Diffusion-weighted Spatiotemporal Encoding Schemes in the Assessment of SPIO-labeled Cell Therapy for Ischemic Stroke

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Target Audience: Researchers and clinicians interested in rapid and susceptibility-free imaging in ischemic stroke and stem cell therapy.

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 (particularly with increased magnetic field strength) is largely based on susceptibility-induced contrast, which can disrupt other quantitative methods used to assess the underlying pathology that is the target of intended cellular therapy. For example, in stroke, diffusion weighted imaging (DWI) is commonly used to diagnose and evaluate stroke progression by quantifying the apparent diffusion coefficient (ADC). The susceptibility-induced contrast generated by SPIO-labelled hMSCs used to treat stroke provides additional magnetic field gradients that may lead to inaccurate quantification of ADC, resulting from uncompensated susceptibility gradients, when fast imaging sequences such as echo-planar imaging (EPI) are employed. 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, particularly with respect to susceptibility artifacts, reconstruction distortions and high temporal resolution. DW-SPEN provides at least comparable ADC measurements as conventional DW spin-echo or EPI sequences [2] with distinctly reduced variation and potentially more accuracy in the absolute quantification of diffusion parameters. 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 and are a good candidate for a cellular-based stroke therapies. The study was carried out at 21.1 T to achieve the highest detectability of labeled cells. While providing the highest sensitivity available, this system challenges DW-EPI because of susceptibility artifacts and gradients that are prominent at the ultra-high field. This work compares *in vivo* diffusion quantification in ischemic stroke with iron oxide labeled hMSCs of rats using DW-SPEN, DW-EPI and DW spin-echo (SE) acquisition methods.

Purpose: To determine if diffusion-weighted spatiotemporally encoded imaging can provide more accurate quantification of in *vivo* ADC in stroke in the presence of SPIO-labeled hMSCs.

Methods: The DW-SPEN sequence (Fig. 1) is based on an EPI readout, with the 90° excitation substituted by a chirped pulse imparting the SPEN encoding while in the presence of a gradient [3]. For slice selection, a standard three-lobed 180° sinc pulse was used, with diffusion encoding gradients surrounding the pulse. Fully refocused SPEN signals were acquired with a 30-40 ms EPI readout covering a FOV of 32×32×2 mm using a matrix size of 100×100 and TR = 12 s. DW-SPEN was obtained at six b-values (0, 200, 400, 600, 800 and 1000 mm^2/s) along the principal axes. Post-processing of the DW-SPEN datasets was carried out using MATLAB (MathWorks, Natick, MA) for echo alignment and the application of a super-resolution algorithm [1]. ADC maps were calculated in MATLAB 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) and occluded for 1.0 h following reperfusion [4]. hMSCs were cultured [4] and transfected with a 0.86-μm fluorescent iron oxide (Bangs Laboratories, Inc, Fishers, IN) for 12 h. Immediately following a 1-h transient MCAO, 1×10^6 cells suspended in sterile PBS were injected intra-arterially through the exposed common carotid artery of Sprague-Dawley rats (N=4), which were scanned 24 h after the induced stroke. To display hMSC distributions, 2D GRE images were acquired at high resolution. Significance was assessed using an ANOVA and LSD test between the ipsi- and contralateral hemispheres as well as the acquisition technique ($p<0.5$)

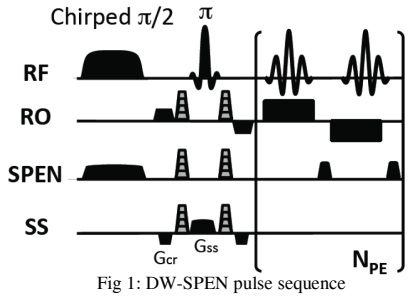

Fig 1: DW-SPEN pulse sequence

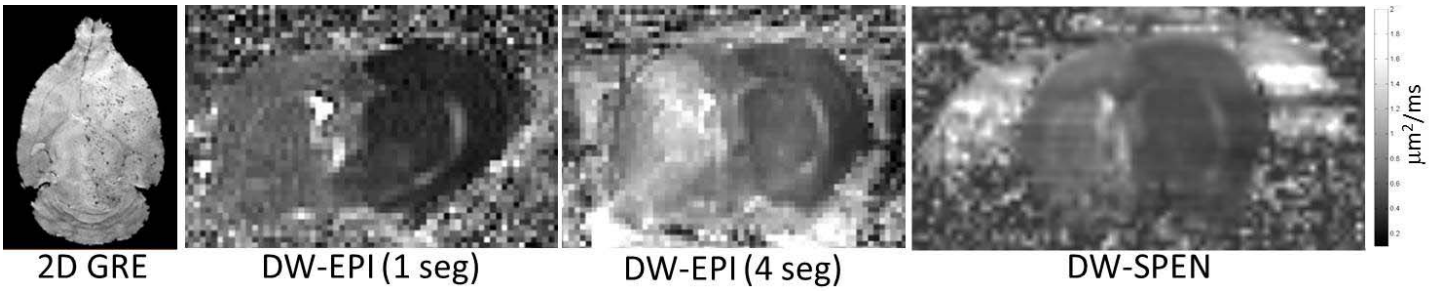

Fig 2: (left) GRE sequence displaying labeled hMSC distribution at time of measurement. (right) ADC maps for DW-EPI (1 & 4 segments) and DW-SPEN for same b-values.

Results and Discussion: Fig. 2 shows representative ADC maps for datasets from DW-EPI (1 and 4 segments) and single-shot DW-SPEN. At 21.1 T, the DW-SPEN sequence is immune to susceptibility artifacts that are particularly strong in non-segmented DW-EPI using similar acquisition parameters. 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 the more accurate quantification 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 histograms of the ADC map) and b) the longer acquisition times and higher ADCs of the 4-shot DW-EPI and DW-SE acquisitions are impacted by motion and susceptibility gradients that also produce an overestimate of the 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 at ultra-high fields and/or heterogeneous signal regions.

Acknowledgement: All work has been conducted in accordance with FSU Animal Care and User committee. Funding provided by the NSF and National High Magnetic Field Laboratory (DMR-1157490), the User Collaboration Group Program (to SCG), the American Heart Association (10GNT3860040), ERC Advanced Grant (246754 to LF), a Helen Kimmel Award for Innovative Investigation (to LF), Kamin-Yeda Grant Israel (711237 to LF), DIP Grant Germany (710907 to LF), and NSF IRFP and Fulbright (to AL).

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