EPILEPSY CURRENTS

Current Literature
In Clinical Science

Epileptic Seizures, Brain Volume Changes, and "Brain Damage": What Do We Know So Far?

Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study.

Whelan CD, Altmann A, Botia JA, Jahanshad N, Hibar DP, Absil J, Alhusaini S, Alvim MKM, Auvinen P, Bartolini E, Bergo FPG, Bernardes T, Blackmon K, Braga B, Caligiuri ME, Calvo A, Carr SJ, Chen J, Chen S, Cherubini A, David P, Domin M, Foley S, França W, Haaker G, Isaev D, Keller SS, Kotikalapudi R, Kowalczyk MA, Kuzniecky R, Langner S, Lenge M, Leyden KM, Liu M, Loi RQ, Martin P, Mascalchi M, Morita ME, Pariente JC, Rodríguez-Cruces R, Rummel C, Saavalainen T, Semmelroch MK, Severino M, Thomas RH, Tondelli M, Tortora D, Vaudano AE, Vivash L, von Podewils F, Wagner J, Weber B, Yao Y, Yasuda CL, Zhang G, Bargalló N, Bender B, Bernasconi N, Bernasconi A, Bernhardt BC, Blümcke I, Carlson C, Cavalleri GL, Cendes F, Concha L, Delanty N, Depondt C, Devinsky O, Doherty CP, Focke NK, Gambardella A, Guerrini R, Hamandi K, Jackson GD, Kälviäinen R, Kochunov P, Kwan P, Labate A, McDonald CR, Meletti S, O'Brien TJ, Ourselin S, Richardson MP, Striano P, Thesen T, Wiest R, Zhang J, Vezzani A, Ryten M, Thompson PM, Sisodiya SM. *Brain* 2018;141(2):391–408.

Progressive functional decline in the epilepsies is largely unexplained. We formed the ENIGMA-Epilepsy consortium to understand factors that influence brain measures in epilepsy, pooling data from 24 research centres in 14 countries across Europe, North and South America, Asia, and Australia. Structural brain measures were extracted from MRI brain scans across 2149 individuals with epilepsy, divided into four epilepsy subgroups including idiopathic generalized epilepsies (n =367), mesial temporal lobe epilepsies with hippocampal sclerosis (MTLE; left, n = 415; right, n = 339), and all other epilepsies in aggregate (n = 1026), and compared to 1727 matched healthy controls. We ranked brain structures in order of greatest differences between patients and controls, by meta-analysing effect sizes across 16 subcortical and 68 cortical brain regions. We also tested effects of duration of disease, age at onset, and age-by-diagnosis interactions on structural measures. We observed widespread patterns of altered subcortical volume and reduced cortical grey matter thickness. Compared to controls, all epilepsy groups showed lower volume in the right thalamus (Cohen's d = –0.24 to –0.73; $P < 1.49 \times 10^{-4}$), and lower thickness in the precentral gyri bilaterally (d = –0.34 to –0.52; $P < 4.31 \times 10^{-6}$). Both MTLE subgroups showed profound volume reduction in the ipsilateral hippocampus (d = –1.73 to –1.91, $P < 1.4 \times 10^{-19}$), and lower thickness in extrahippocampal cortical regions, including the precentral and paracentral gyri, compared to controls (d = –0.36 to –0.52; $P < 1.49 \times 10^{-4}$). Thickness differences of the ipsilateral temporopolar, parahippocampal, entorhinal, and fusiform gyri, contralateral pars triangularis, and bilateral precuneus, superior frontal and caudal middle frontal gyri were observed in left, but not right, MTLE (d = –0.29 to –0.54; $P < 1.49 \times 10^{-4}$). Contrastingly, thickness differences of the ipsilateral pars opercularis, and contralateral transverse temporal gyrus, were observed in right, but not left, MTLE (d = –0.27 to –0.51; $P < 1.49 \times 10^{-4}$). Lower subcortical volume and cortical thickness associated with a longer duration of epilepsy in the all-epilepsies, all-other-epilepsies, and right MTLE groups (beta, b < –0.0018; $P < 1.49 \times 10^{-4}$). In the largest neuroimaging study of epilepsy to date, we provide information on the common epilepsies that could not be realistically acquired in any other way. Our study provides a robust ranking of brain measures that can be further targeted for study in genetic and neuropathological studies. This worldwide initiative identifies patterns of shared grey matter reduction across epilepsy syndromes, and distinctive abnormalities between epilepsy syndromes, which inform our understanding of epilepsy as a network disorder, and indicate that certain epilepsy syndromes involve more widespread structural compromise than previously assumed.

Commentary

There is long-standing interest in the effects of chronic epilepsy on the brain. In 1849, Robert Bentley Todd summarized his neuropathological findings in subjects with chronic epilepsy as follows: "In the more advanced stages of the disease, when the patients have experienced many fits, morbid appearances are met with, and these affect the hemispheres of the brain chiefly. You have among the most common, opacities and thickening of the membranes, shrinking of the convolutions, enlargement of the sulci between them, increased subarachnoid fluid, alterations of colour and consistency of the grey and

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white matter of the hemispheric lobes. These alterations must be looked upon as the accumulated effects produced by the various paroxysms (1)."

In general, Todd's observations that seizures cause progressive long-term effects, or "brain damage," has prevailed as a presumed outcome of uncontrolled epileptic seizures. However, objective confirmation that uncontrolled epileptic seizures themselves are responsible for long-standing neuropathological changes has proved difficult. An important issue is the availability of adequate neuropathological studies, or equivalent biomarker studies, to document changes over time. A recent large multicenter series of 9523 patients reported postoperative neuropathological information about the structural brain lesions in subjects with drug-resistant focal epilepsy who underwent epilepsy surgery (2). While this study describes important information about subjects undergoing epilepsy surgery, it also illustrates the common shortcomings of existing neuropathological series in epilepsy. Many forms of epilepsy, especially the genetic generalized epilepsies, are unsuitable for treatment with resective epilepsy surgery, so postsurgical neuropathological studies only include a highly selected subset of subjects with long-standing epilepsy. Postmortem neuropathological studies are also important, but require extensive effort for correlation with clinical histories and comprehensive analysis. Perhaps most importantly, repeat acquisition of data over time to document changes in longitudinal studies is critical to show progressive changes, which is an obvious obstacle for neuropathological studies.

Given the inherent difficulties of using neuropathological studies to document progressive changes, other biomarkers for such documentation become increasingly important. Measurements of cognitive function (3), or evaluations of intracranial EEG and associated immunohistopathological markers (4) provide interesting avenues for assessing the effects of seizures. While there are several avenues for evaluating progressive changes in epilepsy, each with their advantages and disadvantages, magnetic resonance structural neuroimaging remains one of the most promising as an overall biomarker for progressive brain changes. Previous studies show good correlation with magnetic resonance structural imaging and neuropathological findings (5, 6). Two important issues in the context of structural imaging include 1) longitudinal studies and 2) standardization of data acquisition methods and adequate definition of cohorts.

Documenting changes over time with longitudinal studies, as previously discussed, is very important in subjects with chronic epilepsy. One important clinical factor is that an initial insult (i.e., atypical febrile seizures, trauma, etc.) is often associated with the inciting incident or beginning of epileptic seizures. Therefore, a cross-sectional study design is especially vulnerable to inaccuracy in documenting progressive atrophy, given that a more severe initial brain injury may simply be more predisposing to severe epilepsy, possibly without progression after the initial insult. A second major confounding factor for documenting progressive changes caused by epilepsy over time is ongoing brain changes related to normal aging. Since duration of epilepsy is typically highly correlated with age, statistically controlling for aging can severely affect the sensitivity to detect significant differences in cohorts between effects of epilepsy and normal aging (7). Past studies, however, have addressed this issue in subjects with pharmacoresistant temporal lobe epilepsy by using cortical thickness measurements (7), as well as surface-based mapping of hippocampal, amygdalar, and entorhinal subregions (8), as sensitive measures of morphologic brain changes to convincingly show more progressive age-related volume loss in the participants with epilepsy compared with controls.

From the MRI acquisition perspective, important factors include standardization of MRI acquisition protocols, repeated scans performed on the same hardware, and reproducible and sensitive image postprocessing algorithms (7). Consistent, accurate definition of the epilepsy syndrome involved and an adequately large sample size are also important.

The publication by Whelan et al. represents an important step forward in assessing structural brain abnormalities in epilepsy. Through the ENIGMA-Epilepsy consortium, which consists of 24 research centers, this collaborative study measured structural brain changes in 2149 subjects, and compared results with those of 1727 matched healthy controls. There are many advantages to this collaborative approach, including a very large sample size (the largest neuroimaging study of epilepsy to date), consistent definitions and documentation of epilepsy syndromes, and standardized post-image acquisition algorithms for anatomic analysis. The authors show interesting findings by dividing subjects into four subgroups, including idiopathic generalized epilepsies, left and right mesial temporal lobe epilepsies with hippocampal sclerosis (hsMTLE). and all other epilepsies in aggregate. The investigators postulated that there was a degree of common pathophysiology in all epilepsy syndromes, and they 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. Another interesting finding was the difference between left and right hsMTLE groups, with the left hsMTLE group showing broader regions of subcortical and cortical changes compared with the right hsMTLE group, which supports the hypothesis of differing pathophysiology between left and right and hsMTLE.

There are limitations to the study. As a cross-sectional sample of data, the findings do not differentiate between damage induced by an initial injury or progressive abnormalities, the importance of which was previously discussed. Additionally, the authors reported that some brain measures showed a wide distribution of effect sizes across research centers, which likely reflects sample heterogeneity and differences in scanning acquisition and protocols between centers.

Therefore, the study by Whelan et al. documents important structural neuroimaging changes in subjects with epilepsy. The study design, with multicenter collaborations, standardized epilepsy syndrome definition, and post-image acquisition processing, stands out as a model for future multicenter studies. However, the lack of longitudinal data, as is the case with almost all previous structural neuroimaging studies in epilepsy, remains problematic. Future efforts should focus on this important factor. For now, we can be sure that epileptic seizures are associated with structural brain changes, which we should strive to alleviate through the best available treatments. In the future, we can hope to further specify the factors

associated with structural brain changes to assist in treatment and provide a robust biomarker for long-standing effects of epileptic seizures.

by R. Edward Hogan, MD

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