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

Jens T. Rosenberg[1], Avigdor Leftin[2], Eddy Soloman[2], Lucio Frydman[1,2] and Samuel C. Grant[1,3]

[1]National High Magnetic Field Laboratory, Florida State University, Tallahassee, FL, United States, [2]Chemical Physics, Weizmann Institute of Science, Rehovot, Israel, [3]Chemical & Biomedical Engineering, Florida State University, Tallahassee, FL, United States

INTRODUCTION

Super paramagnetic iron oxides (**SPIO**) are common contrast agents with high detectability and are largely biocompatible. However, the detectability of **SPIO** as a cellular label is largely based on susceptibility-induced contrast, which can disrupt other quantitative methods used to assess the underlying pathology. Diffusion weighted imaging (**DWI**) is commonly used to diagnose and evaluate stroke lesion, including by the apparent diffusion coefficient (**ADC**). **SPIO-labeled** human mesenchymal stem cells (**hMSCs)** used to treat stroke provides additional magnetic field gradients that may lead to inaccurate quantification of **ADC** with traditional echo-planar imaging (**EPI**) sequences. 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. **DW-SPEN** provides at least comparable **ADC** measurements as conventional **DW spin-echo (SE)** or **EPI** sequences [2], and can eliminate diffusional effects (namely susceptibility gradients) unrelated to cerebral ischemia.

Here, a **DW-SPEN** is used to evaluate **ADC** in an *in vivo* model of stroke under treatment with **MPIO-labeled hMSCs** at 21.1 T. This system provides the highest sensitivity available, while also challenging DW-EPI because of susceptibility artifacts and gradients. Traditional DW sequences such as **DW-EPI** and **DW-SE** are used as comparison.

METHODS

CELL CULTURE

- Standard hMSCs were cultured following Rosenberg *et al* [3].
- 12-h exposure with MPIOs (Bangs Laboratories)
- Incubation with 7.5 mg Fe/mL

MIDDLE CERBRAL ARTERY OCCLUSION (MCAO)

- Male Sprague Dawley rats weighing ~250 g
- Rubber coated filament blocked external carotid artery (ECA)
- 1-hr occlusion followed by re-perfusion

CELL INJECTION

- Internal carotid artery (ICA) injection of magnetically labeled hMSCs right after stroke
- Micro-needle injection of $1x10^6$ cells in 50-mL cell suspension [4] MRI at 24 hr. following surgery

MRI METHODS

Single shot DW-SPEN:

- Spatial encoding by 90° frequency swept chirp pulse with a field gradient G_{exc} (Fig. 1) and standard 180° sinc pulse
- Diffusion encoding gradients surrounding the sinc pulse [2,7]
  - Six b-values: 0, 200, 400, 600, 800 & 1000 mm^2/s along principal axes with ” = 9.81 ms and ´ = 3.5 ms
  - TR = 12s, TE = 56 ms; FOV = 32x32x2 with Matrix = 100x100
  - Acq. time 1 min 12s
- Post processing of SPEN with MATLAB (Mathworks, Natick, MA)
- ROI analysis conducted on entire segmented stroke & contralateral side
- Control EPI scans were acquired with same b-values, FOV as DW-SPEN
  - TR = 6 s, TE (1 segment) = 45 ms and TE (4 segment) = 23 ms
  - Acq. time: 1 min 48 s (1 segment) and 7 min 12 s (4 segment)

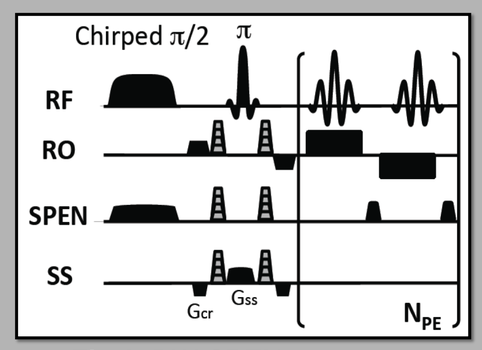


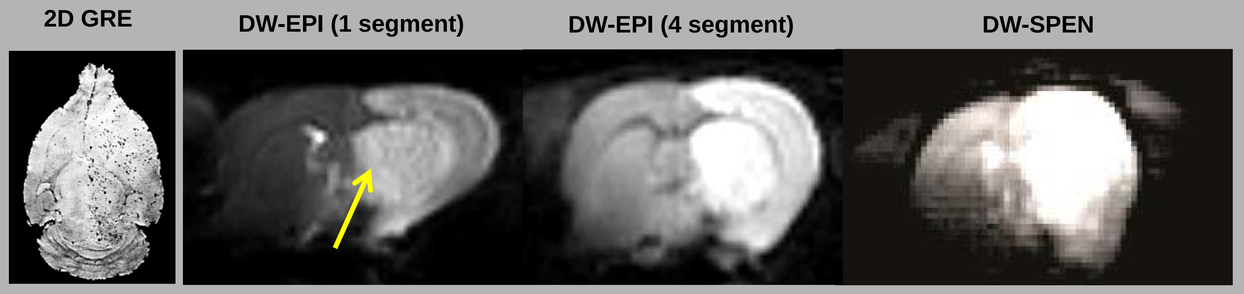
Fig 1: DW-SPEN sequence

MRI System

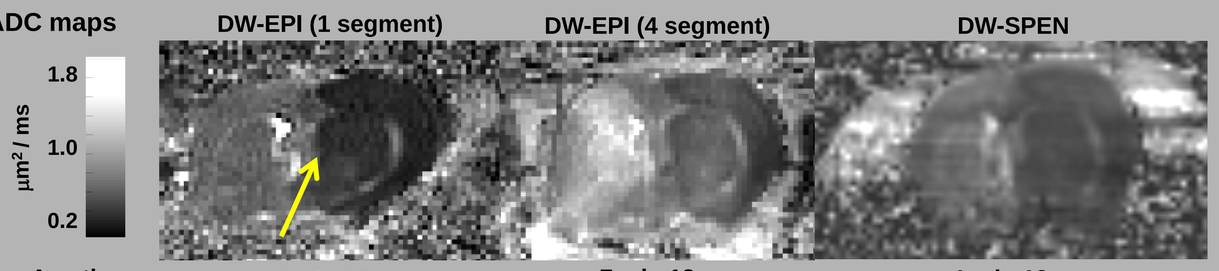
- 21.1 T 900 MHz spectrometer equipped with an Avance III spectrometer (Bruker, Billerica, MA) with 60 G/cm triple axis gradients (RRI, Billerica, MA)
- Homebuilt 33-mm quadrature coil

RESULTS

Magnitude images

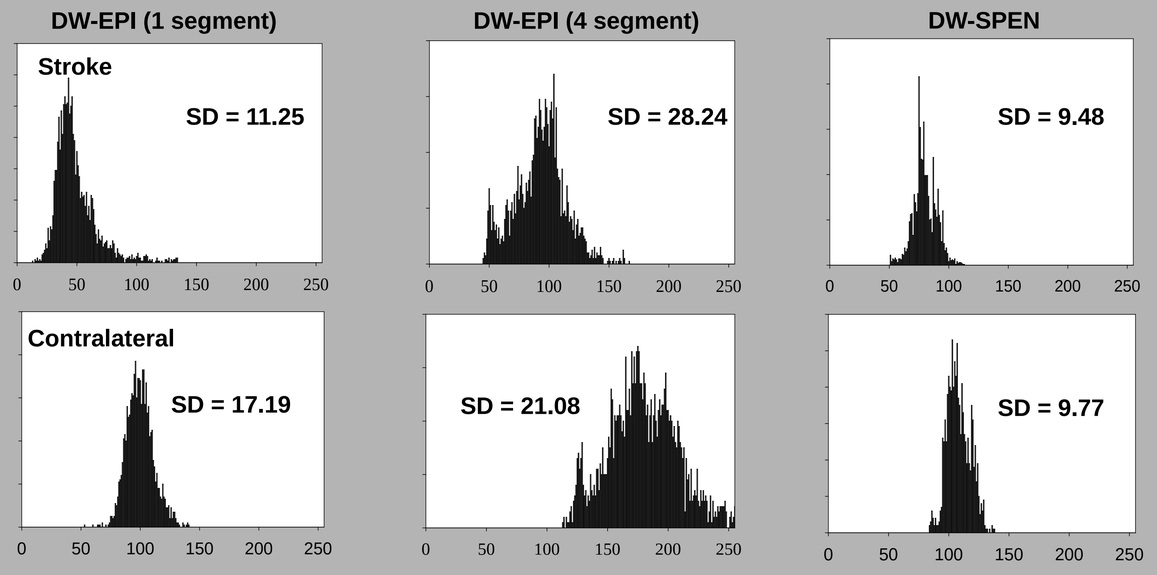


ADC maps



- **At 21.1 T, the DW-SPEN sequence is immune to susceptibility compared to long TE EPI (susceptibility effects noted by yellow arrow)**
- **Artifact-free DW-SPEN reveals a larger hyperintense stroke region characteristic of toxic edema and swelling**
- **Decreases in ADCs were evident for all acquisition techniques**

Histogram Analysis



ADC (μm²/ms): N=5	DW-EPI (1 segment)	DW-EPI (4 segment)	DW-SPEN
Stroke	0.44 ± 0.07*	0.63 ± 0.06*	0.55 ± 0.13
Contralateral	0.68 ± 0.02	0.83 ± 0.07	0.74 ± 001

*DW-EPI 1 and 4 segments are significantly different according to ANOVA and Tukey’s post-hoc test ($P < 0.05$)

- **DW-SPEN has more uniform distribution as seen with histograms & standard deviations (SD)**
- **Less uniform distribution with EPI (1 & 4 segments) is likely due to susceptibility gradients and motion, respectively, affecting ADC quantifications**

CONCLUSION

The quality of the DW-SPEN make this 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.

ACKNOWLEDGEMENTS:

A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by NSF (DMR-1157490 and User Collaborations Group Project) and the State of Florida. Funding was also provided by AHA (SCG), ERC Advanced Grant (LF), Helen Kimmel Award for Innovative Investigation (LF), Kamin-Yeda Grant Israel (LF), DIP Grant German (LF), and NSF IRFP and Fulbright (AL). All work has been conducted in accordance with the FSU Animal Care and Use Committee.

REFERENCES:

1. Ben-Elizer N. Magma. 2012(25).
2. Leftin A *et al.* MRM. 2014.
3. Rosenberg J *et al.* Cytotherapy. 2013.
4. Chua *et al.* J Cereb Blood Flow Metab. 2011.
5. Ben-Elizer N *et al.* MRM. 2010.
6. Ben-Elizer N *et al.* MRM. 2014.
7. Solomon E *et al.* J Magn Reson. 2013.