



Cortico-Thalamic Connections and Temporal Lobe Epilepsy: An Evolving Story

Mapping Thalamocortical Network Pathology in Temporal Lobe Epilepsy.

Bernhardt BC, Bernasconi N, Kim H, Bernasconi A. *Neurology* 2012;78:129–136.

OBJECTIVE: Although experimental work has provided evidence that the thalamus is a crucial relay structure in temporal lobe epilepsy (TLE), the relation of the thalamus to neocortical pathology remains unclear. To assess thalamocortical network pathology in TLE, we mapped pointwise patterns of thalamic atrophy and statistically related them to neocortical thinning. **METHODS:** We studied cross-sectionally 36 patients with drug-resistant TLE and 19 age- and sex-matched healthy control subjects using high-resolution MRI. To localize thalamic pathology, we converted manual labels into surface meshes using the spherical harmonic description and calculated local deformations relative to a template. In addition, we measured cortical thickness by means of the constrained Laplacian anatomic segmentation using proximity algorithm. **RESULTS:** Compared with control subjects, patients with TLE showed ipsilateral thalamic atrophy that was located along the medial surface, encompassing anterior, medial, and posterior divisions. Unbiased analysis correlating the degree of medial thalamic atrophy with cortical thickness measurements mapped bilateral frontocentral, lateral temporal, and mesiotemporal cortices. These areas overlapped with those of cortical thinning found when patients were compared with control subjects. Thalamic atrophy intensified with a longer duration of epilepsy and was more severe in patients with a history of febrile convulsions. **CONCLUSION:** The degree and distribution of thalamic pathology relates to the topography and extent of neocortical atrophy, lending support to the concept that the thalamus is an important hub in the pathologic network of TLE.

Commentary

As an epilepsy community, we *know* temporal lobe epilepsy (TLE) very well. First, it is the most common type of focal epilepsy. Second, it is responsible for the majority of resective surgeries performed for intractable epilepsy. Third, its exhaustively studied pathological substrates fall under the two major umbrellas of either hippocampal sclerosis with characteristic cell loss in the CA1 and CA3 hippocampal subfields, or various extrahippocampal epileptic pathologies such as vascular malformations, tumors, malformations of cortical development, and a growing minority of nonlesional cases with essentially normal structural neuroimaging and no pathological abnormalities on microscopic tissue examination, but with an electro-clinical picture that is highly consistent with a “TLE syndrome.” As such, our work-up of the full *temporal lobe* epilepsy spectrum, ranging from newly diagnosed to medically intractable disease, largely focuses on identifying signs of *temporal lobe* pathology. Yet, in the article chosen for this commentary, Bernhardt et al. used novel and elegant MRI processing techniques to demonstrate a pattern of *bilateral* thinning of the frontocentral, lateral temporal, and mesiotemporal

cortices and *ipsilateral* mesial thalamic atrophy in patients with drug-resistant *unilateral* TLE, whether hippocampal sclerosis was present or not. These findings represent the latest addition to a long, slow but steady stream of evidence driving us to think outside the box of the temporal lobe while evaluating patients with TLE.

Gradually painting the layout of pathology beyond the amygdalo-hippocampal complex in TLE, volumetric MRI studies have consistently shown significant ipsilateral atrophy in the entorhinal and perirhinal cortices (1–3). The degree of this atrophy strongly correlated with the extent of electrophysiological coupling occurring at seizure onset between the entorhinal cortex and the hippocampus, as measured via intracranial stereo-EEG recordings (4), supporting the notion that its main underlying mechanism may be excitotoxic cell loss secondary to chronic stimulation in the setting of long-standing epilepsy. Given the immediate proximity of these mesial temporal structures to the hippocampus and their well-established connectivity to the amygdalo-hippocampal complex, such observations of mesial temporal cortical thinning and volume loss are intuitively understood and accepted. Acknowledging cortical atrophy outside of the mesial temporal cortex is where it gets more challenging. The advent of more advanced MRI volumetric and processing techniques such as voxel-based-morphometry and spherical harmonic shape descriptions exponentially expanded our ability to visualize more



subtle volumetric changes and to evaluate the more “distant” pathological implications of TLE. Similar to the article at hand, McDonald et al. also showed an extension of atrophy beyond the mesial temporal cortex to involve frontal and lateral temporal regions bilaterally in patients with mesial TLE relative to controls (5). The most striking finding was bilateral cortical thinning in the precentral gyrus and immediately adjacent paracentral region and pars opercularis of the inferior frontal gyrus, extending to the orbital region. Within the temporal lobe, bilateral thinning was observed in Heschl’s gyrus only. Strictly ipsilateral thinning was observed in the superior and middle temporal gyri, as well as in the medial orbital cortex (5). The cingulate cortex was also atrophied in another study (2). Although cortical structures such as the orbitofrontal cortex and cingulate gyrus do represent classic recipients of hippocampal efferents and, as such, are understandable targets for excitotoxic cell loss, not all of the above areas of observed cortical thinning do. This brings into question whether other mechanisms besides seizure-related cell loss may be relevant to this extratemporal cortical thinning in TLE.

Analyzing thalamic volumes in the setting of TLE has also yielded evidence of cell loss and atrophy either in the mesial thalamic nuclei, or the anterior nuclei (3, 6), or pulvinar (3). Also, although the thalamus represents a classic “relay nucleus” of hippocampal efferents, most studies have consistently shown a direct relationship of the extent of its atrophy to that of the hippocampus and mesial temporal cortex (2, 3), but not with the severity and distribution of neocortical thinning (3). This discrepancy of findings may be related to differences in techniques and resolution of various imaging modalities. Alternatively, it may again reflect a more nuanced mechanism of atrophy beyond seizure-related cell loss. The question then becomes: what else can cortical thinning mean in this context, and what role does the thalamus play in it? Turning to functional and electrophysiological examinations might help with an answer.

A wide network of perfusion changes was seen in an analysis of ictal SPECT findings during early tracer injections (0–30 seconds) of complex partial seizures in patients with hippocampal sclerosis (7). This network included the ipsilateral middle frontal, precentral gyrus, and precuneus, the contralateral postcentral gyrus and cerebellum, and both occipital lobes, but not the thalamus. While most of these neocortical regions were hyperperfusing with the temporal lobe at ictal onset, both the frontal lobe and precuneus were hypoperfusing, suggesting that while all these cortical structures represent distinct components of a limbic network and demonstrate cortical thinning in various volumetric MRI studies, some are excitatory and others are inhibitory during the evolution of a seizure. Hyperperfusion of the mesial thalamus—demonstrating atrophy in the present study by Bernhardt et al.—was seen in another SPECT study with tracer injections occurring later after seizure onset (8), potentially implying that thalamic involvement occurs in the later stages of a TL seizure evolution. Regardless of its timing, thalamic “gating” may be a significant marker of the extent of the active epileptogenic network, and thus of seizure outcomes following resective epilepsy surgery. In fact, intracerebral recordings do demonstrate that the thalamus and remote cortical structures synchronize their activity

during TLE seizures, further showing poorer surgical outcomes in patients with stronger corticothalamic coupling (9). If cortical thinning represents, then, the anatomic signature of both the distribution and strength of this epileptogenic network, one may understand why both lesional and nonlesional TLE share the same topography of neocortical—likely mostly excitotoxic—volume loss, while the patterns of cortical thinning predictive of surgical outcome are distinct: seizure recurrence was related in one study to temporopolar and insular cortical atrophy in TLE patients with hippocampal atrophy versus posterior quadrant cortical atrophy in nonlesional TLE, suggesting different configurations of epileptogenic networks in these two groups (2).

In summary, the maturity and extent of the epileptogenic network beyond the physical boundaries of the temporal lobe itself represent the true essence of disease in TLE. While considering the extrahippocampal manifestations of TLE, and evoking the thalamus as a critical gatekeeper in hippocampal connections, the real neuroimaging challenge is to develop reproducible and reliable MRI postprocessing tools that can be easily incorporated in the clinical workflow of caring for patients with epilepsy as we finally understand the need to visualize the TLE epileptogenic network and not simply the focus.

by Lara E. Jehi, MD

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