Correlations between ex-vivo MRI and hippocampal sub-field neuronal density in temporal lobe epilepsy

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Introduction

Drug-resistant, or intractable, epilepsy affects close to a third of epilepsy patients most commonly in temporal lobe epilepsy [1]. Surgical resection of the affected region is the only alternative for seizure management in many of these cases. However, traditional localization of the epileptogenic focus can be challenging and inaccurate, thus pre-operative MRI for surgical planning has the potential to improve surgical outcomes by performing a more focused resection with minimal invasiveness. The identification of cellular abnormalities in histological slides of the resected tissue can be used to validate the effectiveness of multi-spectral magnetic resonance imaging (MRI) in pre-operative surgical planning. Previous work has shown smaller hippocampal sub-field volumes on MR images in patients with Mesial Temporal Sclerosis, however, these findings were not confirmed histologically [2]. To this end, our objective here is to investigate whether ex-vivo MRI can detect hippocampal sclerosis as differences in neuronal density of the hippocampal subfields, paving the way for validation of pre-op MRI in detection of pathology.

Methods

Temporal lobe epilepsy patients recommended for anterior temporal lobectomy were recruited for this study (N=3), and surgical resection of the neocortex and hippocampus resulted in two separate tissue specimens. The hippocampus was formalin-fixed, immersed in a silicone-based lubricant, and imaged using a solenoid in a 3T MRI scanner (General Electric). Two 3D SPGR images were acquired for fast T1 mapping 'DESPOT1' [3] (TR=11.7ms, TE=5.56ms, flip angles =4 & 18, matrix=200x200, slice thickness=0.2, FOV=60 mm). In addition, a T2-weighted Fiesta sequence of the specimens was acquired (TR=3.5ms, TE=1.75ms, flip angle=4, N=4, matrix=200x200, slice thickness= 0.2, FOV=50 mm).

Following MR imaging, the specimens then underwent accessioning, grossing, cut-plane identification, embedding in agar, then coronal slicing into 4.4 mm pieces. These were then processed, sectioned, stained (hematoxylin & eosin 'HE'), and digitized. These digital histology images were registered to the ex-vivo MRI images using an iterative 3D/2D rigid registration algorithm followed by non-rigid correction of in-plane warping [4]. A learning and segmentation toolkit 'ilastik' based on the random forest classifier was used to quantify the different cellular components of HE histology slides (down-sampled to a 5 µm/pixel resolution) [5]. Color, edge and texture feature information was computed and incorporated in the decision trees of the classifier. Neuronal cell densities were computed by thresholding the classification maps and performing connected components to count the number of cells per unit area. The hippocampal subfields (Cornus Ammonis 'CA'1-4, dentate gyrus 'DG') were manually labeled on the histology images and automated cell counts were compared against MRI measures within these ROIs. We used T1 values and T2-weighted intensities to compare against the cell counts, and also computed the local entropy of the normalized intensity values to convey textural differences that may be the result of cell loss and/or gliosis.

Results

The target registration error (TRE) for hippocampal ex-vivo and histology images, assessed using anatomically-placed fiducials was 0.61±0.02 and 0.54±0.03 (mm) for rigid and non-rigid registration respectively. Figure 1 shows the aligned images, subfield labels, neuron classification, cell density and local entropy measurements of the Fiesta scan for one of the slices. Figure 2 shows box plots (averaged across patients) of neuronal density, DESPOT1 values and entropy values of the DESPOT1 map, across the labeled layers. Pathology reports of the patients showed neuronal loss in CA1, CA3 and CA4, which is consistent with the automated cell count maps, as well as lower entropy values for the quantitative T1 maps in the same regions. The entropy maps showed to be a better measure of correlation with neuronal loss than the normalized image intensity values. Tissue prone to cell loss (CA1, CA3 & CA4) had lower local entropy values, compared to tissue resistant to neuronal loss (CA2 & DG).

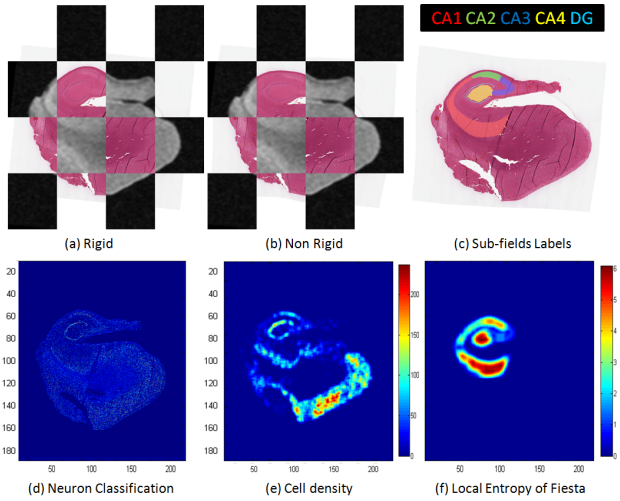

Figure 1: Coronal views of one slice from subject 1: a) MRI rigidly registered to histology, b) MRI non-rigidly warped to histology, c) Sub-fields ROIs, d) Neuron classification probability, e) Cell density (count/mm^2), f) Fiesta Local entropy values

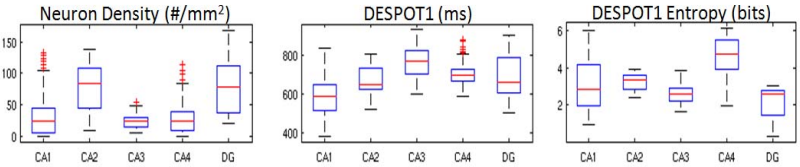

Figure 2: Box Plot of average cell count, T1 values and entropy

Conclusion

Our preliminary results have shown that the classifier-based cell counts were consistent with pathological findings and can be used as markers for neuronal loss in CA1, CA3 and CA4. It has also been suggested that ex-vivo MR images may have the potential to differentiate between the hippocampal sub-fields through local features and entropy measurements. These findings will be further investigated as more datasets becomes available to the study, in order to fully explore the correlation between MRI and hippocampal histopathology with more complex quantitative histology measures.

References

[1] Engel, J., "Etiology as a risk factor for medically refractory epilepsy: a case for early surgical intervention," Neurology 51(5), 1243–4 (1998)
[2] Mueller, S., et al. "Subfield atrophy pattern in temporal lobe epilepsy with and without mesial sclerosis detected by high-resolution MRI at 4 Tesla: Preliminary results," Epilepsia 50(6), 1474-1483 (2009)
[3] Deoni, SCL., Peters, TM., Rutt, BK., "High Resolution T1 and T2 Mapping of the Brain in a Clinically Acceptable Time with DESPOT1 and DESPOT2," Magnetic Resonance in Medicine 53, 237-241 (2005)
[4] Goubran, M., et al. "Robust registration of sparsely sectioned histology to ex-vivo MRI of temporal lobe resections," Proc. SPIE 8314, 66 (2012)
[5] Sommer, C., et al. "Ilastik: Interactive learning and segmentation toolkit," IEEE International Symposium on Biomedical Imaging: From Nano to Macro, 230-233 (2011)