Smaller subcortical volumes in patients with idiopathic generalised epilepsy and their first degree relatives using FIRST analysis

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Background

Idiopathic generalised epilepsies (IGE) have a complex inheritance pattern and are predominantly polygenic. Endophenotypes are subclinical phenotypes that have a simpler genetic basis than the overall phenotype, and may represent a genetic liability to develop symptoms. Characterising such traits could be of considerable use both for understanding seizure pathology, and for identifying individuals at increased risk. Although structural imaging is qualitatively normal in IGE, several studies using quantitative imaging methods have reported focal abnormalities with reduced volumes of the subcortical nuclei such as thalamus, caudate, globus pallidus and putamen in groups of IGE patients compared to controls[1,2,3]. However, there are no published studies of imaging in relatives of patients with IGE.

Objectives

In this study we sought to identify whether patients with idiopathic generalised epilepsy and their first degree relatives had smaller volumes of subcortical nuclei, using FIRST (FSL 4.14, FMRIB http://www.fmrib.ox.ac.uk/fsl/first/ [4,5]), an automated model based segmentation/registration tool which uses a training data set of manually segmented images to investigate shape and volume of subcortical grey matter nuclei (thalamus, putamen, globus pallidus, hippocampus, caudate, amygdala and nucleus accumbens)..

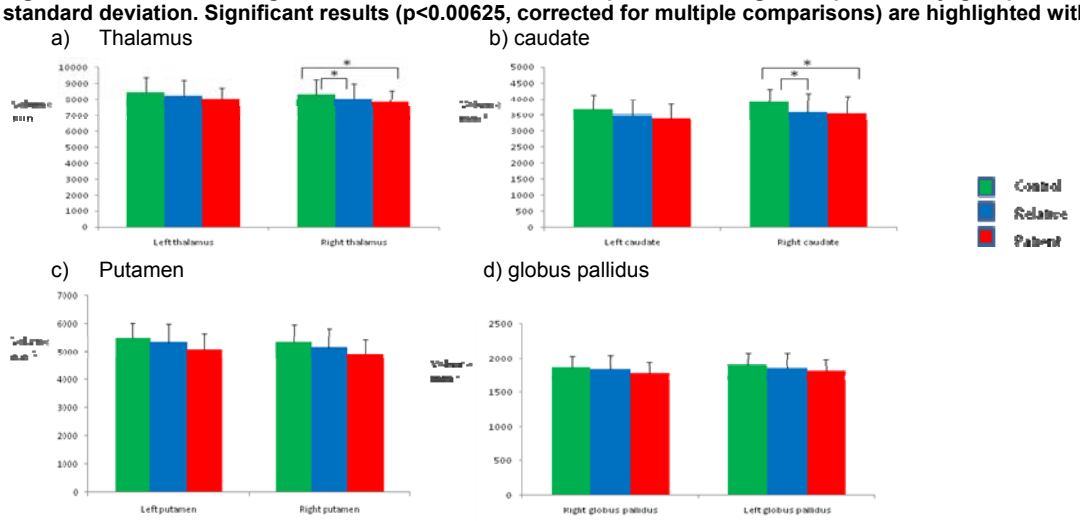
Methods

Subjects: 30 patients with IGE, 36 of their unaffected first degree relatives and 40 controls were scanned using a 3 Tesla GE HDx system (General Electric, Milwaukee, WI). **Image acquisition:** A 3-dimensional isotropic high resolution inversion recovery prepared spoiled gradient-recalled echo (IR-SPGR) scan was obtained in the coronal plane (FOV 28 cm^2, Matrix size 256x256, 160 1.1mm partitions, giving an isotropic voxel size of 1.1mm,, TE 2.8ms, TR 7 ms, Inversion time 450ms, flip angle 20°). **Image processing:** Each axially reoriented coronal SPGR analysis was processed using FIRST. Surface meshes were created for each subcortical structure by parameterising the manually generated labels. The mesh is composed of a set of triangles where the apex of adjoining triangles is called a vertex. A deformable mesh model is used so that the cross-subject vertex correspondence is preserved and the number of vertices for each structure is fixed, enabling corresponding vertices to be compared across individuals. FIRST gives outputs of total volume for each subcortical structure. **Statistical analysis:** ANOVA was used to investigate group differences between the three groups with age and total brain volume (SPM 8, VBM toolbox) entered as covariates. In order to correct for multiple comparisons, a Bonferroni correction factor of 8 was used. For those measures where it appeared that patients and relatives both differed in a similar way from controls, a 2-tailed test for linear trends was carried out to investigate whether relatives fell between patients and controls.

Results

Patients and relatives showed significantly lower volumes of right thalamus and right caudate compared with controls (right thalamus: F=5.51, df 2:101, p=0.005, right caudate: F=4.95, df 2:101, p=0.006). There were significant linear trends for right thalamus (p=0.038), right caudate (p=0.006), left caudate (p=0.006), right putamen (p=0.012) and left putamen (p=0.011) with relatives falling between patients and controls for all these regions.

Fig 1: Mean volume of right and left thalamus, caudate, putamen and globus pallidus by group. Error bars show standard deviation. Significant results (p<0.00625, corrected for multiple comparisons) are highlighted with a star.



Discussion

Our data support the hypothesis that IGE is associated with reduced volumes of subcortical nuclei, which is consistent with the theory that abnormal cortico-subcortical connections underlie the pathophysiology of IGE. Our data also provides evidence that such changes are found in clinically unaffected relatives of patients with IGE, suggesting that such abnormalities are a heritable endophenotype.

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