“Connectionology” Provides Further Evidence for Nociferous Epileptic Cortex

**Frequent Seizures Are Associated with a Network of Gray Matter Atrophy in Temporal Lobe Epilepsy with or without Hippocampal Sclerosis.**


**OBJECTIVE:** Patients with temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS) have diffuse subtle gray matter (GM) atrophy detectable by MRI quantification analyses. However, it is not clear whether the etiology and seizure frequency are associated with this atrophy. We aimed to evaluate the occurrence of GM atrophy and the influence of seizure frequency in patients with TLE and either normal MRI (TLE-NL) or MRI signs of HS (TLE-HS). METHODS: We evaluated a group of 172 consecutive patients with unilateral TLE-HS or TLE-NL as defined by hippocampal volumetry and signal quantification (122 TLE-HS and 50 TLE-NL) plus a group of 82 healthy individuals. Voxel-based morphometry was performed with VBM8/SPM8 in 3T MRIs. Patients with up to three complex partial seizures and no generalized tonic-clonic seizures in the previous year were considered to have infrequent seizures. Those who did not fulfill these criteria were considered to have frequent seizures. RESULTS: Patients with TLE-HS had more pronounced GM atrophy, including the ipsilateral mesial temporal structures, temporal lobe, bilateral thalami and pre/post-central gyri. Patients with TLE-NL had more subtle GM atrophy, including the ipsilateral orbitofrontal cortex, bilateral thalami and pre/post-central gyri. Both TLE-HS and TLE-NL showed increased GM volume in the contralateral pons. TLE-HS patients with frequent seizures had more pronounced GM atrophy in extratemporal regions than TLE-HS with infrequent seizures. Patients with TLE-NL and infrequent seizures had no detectable GM atrophy. In both TLE-HS and TLE-NL, the duration of epilepsy correlated with GM atrophy in extra-hippocampal regions. CONCLUSION: Although a diffuse network GM atrophy occurs in both TLE-HS and TLE-NL, this is strikingly more evident in TLE-HS and in patients with frequent seizures. These findings suggest that neocortical atrophy in TLE is related to the ongoing seizures and epilepsy duration, while thalamic atrophy is more probably related to the original epileptogenic process.

**Commentary**

A recent prior issue of Epilepsy Currents included two commentaries on studies of network activation in temporal and frontal lobe epilepsies and the association of network changes with cognitive deficits (1, 2). Both reviews emphasize the lack of evidence for the cause of the identified network abnormalities. The recent paper by Coan et al. from the Neuroimaging Laboratory at the State University of Campinas, Brazil, contributes further support that unique patterns of network dysfunction are associated with specific types of epilepsy. Additionally, their findings indicate that frequency of seizures and duration of temporal lobe epilepsy are associated with abnormalities in neuronal networks beyond the mesial temporal structures, which could have significant implications for the treatment and prevention of temporal lobe epilepsy. If recurrent seizures damage components of extended brain networks, perhaps stopping or reducing seizure frequency or severity by pharmacological or surgical interventions could prevent progressive dysfunction.

The study by Coan and colleagues found volume loss in specific regions of extratemporal gray matter (GM) in patients with temporal lobe epilepsy. They present one of the largest published series, including 122 subjects with TLE and unilateral hippocampal sclerosis (TLE-HS), 50 with TLE and normal hippocampi TLE-NL), and 82 normal controls. Using established techniques of voxel based morphometry and statistical parametric mapping to analyze 3T MRI, they demonstrated that TLE-HS patients had severe volume loss of bilateral thalamus and, bilateral pre-central and postcentral gyri, and ipsilateral temporal neocortex. Patients with TLE-NL had less severe GM volume loss but still had significantly smaller volumes in the bilateral thalamus and pre-central and postcentral gyri, and the ipsilateral orbitofrontal cortex. It is noteworthy that patients with infrequent seizures and TLE-NL did not have significant GM loss in any regions. Patients with TLE-HS and frequent seizures had more severe volume loss than similar patients with infrequent seizures (e.g., see figure 1 from the article by Coan.
et al.), and in both TLE-HS and TLE-NL groups the duration of epilepsy correlated with degree of GM volume loss.

The clinical consequences expected from these extratemporal regions of GM volume loss include impairments in motor function, memory, and possibly language. In a highly relevant prior study, Hermann et al. prospectively evaluated 47 patients with temporal lobe epilepsy and 65 healthy controls at baseline and 4-year follow up to demonstrate progressive decline in cognitive domains, which fit closely with the regions of GM volume loss in the Campinas paper (3). The neuropsychological testing domains with the greatest decline were language, verbal memory, and motor function. Interestingly, the Grooved Pegboard Test that quantitates motor function had the most severe worsening of any of the tests in the comprehensive neuropsychological battery, even after controlling for potential medication effects. The regions of GM volume loss reported by Coan et al. provide neuroanatomical support for the potential pathophysiology of progressive cognitive and motor decline in temporal lobe epilepsy.

Although the association of severity of GM volume loss with seizure frequency and duration of epilepsy suggests a possible causal relationship, this observation does not constitute proof of causality. It is possible that the original brain insult that caused the epilepsy—such as viral or hypoxic injury—could predispose to accelerated cerebral atrophy and associated cognitive decline, independent of the effects of recurrent seizures. Limited prospective observations have supported the association of recurrent seizures and hippocampal volume loss (4). Further prospective studies with repeated imaging and detailed seizure assessments with adequate control subjects are necessary to confirm seizures as the cause of progressive atrophy and dysfunction.

Findings by Coan et al. evoke Drs. Penfield and Jasper’s concept of nociferous cortex postulated more than a half century ago (5). This theory proposes that seizures can cause enduring injury to connected regions distant from the epileptogenic zone. Hermann and Seidenberg previously provided indirect evidence for nociferous mesial temporal cortex with the analysis of neurocognitive testing of executive function in temporal lobe epilepsy (6). Coan et al. provide more direct evidence through the association of temporal lobe seizure frequency over time with severity of gray matter volume loss in extratemporal brain regions. Could stopping seizures or decreasing seizure rate early in the course of epilepsy prevent progressive atrophy and associated neuropsychological decline in temporal lobe epilepsy? Answering this question will require prospective comparison of persons with temporal lobe epilepsy who have had their seizures stopped in relation to a group with similar key clinical characteristics, including potential etiologies, with continued seizures. This question was partially addressed by a prior longitudinal study (7). Although data from a randomized interventional trial would be optimal, we are not likely to obtain such data in the near future. Valid conclusions may be able to be drawn from data from other study designs. For example, patients who decline epilepsy surgery after meeting stringent criteria could be prospectively compared to similar patients who elect to have surgery. The results would allow more robust comparisons of long-term

**FIGURE 1.** Patterns of gray matter atrophy according to seizure frequency in TLE-HS and TLE-NL. VBM demonstrated significant areas of diffuse gray matter atrophy in TLE-HS patients with infrequent and frequent seizures but only in TLE-NL with frequent seizures. A: areas of gray matter atrophy in TLE-HS with infrequent seizures (two-sample t-test, p < 0.001, uncorrected, minimum threshold cluster of 30 voxels); B: areas of gray matter atrophy in TLE-HS with frequent seizures (two-sample t-test, p < 0.001, uncorrected, minimum threshold cluster of 30 voxels); C: areas of gray matter atrophy in TLE-NL with frequent seizures (two-sample t-test, p < 0.001, uncorrected, minimum threshold cluster of 30 voxels). TLE-HS: temporal lobe epilepsy with MRI signs of hippocampal sclerosis; TLE-NL: temporal lobe epilepsy with normal MRI; VBM: voxel based morphometry; T: t-value; L: left; R: right. Reprinted with permission from Coan, et al.
neuropsychological outcomes; the initial declines in verbal memory and naming ability experienced by some patients after dominant temporal resection may compare favorably to the language, memory, and motor dysfunction from years of recurrent seizures. Perhaps Drs. Penfield and Jasper were correct: Preventing the long-term harm of nociferous cortex may be preferable to the potential risk of surgical removal of the epileptic cortex. If definitive evidence was available to support that preventing harm from recurrent seizures was advantageous to the potential harm of surgical removal of nociferous cortex, then perhaps many neurologists would no longer consider epilepsy surgery a “final, desperate option” (8). We would also have additional support for the importance of studies of prevention of epilepsy to eliminate the risk of damage from the seizures themselves. Coan and colleagues appear to have another victory for the application of advances in neuroscience, including innovative neuroimaging and “connexionology,” to epilepsy. Through better knowledge of the consequences of recurrent seizures, we can begin to understand and develop potential solutions to stop them.

by Frank Gilliam, MD, MPH

References
2. Chang BS. It’s all about who you know: The importance of connections in understanding epilepsy and associated cognitive dysfunction. Epilepsy Curr 2014;14:14–16.
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