seizures, large-artery atherosclerotic etiology, and middle cerebral artery territory involvement are factors predictive of post-stroke epilepsy.[6] Similar to these, authors found that after stroke, bigger lesions and higher cortical damage were associated with a higher epilepsy risk, while subcortical damage was associated with a reduced epilepsy risk.[5] Contrary to previous literature, authors found no difference in epilepsy risk based on vascular territory or lobar location.[5] They controlled all further analyses for these potential risk factors for post-stroke epilepsy.

The strengths of the study lie in the use of advanced lesion location and mapping techniques, highly sophisticated analyses including multiple control analyses, and extensive external validation of results in 4 separate datasets. Perhaps the study's most significant and notable contribution to existing knowledge of brain connectivity and epilepsy networks is that it analyzed the link between functional connectivity of lesions and epilepsy irrespective of the lesion location and etiology, something that has never been studied before. Schaper et al found that despite the heterogeneity of the location and distribution of lesions related to epilepsy, the lesion locations were involved in certain brain networks described by functional connections to subcortical regions, namely cerebellum and substantia nigra and globus pallidus interna in basal ganglia. Negative functional connectivity of lesion locations to this network was independently associated with an increased risk of epilepsy across 5 different datasets. This association was irrespective of the type and etiology of the lesions. Negative functional connectivity to subcortical regions may explain why epilepsy occurs in certain cortical lesions but not others. However, prospective studies are needed to validate these findings and combine connectivity with other variables to build more accurate risk stratification models for epilepsy prediction.

It has been hypothesized that the therapeutic benefit of deep brain stimulation (DBS) in various neurological disorders is largely via neuromodulation of brain networks.[7] In other neurological disorders, including Parkinson's disease, structure and functional connectivity between stimulation sites and remote brain regions have been shown to be independent predictors of clinical outcomes.[7] Therefore, to understand the therapeutic implications and relevance of subcortical functional connectivity and brain networks, the authors analyzed a fifth dataset of drug-resistant focal epilepsy (DRE) patients with thalamic DBS. Positive functional connectivity of the DBS sites to basal ganglia and cerebellum was associated with better seizure outcomes. Some evidence from previous studies also suggests that direct neuromodulation of basal ganglia and cerebellum via DBS may offer therapeutic benefits in epilepsy. A double-blinded randomized control trial of bilateral cerebellar stimulation showed a significant reduction in tonic and tonic–clonic seizures.[8] In another study, high-frequency stimulation of the subthalamic nucleus has shown promising results for DRE.[9] Overall, these findings support the hypothesis that DBS reduces seizures by neuromodulation of subcortical brain networks, especially basal ganglia and cerebellum. These findings can inform therapeutic targets for future neuromodulation clinical trials in epilepsy and may help select patients who are most likely to benefit from DBS in clinical practice.

The biggest shortcoming of the current study is its retrospective study design, which has many inherent limitations, including confounding factors and the inability to control for a wide variety of factors that may have impacted the study findings, such as stroke severity, etiology, and seizure frequency to name a few. Additionally, the subcortical network identified in this study is derived from people with focal lesions in the brain. It remains unclear whether this can be applicable to other common epilepsies, including generalized epilepsies, mesial temporal lobe epilepsies, and nonlesional focal epilepsies. Another pitfall of the study is that the nonepilepsy controls in the stroke cohort were likely underestimated because they were not specifically evaluated for epilepsy. Lastly, functional connectivity in epilepsy is often altered. Therefore, network studies should utilize age-matched, patient and disease-specific connectivity data. The current study did not analyze the data in such a fashion, and functional connectivity data for lesion network mapping was utilized from healthy participants.

In summary, this study addresses a longstanding controversy of whether epilepsy is largely a cortical disease or if the subcortex also has an important role to play. Its findings suggest that despite individual epilepsy networks, common subcortical networks likely play a significant role in focal epilepsies. It demonstrates that basal ganglia and cerebellum represent subcortical regions, which may represent a common subcortical network across different types of focal epilepsies. Negative functional connectivity of lesions to this subcortical network is associated with higher epilepsy risk and positive functional connectivity of the DBS site to this network is associated with better therapeutic response in epilepsy. While these findings can have significant prognostic and therapeutic implications in epilepsy across a wide variety of locations and etiologies of lesions, future prospective studies are needed to ascertain if this network can be utilized in clinical practice for the prognosis and management of epilepsy.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financialsupport for the research, authorship, and/or publicationof this article: American Epilepsy Society and BAND foundation funding supported this research work.

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