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Chronicles of Change: The Shrinking Brain in Epilepsy

Identification of Different MRI Atrophy Progression Trajectories in Epilepsy by Subtype and Stage Inference

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Artificial intelligence (AI)-based tools are widely employed, but their use for diagnosis and prognosis of neurological disorders is still evolving. Here we analyse a cross-sectional multicentre structural MRI dataset of 696 people with epilepsy and 118 control subjects. We use an innovative machine-learning algorithm, Subtype and Stage Inference, to develop a novel data-driven disease taxonomy, whereby epilepsy subtypes correspond to distinct patterns of spatiotemporal progression of brain atrophy. In a discovery cohort of 814 individuals, we identify two subtypes common to focal and idiopathic generalized epilepsies, characterized by progression of grey matter atrophy driven by the cortex or the basal ganglia. A third subtype, only detected in focal epilepsies, was characterized by hippocampal atrophy. We corroborate external validity via an independent cohort of 254 people and confirm that the basal ganglia subtype is associated with the most severe epilepsy. Our findings suggest fundamental processes underlying the progression of epilepsy-related brain atrophy. We deliver a novel MRI- and AI-guided epilepsy taxonomy, which could be used for individualized prognostics and targeted therapeutics.

Commentary

Epilepsy leads to numerous deleterious effects on the brain, particularly when seizures are drug resistant. These effects include diffuse gray matter atrophy, widespread neocortical hypometabolism,[1] extensive neurocognitive deficits,[2] and brain network perturbations.[3] While these widespread detrimental effects of epilepsy may not be surprising in severe generalized seizure disorders, such as idiopathic generalized epilepsy (IGE), they are also surprisingly prominent in focal epilepsy syndromes, such as mesial temporal lobe epilepsy (MTLE). Many of these sequelae are related to duration of disease and frequency of seizures, suggesting they may be progressive over time.[4] Longitudinal studies of epilepsy patients are relatively rare, however, limiting our understanding of the trajectory of this progression.

In the currently highlighted manuscript, Xiao and colleagues present a large structural MRI study examining epilepsy patients and controls using a novel machine-learning approach that achieves longitudinal inference from cross-sectional data.[5] The authors' goal was to discern patterns of brain atrophy progression in epilepsy by examining a discovery cohort of nearly 700 individuals with both focal epilepsy and IGE, most of whom had drug-resistant seizures, and more than 100 controls. After adding an independent external cohort that was examined to validate models, 1105 epilepsy patients were investigated. The authors used an unsupervised and data-driven machine learning algorithm called SuStaIn (Subtype and Stage Interference), recently developed to study disease progression in neurodegenerative disorders. Projection-based cortical thickness was measured using 3D T1-weighted MRI, and region-wise cortical thickness was adjusted for age, sex, and total intracranial volume. SuStaIn then clustered individuals into subtype groups based on the predominant expression of a given progression pattern. By determining whether a single biomarker becomes abnormal before another individual biomarker, the model decides which subject groups have which abnormal biomarker and compares the relative likelihood of different candidate progression patterns. Focal epilepsy and IGE patients were examined separately in the study.

In focal epilepsy patients, the authors report that SuStaIn identified 3 epilepsy progression subtypes, including (i) a cortical progression subtype with predominantly neocortical atrophy and subcortical atrophy that developed later (dominant in 49%; mostly extratemporal and temporal neocortical epilepsy patients), (ii) a subtype involving early basal ganglia and pallidal atrophy with later cortical atrophy (dominant in 18%; mostly patients with recent generalized seizures), and (iii) a subtype with early hippocampal atrophy, followed by

thalamus, temporal neocortex, and then extratemporal neocortex atrophy (dominant in 33%; mostly MTLE patients). In IGE, individuals were split between a cortical progression subtype (two-thirds of whom had absence or juvenile myoclonic epilepsy) and a basal ganglia subtype (two-thirds of whom had unclassified IGE with primarily tonic–clonic seizures). These 2 subtypes in IGE resembled those in focal epilepsy patients, but no hippocampal subtype was found. In both focal epilepsy and IGE, while some results and proportions differed when analyses were repeated in the validation cohort, for the most part, similar progression subtypes were identified. The authors argue that in the future, machine-learning approaches may prove useful to guide prognostication and treatment planning in individual epilepsy patients.

This study by Xiao and others follows the group's prior work demonstrating cortical thinning in focal epilepsy patients that is greater than expected with aging and is related to epilepsy duration.[6] A success in the present analysis is the use of a relatively interpretable machine learning algorithm to both identify progressive nature of gray matter atrophy, and stratify progression subtypes that seem to correlate with clinical factors. Of note, earlier basal ganglia and subcortical region disruption in both focal epilepsy and IGE patients who had more frequent bilateral to tonic–clonic seizures supports recent observations that these subcortical loops play an important role in seizure generalization. As these machine learning methods are improved, they may be useful to predict the expected clinical course in individual patients without requiring serial longitudinal imaging. The use of an external validation dataset and test framework in the present study is also quite welcome, as validation steps are often absent from modeling studies. It is notable that similar loadings are surfaced for the top principal component in the discovery and validation cohorts. Since the 2 cohorts are from different sites, mixing patients between the 2 groups (albeit ones that use different scanning protocols) may be worthwhile for further validation.

A few limitations of the highlighted study relate to how elements of human interpretation are still required in the methods. The study utilized an anatomical atlas with limited preselected regions of interest, likely to make the analysis computationally tracible, but it is unclear if the results would be replicated using a less biased voxel-wise analysis. Also, patients were classified into one subtype at the threshold of >50% which may be somewhat arbitrary, and a subanalysis of patients who were borderline between groups may be of interest. Further, it may be worthwhile to separate patients with drug resistant and medically controlled seizures to determine if medical control portends a lower risk of progressive gray matter atrophy.

In this study and others, it remains striking that even patients with focal epilepsy with a presumed anatomically restricted focus develop relatively widespread neocortical consequences. While early hippocampal atrophy was noted in several MTLE patients, temporal neocortical and frontoparietal gray matter loss then followed. In the Extended Network Inhibition Hypothesis, it suggested that perhaps progressive connectivity perturbations between subcortical arousal structures and broad neocortical regions may lead to more global problems in MTLE, such as diffuse neocortical atrophy, hypometabolism, and neurocognitive deficits.[7] Another compelling implication of the highlighted study is considering early surgical intervention in focal epilepsy patients with persistent drug-resistant seizures, to prevent progression of broad network problems. Prior work by the highlighted group has demonstrated that successful surgery can prevent progressive cortical thinning in MTLE patients,[8] and other studies have shown improvement in certain disturbed functional connections between subcortical arousal regions and the neocortex after MTLE surgery.[9] Furthermore, while few surgical approaches for generalized epilepsy syndromes were previously available, novel neurostimulation paradigms are being increasingly explored to reduce seizure burden and improve quality of life in these patients.

Overall, interest in improved modeling methods to predict disease trajectory and personalize patient care in epilepsy is rapidly growing.[10] Both hypothesis-driven and machine-learning approaches have shown value. There are challenging practical barriers to integrating new analytical methods and technologies into the treatment pipeline in epilepsy, but the chronicles of change may be upon us in this field.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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