Application of Ultra-Short Echo Time Imaging for Visualization of SPIO-loaded Tumor Cells in Brain

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Introduction: There has been recent interest in positive-contrast MRI methods for tracking cells labeled with superparamagnetic iron oxide (SPIO) nanoparticles. Due to signal variations caused by SPIO-induced field inhomogeneities, in tissues with highly concentrated iron labeled cells, T2* values can decrease to values below 1 millisecond. Therefore, the signal may have decayed to the noise level even at echo times as sort as a few milliseconds typical of clinical gradient echo pulse sequences. Ultra-short echo time (UTE) imaging has been proposed as a method for visualizing short T2 relaxation components and recently has demonstrated the ability for positive contrast detection of iron based contrast agents.[7,8].Previous work has demonstrated UTE imaging using 2D radial [1], 2D spiral [2] and 3D stack-of-spirals [3] imaging approaches. Recently the 3D Cones technique [4] has been presented that combines ultra-short TE capability with an efficient, isotropic 3D acquisition strategy. This work presents preliminary feasibility for applying the 3D Cones technique in UTE imaging of SPIO-labelled tumour cells in mouse brain.

Methods: For SPIO labeling, GL261 mouse glioma cells were incubated with Feridex and Lipofectamine complex at concentrations of 200:5µg/ml for 24 hours, which maximized iron uptake to 15pg/cell. C57/Bl6 mice were anaesthetized, then $5x10^4$ GL261 cells were injected over 10mins into the striatum. Intracranial tumors were allowed to develop for 3 weeks. Mice were then euthanized by intraperitoneal injection of Euthanyl and perfused with cold saline followed by cold 3.75% formalin. Ex vivo UTE imaging of the mouse head was performed with the 3D Cones sequence on a 1.5T MR scanner (Signa HDx, GE Healthcare) using a home made T/R solenoid coil. Short-T2-selective UTE images were obtained through the subtraction of interleaved, alternating-TE data acquired using an RF-TE1-RF-TE2 scheme. The TE1 and TE2 echo times were 0.08 ms and 5.0 ms, respectively. Other scanning parameters for this protocol were: isotropic 300µm resolution, 3 NEX, 125 kHz bandwidth, 20^o flip angle, 9.3 ms TR, and 20771 cone trajectories to fill the 3D K-space with 512 points per cone for a total scan time of 19.2mins. Following MRI, the brains were removed and cryostat sections (20µm) were collected. Consecutive slides were stained for Perls' Prussian Blue for iron with eosin counterstain.

Results: Fig.1 shows example 3D Cones UTE images of the mouse head, demonstrating tumour visualization and sensitivity to iron contrast. SPIO loaded tumour cells created signal voids in the long TE (5ms) images due to dephasing caused by the magnetic field inhomogeneity (and resultant short T2*) near the cells. On the other hand, the signal from the SPIO labeled tumour is largely preserved in the short TE images (0.08ms). By subtracting long from short TE images, the SPIO loaded tumour in the difference image exhibits positive contrast. In Fig. 2, the iron loaded cells were further examined with histological study. Prussian Blue staining for iron validated that the positive signal in combined MR images correlated spatially with the presence of iron.

Discussion: Contrast agents incorporating SPIO nanoparticles have shown promise to visualize labeled cells using MRI [6]. However, the standard negative-contrast can lead to confusion about the location and quantitative burden of iron-loaded cells, given that signal voids can be the result of other mechanisms, such as field and tissue inhomogeneity or partial volume effect. Therefore, selective positive-contrast imaging of SPIO-labeled cells, with simultaneous suppression of signals from background tissues, remains an important research objective which has not been adequately addressed to date. What is known at present is that it is feasible to visualize SPIO-labeled cells with positive-contrast by using UTE imaging. 3D Cones acquisitions have scan time advantages over previously reported UTE imaging methods. The naturally isotropic 3D nature of the 3D Cones data may be useful for characterizing the morphology of more complex short T2 structures in reasonably short scan times. We are presently investigating more precise gradient tuning, gradient compensation blips [2] and long-T2 suppression pre-pulses [5], as means of further improving 3D Cones image quality.

References:

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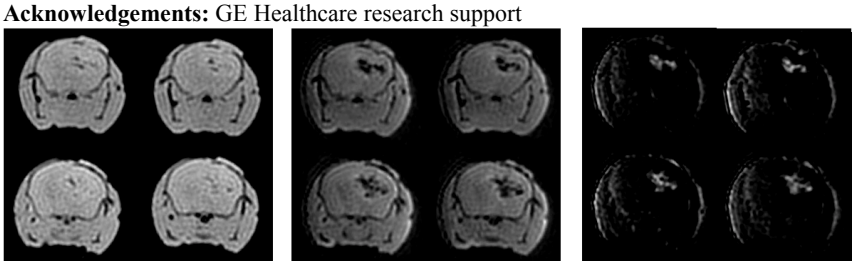

Figure 1, 3D Cones UTE protocol for tumour visualization. Left: TE=0.08ms images; Middle: TE=5ms images; Right: Subtracted Short-T2 images. The SPIO loaded tumour exhibits signal voids in the long TE images, and positive contrast in the subtracted images.

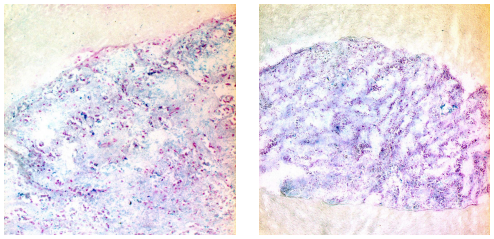

Figure 2. Prussian Blue staining for iron in the mouse brain. The significant iron staining in the area of tumour and corresponds with the area of positive signal on the MR images. (Left, 5x; right. 2.5x)