The influence of temporal lobe epilepsy on thalamocortical connectivity

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Introduction: Temporal lobe epilepsy (TLE) refractory to antiepileptic drugs often has hippocampal sclerosis (HS) as its presumed underlying basis. Previous studies have demonstrated gray matter atrophy in patients with HS located in the thalamus as well as in the hippocampus and the rest of the limbic system (1). The mechanism of the thalamic damage is not clear but is believed to represent the secondary effect of seizure activity. This reflects the crucial role of the thalamus as the "central post office" of the brain. Everything that reaches the brain goes through the thalamus and is then distributed to widespread cortical fields. The thalamus is reciprocally connected with the cortex and the thalamocortical relationship is very tightly coupled. A tool has recently been developed to probe this relationship that is based on probabilistic DTI tractography (2). Seed voxels in the thalamus are classified according to the probability of connection to different cortical target masks. The connectivity distributions thereby revealed are in accordance with those expected and are reproducible. In this study, we used this approach to evaluate the influence of HS on thalamic connectivity to the cortex and especially to the limbic and temporal cortices.
Methods: *Imaging*: DTI was performed with a 28 direction spin echo EPI sequence (3T GE scanner). The imaging parameters were as follows: TR/TE=5.8sec/83ms, 96×96 matrix, voxel size: 2.5×2.5×2.5mm, 50 contiguous slices, 3 pass interleaving, b=1100s/mm^2, 5 repeats of b=0 image, 28 directions. T1-weighted structural imaging was performed with a inversion-recovery prepared FSPGR sequence (voxel size: 0.5×0.5×2mm).
Subjects: 14 subjects with unilateral left HS were compared to a set of 14 age and gender matched control subjects (mean age: 35±12 years, 9 males).
DTI analysis: The DTI images were analysed with the FDT toolbox in FSL (http://www.fmrib.ox.ac.uk/fsl/). This toolbox also includes the module for connectivity based segmentation classification (CSBC). Affine registration between EPI-space and standard space are carried out via the high resolution structural image and the masking of the thalamus and the cortex can therefore be carried out in standard space. The cortical masks are supplied in the distribution (7 in total). The probabilistic tractography algorithm was used to define probability levels for connectivity to each target mask. Two distinct CBSC analyses were carried out to assess disturbance of thalamic connectivity in HS. The first was the standard thalamocortical mapping using all the cortical masks. The second was a simplified run in which a single target mask, the ipsilateral hippocampus/amygdala was used. In both cases, the output is an image depicting for each thalamic voxel the number of tracts (out of 5000 drawn through the probability distributions) that reach the target mask (the seeds-to-target image). A simple hard segmentation approach can then be used to classify the seed voxels according to the target mask with which they show the highest probability of connection (Behrens). Both analyses were carried out separately for left and right thalami in the HS and control subjects.
Image analysis: *Thalamocortical mapping*: A qualitative measure of mean thalamic connectivity mapping in each group was obtained by averaging the seeds-to-target image across the subjects and running the hard segmentation. Differences in the distribution of cortical connectivity were then evaluated by calculating in each subject the number of tracts reaching each target and comparing the pooled results between the 2 groups using simple unpaired t-test analysis. The distribution of connections to the temporal cortex was further investigated by masking the two expected zones of thalamic projections to that area, the anterior and lateral dorsal nuclei, and the lateral and inferior pulvinar, and determining the number of tracts reaching the temporal cortex from each of those zones. *Hippocampal masking*: The thalamo-hippocampal connectivity was evaluated in a similar manner by comparing the number of tracts reaching the hippocampal target.
Results: *Thalamocortical mapping*: Figure 1 shows the mean thalamic connectivity maps for the cortical and HS subject groups. Inspection of these maps revealed that in the thalamus ipsilateral to the hippocampal atrophy, the probability of connections to the somatosensory area (S1) in the ventral nuclei was increased in extent at the expense of a reduction in connectivity to the motor (M1) areas (Fig. 1). Connectivity to the posterior parietal cortex (PPC) in the lateral posterior nuclei was also reduced in extent. Quantitative evaluation of these differences indicated statistically significant reductions ($p<0.05$) of probability of thalamic connections to the ipsilateral prefrontal cortex (PFC) and PPC in the HS group. An increase in tract numbers reaching ipsilateral S1 was observed and, in the temporal lobe, this trend was repeated but was not significant. In the contralateral (right) thalamus the overall trends were similar to the ipsilateral results but changes were insignificant. In order to better depict the overall pattern of connectivity distribution, a "doughnut" chart is shown in Fig. 2. Further evaluation of the distribution of temporal connections revealed that in the anterior thalamic zone, temporal lobe connectivity was significantly decreased in the HS subjects in both the left and right thalami. On the other hand, in the posterior pulvinar area, the number of tracts displayed a non-significant increase in both thalami, implying a regional sensitivity. *Hippocampal masking*: The number of tracts reaching the hippocampal target was not statistically different between the 2 groups with again a non-significant increase in tract counts being observed ipsilaterally in the HS subjects.
Discussion: The use of this technique in a group of subjects with HS has enabled abnormalities in the connectivity of the thalamus to be probed. Seizure activity in TLE is relayed through the thalamus to the rest of the brain and the resultant thalamic atrophy is a well characterized phenomenon. However, although volume loss is consistently observed in the thalamus, T2 changes have not been observed. This indicates that the mechanism behind apoptosis in the thalamus is not severe enough to cause more substantial cellular changes reflecting the secondary nature of the damage. The results of our study confirm that the major thalamocortical connections remain largely unharmed by the seizure activity. Disturbances of the pathways to the prefrontal cortex dominate and this reflects the pathway of common seizure spread to this area. Impairments of connections to the temporal and hippocampal areas display a regional sensitivity with the anterior nuclei pathways displaying significant impairment. This has been shown to be the main area of thalamic volume loss (1). However, the connections to the limbic cortex from the lateral pulvinar area remain unimpaired and even show an increasing trend in the HS subjects. It is from this posterior thalamic region that the tracts leave the thalamus and, following the fornix, reach the hippocampal formation and temporal cortex (2).
References: (1) Bonilha L. et al, NI, 25:1016 (2005); (2) Behrens TEJ et al., Nature Neurosci, 6:750 (2003)

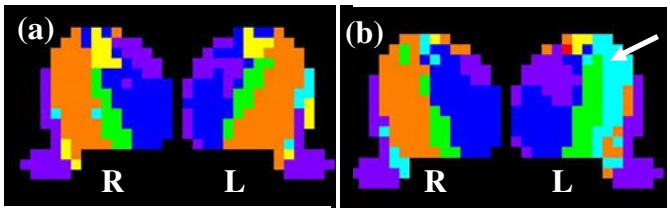

Fig 1: Connectivity based segmentation of the thalamus in the (a) control and the (b) HS groups. The left and right thalami are shown in each case. The arrow points to the area of increased S1 connections in the HS group. The scheme relating each color to the cortical mask is as shown in Fig. 2

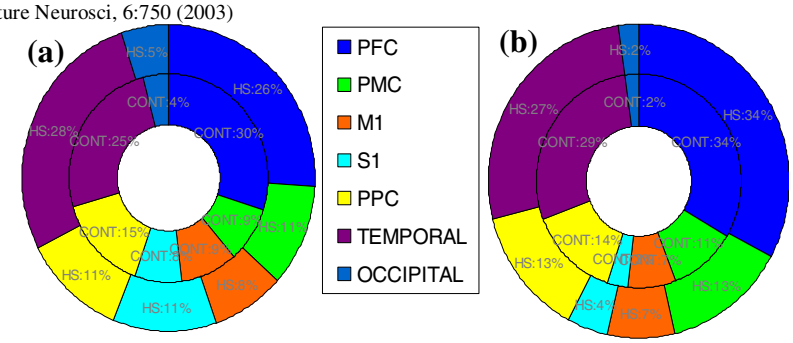

Fig 2: Doughnut plots showing the distribution of connection probabilities in (a) left, ipsilateral thalamus and (b) the right thalami. The HS subjects are on the outer ring in each case, and percentages are given in each category.