Stacked In-plane Histology for Quantitative assessment of MRI markers: Application to an Infiltrative Brain Tumour Model

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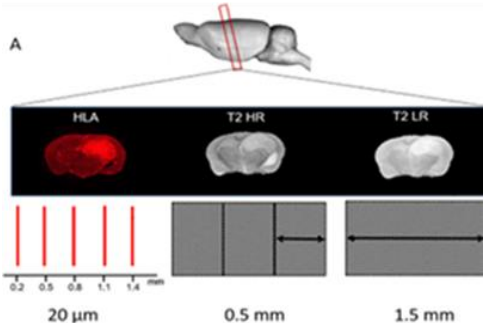
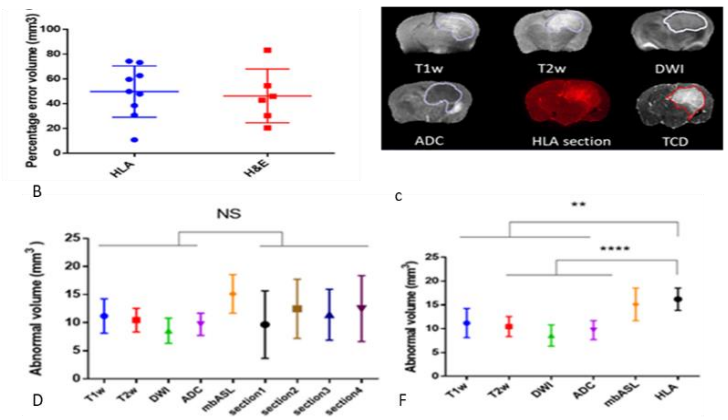
Introduction: While medical imaging provides valuable in-vivo information for prognosis and in guiding therapies, histological analysis is still the gold standard (ground truth) for definitive diagnosis and for detailed characterization of brain tumours and the normal brain. However, the methods currently employed to validate non-invasive imaging biomarkers of brain tumours are inadequate. To improve the validation of magnetic resonance imaging (MRI), we have developed a new method to achieve high-quality registration of histology with MRI by improving the quality of the histological technique used.

Materials and Method: Ten CD1 nude mice were injected intracranially with G7 glioblastoma stem-like cells ($1x10^5$ cells per mouse). Immediately following MRI (which acquired T1w, T2w, DWI ,ADC, and multi bloi Arterail Spin label (mbASL)(1) the mice were sacrificed and the brains removed and fresh frozen. After that, the brains were sectioned by adjusting the orientation of brain in x and y-axis according to high resolution T2w MR images (0.5 mm thickness), which were used as a guide to match the histology (20µm thickness) (fig.A). Tissue sections were stained for Human Leukocyte Antigen (HLA), hematoxylin, and eosin (H&E). Three histological sections were selected for each MRI image (front, middle and rear) and co-registered to create a Tumour Cell Density (TCD) map, which was co-registered with a multi contrast MRI dataset to create a 3D matrix.



Results: Important variations in volume of the tumour-related abnormality were observed between individual histology sections (HLA and H&E) within the thickness of each MR image (40±50% difference between the max. and min. abnormal volume) (fig.B).This demonstrates the inadequacy of single slice techniques to properly assess tumour volume (fig.C). In contrast, TCD maps exhibited significantly higher abnormal volumes to MRI modalities ($p<0.01$) allowing us to better assess MRI sensitivity limits, which single slice assessment cannot evaluate due to volume underestimation and large standard deviations (fig.D,F) . Power calculations show that, depending on the histology slice (HLA) used, up to 72 animals would be required to achieve $p<0.05$, several times more than with the a multiple slice approach.

Conclusion: We present a new method whereby stacked in-plane histological sections are used to generate histological probability maps, taking into account both orientation and thickness of the MRI slice. The substantial increase in accuracy achieved by the TCD map technique allows a significant reduction in the number of animals required for each experiment.



[1] Vallatos and et al, Magnetic Resonance in Medicine, 2017.