The Disruptive Nature of Focal Developmental Insults

The Spectrum of Structural and Functional Network Alterations in Malformations of Cortical Development.

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Neuroimaging studies of malformations of cortical development have mainly focused on the characterization of the primary lesional substrate, while whole-brain investigations remain scarce. Our purpose was to assess large-scale brain organization in prevalent cortical malformations. Based on experimental evidence suggesting that distributed effects of focal insults are modulated by stages of brain development, we postulated differential patterns of network anomalies across subtypes of malformations. We studied a cohort of patients with focal cortical dysplasia type II ($n = 63$), subcortical nodular heterotopia ($n = 44$), and polymicrogyria ($n = 34$), and compared them to 82 age- and sex-matched controls. Graph theoretical analysis of structural covariance networks indicated a consistent rearrangement towards a regularized architecture characterized by increased path length and clustering, as well as disrupted rich-club topology, overall suggestive of inefficient global and excessive local connectivity. Notably, we observed a gradual shift in network reconfigurations across subgroups, with only subtle changes in focal cortical dysplasia type II, moderate effects in heterotopia and maximal effects in polymicrogyria. Analysis of resting state functional connectivity also revealed gradual network changes, with most marked rearrangement in polymicrogyria; contrary to findings in the structural domain, however, functional architecture was characterized by decreases in both local and global parameters. Diverging results in the structural and functional domain were supported by formal structure–function coupling analysis. Our findings support the concept that time of insult during corticogenesis impacts the severity of topological network reconfiguration. Specifically, late-stage malformations, typified by polymicrogyria, may selectively disrupt the formation of large-scale corticocortical networks and thus lead to a more profound impact on whole-brain organization than early stage disturbances of predominantly radial migration patterns observed in cortical dysplasia type II, which likely affect a relatively confined cortical territory.

Commentary

Neuroembryology has taught us that before it becomes what it is as a mature organ, the brain undergoes several stages of development starting with neural tube formation in the first few weeks of embryogenesis, which result in orderly localization of structures (and functions) in the brain. All stages of neural tube formation are subject to various genetic, epigenetic, and environmental influences that can potentially cause aberrations in the proliferative activity (or cell proliferation), migration, and differentiation. As such, abnormal neuronal and glial proliferative activity that is most active in the 8th to 16th weeks of gestation typically results in developmental abnormalities like microcephaly or focal cortical dysplasia type II (FCD-II). Later aberrations in migration (12th–20th weeks of gestation) typically result in, for example, heterotopias, while aberrations secondary to abnormal postmigrational development, which typically occur between the sixth gestational month and maturity, result in focal or widespread functional and structural

abnormalities, for example, polymicrogyria or focal cortical dysplasias type I (FCDs-I) (1).

Neuroimaging has allowed us to build dynamic models of brain activity, including models of structural and functional connectivity (2). Structural connectivity can be measured directly (e.g., with diffusion tensor imaging) or indirectly by examining structural interactions between various brain locations (e.g., whether changes in cortical thickness occur in different areas simultaneously); functional connectivity measured with fMRI can be further divided into resting state functional connectivity, which takes advantage of slow oscillations in the brain that occur in the resting state (as in this study), or task-related functional connectivity, which takes advantage of the effects of fMRI task activations and the relationship between these activations (3, 4). Thus far, these concepts have been applied to patients with new onset and chronic focal and generalized epilepsies, but, Hong et al. take their investigation one step further. Instead of investigating the effects of seizures and epilepsy on brain networks, they investigate the effects of epileptogenic lesions—FCDs-II, heterotopias, polymicrogyrias, and FCDs-I—on structural and functional connectivity (5). Thus, while numerous studies examine the effects of seizures and epilepsy on structural and functional connectivity, this

particular study stands out in that it examines the effects of epileptogenic lesions, rather than epilepsy itself, on brain connectivity.

Their findings are surprising: the earlier the lesion appears in the prenatal brain development, the less pronounced are the effects on structural and functional connectivity. Shouldn't it be the opposite, that is, earlier lesions cause more disruption? Or, do the findings make intuitive sense: lesions that occur earlier have more chance to induce plasticity and, thus, more adjustment and rewiring of the networks so that, in the end, they create less long-term disruption? The intuitive approach appears to make sense in view of the literature coming from another type of unfortunate prenatal and postnatal event—stroke—where earlier lesions result in more pronounced functional plasticity and fewer deficits (6). Another strength of the study is combining structural and functional connectivity analyses in one study to provide convergent evidence for their findings.

In general, this is an imaging study of brain development and how brain maturation evolves in the presence or absence (healthy control subjects) of lesions. It documents in a convincing way how the lesions affect the brain's structural and functional connectivity and shows that there is more to these lesions than the simple fact that they occupy a certain space. These lesions affect how brain structures interact and, as such, this study details the rearrangement of structural and functional networks in response to early versus late structural lesions. Besides being a great neuronetworks study, however, this work poses several additional and important questions:

1. Is the location of lesion (and its extent) related to the degree of network disruption and, in turn, to epileptogenicity?
2. Can these or other connectivity-related measures detect the parts of the lesion and adjacent cortex that need to be removed in order for the patient to become seizure free? Can they predict which part of the lesion does not need to be removed to achieve seizure freedom?
3. Is there a point no return? That is, can neuroimaging of networks, whether structural, functional, or combined, be utilized to predict who will or will not benefit from epilepsy surgery? In other words, can neuroimaging predict the patients who will not be helped with surgery? Or is there a level of network dysfunction that negates the need for surgery (or even entering the taxing and costly evaluation process) as there is no chance for a good seizure outcome?
4. Is the existence of abnormalities in connectivity related to the presence of the lesion itself, epileptiform discharges, seizures, epilepsy, or drugs? Or is this a combination of fac-

tors known and unknown at this time? What is the role of genetics and epigenetic factors?

5. Is there a relationship between the degree of abnormalities in connectivity and surgery outcomes similar to that present in retrospective studies of temporal lobectomy?
6. If there is a relationship between network disruption in patients with lesional epilepsies and epilepsy surgery outcomes, is there an intervention that can improve or minimize the network disruption and, thus, make the patient more amenable to surgical success?

These and probably other questions need to be answered before connectivity analyses are used to decide a patient's candidacy for epilepsy surgery. For now, we know that detecting the lesion in extratemporal neocortical epilepsy increases two- to threefold the chance of a seizure-free surgical outcome over nonlesional cases (7). Also, besides our own eyes, which sometimes miss small or inconspicuous lesions, we now have excellent methods for identifying lesion, for example, morphometric analysis program (MAP) (8), that increase the chance of detecting previously unidentified lesions and possibly resulting in better surgical outcome. Do connectivity measures in lesional epilepsies measure up to MAP or other imaging and clinical modalities? Only time will tell.

by Jerzy P. Szaflarski, MD, PhD

References

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