Epilepsy as a Disease of White Matter

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White Matter Abnormalities Across Different Epilepsy Syndromes in Adults: An ENIGMA-Epilepsy Study

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The epilepsies are commonly accompanied by widespread abnormalities in cerebral white matter. ENIGMA-Epilepsy is a large quantitative brain imaging consortium, aggregating data to investigate patterns of neuroimaging abnormalities in common epilepsy syndromes, including temporal lobe epilepsy, extratemporal epilepsy, and genetic generalized epilepsy. Our goal was to rank the most robust white matter microstructural differences across and within syndromes in a multicenter sample of adult epilepsy patients. Diffusion-weighted magnetic resonance imaging (MRI) data were analyzed from 1069 healthy controls and 1249 patients: temporal lobe epilepsy with hippocampal sclerosis (n = 599), temporal lobe epilepsy with normal MRI (n = 275), genetic generalized epilepsy (n = 182), and nonlesional extratemporal epilepsy (n = 193). A harmonized protocol using tract-based spatial statistics was used to derive skeletonized maps of fractional anisotropy and mean diffusivity for each participant, and fiber tracts were segmented using a diffusion MRI atlas. Data were harmonized to correct for scanner-specific variations in diffusion measures using a batch-effect correction tool (ComBat). Analyses of covariance, adjusting for age and sex, examined differences between each epilepsy syndrome and controls for each white matter tract (Bonferroni corrected at $P < .001$). Across "all epilepsies" lower fractional anisotropy was observed in most fiber tracts with small to medium effect sizes, especially in the corpus callosum, cingulum, and external capsule. There were also less robust increases in mean diffusivity. Syndrome-specific fractional anisotropy and mean diffusivity differences were most pronounced in patients with hippocampal sclerosis in the ipsilateral parahippocampal cingulum and external capsule, with smaller effects across most other tracts. Individuals with temporal lobe epilepsy and normal MRI showed a similar pattern of greater ipsilateral than contralateral abnormalities, but less marked than those in patients with hippocampal sclerosis. Patients with generalized and extratemporal epilepsies had pronounced reductions in fractional anisotropy in the corpus callosum, corona radiate, and external capsule, and increased mean diffusivity of the anterior corona radiata. Earlier age of seizure onset and longer disease duration were associated with a greater extent of diffusion abnormalities in patients with hippocampal sclerosis. We demonstrate microstructural abnormalities across major association, commissural, and projection fibers in a large multicenter study of epilepsy. Overall, patients with epilepsy showed white matter abnormalities in the corpus callosum, cingulum, and external capsule, with differing severity across epilepsy syndromes. These data further define the spectrum of white matter abnormalities in common epilepsy syndromes, yielding more detailed insights into pathological substrates that may explain cognitive and psychiatric comorbidities and be used to guide biomarker studies of treatment outcomes and/or genetic research.

Commentary

The understanding of the pathogenesis of epileptic seizures has evolved, changing with our understanding of the nervous system over time. Early definitions describe epilepsy as a disease of the cortex. In 1888, Hughlings-Jackson stated that epileptic seizures show "particular symptoms as pointing to a 'discharging lesion' of this or that particular part of cortex."[1] Advances in electroencephalogram (EEG), including cortical stimulation studies, allowed formal investigations to further substantiate the role of the cortex in epilepsy.[2]

However, concepts evolve over time. Although cerebral cortex is the primary element in the generation of epileptic seizures, it is not the only one. In some circumstances, epileptic seizures can originate in thalamocortical interactive systems, or in the brainstem.[3] Additionally, EEG and neuroimaging studies provide compelling evidence for the existence of specific cortical and subcortical networks in the genesis and expression of focal-onset and generalized-onset seizures, which involve functionally and anatomically connected structures in which one part of the network affects activity in all the others.[4] Given that multiple cortical and subcortical regions are involved in

seizure networks, it follows that the structures connecting these regions, within the white matter, could also be involved.

More recent neuroimaging studies definitively confirm involvement of white matter in patients with epilepsy.[5,6] The introductory text by Hatton et al[7] nicely summarizes previous studies about white matter changes in epilepsy, which document white matter changes in patients with temporal lobe epilepsy (TLE) and genetic generalized epilepsy (GGE). White matter changes also correlate with cognitive changes as well as postoperative seizure outcomes in people with long-standing epilepsy. Given the documented involvement of the white matter in epileptic seizures, the ENIGMA-epilepsy consortium publication by Hatton et al represents an important step forward in assessing white matter brain abnormalities in epilepsy.

The ENIGMA-epilepsy consortium recently published another study evaluating structural brain changes, ranking brain structures in order of differences between brains of epilepsy patients and controls, and analyzing effect sizes across 16 subcortical and 68 cortical brain regions.[8] The investigators showed interesting findings by dividing patients into 4 subgroups, including GGE, left and right mesial temporal lobe epilepsies with hippocampal sclerosis (TLE-HS) and all other epilepsies in aggregate. The investigators postulated that there was a degree of common pathophysiology in all epilepsy syndromes and documented lower volumes in the right thalamus, and cortical thinning in the precentral gyri bilaterally to support this hypothesis when they evaluated all epilepsies as a single group. Interestingly, patients with GGE also showed reduced volume of the right thalamus and bilaterally thinner precentral gyri as the most prominent finding. In TLE-HS, there were differences between left and right TLE-HS groups, with the left TLE-HS group showing broader regions of subcortical and cortical changes than the right TLE-HS group, which supported the hypothesis of differing pathophysiology between left and right TLE-HS.

The current study from the ENIGMA-Epilepsy consortium by Hatton et al includes diffusion magnetic resonance imaging (MRI) scans from 21 cohorts, including all 1249 adult epilepsy patients and 1069 healthy controls. The patient groups were similar to those in the previous ENIGMA-epilepsy study except that right and left nonlesional TLE (TLE-NL) and nonlesional extratemporal epilepsy groups were included. Functional anisotropy (FA), mean diffusivity (MD), axial diffusivity, and radial diffusivity were obtained for 38 regions of interest. Evaluation of all epilepsy patients in aggregate showed lower FA with small to medium effect sizes in most fiber tracts, most prominently in the corpus callous, cingulum, and external capsule. In TLE-HS, FA and MD changes were most prominent in the ipsilateral parahippocampal cingulum. Also, the TLE-HS group showed greater diffusion abnormalities in patients with earlier age of seizure onset and longer disease duration. In comparison to the TLE-HS group, the TLE-NL group showed ipsilateral but less prominent findings. In patients with generalized and extratemporal epilepsies, there were increases in MD of the anterior corona radiata and pronounced reductions in fractional anisotropy in the corpus callosum, corona radiata, and external capsule.

The many advantages to this collaborative approach include a very large sample size, consistent definitions of epilepsy syndromes, and standardized post-image acquisition processing algorithms for analysis of results. Because of differences in image acquisition between centers, there are unavoidable uncertainties induced by harmonizing data between centers. The authors clearly describe and discuss their use of the batch-effect correction tool, ComBat, which allows harmonization of diffusion metrics between different sites and MRI acquisition protocols. Although a necessity to adequately compare data between different centers, the statistical batch normalization process may also affect pathophysiological changes directly caused by epilepsy, resulting in loss of differentiation between epilepsy syndromes.

As discussed previously, cerebral cortex plays a central role in epileptic seizures. There is extensive clinical experience in measuring cortical function with scalp surface and intracranial EEG to successfully diagnose and treat epileptic seizures. Therefore, postulating the cerebral cortex as responsible for the primary pathophysiological process in epilepsy, which drives secondary change in the cerebral white matter, is an attractive hypothesis. However, as the authors discuss, the cross-sectional design of this study, and therefore lack of longitudinal follow-up, obviates any definitive conclusions about the epileptogenic process over time. Studies focusing on new-onset seizures, and following changes over time, are necessary to document the progression of gray and white matter disease in epilepsy.

Given 2 large-scale ENIGMA-epilepsy studies, one focusing on gray matter and the other on white matter changes, the next obvious question is how these results may relate to each other in this large data set. One interesting finding is the more extensive structural gray matter volume changes in left than right TLE-HS in the initial study, and the more comparable changes between these groups demonstrated by diffusion magnetic resonance measures in the current study. Future use of the ENIGMA-epilepsy databases to objectively compare and correlate gray and white matter changes is an obvious opportunity for further study.

As with all diagnostic tests in patients with epilepsy, individual patient data should be interpreted in the context of clinical findings and other tests. One important factor in this study is inclusion of only "non-lesional" patients, showing no definitive cerebral structural MRI lesions by visual inspection (other than HS). Therefore, patients with more definitive structural MRI lesions that affect diffusion MRI may show different diffusion MRI patterns and would need to be interpreted accordingly. However, Hatton et al provide an interesting framework describing white matter changes in epilepsy, substantiating earlier findings in both generalized and focal epilepsy. These findings will provide important information for correlations with other diagnostic tests, including electrophysiological, imaging, and neuropsychological studies.

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