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The Dilemma of the Chicken or the Egg—What Appears First in TLE—Seizures or Morphometric Changes in the Temporal Lobe?

Abstract

Abnormal Temporal Lobe Morphology in Asymptomatic Relatives of Patients With Hippocampal Sclerosis: A Replication Study

Yaakub SN, Barker GJ, Carr SJ, et al. *Epilepsia*. 2019;60(1):e1-e5. doi:10.1111/epi.14575.

We investigated gray and white matter morphology in patients with mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE + HS) and first-degree asymptomatic relatives of patients with mTLE+HS. Using T1-weighted magnetic resonance imaging (MRI), we sought to replicate previously reported findings of structural surface abnormalities of the anterior temporal lobe in asymptomatic relatives of patients with mTLE+HS in an independent cohort. We performed whole-brain MRI in 19 patients with mTLE+HS, 14 first-degree asymptomatic relatives of patients with mTLE+HS, and 32 healthy control participants. Structural alterations in patients and relatives compared to controls were assessed using automated hippocampal volumetry and cortical surface-based morphometry. We replicated previously reported cortical surface area contractions in the ipsilateral anterior temporal lobe in both patients and relatives compared to healthy controls, with asymptomatic relatives showing similar but less extensive changes than patients. These findings suggest morphologic abnormality in asymptomatic relatives of patients with mTLE+HS, suggesting an inherited brain structure endophenotype.

Commentary

The question is whether temporal lobe epilepsy (TLE) causes changes in brains' anatomy (morphometric changes) or whether the presence of such changes is a precursor for the development of temporal lobe seizures—that is, what was first, *the chicken or the egg*, argument. In the present study, Yaakub et al, find cortical surface abnormalities in the temporal lobes of patients with sporadic medial TLE with hippocampal sclerosis (MTLE-HS) and relatives of patients with MTLE-HS (not necessarily relatives of the probands) when comparing them to healthy controls. This would not be unusual or unexpected in patients with familial MTLE-HS as various morphometric alterations have been well documented in this population over the last 3 decades. However, this is only the second (thus "replication") study of nonfamilial (sporadic) cases of MTLE-HS to show cortical surface abnormalities.[1] With their somewhat unusual design of nonfamilial recruitment and different (whole-brain rather than region-of-interest) data-analytical methods compared to previous studies, their positive results and their robustness may be, to some, surprising. Since their sample was small (19 patients and 14 asymptomatic relatives), the cortical surface abnormalities—reduction in ipsilateral temporal lobe surface—must be robust to be identified in such a small sample and, thus, may have other than "sporadic" underlying etiology.

Morphometric abnormalities (typically gray and/or white matter atrophy) in patients with MTLE with or without HS have been reported repeatedly. For example, one study documented correlation between hippocampal and regional gray matter volume loss in various temporal and extra-temporal brain regions including bilateral parahippocampal gyri and frontal and parietal regions with differences present between patients with left and right MTLE that could potentially explain some of their behavioral or neuropsychological deficits.[2] A more recent study identified, in a cross-sectional and longitudinal design, atrophy of the hippocampus, entorhinal cortex, amygdala, and lateral temporal cortex in candidates for anterior temporal lobectomy. Those who delayed the surgery had progressive atrophy of the ipsilateral and contralateral temporal lobe structures and the observed morphometric changes were, at least to some degree, related to the duration of epilepsy and seizure frequency.[3] Hence, while the presence of morphometric abnormalities in MTLE is unquestionable, their etiology remains murky. However, there are differences in what has been studied to date. Cortical and/or white matter thickness/atrophy were investigated in the majority of studies versus cortical surface in the initial and replication study: while both are highly heritable, they may not reflect the same genetic concept.[4] Thus, what is being studied may affect the conclusions.[5]

As we all know, the normal development of the temporal lobe does not end in the prenatal period. Although specific gains and differences in the shape, surface, and size of the hippocampi and other temporal lobe structures are already noted in the gestational period, this process is well known to continue postnatally.[6,7] In the postnatal period noted are nonlinear increases in the volume of the gray and white matter; the magnitude of these changes varies with brain region, age, and sex with the maximum of the changes peaking around preadolescence.[7,8] The sequence and degree of the developmental changes in the brains' gray matter thickness and surface are likely to be influenced by anatomically driven and age-specific variability in gene expression, in parallel to environmental factors.

In epilepsy in general, and TLE in particular, specific changes in brain structure and connectivity are expected and have been reported repeatedly.[9] Although MTLE is considered a sporadic disorder, there is mounting evidence that this may not be so for all cases. For example, recent advances in genetics and testing of large samples of patients with MTLE identified relatively robust associations between the sodium channel gene *SCN1A* and MTLE-HS with febrile seizures.[10] A recent whole-exome sequencing study in ethnic Han Chinese population from Hong Kong identified several potential rare genetic variants or gene sets for example, *SEC24B*, or fragile X mental retardation-target with possible relationship to MTLE-HS.[11] While advances in disentangling the relationship between MTLE-HS and genetics are needed and welcome, it is clear that there is not a single gene that underlies MTLE-HS but, rather, that it is a complex disorder with genetic and environmental contributions to its etiology. The extent of the genetic contribution to the development of MTLE-HS remains unclear.

The study by Yaakub et al, is, in many ways, confirmatory of the findings of other studies that identified neuroimaging changes in patients with MTLE and unaffected family members. Hence, their findings of cortical surface abnormalities in the temporal lobe in patients and their asymptomatic first-degree relatives are not surprising. Perhaps, the most interesting finding is the one in the unaffected individuals—they all are unaffected family members of patients with MTLE-HS who were not necessarily related to the probands. While this may, on the surface, complicate the interpretation, it actually makes it a bit simpler. The cortical surface differences between healthy controls and relatives of patients with MTLE-HS must be present "across the board" for them to be observed in this study that included unrelated patients and family members. These findings were observed despite using methods that are, in general, of lesser sensitivity when compared to the previous study.[1] By definition, the analyses used in the first study increased the chance of detection of abnormalities since they were performed over a smaller area of the brain (region-of-interest) rather than over the whole brain as in the present replication study—an approach that decreases sensitivity but is more conventional and likely less prone to false positives. Hence, this approach and its results support the notion that MTLE-HS may not be a sporadic disease but rather a genetic trait with variable expression modulated by environmental (and other) factors. However, such associations cannot be solved by a study that does not collect all potential contributing variables. Such associations can only be solved by studies asking very specific questions or large and multicenter studies that address the relationship between genes and neuroimaging—for example, the studies conducted by the ENIGMA Consortium.[12] Hence, the "what was first, *the chicken or the egg*" conundrum remains unanswered for now. However, studies like this one bring us closer to answering this important question.

By Jerzy P. Szaflarski

References

1. Alhusaini S, Whelan CD, Doherty CP, Delanty N, Fitzsimons M, Cavalleri GL. Temporal cortex morphology in mesial temporal lobe epilepsy patients and their asymptomatic siblings. *Cereb Cortex*. 2016;26(3):1234-1241.
2. Bonilha L, Rorden C, Halford JJ, et al. Asymmetrical extra-hippocampal grey matter loss related to hippocampal atrophy in patients with medial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. 2007;78(3):286-294.
3. Bernhardt BC, Kim H, Bernasconi N. Patterns of subregional mesiotemporal disease progression in temporal lobe epilepsy. *Neurology*. 2013;81(21):1840-1847.
4. Panizzon MS, Fennema-Notestine C, Eyler LT, et al. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex*. 2009;19(11):2728-2735.
5. Alhusaini S, Kowalczyk MA, Yasuda CL, et al. Normal cerebral cortical thickness in first-degree relatives of temporal lobe epilepsy patients. *Neurology*. 2019;92(4):e351-e358.
6. Ge X, Shi Y, Li J, et al. Development of the human fetal hippocampal formation during early second trimester. *Neuroimage*. 2015;119:33-43.
7. Tanaka C, Matsui M, Uematsu A, Noguchi K, Miyawaki T. Developmental trajectories of the fronto-temporal lobes from infancy to early adulthood in healthy individuals. *Dev Neurosci*. 2012;34(6):477-487.
8. Uematsu A, Matsui M, Tanaka C, et al. Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *Plos One*. 2012;7(10):e46970.
9. Middlebrooks EH, Ver Hoef L, Szaflarski JP. Neuroimaging in epilepsy. *Curr Neurol Neurosci Rep*. 2017;17(4):32.
10. Kasperaviciute D, Catarino CB, Matarin M, et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. *Brain*. 2013;136(pt 10):3140-3150.
11. Wong JKL, Gui H, Kwok M, et al. Rare variants and de novo variants in mesial temporal lobe epilepsy with hippocampal sclerosis. *Neurol Genet*. 2018;4(3):e245.
12. Thompson PM, Stein JL, Medland SE, et al; Alzheimer's Disease Neuroimaging Initiative, EPIGEN Consortium, IMAGEN Consortium, Saguenay Youth Study (SYS) Group. The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging Behav*. 2014;8(2):153-182.