It's All About the Networks

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Interictal stereotactic-EEG functional connectivity in refractory focal epilepsies

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Drug-refractory focal epilepsies are network diseases associated with functional connectivity alterations both during ictal and interictal periods. A large majority of studies on the interictal/resting state have focused on functional magnetic resonance imaging (MRI)-based functional connectivity. Few studies have used electrophysiology, despite its high-temporal capacities. In particular, stereotactic-electroencephalogram (EEG) is highly suitable to study functional connectivity because it permits direct intracranial electrophysiological recordings with relative large-scale sampling. Most previous studies in stereotactic-EEG have been directed toward temporal lobe epilepsy, which does not represent the whole spectrum of drug-refractory epilepsies. The present study aims at filling this gap, investigating interictal functional connectivity alterations behind cortical epileptic organization and its association with postsurgical prognosis. To this purpose, we studied a large cohort of 59 patients with malformation of cortical development explored by stereotactic-EEG with a wide spatial sampling (76 distinct brain areas were recorded, median of 13.2 per patient). We computed functional connectivity using nonlinear correlation. We focused on 3 zones defined by stereotactic-EEG ictal activity: the epileptogenic zone (EZ), the propagation zone (PZ), and the noninvolved zone. First, we compared within-zone and between-zones functional connectivity. Second, we analyzed the directionality of functional connectivity between these zones. Third, we measured the associations between functional connectivity measures and clinical variables, especially postsurgical prognosis. Our study confirms that functional connectivity differs according to the zone under investigation. We found: (1) a gradual decrease in the within-zone functional connectivity with higher values for EZ and PZ, and lower for noninvolved zones; (2) preferential coupling between structures of the EZ; (3) preferential coupling between EZ and PZ; and (4) poorer postsurgical outcome in patients with higher functional connectivity of non-involved zone (within-noninvolved zone, between noninvolved zone, and PZ functional connectivity). Our work suggests that, even during the interictal state, functional connectivity is reinforced within epileptic cortices (EZ and PZ) with a gradual organization. Moreover, larger functional connectivity alterations, suggesting more diffuse disease, are associated with poorer postsurgical prognosis. This is consistent with computational studies suggesting that connectivity is crucial in order to model the spatio-temporal dynamics of seizures.

Dynamic brain network states in human generalized spike-wave discharges

Tangwiriyasakul C, Perani S, Centeno M, et al. *Brain*. 2018;141(10):2981-2994. doi:10.1093/brain/awy223

Generalized spike-wave discharges in idiopathic generalized epilepsy are conventionally assumed to have abrupt onset and offset. However, in rodent models, discharges emerge during a dynamic evolution of brain network states, extending several seconds before and after the discharge. In human idiopathic generalized epilepsy, simultaneous EEG and functional MRI shows cortical regions may be active before discharges, and network connectivity around discharges may not be normal. Here, in human idiopathic generalized epilepsy, we investigated whether generalized spike-wave discharges emerge during a dynamic evolution of brain network states. Using EEG-functional MRI, we studied 43 patients and 34 healthy control subjects. We obtained 95 discharges from 20 patients. We compared data from patients with discharges with data from patients without discharges and healthy controls. Changes in MRI (blood oxygenation level dependent) signal amplitude in discharge epochs were observed only at and after EEG onset, involving a sequence of parietal and frontal cortical regions then thalamus ($P < .01$, across all regions and measurement time points). Examining MRI signal phase synchrony as a measure of functional connectivity between each pair of 90 brain regions, we found significant connections ($P < .01$, across all connections and measurement time points) involving frontal, parietal and occipital cortex during discharges, and for 20 seconds after EEG offset. This network prominent during discharges showed significantly low synchrony (below 99% confidence interval for synchrony in this network in nondischarge epochs in patients) from 16 seconds to 10 seconds before discharges, then ramped up steeply to a significantly

high level of synchrony 2 seconds before discharge onset. Significant connections were seen in a sensorimotor network in the minute before discharge onset. This network also showed elevated synchrony in patients without discharges compared to healthy controls ($P = .004$). During 6 seconds prior to discharges, additional significant connections to this sensorimotor network were observed, involving prefrontal, and precuneus regions. In healthy subjects, significant connections involved a posterior cortical network. In patients with discharges, this posterior network showed significantly low synchrony during the minute prior to discharge onset. In patients without discharges, this network showed the same level of synchrony as in healthy controls. Our findings suggest persistently high sensorimotor network synchrony, coupled with transiently (at least 1 minute) low posterior network synchrony, may be a state predisposing to generalized spike-wave discharge onset. Our findings also show that EEG onset and associated MRI signal amplitude change is embedded in a considerably longer period of evolving brain network states before and after discharge events.

Commentary

Mr. McGuire: I want to say one word to you. Just one word.
Benjamin: Yes, sir.
Mr. McGuire: Are you listening?
Benjamin: Yes, I am.
Mr. McGuire: Networks.
Benjamin: Exactly how do you mean?
Mr. McGuire: There's a great future in networks. Think about it. Will you think about it?

For film aficionados and people who still remember movies from the last century, the above quote adapted and modified from the 1967 movie "The Graduate" could easily be something you hear at the next American Epilepsy Society meeting. For many years, we learned (and taught) that epilepsy can be classified into 2 major categories: focal and generalized.[1] While that classification system is still quite useful, the studies demonstrating altered functional and structural connectivity in many of the epilepsies have forced a reevaluation of how we think about seizures, especially ones that are of "focal" onset.

The work of Lagarde et al adds to the growing literature that focal seizures are not really that "focal" and involve multiple regions of the brain not necessarily in close physical proximity. The authors studied a cohort of 59 patients with drug-resistant epilepsy from malformations of cortical development and undergoing stereotactic-EEG monitoring. Using a nonlinear correlation method, they used resting state data to determine the connectivity between the EZ, the PZ, and noninvolved or electrically quiet zones, as defined by ictal data. These results showed a higher degree of coupling between contacts in the EZ compared to contacts in noninvolved regions, and preferential coupling between the EZ and PZ. Patients with a poor surgical outcome had higher connectivity indices between the EZ and noninvolved zones compared to those with good surgical outcome, suggesting that while the "noninvolved areas" in those patients with poor outcomes may not have been part of the ictal onset or spread by clinical test standards, they nevertheless may have been part of the distributed network of epileptogenicity. The results of this study build upon previous work demonstrating enhanced EEG functional connectivity between epileptogenic structures in mesial temporal lobe epilepsy.[2,3] The findings also advance our knowledge in highlighting the different relative strengths of coupling within and between the epileptogenic region, propagations areas and noninvolved areas.

Tangwiriyasakul et al show that the interictal discharges in human idiopathic generalized epilepsy are preceded by alterations in brain synchrony suggesting that evolving network states may predispose to the development of generalized spike-wave discharges. The authors recorded resting state EEG-triggered fMRI data in patients with epileptiform discharges, patients without epileptiform discharges and normal controls. Using MRI signal phase synchrony as a measure of functional connectivity, they found significant coupling between frontal, parietal and occipital cortices during the generalized discharges, which is not surprising. An interesting finding was that the network showed significantly low synchrony in the 10 to 16 seconds before the epileptiform discharge before changing to a high level of synchrony in the 2 seconds before the discharge. This implies a resting network that changes into a dyssynchronous state before rapidly ramping up to a hypersynchronous state immediately before the spike. An additional finding was that the underlying network features were different between controls and patients, even in the absence of spike-wave discharges. While some of these data have previously been seen in a rodent model,[4] this is the first demonstration in humans of dynamic network changes around the time of a generalized spike-wave discharge.

These 2 studies reinforce the understanding of epilepsy as a network disease. While there is often a discrete localized region to resect, ablate, or neuromodulate in many patients with drug-resistant focal epilepsy, functional and structural connectivity studies have convincingly shown that multiple regions of the brain are involved in the genesis of seizures or in the maintenance of epileptogenicity. Some may find this statement incongruous. After all, if one can eliminate seizures by removing a small part of the brain, how can one say that multiple regions are involved? The answer is that the issue is not whether different brain regions form a network of increased epileptogenicity. Rather, the important feature may be the degree of functional connectivity between the various nodes. The findings from Legarde et al firmly support this hypothesis.

As the 2 reviewed articles highlight, the field of connectivity research is heterogenous. Different methods for network analysis include nonlinear correlation coefficient, phase lag index, synchronization likelihood, partial directed coherence, and Granger causality. All of these analysis methods have their unique advantages and limitations. In addition, data for analysis can be obtained not only from stereotactic-EEG and fMRI, but also from scalp EEG and magnetoencephalography. Each of these recording methods has their own individual strengths and weaknesses. No matter how extensive the coverage, data from clinical stereotactic-EEG recordings will not achieve the spatial resolution needed for whole brain network analysis. Given this myriad of recording and analytical techniques, the results from different connectivity studies may lead to contradictory conclusions. We can expect some initially promising research pathways to ultimately lead to a dead end.

Beyond demonstrating that epilepsy is a network disease process, the field of connectivity research has the potential to impact diagnosis and treatment in clinical practice. Some groups suggest that network analysis may be superior to conventional EEG in the diagnosis of epilepsy.[5,6] Other groups have put forth various connectivity features as potential biomarkers to guide surgical resection and improve outcomes.[7,8] One promising clinical application is the use of these methods in seizure detection. A reliable method to predict seizures will significantly impact clinical practice, and mitigate disability for our patients who usually don't know when the next seizure will occur. The work of Tangwiriyasakul et al adds to previous studies suggesting that network analysis may hold the key to revealing biomarkers of an impending seizure. If patients can know with a high degree of accuracy of seizures minutes before their occurrence, personal safety measures and notification algorithms can be implemented. This can lead to greater independence, less injuries and potentially a lower risk for sudden death in epilepsy.

The field of functional connectivity analysis has not thus far produced enough clinically validated results to be useful in the day to day care of individual patients. There clearly is more work to be done. And yet, there's a great future in networks. Think about it.

By Jerry J. Shih

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