

# THALAMUS: THE “INNER CHAMBER” REVEALS ITS SECRETS

**A Subcortical Network of Dysfunction in TLE Measured by Magnetic Resonance Spectroscopy.** Hetherington HP, Kuzniecky RI, Vives K, Devinsky O, Pacia S, Luciano D, Vasquez B, Haut S, Spencer DD, Pan JW. *Neurology* 2007;69(24):2256–2265. **OBJECTIVE:** The goal of this work was to evaluate the relationship between neuronal injury/loss in the hippocampus, thalamus, and putamen in temporal lobe epilepsy (TLE) patients using  $^1\text{H}$  magnetic resonance spectroscopic imaging. **METHODS:**  $^1\text{H}$  spectroscopic images from the hippocampus and thalamus of controls and patients with TLE were acquired at 4 T. The spectroscopic imaging data were reconstructed using an automated voxel-shifting method based on anatomic landmarks providing four, six, and three loci for the hippocampus, thalamus, and putamen, respectively. For correlation analysis, the hippocampal and striatal loci were averaged to provide single estimates of the entire structure, whereas the thalamus was divided into two regions, an anterior and posterior measure, using the average of three loci each. **RESULTS:** The ratio of *N*-acetyl aspartate to creatine (NAA/Cr), a measure of neuronal injury/loss, was significantly reduced in both the ipsilateral and contralateral hippocampi and thalami. NAA/Cr in the ipsilateral hippocampus was significantly correlated with the ipsilateral and contralateral anterior and posterior thalami, putamen, and contralateral hippocampus. In control subjects, the hippocampi were only correlated with each other. **CONCLUSIONS:** The data demonstrate that there is significant neuronal injury/loss in both the ipsilateral and contralateral thalami in temporal lobe epilepsy patients, with greater impairment in the anterior portions of the ipsilateral thalamus. The degree of injury/loss in the ipsilateral and contralateral thalamus and putamen is directly correlated with that of the ipsilateral hippocampus. This is consistent with the hypothesis that the impairment and damage associated with recurrent seizures as measured by *N*-acetyl aspartate originating in the hippocampus results in injury and impairment in other subcortical structures.

## COMMENTARY

Thalamic involvement in human temporal lobe epilepsy (TLE) was first documented in 14 of 55 patients in a macroscopic and microscopic autopsy study; prospectively obtained ictal semiologies and EEGs had indicated the presence of TLE (1). Abnormalities ranged from gross atrophy to microscopic neuronal loss and gliosis. The lack of predilection to any single thalamic area suggested to the authors that retrograde degeneration from cortical destruction was not a pathogenetic factor. Of the 14 patients, hippocampal sclerosis appeared in 11 and amygdala lesions in 9.

Abundant axons extend from mesial temporal structures to the thalamus, with the medial dorsal and anterior thalamic nuclei being the principal recipients. Fibers, originating from the basolateral nuclei of the monkey amygdala, project to the mag-

nocellular portion of the mediodorsal thalamic nucleus, while the central and medial nuclei go to midline thalamic nuclei (2). In primates, two systems connect the hippocampal region to the thalamus: 1) the mediodorsal nucleus receives afferents via the cingulum and anterior commissure, and 2) the anterior thalamic nucleus receives afferents via the fornix, mammillary bodies, and mammillothalamic tract (3–5). Projections from the entorhinal cortex extend to the pulvinar and lateral dorsal thalamic nucleus.

These abundant connections likely contribute to the reduced thalamic *N*-acetyl aspartate to creatine (NAA/Cr) ratios demonstrated in the study by Hetherington and colleagues. Although no mention of observed thalamic propagation of temporal lobe seizures could be found in the references cited in this article, thalamic ictal involvement (usually delayed) was found, using depth recordings, in 11 of 13 patients with mesial TLE in another study (6). Recovery of NAA in the nonepileptogenic temporal lobe after resection of the epileptogenic side (7) suggests that low thalamic NAA levels may reflect ictal spread and

not simply neuronal loss—a possibility also indicated by the authors of this paper.

Results of this study suggest that thalamic dysfunction may contribute to memory impairment in some patients with medial temporal epilepsy. Lesions of the human anteromedial thalamus have long been associated with memory impairments (8). Memory deficits from mediodorsal thalamic lesions in humans resemble those of anterior mesial temporal lesions sufficiently enough to suggest a memory system involving the amygdala, the hippocampal region, and the anteromedial thalamus (9). Although thalamic lesions causing amnesia commonly involve the mediodorsal nucleus, such lesions often encompass neighboring thalamic structures. The severity of the amnesia appears to correlate with thalamic lesion size (10). The finding that NAA/Cr ratios were decreased in all thalamic areas tested in the study by Hetherington et al. (especially anterior mesial) indicates that dysfunction was amply widespread to cause or contribute to any amnesia. Note also that ratios were diminished bilaterally but asymmetrically. Among asymmetrical bilateral lesions, left- and right-accentuated ones produce primarily verbal and nonverbal memory deficits, respectively (11,12). Such bilaterality of lower NAA/Cr ratios may underlie the mixed (i.e., verbal and nonverbal) memory deficits seen in patients with unilateral temporal seizures. The lower NAA/Cr ratios found in this study are not only indicative of thalamic dysfunction but also suggest that any memory impairment in these patients would reflect more than mesial temporal pathophysiology.

Reciprocal connections between the magnocellular portion of the mediodorsal thalamic nucleus and the orbital frontal and medial frontal cortex provide a supplementary pathway to the direct pathway of temporal frontal fibers involved in ictal propagation (2). During pentylenetetrazol-induced seizures in the rat, anterior thalamus activity more closely correlated with what was occurring in the cerebral cortex than did any other thalamic nuclei to cortex activity, suggesting a greater contribution of the anterior thalamus to an ictal network (13). A matrix of calbindin-immunoreactive neurons extending throughout the primate thalamus effects synchronous, high-frequency activity with the cerebral cortex (14), which may influence coherence and ictal propagation. The various anatomical connections and physiological mechanisms described here may contribute to the presence of a generalized seizure tendency among TLE patients (15).

The correlation between NAA/Cr decreased ratios and number of seizures—but not between NAA/Cr decreased ratios and duration of the seizure disorder—found in the Hetherington et al. study is at variance with an investigation disclosing a progressive decline in human hippocampus neuronal densities that corresponded to duration of seizure disorder (16). Similarly, another study found that rat hippocampal damage correlated with “time to perfusion” and not

to seizure number in a study of status epilepticus-induced epileptogenesis (17).

This study reemphasizes the role of subcortical structures in TLE. It also demonstrates that interactions between clinical and basic neuroscience are required to unravel the complexities of human epilepsy. Hopefully, technological advances will disclose point-to-point anatomical and physiological relationships between mesial temporal structures and individual thalamic nuclei.

by Warren T. Blume, MD

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