Increased Folding Complexity of the Left Temporal Pole in Temporal Lobe Epilepsy

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Introduction

Converging histological and radiological data suggest neurodevelopmental abnormalities may play a role in the pathogenesis of drug-resistant temporal lobe epilepsy (TLE). Gross morphological evaluation of medial temporal lobe structures has identified unusual shape and positioning of the hippocampus in TLE patients (1). However, the anatomical extent of potential neurodevelopmental changes in TLE remains largely unknown. Cortical folding is thought to result from mechanical and tension-based processes including the establishment of axonal cortico-cortical connections during fetal growth (2,3). Automated measures of cortical surface curvature allow direct measurement of changes in gyral folding at every vertex on the brain surface, and may offer a sensitive index of cortical neurodevelopmental changes. Very few studies have investigated cortical complexity changes in TLE, and employed only visual ratings or poorly localised indices of whole-brain or lobar-level complexity. Using surface-based methods of cortical curvature sensitive to focal changes in gyrification, we tested whether: (i) TLE is associated with abnormal cortical folding (ii) cortical complexity relates to hippocampal positioning, and (iii) changes in gyrification impact on epilepsy surgery outcome.

Methods

High-resolution T1-weighted MRI images were acquired at 1.5T in 40 healthy volunteers (mean age 33.1, range 20-66 years) and 62 patients with unilateral TLE (mean age 35.8, range 18-63 years; 32 with left TLE, 28 with right TLE) being evaluated for temporal lobe surgery using a 3D fast field echo sequence (TR=18ms, TE=10ms, 30° flip angle, 1x1x1mm resolution). For *cortical surface measures*, individual subjects' T1 images were input to the CIVET pipeline (http://wiki.bic.mni.mcgill.ca/index.php/CIVET), which carries out correction for intensity non-uniformity, tissue segmentation, cortical surface extraction using the Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) algorithm, nonlinear surface registration and cortical surface measurements. Absolute mean curvature was calculated on the mid-surface between the white and pial matter as a measure of changes in the frequency of sulcal and gyral folds and smoothed at both 10mm and 30mm FWHM. Group t-statistic maps of absolute mean cortical curvature (thresholded at $p< 0.05$, corrected using random field theory) were generated to test for differences in cortical folding between healthy volunteers and left and right TLE patients. To separate folding differences from potential atrophy confounds, we also measured cortical thickness in native T1 space as the distance between corresponding vertices on the inner and outer surfaces in each hemisphere (4) and repeated the curvature analysis, correcting for cortical thickness at every vertex. Curvature results were then related to measures of hippocampal positioning. For *hippocampal rotation measurements*, 3D hippocampal models were created as previously described (5) from manual segmentations to determine (i) positioning of the hippocampus relative to the midline, (ii) a medial-lateral deflection in the tail of the hippocampus and (iii) relative vertical deviation of the entire hippocampus from its normally horizontal orientation. Surgical outcomes (mean follow-up 5.1 years, range 1-11 years) were available for 42 patients. Twenty-seven were seizure-free following temporal lobe surgery (Engel Class I) while 15 patients had Class II, III or IV outcomes. Seventy-six percent of patients had histologically confirmed hippocampal sclerosis.

Results

Group t-stat maps demonstrated increased cortical curvature in patients with TLE relative to healthy controls in the left temporopolar region (Figure), irrespective of side of seizure onset. These folding changes were robust across smoothing levels. Areas of abnormal cortical folding were independent of those of cortical thinning, which affected the lateral temporal, frontal and occipital regions. Consistent with previous qualitative reports (1), the left hippocampus in TLE patients with a left-sided seizure focus showed an abnormal vertical orientation relative to controls ($t=3.72$, $p<0.001$, corrected for multiple comparisons), which was associated with greater folding of the left temporopolar region in the same patients ($r=0.37$, $p=0.031$). In right TLE patients, left temporopolar folding was associated with post-operative seizure outcome ($t=1.79$, $p=0.045$), such that patients with pre-operatively increased left temporal curvature were less likely to be seizure free after right temporal pole surgery than those with normal folding.

Discussion

Increased cortical folding of the left temporopolar region in drug-resistant TLE may be an indicator of neurodevelopmental deviance associated with this condition. This is further supported by the direct relationship between hippocampal malrotation and temporopolar folding complexity. The association between left temporopolar folding and unfavourable outcome in patients with a right-sided seizure focus suggests that the left hemisphere plays an important role in temporal lobe epileptogenesis.

References

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