SPHARM detects hippocampal subfield pathology in temporal lobe epilepsy

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Introduction. The most common form of pharmacoresistant epilepsy in adults is temporal lobe epilepsy (TLE) related to hippocampal sclerosis (HS). Histopathologically, HS is typically characterized by neuronal loss, gliosis, and mossy fiber sprouting in CA1 to CA4 subfields, with the least damage in CA2 and dentate gyrus. Although HS is usually unilateral, there may be varying degree of contralateral changes. *In vivo*, HS is typically associated with hippocampal atrophy. Global hippocampal volume changes can be reliably quantified using manual MRI volumetry. However, this procedure does not allow capturing focal changes. We hypothesized that shape analysis based on statistical surface models using spherical harmonic (SPHARM) description [1] is an efficient method to capture local volume and shape changes (i.e., inward/outward deformation) reflecting microstructural abnormalities in hippocampal subfields not detected otherwise.

Methods. We selected 95 TLE patients and 46 age- and sex-matched healthy controls from our database. The seizure focus was right-sided in 45 (RTLE) patients and left-sided in 50 (LTLE). All patients had hippocampal atrophy ipsilateral to the focus (i.e., volume 2SD below mean of controls). We applied SPHARM to manually segmented hippocampal labels to obtain triangulated surfaces. Hippocampal surfaces were rigidly aligned to a template constructed from the mean surface of controls using the centroid and the axis of the 1st order ellipsoids. Then, a distance difference (in mm) between groups was computed at each vertex. Statistical significance was assessed by permutation test and p-values were visualized in 3D after correction for multiple comparisons (FDR). For individual analysis, the measurement at each vertex was z-transformed. We used a leave-one-out approach to avoid biased estimation within controls. The proportion of individuals with abnormal measurements (i.e., ± 2 SD) was visualized on a 3D surface rendering. Linear regression was used to investigate relations between deformations and disease duration, history of secondarily generalized tonic-clonic seizures (GTCS) and febrile convulsions (FC). To provide a meaningful anatomical interpretation of our findings, we manually traced hippocampal subfields in a control subject using an atlas [2] (*Figure 1*)

Results. In TLE, group comparison for volumetry showed that global atrophy was present ipsilateral to the focus ($p<0.00001$) and not contralateral. Group comparison for SPHARM (*Figure 2A*) revealed inward deformation ipsilateral to the focus in both LTLE and RTLE (>1.5mm, $p<0.001$) involving the entire CA1 region. Contralateral to the focus, we found a similar, but less marked inward deformation (>0.8mm; $p<0.05$). Furthermore, in RTLE there was a tendency to an outward deformation in the medial portion of CA2, CA3 and the dentate gyrus (>0.5mm; $p<0.05$ uncorrected). Individual analysis showed that ipsilateral CA1 atrophy is present in more than 40% of TLE patients, and that contralateral inward and outward deformation are found in more than 20% of them (*Figure 2B*). Disease duration was negatively correlated with CA1 inward deformation (*Figure 2C*), which was stronger and broader ipsilateral to the focus ($r<-0.55$; $p<0.001$ *vs.* $r<-0.35$; $p<0.05$). There was no effect of either GTCS or FC.

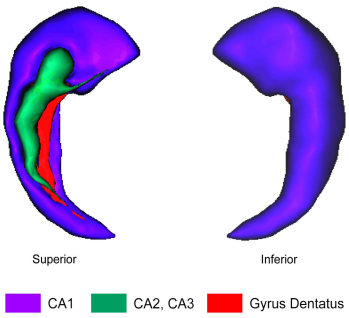

***Figure 1**. Hippocampal subfields*

Discussion. In TLE with unilateral hippocampal atrophy on MR volumetry, SPHARM reveals predominently CA1 atrophy, a finding in accordance with classical HS. Furthermore, our imaging data show that, while CA1 atrophy is more striking ipsilateral to the focus, it also occurs contralaterally. The relationship to disease duration suggest that neuronal damage due to recurrent seizure activity may affect both hippocampi. Other subfields appear to be relatively spared. In particular, contralateral outward deformation in dentate gyrus may indicate seizure-induced neurogenesis [3].

References

1. Styner M et al., Med Image Anal (2004); 2. Duvernoy HM, Springer (1988); 3. Scharfman HE et al., Epilepsia (2007)

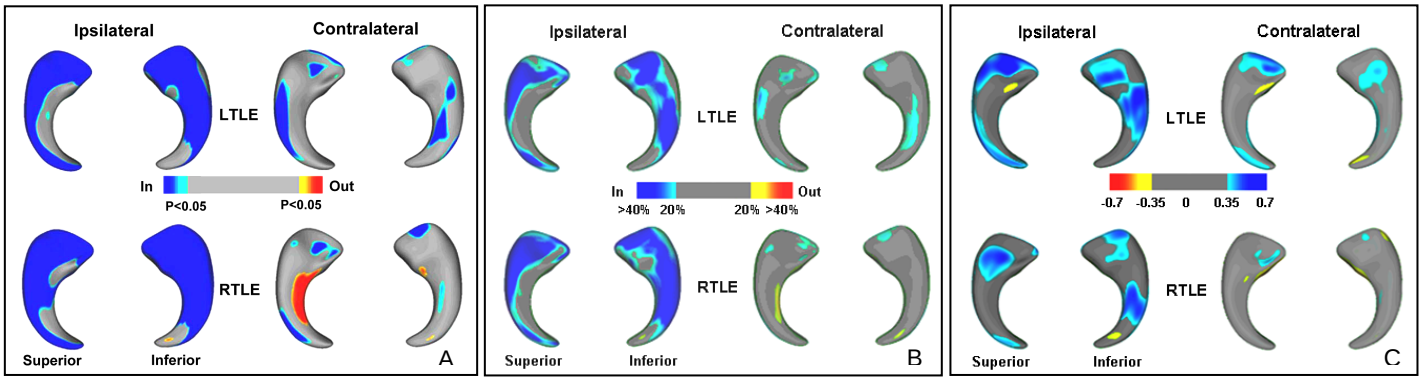

***Figure 2**. **A)** Group comparison. **B)** Individual analysis. Significant inward (blue) and outward (red) deformations are shown. To facilitate the left/right comparison, the right hippocampus is flipped. **C)** Effects of disease duration. Negative (blue) and positive (yellow) correlations are shown.*