Thalamocortical atrophy in patients with primary generalized tonic and clonic seizures

B. C. Bernhardt[1], D. Rozen[1], L. Horwood[1], and A. Bernasconi[1]

[1]Brain Imaging Center, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada

Introduction. Idiopathic generalized epilepsy (IGE) is clinically characterized by typical absences, generalized tonic-clonic seizures (GTCS) and myoclonic jerks. Patients with different IGE sub-syndromes manifest all or some of these seizure types. The cardinal EEG features are widespread, generalized spike and waves discharges, with higher amplitude in both frontal areas. Although experimental work in animal models of IGE indicate that the thalamocortical circuitry is involved in the generation of the epileptic discharges (1, 2), the neuropathological substrate of IGE is not fully defined. Structural MRI studies have yielded preliminary evidence of diffuse abnormalities in IGE, but results have been conflicting. Functional studies reported BOLD and perfusion changes in frontal, parietal, posterior cingulate and thalamic areas. Furthermore, MR spectroscopy has shown thalamic dysfunction. Our purpose was to assess thalamic and neocortical atrophy in IGE by measuring cortical thickness and thalamic volumes. We hypothesized that neocortical atrophy is primarily localized in areas connected to the thalamus. Connections were inferred by correlating thalamic volume with gray matter thickness data across the neocortex (3).

Methods. We studied 24 consecutive IGE patients with GTCS and 47 healthy controls. We measured cortical thickness using an unbiased automatic surface-based deformation algorithm (4, 5) and calculated the volumes of thalami automatically by applying a non-linear matching algorithm to a probabilistic anatomical atlas (6) on high-resolution MRI (3D T1-spoiled gradient echo sequence; TR = 18; TE = 10; voxel size: $1mm^3$). Images were corrected for intensity non-uniformity (7) and linearly registered to a standardized stereotaxic space (8). We statistically corrected all data for age and gender prior to all analyses. Group comparisons assessed the extent of atrophy in IGE patients. We correlated the volume of the thalamus with cortical thickness values. Thalamic volumes and cortical thickness data were further correlated with disease duration to estimate seizure-related damage.

Results. Compared to healthy controls, IGE patients had a bilateral decrease in thalamic volumes ($t<-3.33$, $p<0.001$) and in mean cortical thickness ($t<-2.54$, $p<0.02$). Cortical thickness was decreased in fronto-centro-parietal areas (*Figure, top*). In controls and in IGE patients, thickness in the same regions had a high positive correlation ($p<0.005$) with thalamic volumes. Correlations were more widespread on the right hemisphere and more prominent in IGE patients, where additional occipital areas displayed a high degree of positive correlation *(Figure, middle*). Duration of epilepsy negatively affected thickness in central, parietal and occipital areas (*Figure, bottom*) and volumes of the thalamus bilaterally ($p<0.04$, $r<-0.37$).

Discussion. We demonstrate that IGE is associated with bilateral and progressive atrophy of the thalamus. Moreover, neocortical atrophy occurs in areas functionally connected to the thalamus, supporting the pivotal role of thalamocortical connectivity and damage secondary to seizures in IGE.

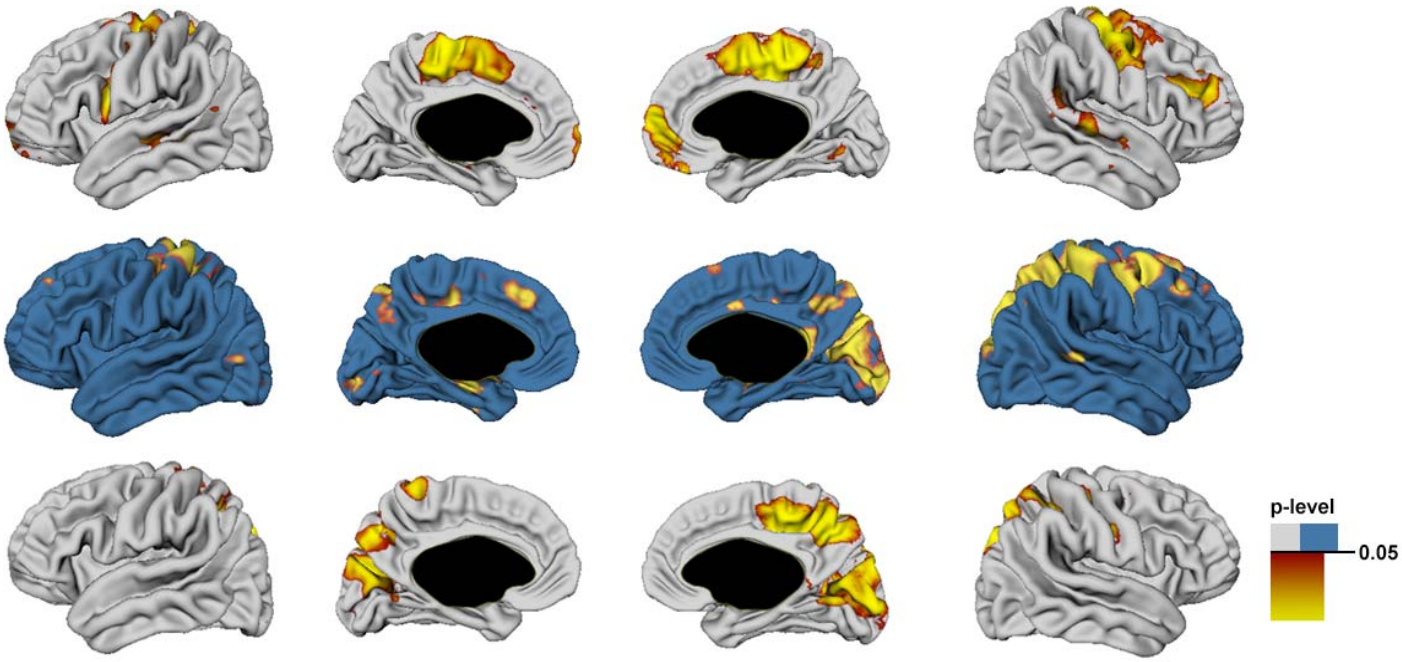

Figure. *Top:* group differences between IGE patients and healthy controls (FDR<0.05,). *Middle:* positive correlations between ipsilateral thalamic volume and cortical thickness at each vertex ($p<0.05$, $r>0.34$). *Bottom:* negative effects of duration of epilepsy at each vertex ($p<0.05$, $r<-0.34$).

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