Unilateral Diffusion and Bilateral Volumetric Differences of the Thalamus in Temporal Lobe Epilepsy

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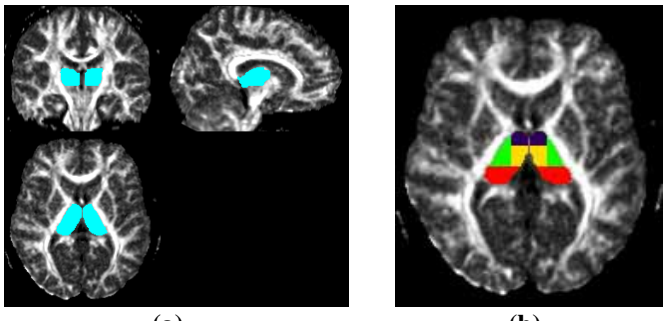
Introduction: Previous studies have suggested that various thalamic nuclei may have unique roles in certain epilepsies due to their specific interconnections with different cortical regions [1]. In temporal lobe epilepsy (TLE) with unilateral Mesial Temporal Sclerosis (MTS), bilateral atrophy of the thalamus has been observed by using high resolution structural MRI [2]. Recently, diffusion tensor imaging (DTI) has demonstrated water diffusion changes of the hippocampus [3] and white matter [4] in TLE. However, the thalamus in TLE has been rarely studied by DTI. The primary objective of this study was to explore regional diffusion changes of the thalamus in TLE with MTS by DTI. A secondary objective is to determine whether any diffusion changes are consistent with volumetric findings. Diffusion and volumetric analyses in the same subjects are infrequent, but they may provide novel insight into the understanding of the involvement of the thalamus in TLE with MTS.

Method: Ten medically intractable TLE patients with left MTS (38 ± 14 years) and twenty age-matched controls were included in our study. Coronal T2 relaxometry was used to quantify MTS. DTI was performed on a 1.5 T Siemens Sonata using a single-shot EPI-based sequence (63 slices, 2 mm thickness with no inter-slice gap, TR=10s, TE=88ms, 6 diffusion directions, b=1000s/mm^2, 8 averages, 128×128 matrix, FOV=256×256 mm^2). A magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was used to get high resolution (1×1×1 mm^3) structural MRI of the whole brain. Specifically, our processing included several steps as follows: 1) Quantitative diffusion maps (*i.e.* fractional anisotropy (FA) and mean diffusivity (MD)) were generated; 2) Diffusion maps were coregistered to structural MRI; 3) Structural MRI were mapped into MNI space, and the same transformation was applied to diffusion maps; 4) WFU-pickup-atlas [5] was used to mask out the thalamus in MNI space, and we further polished the mask by removing the voxels within the masked thalamus if FA >0.5 (to ignore voxels in internal capsule) or MD > 1.3×10^{-3}mm^2/s (to ignore voxels in lateral ventricle). Final quality of the extraction for whole thalamus was manually checked and was deemed acceptable for all subjects (*Fig 1a*); 5) Based on a relatively simple but robust scheme, the unilateral thalamus was further subdivided to four parts: anterior, mesial, lateral and posterior sub-regions (*Fig 1b*); 6) Mean FA and MD of each sub-region were taken as the typical diffusion measurements, and each thalamic sub-regions' volume in native space was estimated by the Jacobian determinants of deformation field, which represent the amount of expansion or contraction from MNI space to native space; 7) The comparison of FA, MD and volume between patients and controls was made by an independent t test respectively. Considering the multiple comparison in our study, $p < 0.01$ was considered significant.

Results: In our left MTS patients, significant ipsilateral elevation of mean diffusivity (MD) was identified in anterior thalamus (p<0.001, difference: 5.3%) and mesial thalamus (p=0.007, difference: 3.8%), and an ipsilateral elevation tendency was found in lateral thalamus (p=0.02) and posterior thalamus (p=0.02) (*Fig2a*). The contralateral thalamus had no subregion showing significant MD changes, although the posterior thalamus had a weak tendency of elevation (p=0.05) (*Fig2b*). Interestingly, significant reduction of fractional anisotropy (FA) was found only in ipsilateral posterior thalamus (p=0.005, difference: 5.2%) (*Fig2c, d*). For the volume, all thalamic sub-regions in TLE with left MTS showed strongly significant reduction bilaterally (ipsi-difference: 16.7%, contra-difference: 15.2 %) (*Fig2e, f*).

Discussion: Unlike the volume finding demonstrating diffuse bilateral thalamic abnormalities, the diffusion changes exhibited obvious lateralization and intra-thalamus variation in patients with TLE and unilateral MTS. More interestingly, the three sub-regions (*i.e.* ipsilateral anterior, mesial, and posterior) with diffusion changes all contain nuclei that have significant interconnections with the temporal lobe (*i.e.* anterior nucleus, mesial-dorsal nucleus and pulvinar). As patients with TLE and MTS are known to have significant cell loss in the mesial temporal structures, our DTI findings would be consistent with downstream degeneration along limbic pathways arising from the affected temporal lobe. As these hemispheric and intra-thalamic variations were not apparent with volumetric analysis, our findings suggest that DTI can provide unique information that may provide new insights into the pathogenesis of temporal lobe epilepsy.



(a) **(b)**

Fig1. Exaction and subdivision of thalamus: (a) Bilateral thalamus extracted by our automated criterion in one subject and (b) its subdivision into anterior (purple), mesial (yellow), lateral (green), and posterior (red) thalamus. The detailed scheme is as follow: Anterior (11>x>-11, y>-10); Mesial (11>x>-11, -9>y>-26); Lateral (x>10 or x<-10; y>-26); Posterior(y<-25). All coordinates are in MNI space.

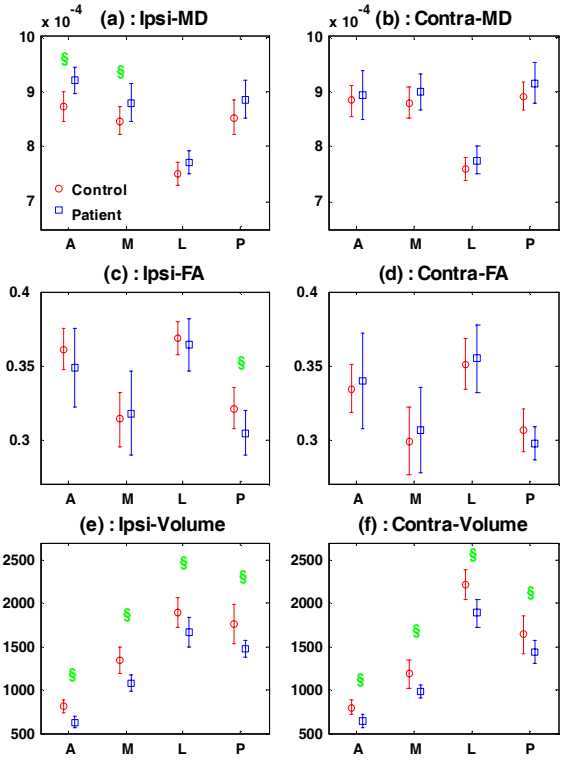


Fig2. Bilateral MD (mm^2/s) (*a,b*), FA (*c,d*) and volume (mm^3) (*e,f*) of thalamic sub-regions (*mean ± standard deviation*) in TLE with left MTS patients (N=10, blue with rectangle) and controls (N=20, red with circle). A, M, L and P denotes anterior, mesial, lateral and posterior sub-region, respectively; § indicates p<0.01.

Reference: [1] Juhasz C *et.al*, Neurology, 1999. 53: 2037-45. [2] Bernasconi N *et.al*, Neuroimage, 2004. 23:717-723. [3] Assaf BA *et.al*, Am J Neuroradiol, 2003. 24: 1857-62. [4] Concha L *et.al*, Ann Neurol, 57: 188-196. [5] Maldjian JA *et.al*, Neuroimage, 2003. 19: 1233-39.