Diffusion-Weighted Spatiotemporal Encoding Schemes in the Assessment of SPIO-Labeled Cell Therapy for Ischemic Stroke

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Introduction

Super-paramagnetic iron oxide particles (SPIOs) of different sizes are common MRI contrast agents for the tracking of implanted cells, including human mesenchymal stem cells (hMSCs). Generating high contrast for assessing initial cell biodistribution and longer term engraftment, SPIOs exhibit high cell labeling efficiency and are largely biocompatible. However, the detectability of SPIOs as a cellular label is largely based on susceptibility-induced contrast, which can disrupt other quantitative methods used to assess the underlying stroke. Recently, a new suite of ultra-fast single-shot, super-resolved, diffusion-weighted spatiotemporally encoded (DW-SPEN) sequences have been introduced [1,2] that offer additional robustness for high field imaging. In this work, DW-SPEN sequences are used to evaluate a pre-clinical *in vivo* model of ischemic stroke under treatment with SPIO-labeled hMSCs, which are known to target stroke lesions as a cellular-based therapy.

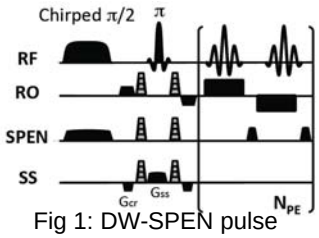

Fig 1: DW-SPEN pulse sequence

Experimental

The DW-SPEN sequence (Fig. 1) is based on an echo planar imaging (EPI) readout, with the 90° excitation substituted by a chirped pulse imparting the SPEN encoding while in the presence of a gradient [3]. Fully refocused SPEN signals were acquired with a 30-40 ms EPI readout using a matrix size of 100×100 and TR = 12 s. DW-SPEN was obtained at six b-values along the principal axes to generate apparent diffusion coefficient (ADC) maps incorporating all background gradient corrections for the SPEN-DWI sequence [3]. Complementary ADC data also were acquired using DW-SE and DW-EPI (1 & 4 segments) sequences. For all *in vivo* experiments, ischemic stroke was induced by middle cerebral artery occlusion (MCAO) for 1.0 h followed by reperfusion [4]. hMSCs were cultured [4] and transfected with a 0.86-μm iron oxide for 12 h. Immediately following MCAO, 1×10^6 cells suspended in sterile PBS were injected intra-arterially in stroked Sprague-Dawley rats (N=4).

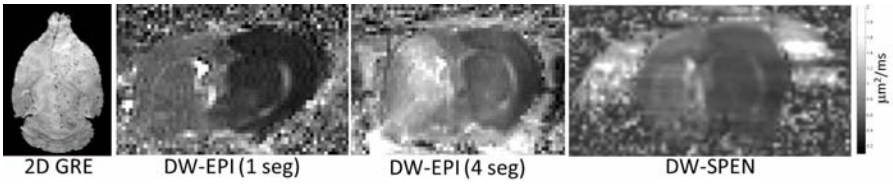

Fig 2: (left) GRE sequence displaying labeled hMSC distribution at measurement. (right) ADC maps.

Results and Discussion

At 21.1 T (Fig 2), the artifact-free DW-SPEN reveals a large hyperintense stroke region characteristic of toxic edema and swelling associated with MCAO. Decreases in ADCs were evident for all acquisition techniques between hemispheres, with only the long DW-SE acquisition not showing significance. However, the DW-SPEN provided an ipsilateral ADC value (0.55 μm^2/ms) between the low of the 1-shot DW-EPI (0.44 μm^2/ms) and high of the DW-SE (0.74 μm^2/ms). We theorize that DW-SPEN acquisition provides more accuracy in the presence of susceptibility induced diffusion gradients because: a) the ADC of 1-shot DW-EPI is lower and has a less uniform distribution (based on pixel-by-pixel ADC histograms) and b) the longer acquisition times and higher ADCs of the 4-shot DW-EPI and SE acquisitions are impacted by motion and susceptibility that produce an overestimate of true ADC.

Conclusions

The quality of the DW-SPEN and resulting ADC maps make this form of single-shot acquisition a clear choice for comprehensive, high-throughput *in vivo* stroke studies in the presence of background susceptibility gradients.

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References

[1] Ben-Elizer, N., MAGMA, **25** (2012). [2] Leftin, A., *et al.,* Magn. Reson. Med. (2014). [3] Ben-Eliezer, N., *et al.,* Magn. Reson. Med., **63** (2010). [4] Rosenberg, J.T., *et al.,* Cytotherapy, **15(3)** (2013). [5] Solomon, E., *et al.,* J Magn Reson, **232** (2013).