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Flattening the Curve: Slowing Age-Accelerated Brain Atrophy With Epilepsy Surgery

Resective Surgery Prevents Progressive Cortical Thinning in Temporal Lobe Epilepsy

Galovic M, de Tisi J, McEvoy AW, et al. *Brain.* 2020;43(11):3262-3272. doi:10.1093/brain/awaa284

Focal epilepsy in adults is associated with progressive atrophy of the cortex at a rate more than double that of normal aging. We aimed to determine whether successful epilepsy surgery interrupts progressive cortical thinning. In this longitudinal case–control neuroimaging study, we included patients with unilateral temporal lobe epilepsy (TLE) before (n = 29) or after (n = 56) anterior temporal lobe resection and healthy volunteers (n = 124) comparable regarding age and sex. We measured cortical thickness on paired structural magnetic resonance imaging scans in all participants and compared progressive thinning between groups using linear mixed effects models. Compared to aging-related cortical thinning in healthy patients, we found progressive cortical atrophy on vertex-wise analysis in TLE before surgery that was bilateral and localized beyond the ipsilateral temporal lobe. In these regions, we observed accelerated annualized thinning in left (left TLE 0.0192 ± 0.0014 vs healthy volunteers 0.0032 ± 0.0013 mm/year, $P < .0001$) and right (right TLE 0.0198 ± 0.0016 vs healthy volunteers 0.0037 ± 0.0016 mm/year, $P < .0001$) presurgical TLE cases. Cortical thinning in these areas was reduced after surgical resection of the left (0.0074 ± 0.0016 mm/year, $P = .0006$) or right (0.0052 ± 0.0020 mm/year, $P = .0006$) anterior temporal lobe. Directly comparing the post- versus presurgical TLE groups on vertex-wise analysis, the areas of postoperatively reduced thinning were in both hemispheres, particularly, but not exclusively, in regions that were affected preoperatively. Participants who remained completely seizure-free after surgery had no more progressive thinning than that observed during normal aging. Those with postoperative seizures had small areas of continued accelerated thinning after surgery. Thus, successful epilepsy surgery prevents progressive cortical atrophy that is observed in TLE and may be potentially neuroprotective. This effect was more pronounced in those who remained seizure-free after temporal lobe resection, normalizing the rate of atrophy to that of normal aging. These results provide evidence of epilepsy surgery preventing further cerebral damage and provide incentives for offering early surgery in refractory TLE.

Commentary

Whether or not temporal lobe epilepsy (TLE) is a progressive disorder has been debated since the late 1800s, and this debate has enjoyed renewed interest in recent years.[1] Cognitive decline has been at the center of the debate, with studies arguing both for[2] and against[3] cognitive deterioration in TLE over time. These studies are complemented by recent longitudinal imaging studies demonstrating progressive hippocampal atrophy[4] and cortical thinning[5] in young to middle-aged adults with TLE over an average duration of 3 years. However, most existing studies are small, retrospective, or lack an adequate comparison group. The latter is of particular concern because cortical thinning is a natural process that occurs throughout much of the life span with annualized thinning estimated at 0.17% to 0.26% by midlife.[6] Therefore, *pathological* thinning of the cortex associated with a specific disease or epilepsy syndrome must be benchmarked against cortical thinning that occurs as a part of the normal aging process.

A recent study by Galovic et al[5] has provided new support for age-accelerated atrophy in patients with focal epilepsy, revealing annualized cortical thinning rates in patients with TLE that are nearly double the rates of age-matched controls. Although atrophy rates were most pronounced ipsilateral to the seizure focus and in areas structurally connected to the hippocampus, widespread atrophy was also observed in both hemispheres and was particularly pronounced in patients older than the age of 55. Interestingly, progressive atrophy was not directly associated with seizure frequency, number of antiseizure medications, or a history of generalized seizures. These findings suggest that age-accelerated atrophy is present in many patients with TLE, is characterized by a diffuse pattern, and may intensify with age. However, the processes that leads to accelerated cortical atrophy in these patients remain a mystery.

An interesting question that emerges is *what impact does resective surgery have on the brain of patients with epilepsy*? Does resecting the epileptic focus set off a cascade of

neurodegenerative changes, including deafferentiation of white matter and downstream cortical damage? Or does surgery provide the opportunity for the brain to stabilize, heal, and reorganize over time in seizure-free patients? Although there are some data to support surgically-induced neurodegeneration,[7] compelling support for adaptive changes following surgery comes from neuropsychological studies demonstrating stable or improved cognitive functioning in patients with good seizure control, and conversely, poorer cognitive outcomes in patients with continuing seizures.[8]

In the highlighted article, Galovic et al[9] build upon their previous findings of progressive brain atrophy in focal epilepsy and ask the question, *what impact does resective surgery have on progressive cortical thinning in TLE and does this differ in patients with seizure-free versus non seizure-free outcomes*? The authors examined annualized atrophy rates in patients with TLE who had paired structural magnetic resonance imaging scans at least six months apart either before (N = 29) or after (N = 56) anterior temporal lobe resection and compared their annualized atrophy rates to 124 age- and sex-matched healthy controls. They find that prior to surgery, annualized thinning exceeded healthy controls in multiple regions in TLE, including the bilateral pre- and post-central gyri, with broader patterns of thinning in patients with left TLE. Following surgery, cortical thinning was attenuated in most regions in left TLE and did not differ from healthy controls in any region in right TLE. Interestingly, when atrophy rates were stratified by seizure outcome, the seizure-free group alone showed cortical thinning similar to healthy controls and even evidenced areas of focal cortical thickening. Conversely, the non-seizure-free group showed continued age-accelerated atrophy in multiple posterior temporoparietal and occipital regions. These data provide evidence that resective surgery may *flatten the curve*, normalizing the rate of atrophy in patients with TLE to that observed with normal aging and providing further evidence that seizure cessation may be the most important factor in halting disease progression.

This article adds to a growing body of literature underscoring the advantages of early surgical intervention in patients with drug-resistant epilepsy. These data also raise the possibility that adaptive structural changes ensue postoperatively that may underlie observations of cognitive improvements over time. This is supported by neuropsychological studies demonstrating improvements in both nonmemory (attention and language fluency) and memory functions in seizure-free patients up to 10 years post-surgery.[8] Notably, Helmstaedter et al found that in seizure-free patients, nonmemory functions had the potential to improve soon after surgery (~1 year post-surgically), whereas memory functions recovered more slowly (between 1 and 10 years post-surgically), suggesting that functions subserved by cortex more distant from the seizure focus recover earlier than functions directly associated with the seizure zone. This new study by Galovic et al may provide a neurobiological explanation for reported cognitive improvements following surgery. However, longer term imaging studies that directly relate patterns of cortical atrophy (or hypertrophy) to dynamic changes in cognition over time are needed to directly answer this question. In addition, it is imperative to know whether surgery slows age-accelerated cortical thinning and/or other neural markers of disease progression *across* the adult age span. This is an area ripe for additional investigation as we push the age window for surgical interventions into the 60 and 70s—an age-group whose brains may be less capable of neural repair and more vulnerable to the deleterious effects of open brain surgery. This has been born out in neuropsychological studies demonstrating poorer cognitive outcomes following epilepsy surgery in adults older than 50,[10] which could reflect less cognitive and brain reserve in older adults.

Strengths of this study include the longitudinal design, comparison to a large, age- and sex-matched healthy control cohort, and consistency in image processing and neurosurgical procedures employed across patients. However, as the authors note, this study only addresses how *resective* surgery mitigates age-accelerated atrophy in the short term (ie, first postoperative year). Thus, longer term data and comparison to atrophy rates following other surgical procedures (ie, laser ablation, neurostimulation, or neuromodulation) would be quite informative. Second, there was little overlap between the presurgical and postsurgical patient cohorts. Although the authors take great care to match the 2 patient groups closely on key clinical and demographic variables, longitudinal follow-up in the same patients before and after resective surgery or other epilepsy treatments would be ideal. Despite these limitations, Galovic et al provide another key piece of the puzzle regarding the effects of resective surgery on the epileptic brain. Whether epilepsy surgery is truly *neuroprotective* remains to be determined. But, we are now one step closer to answering this question.

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References

1. Tai XY, Bernhardt B, Thom M, et al. Review: neurodegenerative processes in temporal lobe epilepsy with hippocampal sclerosis: clinical, pathological and neuroimaging evidence. *Neuropathol Appl Neurobiol*. 2018;44(1):70-90.
2. Helmstaedter C, Elger CE. Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease? *Brain*. 2009;132(pt 10):2822-2830.
3. Thompson PJ, Duncan JS. Cognitive decline in severe intractable epilepsy. *Epilepsia*. 2005;46(11):1780-1787.
4. Fuerst D, Shah J, Shah A, Watson C. Hippocampal sclerosis is a progressive disorder: a longitudinal volumetric MRI study. *Ann Neurol*. 2003;53(3):413-416.
5. Galovic M, van Dooren VQH, Postma T, et al. Progressive cortical thinning in patients with focal epilepsy. *JAMA Neurol*. 2019;76(10):1230-1239.
6. Shaw ME, Abhayaratna WP, Sachdev PS, Anstey KJ, Cherbuin N. Cortical thinning at midlife: the PATH through life study. *Brain Topogr*. 2016;29(6):875-884.

7. Concha L, Beaulieu C, Wheatley BM, Gross DW. Bilateral white matter diffusion changes persist after epilepsy surgery. *Epilepsia*. 2007;48(5):931-940.
8. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Ann Neurol*. 2003;54(4):425-432.
9. Galovic M, de Tisi J, McEvoy AW, et al. Resective surgery prevents progressive cortical thinning in temporal lobe epilepsy. *Brain*. 2020;43(11):3262-3272.
10. Thompson PJ, Baxendale SA, McEvoy AW, Duncan JS. Cognitive outcomes of temporal lobe epilepsy surgery in older patients. *Seizure*. 2015;29:41-45.