



## Teasing Out the Anatomy of Mesial Temporal Lobe Epilepsy

### Cortical Thickness Analysis in Temporal Lobe Epilepsy: Reproducibility and Relation to Outcome.

Bernhardt BC, Bernasconi N, Concha L, Bernasconi A. *Neurology* 2010;74:1776–1784.

**OBJECTIVE:** To assess the reproducibility of neocortical atrophy and its clinical significance across the spectrum of temporal lobe epilepsy (TLE), in particular with respect to postsurgical outcome. **METHODS:** MRI-based cortical thickness measurement was obtained in 105 patients. A total of 58 had hippocampal atrophy on magnetic resonance volumetry (TLE-HA) and 47 had normal hippocampal volumes (TLE-NV). Twenty-seven patients had repeated scans with a mean interval of 28 months. Patients were compared to 48 age- and sex-matched healthy controls. We used linear models to assess cortical thinning and the effect of seizure control after surgery. Reproducibility of finding cortical atrophy was statistically evaluated using bootstrap simulations. **RESULTS:** Cross-sectional and longitudinal analyses revealed highly similar topology and rates of neocortical thinning in both TLE groups, predominantly in frontocentral, temporal, and cingulate regions. Bootstrap methods showed that at least 20 subjects per group were necessary to reliably observe these patterns of atrophy in TLE. Moreover, power analysis showed that even with sample sizes of 80 subjects per group, differences in thickness between TLE-HA and TLE-NV would be marginal. With respect to postsurgical outcome, we found an association between residual seizures and atrophy in temporopolar and insular cortices in TLE-HA, and in the posterior quadrant in TLE-NV. **CONCLUSION:** We demonstrated with a high degree of confidence that static and dynamic effects of epilepsy impact similarly the neocortex of patients with hippocampal atrophy and patients with normal hippocampal volumes. On the contrary, areas predicting unfavorable postsurgical outcome were distinct, suggesting different configurations of epileptogenic networks in these two groups.

### Commentary

While most patients receiving neurosurgical treatment for medically intractable temporal lobe epilepsy have hippocampal atrophy (HA) on MRI, there is another subgroup with mesial temporal epilepsy with a normal appearing hippocampus, with different clinical features and surgical outcome (1). Both of these subtypes of mesial temporal epilepsy are associated with widespread atrophy outside the hippocampus, particularly in bilateral neocortices (2–6). What causes this extrahippocampal abnormality? What is its distribution? How does this distribution vary among individuals, and does it differ between the subgroups of mesial temporal epilepsy patients with and without HA? Does the degree of extrahippocampal abnormality predict surgical outcome? This work by Bernhardt et al. joins a growing body of investigation that is starting to address some of these questions.

Extrahippocampal abnormalities in mesial temporal epilepsy have been documented by MR spectroscopy and morphometry. MR spectroscopy measures N-acetyl-aspartate, which is typically reduced in the epilepsy focus and reflects neuronal loss. Mueller et al. reported that N-acetyl-aspartate was reduced in a bilateral frontotemporal distribution in HA

patients but was more diffusely decreased in those without HA (6), with considerable variation among individual patients. MRI morphometric analysis demonstrated bilateral atrophy in the amygdala, and in the entorhinal, cingulate, temporo-polar, lateral temporal and frontocentral cortices, as well as in the thalamus, in some patients with HA (2–7). Although past reports of MRI analysis in patients without HA have shown some inconsistency as to the distribution of extrahippocampal atrophy (4, 6), the present study by Bernhardt et al. shows a pattern of cortical thinning very similar to the HA group.

Key findings that shed light on the significance of cortical thinning in mesial temporal epilepsy are that it is progressive and that it has a robust association with seizure control (8, 9). In mesial temporal epilepsy, with or without HA, serial MRIs over a mean interval of 2.5 years demonstrated progressive atrophy in the mesial and superior lateral frontal and parietal cortices, with more rapid worsening in patients with more than a 14-year history of epilepsy, and greater thinning in those with a higher seizure frequency (8). Serial MRIs in a control group documented that these changes could not be attributed to normal aging (8). Other investigators independently showed that MRIs with a median interval of 39 months showed progressive white and gray matter atrophy, especially in patients with a longer history of epilepsy, with more intense progression with a higher seizure frequency, and left temporal onset (9). It has been argued that this extrahippocampal atrophy represents seizure-induced damage (8). While this is a



plausible and parsimonious explanation of the findings, even a strong association between seizure frequency and atrophy cannot, by itself, conclusively prove that one causes the other.

It should also be noted that mesial temporal lobe epilepsy is associated with not only impairment of memory but also of other cognitive functions (10). This cognitive decline has been proposed to result from network disruption that correlates with the extensive, progressive extrahippocampal abnormalities seen in mesial temporal epilepsy, and not just with damage to the hippocampus or any other specific structure (10).

The current study used an analysis method that generates a map defining the gray/white matter junction and the gray matter/CSF boundary to measure cortical thickness in different regions. Comparisons were made with control subjects, and between epilepsy patients with and without HA. The strength of the statistical approach used in this study is that it combines data from many patients, so that subtle anatomic changes can be detected and compared. The limitation of this approach is that it may pool heterogeneous information—individual patients that might have different degrees and patterns of atrophy, and brain regions that may be composed of smaller areas with distinct connections and functions.

Surgery was performed in 62 of the 105 patients. It should be noted that hippocampal sclerosis was confirmed pathologically in 81% of the HA patients and in 64% of those without, indicating a substantial overlap between these subgroups. Because of this, and because of insufficient patient numbers to detect small differences, it is not surprising that no differences in cortical atrophy between patients with and without HA were seen, although both subgroups had significant widespread cortical thinning compared with controls.

Comparison between patients that were seizure-free postoperatively, and those that were not, yielded significant differences. Patients who were not seizure-free had more ipsilateral posteriolateral temporal and contralateral parieto-occipital thinning in the subgroup without HA, and more ipsilateral temporopolar and bilateral insular atrophy in the HA subgroup. Not only does this indicate that cortical atrophy is a predictor of surgical outcome, but also it suggests that different clinical subgroups of mesial temporal epilepsy may involve different networks. It is especially intriguing that a longitudinal analysis over time showed significantly less progression of atrophy in bilateral frontocentral cortices in eight patients that were seizure-free after surgery, as compared with four who were not. It cannot be confidently assumed that this indicates that control of seizures with surgery arrests the progression of cortical thinning, since it is unknown whether there were other factors that could account for this difference (such as disparity in the duration and preoperative severity of epilepsy between these two postsurgical subgroups).

It is, therefore, established that uncontrolled mesial temporal epilepsy is a progressive condition, with cognitive

dysfunction that correlates with gradually worsening anatomic changes in widespread regions of the forebrain. The seizures themselves are the prime suspect as the cause of this deterioration. Do seizures damage the brain? If the findings of Bernhardt et al.—that control of seizures by successful epilepsy surgery reduced the progression of extrahippocampal atrophy—were confirmed by a larger, well-controlled series, it would help confirm that these structural changes are actually the direct effect of seizures. This would create a compelling argument for more aggressive intervention early in the course of mesial temporal epilepsy to forestall development of these anatomic changes and their functional consequences.

by John W. Miller, MD, PhD

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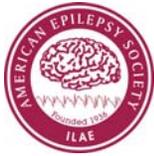
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