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Targeting Epileptogenesis: A Conceptual Black Hole or Light at the End of the Tunnel?

Keywords
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Topographical Reorganization of Brain Functional Connectivity During an Early Period of Epileptogenesis

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Objective: The current study aims to investigate functional brain network representations during the early period of epileptogenesis. Methods: Eighteen rats with the intrahippocampal kainate model of mesial temporal lobe epilepsy were used for this experiment. Functional magnetic resonance imaging (fMRI) measurements were made 1 week after status epilepticus, followed by 2-4-month electrophysiological and video monitoring. Animals were identified as having (1) developed epilepsy (E+, n = 9) or (2) not developed epilepsy (E−, n = 6). Nine additional animals served as controls. Graph theory analysis was performed on the fMRI data to quantify the functional brain networks in all animals prior to the development of epilepsy. Spectrum clustering with the network features was performed to estimate their predictability in epileptogenesis. Results: Our data indicated that E+ animals showed an overall increase in functional connectivity strength compared to E− and control animals. Global network features and small-worldness of E−rats were similar to controls, whereas E+ rats demonstrated increased small-worldness, including increased reorganization degree, clustering coefficient, and global efficiency, with reduced shortest path length. A notable classification of the combined brain network parameters was found in E+ and E−animals. For the local network parameters, the E−rats showed increased hubs in sensorimotor cortex, and decreased hubness in hippocampus. The E+ rats showed a complete loss of hippocampal hubs, and the appearance of new hubs in the prefrontal cortex. We also observed that lesion severity was not related to epileptogenesis. Significance: Our data provide a view of the reorganization of topographical functional brain networks in the early period of epileptogenesis and how it can significantly predict the development of epilepsy. The differences from E−animals offer a potential means for applying noninvasive neuroimaging tools for the early prediction of epilepsy.

Commentary

Epileptogenesis is a well-established concept that has gained new traction with the identification of novel preclinical and clinical biomarkers proposed to have the potential[1,2] to alter the trajectory of disease development (Figure 1A). This strategy could hypothetically prevent the onset of epilepsy in identified high-risk patients (Figure 1B I), or modify the natural history of its progression with increased seizure severity/frequency over time and appearance of new seizure phenotypes and epileptic foci (Figure 1B II) in patients with an identified first seizure. One prevalent concept in targeting epileptogenesis is that of the "latent period" which has been updated from the older understanding of epileptogenesis as a graded step-up process after a brain insult which ends when the first seizure occurs. It is now understood as a progressive worsening of the underlying acute and sub-acute mechanisms that initiate the first seizure but continues well after the first seizure with the occurrence of recurrent spontaneous seizures.[1]

Several molecular, EEG and imaging biomarkers identified in preclinical research using animal models of chronic epilepsy have been proposed as targets for anti-epileptogenesis. However, corroborating clinical trial confirmations are currently sparse and even discouraging.[2,3] There are 2 big stumbling blocks for the clinical application of the preclinical biomarker data. Firstly, unlike animal models where the time point of the aggravating insult is always known, it is rarely well established in the clinic for most patients presenting with a first seizure especially when the brain imaging is reported normal. This raises the question, when would anti-epileptogenesis treatments ideally be initiated? Secondly, even when an aggravating insult like stroke or trauma can be identified, a much smaller percentage of the at-risk patient population go on to develop epilepsy.[2] Identification of biomarkers using noninvasive techniques that reliably identify the sub-cohort of individuals with the highest risk to develop epilepsy or accelerated progression of epilepsy after first seizure carries the most translational value (Figure 1B). For example, early biomarker identification after brain insult or

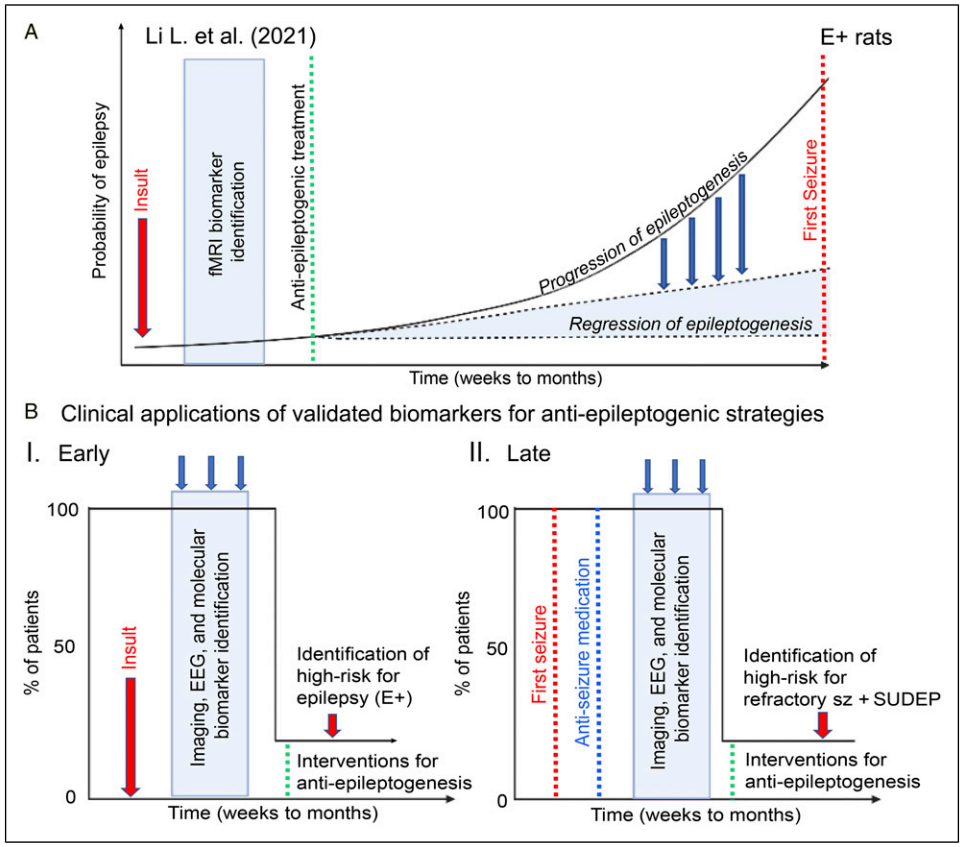

Figure 1. (A). Overview of Li L et al experimental paradigm using fMRI as a biomarker for epileptogenesis- Following unilateral hippocampal insults, fMRI imaging was used to search for the presence of biomarkers to distinguish between rats that became epileptic (E+) or remained seizure free (E−). Validation of such a biomarker could be used to identify and target the E+ rats displaying the early biomarker for interventions targeting antiepileptogenesis before their first seizure (B). Clinical applications–A small percentage of at risk patients develop epilepsy therefore it remains unclear who to target for antiepileptogenesis strategies. For example, of all the patients with a history of brain insult or first seizure, only 20% are at high risk for developing epilepsy or refractory seizure/SUDEP (I. and II. respectively) (I). Using multiple validated biomarkers to identify high-risk patients among a pool of at-risk patient populations with a known brain insult before the occurrence of a first seizure. The use of a panel of validated tests for biomarker identification, could possibly identify patients deemed at highest-risk for epilepsy that could be targeted for long-term antiepileptogenic interventions (II). Prevention of complication of epilepsy (refractory sz + SUDEP) in epileptic patients: Panel of validated biomarker testing to evaluate the efficacy of ongoing antiseizure treatments and identify patients at highest-risk for developing refractory seizures and SUDEP who could be targeted for long-term antiepileptogenic interventions.

injury would help design effective clinical-trials for anti-epileptogenesis studies and would help bolster compliance for long-term study participation from the identified high-risk individuals who have not yet had their 1st seizure (Figure 1B I). Biomarker workups after the 1st seizure could also help identify sub-cohorts of patients at highest risk for severe temporal progression, SUDEP and/or emergence of refractoriness for the recurrent seizures (Figure 1B II). The brain has tremendous capacity for adaptive plasticity both for acquired insults/injury and pathogenic genetic mutations that impair brain function, and these are mostly beneficial.[4] Studies investigating such plasticity after brain injury in preclinical models have identified criteria for maladaptive plasticity where excessive plasticity associated with upregulation of neurotrophic factors and neuropeptides have been implicated in the pathogenesis of neurological disorders like epilepsy.[5] It is important to note that recurrent seizures can also induce plasticity changes not only in the circuits involved in seizure generation but also at distant mirror foci over time.[6] Neuronal changes that contribute to this adaption include overproduction or deletion of synapses, neurogenesis or neuronal death, impaired maturation and axonal sprouting which can alter network connectivity.

In this study, fMRI and graph-theoretic approaches were used to understand the changes in network connectivity in the rodent brain following unilateral intra-hippocampal kainic acid injection.[7] By comparing rats that develop epilepsy (E+) with those that did not develop epilepsy (E−) with the same insult, the goal of this study was to identify and distinguish connectivity changes in epileptogenesis using fMRI. With 40 nodes representing brain regions and edges for functional connectivity, this study performed global and local connectivity analyses. Global connectivity in brain networks can be divided into random, small-world, or regular networks. This classification depends on the clustering coefficient (C_p) and shortest path length

(L_p), where C_p and L_p represent the degree of local and global network connectivities, respectively. Small-worldness is when the ratio to the normalized C_p and the normalized average L_p is greater than one, achieving an appropriate balance in local and global connectivities. In this study, E+ rats showed decreased small-worldness, which indicates inefficient network dynamics. Additionally, this study analyzed global efficiency (E_{glob}), representing the efficiency of global information transfer as the name suggests. Increased C_p and E_{glob} in E+ rats indicated an abnormally synchronized brain and high information transfer efficiency, which contradict with previous studies where the connectivity decreased in epileptogenesis.[8] The authors clarify that the discrepancy may be due to more focal brain lesions in intrahippocampal KA model compared to intraperitoneal KA models.

In a local connectivity level, this study computed the nodal degree (K_i), which is the number of edges connected to the node of interest, to identify the regional hubs in the brain network. This study also calculated the local efficiency (E_{nod}), which is the average inverse shortest path length of a node to its neighborhood. The local connectivity analysis showed obliterated K_i in the hippocampal hub in E+ rats. Increased K_i in the right retrosplenial cortex (RSC) in E−rats and a decreased K_i in E+ rats may insinuate a mechanism in the RSC that prevents epileptogenesis in this model of TLE. The RSC has long been studied for its role in generating seizure activity due to its anatomical connections and, therefore, as a target to modulate seizure activity.[9] fMRI data from a mouse model of genetic epilepsy have shown the RSC forming more connections as a hub between subcortical and cortical regions in the epileptic rats.[9] Apparent difference in the hub dynamics in the RSC across different epilepsy models indicates model specific mechanisms in epileptogenesis. Additional analyses on different centralities could have provided insights into identifying important nodes based on different features.[10] For example, betweenness centrality, which ranks the nodes with the number of shortest path crossing, can highlight the translocation of bridges of brain connectome pathways due to plasticity during epileptogenesis. However, differences highlighted here in fMRI results for preclinical biomarker research indicate that for translational application a cohort of validated biomarkers (Figure 1B) would be more reliable in identifying highest-risk patients.

Of interest was also the analysis of the extent and severity of the T2-weighted signal intensity induced by the unilateral intrahippocampal kainic acid injection. The study reported no significant correlation of the size and severity of these imaging lesions detected in the bilateral hippocampi to the eventual evolution of epilepsy. This is not surprising, since long-term telemetric EEG monitoring recorded over a period of 1 year in a model of perinatal stroke related epilepsy also failed to show significant correlations between the severity of the perinatal stroke injury and the severity of seizure frequency in the epileptic rats.[11] The intrahippocampal kainic acid model for temporal lobe epilepsy is known to cause severe cell death in the hippocampus, however the authors do not report on the differences of histological findings for the chronic hippocampal injury between the E+ and E−rats in this study. It is possible that the E+ rats were also having early clusters of subclinical epileptiform discharges within the first 2 weeks after insult, and that kindling played a role in the alterations of the functional connectivity quantified using the fMRI data at the later time points and in the detection of the epilepsy 3 months later. Overall, these findings suggest that the lesion in itself is not sufficient to cause epileptogenesis, but that lesion-initiated changes in functional connectivity may be more critical for the development of epilepsy.

Epilepsy is a complex disorder and represents a large gamut of developmental, adult and geriatric neurological disorders. For neurodevelopmental disorders associated with epilepsy, there is already some understanding that efficient control of the early-life seizures itself positively changes the trajectory of the disorder.[12] Non-invasive methods like quantitative analysis on imaging and EEG data can provide biomarkers that can be readily used in the patient population. The light at the end of the tunnel for anti-epileptogenesis strategies lies in the ability to reliably identify individuals with the highest-risk to develop epilepsy or complications of epilepsy using validated biomarkers combined with efficacious early anti-seizure interventions.

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