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Assessment of a combined spin- and gradient-echo (SAGE) DSC-MRI method for preclinical neuroimaging

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Abstract

The goal of this study was to optimize and validate a combined spin- and gradient-echo (SAGE) sequence for dynamic susceptibility-contrast magnetic resonance imaging to obtain hemodynamic parameters in a preclinical setting. The SAGE EPI sequence was applied in phantoms and *in vivo* rat brain (normal, tumor, and stroke tissue). Partial and full Fourier encoding schemes were implemented and characterized. Maps of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), vessel size index (VSI), volume transfer constant (K^{trans}), and volume fraction of the extravascular extracellular space (v_e) were obtained. Partial Fourier encoding provided shortened echo times with acceptable SNR and temporal stability, thus enabling reliable characterization of T_2 , T_2^* and T_1 in both phantoms and rat brain. The hemodynamic parameters CBV, CBF, and MTT for gradient-echo and spin-echo contrast were determined in tumor and stroke; VSI, K^{trans} , and v_e were also computed in tumor tissue. The SAGE EPI sequence allows the acquisition of multiple gradient- and spin-echoes, from which measures of perfusion, permeability, and vessel size can be obtained in a preclinical setting. Partial Fourier encoding can be used to minimize SAGE echo times and reliably quantify dynamic T_2 and T_2^* changes. This acquisition provides a more comprehensive assessment of hemodynamic status in brain tissue with vascular and perfusion abnormalities.

Keywords

Dynamic susceptibility contrast imaging; Perfusion; Permeability; Gadolinium contrast agent; Iron oxide contrast agent; Spin-echo; gradient-echo EPI

1. Introduction

Dynamic susceptibility-contrast magnetic resonance imaging (DSC-MRI) can be used to derive various hemodynamic parameters including cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) in patients with vascular abnormalities such as tumors [1–3] and stroke [4,5]. Unlike other tracer-based perfusion imaging modalities, DSC-MRI is unique in its acquisition-dependent vessel size sensitivity. When acquired with

spin-echo (SE) sequences, which assess changes in the transverse relaxation rate constant R_2 , the DSC parameters are maximally sensitive to capillary-sized vascular structures [6]. When acquired with gradient-echo (GE) sequences, which assess changes in the effective transverse relaxation rate constant R_2^* , the hemodynamic parameters are sensitive to vessels of all sizes [7]. When acquired simultaneously, SE and GE DSC-MRI signals may be used to assess vessel size index (VSI) [8–10]. Although sensitivity to microvasculature is desirable, SE sequences often suffer from lower contrast-to-noise ratio, and thus GE acquisitions are preferred for clinical applications. Combined sequences have been proposed to obtain both SE and GE contrast, although early implementations either were not well suited for dynamic studies or were sensitive to T_1 effects that can induce errors in the DSC measurements [1,2,11–14]. Recently, a T_1 -insensitive combined spin- and gradient-echo (SAGE) EPI method was proposed to simultaneously obtain absolute R_2 , R_2^* and T_1 -weighted dynamic time-courses [15,16].

The SAGE sequence is comprised of a series of echoes acquired using an EPI readout, starting with two GEs, followed by a 180° refocusing pulse, two asymmetric echoes, and an SE. In previous implementations, parallel imaging was used to reduce the EPI readout time. The derived measures of R_2 and R_2^* from SAGE acquisitions have been previously validated in phantoms and healthy human subjects [15,16]. In contrast to traditional single-echo DSC-MRI, SAGE-based measures in stroke and tumor patients were found to be insensitive to contrast agent (CA) leakage-induced T_1 effects in regions exhibiting a disrupted blood–brain barrier [16]. Relative VSI was also determined using a SAGE acquisition. More recent applications of SAGE EPI have focused on extracting R_1 dynamic curves and estimating dynamic contrast enhanced (DCE)-MRI kinetic parameters K^{trans} , the volume transfer constant, and v_e , the volume fraction of the extravascular extracellular space. The R_1 information derived from SAGE can also be leveraged to correct for T_2 and T_2^* CA leakage effects [17]. Given the quantitative nature of the SAGE acquisition and its insensitivity to T_1 leakage effects, it is also ideally suited for acquiring vessel architectural imaging data, an approach that provides additional hemodynamic characterization of tissue using the information in dynamic R_2 and R_2^* DSC-MRI time-courses [18].

While prior SAGE studies have focused on development and validation in humans, a similar pre-clinical evaluation has not been performed. In this setting, the biophysical basis for SAGE contrast, the influence of CA type, and the accuracy of the derived hemodynamic parameters can be explored in well-controlled and reproducible disease models and systematically validated against gold-standard measures. Here we focus on optimizing and validating the SAGE acquisition methods, and its initial application in animal models of brain tumor and ischemia. Given the limited availability of parallel imaging methods on small animal MRI systems, partial Fourier encoding is explored as a means to reduce the EPI readout time and provide acceptable echo times for accurate characterization of the short T_2 and T_2^* times encountered during the CA first pass. Using phantoms and *in vivo* rat data, the SAGE-derived R_2 and R_2^* values are compared with two conventional methods for measuring R_2 and R_2^* , one using an EPI read-out to match the distortions of the SAGE sequence and one using conventional (single-line) acquisition. SAGE-based changes in T_1 times between phantoms are also compared to those derived from a conventional inversion-

recovery (IR) sequence. SAGE DSC-MRI signals are compared following injections of gadopentetate dimeglumine (Gd-DTPA) and an intra-vascular magnetic iron oxide nanoparticle (MION)-based CA. The SAGE-based DSC parameters are compared to those calculated using a single echo of the SAGE acquisition, typical of clinical DSC-MRI. VSI maps are also computed and compared using Gd-DTPA and MION-based CAs. For *in vivo* validation of the R_1 data, pre- and post-contrast SAGE R_1 estimates were compared to those derived from a conventional IR approach. The R_1 time-courses were then used to estimate maps of K^{trans} and v_e , in brain tumor tissue. Given the interest in the DSC-MRI community for more quantitative and comprehensive measures of vascular and hemodynamic features, the studies explored herein, specifically the technical advancements in SAGE methodology, its *in vitro* and *in vivo* validation, and the demonstration of its pre-clinical utility, lay the foundation for future pre-clinical neuroimaging investigations.

2. Materials and methods

2.1. Sequence optimization

MRI was performed at a 4.7 T scanner (Agilent, Santa Clara, CA). A SAGE-EPI sequence was used to obtain five echoes – two GEs before a 180° pulse, following by two mixed SAGEs, and an SE. Standard slice-selective sinc pulses were used for excitation and refocusing, with crusher gradients surrounding the refocusing pulse. A 64×64 acquisition matrix within a $36 \times 36 \text{ mm}^2$ FOV was acquired with eight 1-mm thick slices. Using full Fourier encoding (64 of 64 lines acquired), the EPI readout duration was 26 ms, yielding echo times TE_1 – $TE_5 = 15.1/41.2/73.0/99.1/125$ ms (Table 1). With partial Fourier encoding (48 of 64 lines acquired), the EPI readout duration was 18 ms, yielding echo times TE_1 – $TE_5 = 8.6/35/56/82/95$ ms (Table 1). The partially sampled k-space data were reconstructed to full Fourier space using an iterative homodyne reconstruction algorithm [19,20] in Matlab (Mathworks, Inc.). In addition to the fully and partially sampled k-spaces with the minimum TEs, a partially sampled dataset was created from the fully sampled dataset by removing 25% of the k-space lines, thus permitting analysis of the effects of partial Fourier reconstruction with the same TEs used for full Fourier encoding. To obtain adequate temporal resolution for dynamic studies, a repetition time (TR) of 1 s was used. The SAGE-derived R_2 and R_2^* time-courses were obtained using nonlinear least squares fits to a piecewise function (Eq. (1)) as previously described [15]. Due to slice profile imperfections between the excitation and refocusing pulses [15], the signal intensities S_0^I and S_0^{II} were permitted to differ in the fitting. The root mean square percentage error (RMSPE) was calculated as a measure of model goodness-of-fit. The signal stability for each echo was assessed using the voxel-wise temporal relative standard deviation (RSD) over 200 time-points.

$$S(\tau) = \begin{cases} S_0^I \times e^{-\tau \times (R_2^*)} & 0 < \tau < TE/2 \\ S_0^{II} \times e^{-TE \times (R_2^* - R_2)} \times e^{-\tau \times (2 \times R_2 - R_2^*)} & TE/2 < \tau < TE \end{cases} \quad (1)$$

2.2. Phantom and animal methods

A phantom was prepared with four tubes of varying MnCl_2 concentration (0.339, 0.167, 0.080, and 0.038 mM), yielding approximate T_2 values of 15, 30, 60, and 120 ms. All animal studies were performed in accordance with Vanderbilt University Institutional Animal Care and Use Committee protocols. For all procedures and imaging, the animals were immobilized in a stereotactic head holder. Anesthesia was induced using 3–5% isoflurane in air and maintained with 1–2.5% isoflurane in air. Body temperature was maintained at 38 °C using forced warm air. Normal Wistar rats ($n = 5$) were used for the validation of SAGE T_2 and T_2^* measurements. For the tumor studies, male Wistar rats (Harlan Laboratories, Indianapolis, IN) ($n = 10$) were inoculated with 1×10^5 C6 glioma cells (American Type Culture Collection, Manassas, VA) at 1 mm anterior and 3 mm lateral to the bregma and 4 mm depth from the dural surface. Imaging was performed after 14–18 days. For the ischemia studies, stroke was induced via middle cerebral occlusion in a spontaneously hypertensive rat ($n = 1$) using the intraluminal suture method.

2.3. Validation of T_2 and T_2^* : phantom and healthy rat brain

To obtain reference values, pre-contrast T_2 and T_2^* maps were acquired using conventional techniques. The conventional T_2 map was acquired with a multiple SE sequence with 20 echoes ($\text{TE} = 10\text{--}200$ ms ($\text{TE} = 10$ ms)), $\text{TR} = 3$ s, and an acquisition matrix of 128×128 (versus 64×64 for the EPI and SAGE T_2 maps) over the same FOV. For the *in vivo* animal studies, conventional T_2^* maps were acquired using a 3-dimensional multi-gradient-echo sequence to reduce the effects of macroscopic field inhomogeneities in the slice direction. These maps were acquired with 20 echoes ($\text{TE} = 2.8\text{--}68.8$ ms ($\text{TE} = 3.3$ ms)), $\text{TR} = 100$ ms, and a $256 \times 256 \times 20$ acquisition matrix with a $36 \times 36 \times 4$ mm³ FOV. Magnitude averaging of the high-resolution GE data was used to produce a $128 \times 128 \times 4$ matrix that was then fit for T_2^* .

To match the geometrical distortions of the SAGE EPI T_2 and T_2^* maps, conventional T_2 and T_2^* maps were also acquired using an EPI sequence readout. The EPI T_2 map was acquired with 10 SE EPI acquisitions ($\text{TE} = 25\text{--}115$ ms ($\text{TE} = 10$ ms)) and $\text{TR} = 5$ s. The EPI T_2^* map was acquired with 10 GE EPI acquisitions ($\text{TE} = 9.65\text{--}77.15$ ms ($\text{TE} = 7.5$ ms)) and $\text{TR} = 5$ s. The acquisition matrix and other parameters matched that of the SAGE sequence.

2.4. SAGE DSC-PWI

For the dynamic studies, the data were acquired at a 1 s TR for at least 3 minutes and up to 16.67 minutes for DCE-MRI parameter estimation. After 80 s of baseline images, 0.4 mmol/kg Gd-DTPA or 3 mg/kg MION was injected via a jugular catheter. The baseline signals were averaged to obtain the pre-bolus signal, and the voxel-wise R_2 , R_2^* , S_0^I , and S_0^{II} were determined from Eq. (1). The ratio S_0^I/S_0^{II} provides a measure of the slice profile mismatch and was assumed to be constant for the dynamic time course [16]. Thus, for the dynamic fit of the data, a 3-parameter fit was used to obtain $R_2(t)$, $R_2^*(t)$ and $S_0^I(t)$ (with $S_0^{II}(t)$ replaced with $S_0^I(t)/(S_0^I/S_0^{II})$ in the fit function).

The SAGE-derived $R_2^*(t)$ and $R_2(t)$ and the 2nd (GE) and 5th echo (SE) signals were used to determine multi-echo- and single-echo-based ΔR_2^* and R_2 time series. The SAGE ΔR_2^* was used for determination of the arterial input function (AIF), which was selected using an automated method [21] specifically adapted for use with multi-echo acquisitions [22]. CBF was taken as the maximum of the impulse response function determined from the circular singular value decomposition of the AIF and tissue ΔR_2^* [23]. CBV was determined from the ratio of the scaled integrals of the tissue ΔR_2^* curve and the arterial input function curve. To avoid artifactually low CBV values in leakage-affected tumor tissue, negative ΔR_2^* values were not included in the integration. MTT was taken as the ratio of CBV to CBF. In lieu of scaling for hematocrit and density, CBV and CBF were normalized to 4% and 60 ml/100 g/min in gray matter for display purposes. For the stroke rat, $T_{\max}$ was calculated as the time-to-maximum of the impulse response function.

2.5. Vessel size imaging

SAGE EPI can be used to provide a measure of the vessel size index (radius) from the ratio of ΔR_2^* and R_2 . More specifically, VSI can be calculated as [1,4,24]

$$VSI = 0.867 \cdot \sqrt{ADC \cdot \zeta} \cdot \frac{\Delta R_2^*}{\Delta R_2^{3/2}} \quad (2)$$

The blood volume fraction ζ was taken as CBV (calculated as stated above and normalized to 4% in normal gray matter) from dynamic Gd-DTPA and MION, as previously reported [1,4]. In a separate study, diffusion data were acquired in three orthogonal directions using 2 b-values (100 s/mm² and 1000 s/mm²), where the 100 s/mm² b-value was chosen to avoid influence of perfusion effects [25]; the ADC was taken as the average ADC from the three orthogonal directions. The mean diffusion values in tumor and normal tissue were used to calculate both Gd-based and MION-based VSI. The ratio $\Delta R_2^*/\Delta R_2^{3/2}$ was calculated from the slope of the least-squares linear fit of $\Delta R_2^{3/2}$ vs. ΔR_2^* during bolus passage. The VSI using SAGE $\Delta R_2^*/\Delta R_2^{3/2}$ and single echo $\Delta R_2^*(TE_2)/\Delta R_2^{3/2}(TE_5)$ were compared.

2.6. Validation of DSC-derived R_1 for DCE-based analysis: phantom and rat brain tumor

To obtain DCE-MRI parameters, the T_1 -based signal changes were extracted from the SAGE signals (using S_0^I from Eq. (1)). The DSC-derived T_1 ($=1/R_1$) data are obtained by combining the DSC T_1 -based signals with a pre-contrast T_1 map, based on the method of Landis et al. [26]. Briefly, using a 90° excitation flip angle, the R_1 time-course can be determined by rearranging the spoiled GE signal equation:

$$R_1(t) = \frac{1}{TR} \ln \left(\frac{S_0}{(S_0 - S(t))} \right) \quad (3)$$

where S_0 is obtained from the pre-contrast T_1 -weighted DSC signal (S_-) and T_{10} maps:

$$S_0 = \frac{S_-}{(1 - e^{-TR/T_{10}})} \quad (4)$$

Using the phantom described above, the DSC-derived T_1 maps from SAGE were compared to a conventional T_1 map acquired using an IR snapshot FLASH GE sequence (8 inversion times exponentially spaced from 250 ms to 6 s, $TR = 8$ s, $TE = 2.9$ ms, and $\alpha = 15^\circ$). To account for possible inversion pulse imperfections, the flip angle was a free parameter in the T_1 fit algorithm. For the phantom validation, the tube with the lowest CA concentration (tube 4) was used as the “pre-contrast” T_1 , from which the T_1 s of the other three tubes were calculated.

Because DCE pharmacokinetic modeling using the Tofts model requires substantially longer time-courses than typical DSC acquisitions for reliable parameter estimation, the *in vivo* SAGE signals were acquired for 16.67 minutes (1000 images at $TR = 1$ s). Furthermore, the extracted K^{trans} and v_e using the full time-course were compared to the estimates of K^{trans} and v_e from a truncated time-course (typical DSC acquisition) using only 2 minutes of data following injection. The SAGE R_1 curves were analyzed using the reference region (RR) Tofts model [27] to extract K^{trans} and v_e [28]. A pre-bolus T_1 map acquired using an IR sequence was used to compute the R_1 time courses for the SAGE data [26]. To validate the SAGE-derived R_1 curves, a post-bolus T_1 map was acquired and used to compute a conventional (IR) R_1 map. The RR was selected from the rat masseter muscles using the SAGE R_1 . The RR K^{trans} and v_e were set to 0.05 min^{-1} and 0.11, respectively [29]. The C6 tumor voxels were selected as the tissue of interest to extract K^{trans} and v_e , with analysis limited to voxels exhibiting $K^{trans} < 0.5 \text{ min}^{-1}$ and $v_e < 1$.

3. Results

Fig. 1 demonstrates the SAGE images acquired at each echo and calculated T_2 and T_2^* maps in healthy rat brain for full Fourier encoding (64 of 64 lines acquired), partial Fourier encoding (75% k-space: 48 of 64 lines acquired), and partial Fourier encoding with longer TEs created from the fully sampled data (75% k-space: 48 of 64 lines reconstructed). The TEs, image SNR, and temporal RSD are summarized in Table 1 for each Fourier encoding scheme. Partial Fourier encoding yields TEs that are less than 10 ms for the first echo and 100 ms for the final echo; full Fourier encoding yields TEs of 15 ms for the first echo and 125 ms for the final echo. Partial Fourier encoding with minimized TEs yields lower SNR for the first two echoes and higher SNR for the last three echoes compared to full Fourier encoding. The partial Fourier encoding with longer TEs suffers from lower SNR in all echoes. The temporal RSD is comparable between partial (short TE) and full Fourier encoding and increases with echo number. Due to the low SNR for partial Fourier with long TEs, the temporal RSD suffers substantially for the last three echoes. Using the SAGE fits with all five echoes, the mean T_2 in brain for partial (short and long TE) and full Fourier encoding are 57.9, 58.3, and 54.5 ms, respectively, and the mean T_2^* for partial (short and long TE) and full Fourier encoding are 41.0, 41.2, and 38.2 ms, respectively. Moreover, the SAGE fit error was smallest for partial Fourier encoding with minimized TE (RMSPE =

4.63; vs. 5.04 and 7.00 for partial with long TE and full Fourier encoding, respectively). Thus, for the remaining studies, partial Fourier encoding (48 of 64 lines acquired) with minimized TEs was used to provide the desired TEs and slightly higher SNR for the late echoes.

Fig. 2a shows T_2 maps derived from conventional SE, SE-EPI, and SAGE for four tubes with T_2 values of approximately 15, 30, 60, and 120 ms. The T_2 maps from the conventional readout were highly homogenous, while the EPI and SAGE maps show increased heterogeneity at the edges. Overall, the values for SAGE T_2 are in good agreement with the conventional and EPI T_2 values (Fig. 2b). Fig. 2c shows the T_1 maps from conventional IR and SAGE data. The SAGE T_1 values match the conventional T_1 map reasonably well (Fig. 2d). The calculated T_2 values (based on $MnCl_2$ concentration) and measured T_2 values using conventional SE, SE-EPI, and SAGE fits, as well as the measured T_1 values using conventional IR and SAGE signals, are summarized in Table 2. There were no statistically significant differences between the SAGE measurements and either the conventional or EPI T_2 measurements or the IR-based T_1 measurements (paired t-test, $p = 0.084$, 0.474 , and 0.442 , respectively). The relatively high standard deviation (SD) for the SAGE T_2 in tube 4 likely reflects the limitations in fitting T_2 values that are much longer than the longest TE. Measurements of T_2 and T_2^* using conventional and EPI readouts were acquired in normal rat brain for comparison with the SAGE T_2 and T_2^* (Table 2). There were no statistically significant differences between the SAGE measurements and either the conventional or EPI measurements in rat brain (paired t-test, SAGE T_2 vs. conventional and EPI T_2 : $p = 0.718$ and 0.059 , respectively; SAGE T_2^* vs. conventional and EPI T_2^* : $p = 0.209$ and 0.128 , respectively).

In Fig. 3, the R_1 from DSC-MRI is compared to the R_1 from IR-based T_1 maps acquired before and after contrast administration. The SAGE R_1 was obtained using S_1^I (Eq. (1)) from the SAGE fit. The conventional and SAGE R_1 maps are shown for a representative rat, showing increased R_1 in the tumor due to T_1 leakage effects following bolus injection. Although the DSC R_1 in tumor is overestimated compared to conventional R_1 , the DSC and conventional R_1 show good spatial correlation and similar signal characteristics in the tumor voxels. The bar plots show the mean tumor R_1 values ($n = 3$). The SAGE R_1 is overestimated compared to the conventional R_1 in the tumor, which is likely attributable to CA washout effects during the relatively long (17 minutes) IR scans needed for T_1 estimation. There was no significant difference between the DSC and conventional R_1 values in tumor tissue (paired t-test, $p = 0.119$).

Fig. 4 illustrates representative examples of dynamic SAGE data following Gd-DTPA (top) and MION (bottom) injection in a C6 rat brain tumor ROI. For Gd-DTPA, the TE_1 and $TE_2 \Delta R_2^*$ time-courses exhibit substantial CA-induced T_1 leakage effects, which present here as negative or transiently decreasing ΔR_2^* values following the first pass of the CA. It should be noted that these effects are absent in the T_1 -insensitive SAGE ΔR_2^* time curves. The SAGE R_2 remains higher than the $TE_5 R_2$, indicating that T_1 leakage effects are also present in the SE signals. The average CNR in a tumor ROI with Gd-DTPA injection was $10.5 (\pm 8.6)$ for $TE_2 \Delta R_2^*$, $7.7 (\pm 4.6)$ for SAGE ΔR_2^* , $4.8 (\pm 2.6)$ for $TE_5 R_2$, and $5.4 (\pm 4.0)$

for SAGE R_2 . The ΔR_2^* time-courses following injection of MION (3 mg Fe/kg dynamic dose) show no signs of leakage effects. The ΔR_2^* and R_2 time-courses show excellent agreement between single-echo (TE_2 and TE_5) and SAGE fits (R_2^* and R_2), indicating no leakage with MION. The average CNR in a tumor ROI with MION injection was 23.2 (± 14.2) for $TE_2 \Delta R_2^*$, 17.1 (± 11.2) for SAGE ΔR_2^* , 5.9 (± 3.7) for $TE_5 R_2$, and 6.4 (± 2.2) for SAGE R_2 .

The corresponding CBF, CBV, and MTT maps are shown in Fig. 5 for the single-echo (TE_2 and TE_5) and the SAGE fits following Gd-DTPA injection. The CBF maps are visually similar between TE_2 and SAGE R_2^* (tumor CBF: 72.8 and 66.2 mL/100 g/min, respectively; normalized to 60 mL/100 g/min in normal tissue), while CBV in the tumor region is substantially underestimated from TE_2 due to the effects of CA leakage on the R_2^* curves (tumor CBV: 4.52% and 5.58% for TE_2 and SAGE R_2^* , respectively; normalized to 4% in normal tissue). Because of the underestimated CBV (TE_2), MTT is also underestimated in the tumor region compared to the MTT computed using SAGE data (tumor MTT: 3.78 and 4.91 s for TE_2 and SAGE R_2^* , respectively). Similar results were observed for CBF, CBV, and MTT using R_2 from TE_5 and SAGE (tumor CBF: 52.5 and 80; tumor CBV: 3.58 and 4.97; tumor MTT: 3.76 and 4.48 for TE_5 and SAGE R_2 , respectively). As expected from the dynamic curves in Fig. 4, the MION CBF, CBV, and MTT are similar between the single-echo (TE_2 and TE_5) and SAGE fits (data not shown).

Fig. 6 shows VSI images obtained with SAGE following dynamic Gd-DTPA bolus. In addition to using ΔR_2^* and R_2 from the SAGE fits, the single-echo ΔR_2^* and R_2 from TE_2 and TE_5 were used to map VSI. Example linear fits of $\Delta R_2^{3/2}$ vs. ΔR_2^* in normal and tumor tissue ROIs show increased slopes in tumor tissue (1.70 and 1.76 in tumor and 1.08 and 1.07 in normal tissue for SAGE and single-echo VSI, respectively), indicative of increased vessel sizes. There was no significant difference observed between the SAGE VSI and the single-echo VSI, indicating that leakage effects occurring over the bolus passage do not affect the resulting VSI. The bar plots show the mean vessel size in tumor and normal tissue using SAGE and single-echo fits during bolus passage with Gd-DTPA ($n = 4$) and MION ($n = 6$). Both Gd-DTPA and MION showed similarly increased VSI in tumors, which was approximately double the normal tissue VSI in all cases (VSI relative to normal tissue: 1.94 and 1.89 for Gd-DTPA using SAGE and single-echo, respectively; 1.91 and 1.97 for MION using SAGE and single-echo, respectively). Comparisons of single-echo and SAGE VSI were not significant for either tissue or contrast agent ($p > 0.2$ in all cases), while tumor tissue was significantly different from normal tissue for both SAGE and single-echo MION (paired t-test, $p = 0.0040$ and $p = 0.0018$, respectively). The tumor tissue was not significantly different using Gd-DTPA contrast, likely due to the small sample size ($n = 4$, paired t-test, $p = 0.0558$ and $p = 0.0554$ for SAGE and single-echo, respectively). In addition, there were no significant differences between Gd-DTPA and MION VSI for SAGE or single-echo in tumor or normal tissue (unpaired t-test; SAGE in tumor and normal tissue: $p = 0.671$ and 0.335 , respectively, single-echo in tumor and normal tissue: $p = 0.396$ and 0.210 , respectively).

An example of SAGE DSC-MRI in a rat with ischemia is shown in Fig. 7. The diffusion-weighted images (DWI) and T_1 map show the extent of the stroke tissue (indicated by the arrow). The SAGE acquisition provides both ΔR_2^* - and R_2 -based CBF, CBV, MTT, and $T_{\max}$. The infarct area exhibited 35% lower CBF and 26% lower CBV compared to normal tissue for R_2^* SAGE; the R_2 SAGE data also showed reduced CBF and CBV (31% and 33% lower than normal tissue, respectively). The MTT and $T_{\max}$ were elevated in the stroke tissue relative to normal tissue for the R_2^* SAGE (8% and 17% higher, respectively) and R_2 SAGE (13% and 12% higher, respectively) data.

Fig. 8 shows an example DCE analysis from SAGE data. The R_1 curves derived from SAGE data in a tumor ROI are shown (top left), along with the SAGE R_1 in muscle tissue used for the RR model. The RR model produced excellent fits for the SAGE R_1 data with reasonable K^{trans} and v_e values (defined here as $0 < K^{\text{trans}} < 0.5 \text{ min}^{-1}$ and $0 < v_e < 1$), as shown (bottom left) for an example voxel taken from the tumor rim. The corresponding maps of K^{trans} and v_e in the tumor region are also shown. This tumor was characterized by a well-perfused rim with K^{trans} and v_e within the expected physiological ranges (defined above and consistent with Ref. [29]) and a necrotic region in the tumor core that exhibited small K^{trans} and highly overestimated v_e (i.e., $v_e > 1$). The RR fits for the tumor produced mean K^{trans} and v_e values of 0.021 and 0.221, respectively, with approximately 27% of voxels excluded from the analysis due to K^{trans} and v_e outside the expected range. When the data were truncated to 2 minutes post-injection (to match typical DSC acquisitions), the resulting RR fits for the tumor produced a slightly underestimated mean K^{trans} value (0.018), while the mean v_e value (0.734) was substantially overestimated (data not shown). In addition, using the truncated data, approximately 79% of voxels fell outside the expected physiological range for K^{trans} and v_e .

4. Discussion

In multi-echo DSC perfusion imaging, a wide range of TEs are useful for accurate R_2^* estimation in both the AIF and tissue of interest. In particular, shorter echo times are important for dynamic contrast studies, as the T_2 and T_2^* can decrease to as low as tens of milliseconds during bolus passage (depending on dose, magnetic field strength, contrast agent, etc.). Previous studies with SAGE used parallel imaging to achieve the desired TEs; here, we use partial Fourier encoding, which is more readily available on small animal scanners. We obtained $TE_1 < 10 \text{ ms}$ and $TE_5 < 100 \text{ ms}$ with 75% partial Fourier encoding (48/64 lines acquired). The SNR with partial Fourier is decreased compared to full Fourier for the early echoes due to reduced k-space coverage; this is offset in the later echoes (TE_3 - TE_5) with minimized TEs because of competing T_2 effects. There are obvious improvements in image quality for TE_{3-5} using partial Fourier with minimized TEs, including higher SNR, which is important for accurate T_2 estimation. Although the images reconstructed from partial Fourier with long TEs suffered from poor temporal stability (higher temporal RSD), there were no major differences in signal stability over time between partial and full Fourier with minimized TEs. In addition, there was good agreement for the T_2 and T_2^* maps between partial (long and short TEs) and full Fourier encoding with minimized TEs, with partial Fourier encoding yielding a smaller fit error. Taken together

these results indicate that partial Fourier encoding is a reliable method for minimizing SAGE echo times and quantifying dynamic T_2 and T_2^* changes.

The SAGE acquisition presented here provides similar T_2 values compared to conventional single-line and EPI T_2 mapping techniques for both the phantom and rat brain. Species with high T_2 values may not be fit as accurately with SAGE when compared to conventional methods that acquire more echoes and a wider range of TEs. As the maximum T_2 observed in normal brain is typically less than 100 ms, this is unlikely to be a problem *in vivo*. Susceptibility-induced signal dropouts were observed near the brain edges (i.e., sinuses and cortex) for both the SAGE acquisition and conventional GE EPI images; this dropout was especially problematic for the first SAGE echo after refocusing (TE_3), leading to inaccurate SAGE R_2 fits. In pixels exhibiting inadequate MR signal at TE_3 (e.g., less than 5% of the maximum TE_3 signal intensity across the brain), the data were excluded from the SAGE analysis, resulting in a fit to echoes TE_1 , TE_2 , TE_4 , and TE_5 . The error parameter (RMSPE) was also used to define poorly fit voxels, often found near the edge of the brain, which were also excluded from analysis. Moreover, this highlights the need for careful shimming to minimize susceptibility-induced drop-offs near the edges of the brain prior to implementation of SAGE (as with other EPI-based sequences). Overall, we observed good agreement between SAGE T_2 and T_2^* and conventional single-line and EPI T_2 and T_2^* in rat brain.

In addition to measurements of T_2 and T_2^* , the SAGE acquisition also provides T_1 -based signals. In the phantom validation, the SAGE T_1 -based signal, along with a reference T_1 value, was used to determine the T_1 in four tubes doped with varying $MnCl_2$ concentrations. The T_1 s obtained from SAGE matched well with those obtained from a conventional IR acquisition. This indicates the ability of the SAGE sequence to provide accurate T_1 information, and thus R_1 information, for DCE kinetic modeling.

Using pre- and post-contrast IR-based T_1 maps, we also validated the R_1 derived from SAGE fits in C6 brain tumors. We observed good agreement between the conventional R_1 and the DSC-derived R_1 in tumor. To our knowledge, this represents the first time DSC-derived R_1 has been validated against conventional techniques and demonstrates the ability to accurately measure R_1 time-courses and thus extract DCE-permeability parameters (K^{trans} and v_e) using DSC-perfusion imaging. In this regard, the SAGE R_1 was slightly overestimated compared to the IR-based values, though the differences were not significant. This is likely due to CA washout.

Following Gd-DTPA injection, the tumor regions showed substantial T_1 leakage effects with single-echo ΔR_2^* , consistent with previous reports in C6 tumors [30,31]. Conversely, the SAGE R_2^* did not exhibit T_1 leakage effects. The SAGE R_2 time-course was higher than that from TE_5 after the bolus passage, indicating that T_1 leakage effects can influence SE data with long echo times. It is important to note that because the R_2 time-courses computed from TE_5 are not negative, it would have been impossible to discern the presence of leakage effects without comparing them to the T_1 -insensitive SAGE data. While multi-echo GE DSC-MRI acquisitions have been used for over a decade to remove T_1 leakage effects, this finding emphasizes the importance of using multi-SE or SAGE acquisition to

improve the reliability of SE-based DSC hemodynamic parameters in tumors. Due to these leakage effects, GE and SE CBV values were underestimated with the single-echo signals compared to the SAGE fits. Following injection of MION, the DSC time-courses for single-echo and SAGE fits were in good agreement, as expected in the absence of CA leakage [32,33]. In the stroke rat, the SAGE fits showed clear perfusion defects in the ischemic regions, which manifested as reduced CBF, CBV, and MTT and increased $T_{\max}$.

The Gd-based VSI maps showed increased tumor VSI relative to normal tissue, consistent with previous reports for C6 tumors [8–10,31]. A pre-load bolus to reduce T_1 sensitivity previously showed a lack of T_1 leakage effects on VSI estimates [31]. Correspondingly, the Gd-based VSI maps were similar between the SAGE fits and single-echo signals (TE_2 and TE_5), and there were no significant differences between Gd-DTPA and MION VSI for SAGE or single-echo data in tumor or normal tissue. Using the SAGE fits can provide reasonable estimates for VSI in tumor and normal tissue.

Using R_1 time-courses from the SAGE acquisition with an RR kinetic model, the DCE parameters K^{trans} and v_e were obtained in C6 tumors. The resulting K^{trans} and v_e were consistent with previous reports in the same tumor model using a conventional DCE acquisition [29]. Overall, the T_1 -weighted time-courses extrapolated from SAGE data were found to be suitable for DCE pharmacokinetic modeling. In this study, Tofts modeling using an RR was implemented to obtain K^{trans} and v_e ; however, conventional Tofts modeling with an arterial input function could also be applied. Specifically, the ΔR_2^* -derived AIF can be converted to CA concentration with accurate knowledge of the effective transverse relaxivity r_2^* , which was not known here. A potential limitation of conventional DSC-MRI acquisitions for K^{trans} and v_e estimation is the duration of the scan, which typically only includes two minutes of post-injection data. In this study, using approximately 15 minutes of post-injection data, the R_1 time-courses were well fit to the RR model, and the K^{trans} and v_e values were within the expected physiological range (approximately 26% of voxels were excluded with $0 > K^{\text{trans}} > 0.5 \text{ min}^{-1}$ or $0 > v_e > 1$). However, truncating the data to 2 minutes post-injection greatly overestimated v_e , with many voxels falling outside the normal physiological range (79% of voxels, with K^{trans} minimally affected). These results indicate that in order to reliably estimate v_e the DSC-MRI scans should be acquired for durations more consistent with clinical DCE-MRI scans (7–10 minutes).

A major advantage of the SAGE sequence is that the data can be acquired and processed in numerous ways. Conventional single-echo techniques provide CBF, CBV, and MTT for a specific vessel-size sensitivity, but both GE and SE cannot be acquired simultaneously. Additionally, single-echo methods are sensitive to CA leakage, although strategies have been proposed to correct or mitigate these effects [33–35]. Likewise, VSI and DCE permeability parameters cannot be obtained from a single-echo analysis. Dual-echo techniques yield T_1 -leakage insensitive CBF, CBV, and MTT with GE contrast, but no analog exists for SE contrast. DCE permeability information can be obtained with dual-echo sequences, but without SE information, VSI cannot be determined. Combined single gradient-echo spin-echo sequences provide CBF, CBV, and MTT with GE and SE contrast, in addition to VSI. However, these sequences are sensitive to leakage effects and do not permit DCE pharmacokinetic modeling. Using a SAGE EPI acquisition, multiple echoes are

provided in one sequence, providing T_1 -leakage insensitive CBF, CBV, and MTT with GE and SE contrast; moreover, VSI and DCE permeability information can be extracted.

In conclusion, SAGE EPI provides acquisition of multiple echoes with both gradient-echo and spin-echo contrast, which can be used to obtain measures of perfusion and permeability, plus vessel size information, in a preclinical setting. This study represents the first pre-clinical implementation and systematic characterization of the SAGE EPI sequence. We have optimized and validated a partial Fourier SAGE acquisition, which was shown to be robust for measuring R_2 and R_2^* in phantom samples and in two different animal models of disease. Moreover, we compared the DSC-derived R_1 to conventional (IR) R_1 in both phantom and rat brain tumor, further validating the ability to measure DCE-based permeability parameters using DSC-MRI. Overall, SAGE EPI provides a more comprehensive assessment of hemodynamic status in brain tissue with vascular abnormalities. This has implications in both clinical and preclinical settings as it serves to improve our understanding of the complex hemodynamics involved in tumor and stroke and may further influence potential treatment regimes.

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Fig. 1.

SAGE images for each echo and calculated T_2 and T_2^* maps in rat brain for full and partial Fourier encoding (top: partial Fourier 48 of 64 lines acquired; middle: full Fourier 64 of 64 lines acquired; bottom: full Fourier with 25% of k-space removed to yield partial Fourier 48 of 64 lines with same TEs as the full Fourier encoding).

Fig. 2.

a. Phantom comparison of T_2 estimates from conventional, EPI, and SAGE T_2 maps for tubes of various concentrations of $MnCl_2$, chosen to provide T_2 values of approximately 15, 30, 60, and 120 ms for tubes 1–4, respectively. b. Bar plot of mean T_2 in all four tubes between conventional, EPI, and SAGE measurements. c. Phantom comparison of T_1 estimates from conventional and SAGE T_1 maps for tubes of various concentrations of $MnCl_2$. b. Bar plot of mean T_1 in all four tubes between conventional and SAGE measurements. See Table 2 for all T_1 and T_2 values.

Fig. 3.

Top: Images in a representative rat showing R_1 maps from conventional (IR) and SAGE DSC. Bottom: Correlation between SAGE R_1 and conventional R_1 in tumor tissue. Bar plot shows comparison of R_1 from conventional and SAGE data in tumor tissue ($n = 3$).

Fig. 4. Dynamic SAGE signal curves and R_2 and ΔR_2^* curves for a tumor ROI following bolus injection of 0.4 mmol/kg Gd-DTPA (top) or 3 mg Fe/kg MION (bottom).

Fig. 5.

CBF, CBV, and MTT from GE (TE₂), SAGE R_2^* , SE (TE₅), and SAGE R_2 from a Gd-DTPA injection in a tumor-bearing rat.

Fig. 6.

a: Anatomical and VSI images for SAGE and single-echo (TE_2 and TE_5) fits during Gd-DTPA bolus passage. b: Slope of $\Delta R_2^{3/2}$ vs. ΔR_2^* during Gd-DTPA bolus passage for SAGE and single-echo in normal tissue (black) and tumor tissue (blue). c: Bar plots showing mean VSI using Gd-DTPA and MION.

Fig. 7. DWI and T_1 maps in a stroke rat showing location of stroke tissue. Corresponding CBF, CBV, MTT, and $T_{\max}$ from SAGE R_2^* and SAGE R_2 .

Fig. 8.

a. R_1 curves derived from SAGE data over a C6 tumor ROI and the reference region in muscle used for kinetic modeling. b. SAGE R_1 curves in a representative C6 tumor voxel, along with the respective RR model fits. c. Resulting K^{trans} and v_e maps in the C6 tumor region.

Table 1
Echo times (TEs), image SNR, and temporal stability (RSD) for each echo and partial Fourier encoding scheme.

% k-space	TE (ms)			SNR			Temporal RSD		
	75%	100%	75%*	75%	100%	75%*	75%	100%	75%*
Echo 1	8.6	15	15	50.2	59.5	42.6	0.04	0.02	0.05
Echo 2	35	41	41	28.8	36.5	23.8	0.08	0.04	0.09
Echo 3	54	73	73	13.3	11.6	7.6	0.16	0.12	0.25
Echo 4	80	99	99	10.5	9.1	6.6	0.21	0.16	0.32
Echo 5	93	125	125	7.1	6.1	4.2	0.25	0.22	0.43

* The 75% k-space data with long TEs were obtained by removing 16 lines (25%) of the raw full Fourier dataset.

Table 2

Comparison of phantom T_2 and T_1 and rat brain T_2 and T_2^* using conventional, EPI, and SAGE acquisitions.

Tube	Calculated T_2 ([CA])	Conventional T_2 (SD)	EPI T_2 (SD)	SAGE T_2 (SD)	Conventional T_1 (SD)	SAGE T_1 (SD)
1	15 ms (0.339 mM $MnCl_2$)	20.4 (0.47)	19.0 (0.96)	18.5 (4.7)	370.3 (2.3)	426.9 (24.2)
2	30 ms (0.167 mM $MnCl_2$)	36.6 (0.98)	39.0 (1.1)	42.8 (2.6)	669.4 (6.6)	638.2 (107.9)
3	60 ms (0.08 mM $MnCl_2$)	69.8 (1.4)	78.4 (3.8)	73.7 (1.3)	1083.2 (8.6)	1289.9 (133.0)
4	120 ms (0.038 mM $MnCl_2$)	129.0 (2.3)	127.5 (6.3)	134.6 (12.5)	1728.5 (18.4)	1631.0 (92.7)
Rat brain	T_2 (SD)	58.9 (0.8)	53.6 (1.9)	58.1 (4.0)	–	–
	T_2^* (SD)	38.8 (2.5)	37.4 (3.4)	43.7 (6.9)	–	–