Published in final edited form as:

Magn Reson Imaging. 2014 December ; 32(10): 1171–1180. doi:10.1016/j.mri.2014.08.032.

Evaluation of a Multiple Spin- and Gradient-Echo (SAGE) EPI Acquisition with SENSE Acceleration: Applications for Perfusion Imaging In and Outside the Brain

Jack T. Skinner^{1,2}, Ryan K. Robison⁴, Christopher P. Elder^{1,2}, Allen T. Newton^{1,2,3}, Bruce M. Damon^{1,2,6,7}, and C. Chad Quarles^{1,2,5,6}

¹Vanderbilt University Institute of Imaging Science, Vanderbilt University

²Department of Radiology and Radiological Sciences, Vanderbilt University School of Medicine

³Monroe Carol Children's Hospital, Vanderbilt University Medical Center

⁴Barrow Neurological Institute, St. Joseph's Hospital, Phoenix, AZ

⁵Department of Cancer Biology, Vanderbilt University School of Medicine

⁶Department of Biomedical Engineering, Vanderbilt University

⁷Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine

Abstract

Perfusion-based changes in MR signal intensity can occur in response to the introduction of exogenous contrast agents and endogenous tissue properties (e.g. blood oxygenation). MR measurements aimed at capturing these changes often implement single-shot echo planar imaging (ssEPI). In recent years ssEPI readouts have been combined with parallel imaging (PI) to allow fast dynamic multi-slice imaging as well as the incorporation of multiple echoes. A multiple spin- and gradient-echo (SAGE) EPI acquisition has recently been developed to allow measurement of transverse relaxation rate (R_2 and R_2^*) changes in dynamic susceptibility contrast (DSC)-MRI experiments in the brain. With SAGE EPI, the use of PI can influence image quality, temporal resolution, and achievable echo times. The effect of PI on dynamic SAGE measurements, however, has not been evaluated. In this work, a SAGE EPI acquisition utilizing SENSE PI and partial Fourier (PF) acceleration was developed and evaluated. Voxel-wise measures of R_2 and R_2^* in healthy brain were compared using SAGE EPI and conventional non-EPI multiple echo acquisitions with varying SENSE and PF acceleration. A conservative SENSE factor of 2 with PF factor of 0.73 was found to provide accurate measures of R_2 and R_2^* in white (WM) ($r_{R_2} = [0.55-0.79]$, $r_{R_2^*} = [0.47-0.71]$) and gray (GM) matter ($r_{R_2} = [0.26-0.59]$, $r_{R_2^*} = [0.39-0.74]$) across subjects. The combined use of SENSE and PF allowed the first dynamic SAGE EPI measurements

©2014 Elsevier Inc. All rights reserved.

Please send correspondence to: C. Chad Quarles, Vanderbilt University Institute of Imaging Science, AA 1105 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2310, USA, Phone: (615) 322-6215, chad.quarles@vanderbilt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

in muscle, with a SENSE factor of 3 and PF factor of 0.6 providing reliable relaxation rate estimates when compared to multi-echo methods. Application of the optimized SAGE protocol in DSC-MRI of high-grade glioma patients provided T_1 leakage-corrected estimates of CBV and CBF as well as mean vessel diameter (mVD) and simultaneous measures of DCE-MRI parameters K^{trans} and v_e . Likewise, application of SAGE in a muscle reperfusion model allowed dynamic measures of R_2' , a parameter that has been shown to correlate with muscle oxy-hemoglobin saturation.

Keywords

perfusion; MRI; DSC; dynamic contrast; parallel imaging; multi-echo; muscle; BOLD; tumor

Introduction

MR signal can change rapidly in response to changes in exogenous or endogenous contrast agents (CA) in an imaging voxel. MR methods used to monitor these changes often focus on extracting information about tissue perfusion and/or blood oxygenation. For example, dynamic susceptibility contrast (DSC)-MRI uses measures of the effective transverse relaxation rate to track a CA bolus as it distributes in the vasculature and tissue spaces (e.g. tumor) (1,2). This method aims to characterize first-pass hemodynamics for the purpose of computing measures of blood volume and blood flow, often in brain lesions. In addition to Gd-based contrast enhanced imaging, quantification of MR signal changes due to endogenous contrast (e.g. deoxy-hemoglobin) have been demonstrated in blood oxygen level dependent (BOLD) imaging studies (3). Applications of BOLD imaging include functional MRI in both brain (4) and skeletal muscle (5,6). Regardless of the target tissue or type of CA, these techniques require acquisitions with high temporal resolution and the ability to quantify changes in NMR relaxation rates.

Single-shot echo planar imaging (ssEPI) has been used to capture such signal changes with a temporal resolution less than 2s. Dynamic gradient-echo (GE) acquisitions with ssEPI readouts have been implemented in many MR studies, including perfusion (1,2) and functional MRI (7,8). Though conventional ssEPI imaging can improve temporal resolution, it may also produce geometric distortions and result in longer readout times, leading to T_2^* decay during signal acquisition (9). Multi-shot EPI acquisitions can be used to help alleviate these problems; however, these come at the expense of temporal resolution or slice coverage. A second solution, which has been implemented more recently, is the addition of parallel imaging (PI) (10,11). Combining PI with EPI can be used to maintain high temporal resolution during dynamic imaging while mitigating some of the aforementioned limitations (12–16). PI methods, such as SENSitivity Encoding (SENSE), can be implemented with EPI to shorten echo times (TE), permitting increased slice coverage or the acquisition of additional echoes in a single TR (17).

In recent years, perfusion MRI studies have started to incorporate multi-echo acquisitions (18–20). In the context of DSC-MRI, dual GE acquisitions have been used to correct T_1 leakage effects in tumor tissue and to allow the extraction of T_1 -weighted signals for use in

dynamic contrast enhanced (DCE)-MRI based pharmacokinetic modeling (21–23). Multi-echo methods that implement a single GE in addition to a spin-echo (SE) acquisition have also been investigated (24–26). More recently, Schmiedeskamp *et al.* developed a multiple echo spin- and gradient-echo (SAGE) EPI sequence for perfusion measurements in the brain (27,28). The SAGE acquisition permits the simultaneous measurement of R_2 and R_2^* during a dynamic event, such as CA distribution. These measurements can be used to generate traditionally acquired GE-based perfusion parameters such as cerebral blood volume (CBV), blood flow (CBF), and mean transit time (MTT), in addition to their SE-based counterparts. In these multi-echo experiments, simultaneous acquisitions of R_2 and R_2^* provide sensitivity to both macro- and microvasculature and, therefore, allow estimation of relative blood vessel size, a potentially important quantitative MR biomarker in perfusion and functional BOLD imaging (29–31).

Previous studies have investigated the effect of PI on ssEPI image quality and neuronal activation in the case of functional MRI (14–16). Few of these studies, however, included multiple-echo acquisitions and, therefore, have not considered the effect of PI on NMR properties such as R_2 and R_2^* . In previous SAGE EPI experiments (27,28,32), data were only acquired with a single GRAPPA PI factor (Reduction Factor (R) = 3). Though a similar reduction in scan time can be afforded by PI techniques using image-based reconstruction (e.g. SENSE), the optimal (or allowable) amount of image acquisition acceleration, in the context of a SAGE EPI experiment, is unknown. Optimization and implementation of a multi-echo SAGE EPI acquisition requires a trade-off between dynamic scan time, spatial and temporal SNR, and echo time. Depending on voxel size and dynamic repetition time (TR), the use of SENSE with SAGE (33) may be limited by the range of TEs necessary to reliably characterize R_2 and R_2^* in a given tissue. This may be particularly true in tissues outside of the brain (e.g. skeletal muscle) that exhibit higher R_2 and R_2^* . The combination of multiple acceleration methods (e.g. PI plus partial Fourier) may help address this issue by further decreasing SAGE TEs; however, a systematic evaluation is needed.

In this study, a multiple-echo SAGE EPI sequence utilizing SENSE acceleration was developed and optimized in the brain and skeletal muscle. Dynamic relaxation rate measurements were computed from SAGE acquisitions in healthy subjects, while varying SENSE and partial Fourier acceleration factors. These measures were compared, on a voxel-wise basis, to those from conventional non-EPI multiple gradient-echo (MGE) and multiple spin-echo (MSE) MRI methods and were evaluated using the mean percent difference between values, the pooled standard deviation and voxel-wise correlations. Optimized SAGE protocols were applied in DSC-MRI perfusion experiments in high-grade glioma patients as well as measurements of muscle reperfusion in healthy subjects undergoing arterial occlusion and leg contractions.

Methods

SAGE Evaluation and Optimization: Brain and Muscle

For evaluation in the brain, dynamic SAGE EPI data were acquired in healthy subjects (n=4, 28–36 y.o., 2 Males) (under Vanderbilt University Institutional Review Board (IRB) guidelines) at 3T (Achieva, Philips Healthcare, Best, The Netherlands) using a 32 channel

head coil for data reception. Scan parameters were: TR = 1.8s, Dynamics = 35; FOV = 240×240mm², Voxel Size = 3.16×3.16×5.0mm³ (reconstructed to a 96×96 square matrix), number of echoes (NE) = 5 (2 GE, 2 asymmetric SE, 1 SE) (27), and slices = 15. The number of dynamics was chosen to provide 30–60s of data, a typical duration for baseline (pre-contrast) measurements in perfusion imaging. Echo times were computed (within the pulse sequence) by minimizing the acquisition time of each EPI readout train and were, therefore, influenced by SENSE acceleration factors (SENSE), partial Fourier acceleration factors (PF), and voxel size. As part of sequence optimization, the SENSE acceleration factor was varied between 1.5 and 4 with and without PF factors of 0.60, 0.73, 0.81, and 1.00. As a prerequisite, all scan parameters were set such that resulting TEs were between ~5ms and 100ms for brain imaging.

The multi-echo SAGE data were fit in a least-squares manner to Eq. (1) (27,28):

$$S(t) = \begin{cases} S_0 \cdot e^{-t \cdot R_2^*} & 0 < t < TE/2 \\ \frac{S_0}{\delta} \cdot e^{-TE(R_2^* - R_2)} \cdot e^{-t(2R_2 - R_2^*)} & TE/2 < t < TE \end{cases} \quad (1)$$

The four resulting fitted parameters were S_0 , R_2 , R_2^* , and δ , where δ accounts for possible slice profile mismatch between echoes before and after refocusing (28). To assess fit quality, the root mean squared percent error (RMSPE) was calculated. Due to the importance of dynamic stability in analyses of perfusion and functional MR studies (34), temporal SNR (tSNR) was assessed on a voxel-wise basis over an ROI encompassing a single brain slice for each SAGE echo. Voxel-wise measures of R_2 and R_2^* from the SAGE acquisition (averaged over 25 dynamics) were compared to those from conventional MGE (TR = 1800ms, TE = 5.0ms, echo spacing (ESP) = 5.0ms, NE = 20) and MSE (TR = 6000ms, TE = 5.91ms, ESP = 5.91ms, NE = 16) acquisitions. The group mean and pooled standard deviation (std_p) were computed along with Pearson's correlation coefficient (r). In addition, the mean percent difference (% diff) in relaxation rates was calculated in a voxel-wise manner over white and gray matter ROIs covering several contiguous slices.

In a similar manner, the SAGE sequence was evaluated and optimized in skeletal muscle. SAGE data was acquired in the legs of healthy subjects (n=4, 29–39 y.o., 3 Females) at 3T (Achieva, Philips Healthcare, Best, The Netherlands) using an 8 channel receive-only knee coil and the body coil for transmission. Scan parameters were: TR = 2.5s, Dynamics = 10, FOV = 180×180mm², Voxel Size = 2.81×2.81×7.6mm³, NE = 5, slices = 1. The SENSE factor was varied between 2 and 4 and the PF factor varied between 0.6 and 0.65, attempting to keep echo times less than 50ms. As with the brain, dynamic stability was assessed by measuring mean tSNR over an ROI encompassing the tibialis anterior (TA). Muscle SAGE data were fitted to Eq. (1) as described above. Resulting measures of SAGE R_2 and R_2^* were compared to those from MGE (TR = 2500ms, TE = 2.5ms, ESP = 2.5ms, NE = 30) and MSE (TR = 2500ms, TE = 10.8ms, ESP = 10.8ms, NE = 8) acquisitions. Due to the homogeneity of muscle tissue over an ROI, the mean percent difference in relaxation rates and the pooled standard deviation were used for comparison in lieu of voxel-wise correlations. For both muscle and brain, the optimal SAGE protocols were selected based on

temporal stability (high tSNR) and agreement with conventional multi-echo methods (small mean percent difference, small std_p , and high voxel-wise correlations).

Brain Tumor Perfusion

SAGE data were acquired in high-grade glioma patients ($n=3$, 40–55 y.o., 3 Males) using the scan parameters listed above and the optimized acceleration scheme (see Results). Measurements were made before, during, and after administration of Gd-DTPA (0.1 mmol/kg, infusion rate of 4ml/s followed by a 20ml saline flush). The scan duration was 7.5 minutes (250 dynamics). The resulting SAGE data were fitted on a voxel-by-voxel basis, first using Eq. (1) to determine an average value of δ over a 60s baseline, and subsequently fixing this parameter when fitting (three-parameter fit to Eq. (1)) the remainder of the dynamic time-course. From this fit, estimates of R_2 and R_2^* were computed with the passage of CA. R_2 and R_2^* were calculated as the difference between the relaxation rates during CA passage and the mean pre-contrast relaxation rate. In addition, a T_1 -weighted signal time course was extracted from the first two echoes of the SAGE data (TE_1 and TE_2) by extrapolating to $S(TE = 0)$ (21–23). Multiple flip angle (MFA) data were also acquired ($TR = 7.6\text{ms}$, $TE = 4.6\text{ms}$, $FA = 2^\circ\text{--}20^\circ$ in 2° increments) to create a pre-contrast T_1 map, which was combined with the T_1 -weighted data to produce R_1 time-courses for each voxel.

DSC-MRI and DCE-MRI Analysis

To compute parametric perfusion maps, an arterial input function (AIF) was extracted from the SAGE GE data, in the region of the medial cerebral artery. An automated selection process based on peak height, bolus arrival time, and correlation between the first two echoes during bolus passage was used to avoid saturation effects in the AIF (35,36). The

R_2^* time-course for the AIF was converted to a concentration time-course using a quadratic relationship for CA inside a blood vessel (37). R_2 and R_2^* time-courses in tissue were converted to CA concentration ([CA]) using the CA's *in vivo* relaxivity. The effective transverse relaxivity of Gd-DTPA (r_2^*) at 3T was assumed to be $87\text{ mmol}^{-1}\text{ ms}^{-1}$ (38) while the value of r_2 used was $20.4\text{ mmol}^{-1}\text{ ms}^{-1}$ (27). Standard DSC analysis was carried out on the AIF and tissue [CA] time courses (70 dynamics, 30 pre- and 40 post-injection) using a circular deconvolution approach with SVD (1,39). Measures of absolute *CBV*, *CBF*, and *MTT* for both GE and SE data were calculated for the entire tumor volume. Based on the simultaneous acquisition of R_2 and R_2^* (and voxel-wise estimates of tissue diffusion (data not shown)), mean vessel diameter (*mVD*) was computed using methods described by Kiselev *et al.* (30). Pharmacokinetic modeling of the computed R_1 time courses (250 dynamics, 30 pre-injection and 220 post-injection) and the AIF (in [CA]) described above was performed using the standard Tofts model in order to estimate voxel-wise measures of K^{trans} (contrast agent transfer rate constant) and v_e (extracellular-extravascular volume) (40,41).

Muscle Perfusion

Healthy subjects ($n=5$, 27–37 y.o., 3 Females) were scanned at 3T using an eight channel RF knee coil for signal reception. Specific methods about patient set-up are described elsewhere (5). Briefly, the coil was aligned with the center of the magnet and the subject was

positioned supine on the patient bed with a foot stabilized by strapping it into an isometric exercise device. The maximum cross-sectional area of the TA was centered in the coil. For the occlusion experiment, a pneumatic cuff was placed around the subject's (n=2, 1 Female) thigh and connected to a Hokanson E20 rapid cuff inflator and AG101 air source (Hokanson, Bellevue, WA). Data were acquired for 1 minute prior to cuff occlusion, after which the cuff was rapidly inflated to 248 mmHg. Arterial occlusion continued for a period of 4–5 minutes, after which the cuff was rapidly released and data were acquired for an additional 7–8 minutes. The remaining subjects (n=3, 2 Females) performed a 10s duration maximal voluntary isometric dorsiflexion contraction followed by 4 minutes of rest. Scan parameters for the dynamic SAGE acquisition were the same as in the validation scans with the optimal acceleration scheme (see Results). Dynamic SAGE data were analyzed using a three-parameter fit to Eq. (1)) as described for the brain tumor perfusion experiment. From this fit, measures of R_2 and R_2^* were extracted before, during, and after arterial occlusion and contraction. The post-contraction R_2^* data were smoothed by fitting them to a 6th order polynomial, similar to the procedure used in (20). The rate of RF-reversible dephasing, $R_2' (= R_2^* - R_2)$, was also computed as this parameter has been shown to correlate with muscle oxy-hemoglobin saturation (5).

Results

The effect of SENSE PI on SAGE image quality can be seen in Fig. 1. Increasing SENSE acceleration, with the minimum allowable PF factor (PF = 0.6), resulted in PI reconstruction artifacts (Fig. 1a–c). In addition, geometry (g)-factor maps were calculated at each SENSE factor (Fig. 1d–f) in order to assess image noise associated with increased PI. Though the SAGE measurements demonstrated temporal signal stability sufficient for signal modeling in perfusion and functional MRI (Fig. 1g–i), the tSNR decreased by up to 29% in the first two echoes when the SENSE acceleration factor was increased to 4.

Validation of the current technique in an example subject is presented in a voxel-wise comparison of relaxation rate estimates with varying image acceleration (Fig. 2). Fig. 2 demonstrates the influence of combining SENSE acceleration and PF on SAGE measures of R_2 and R_2^* in white matter. A wide range of voxel-wise correlations were observed across the different SENSE/PF combinations, with white matter $r_{R_2} = [0.01–0.84]$ and $r_{R_2^*} = [0.03–0.74]$ and gray matter $r_{R_2} = [0.01–0.92]$ and $r_{R_2^*} = [0.07–0.77]$. Estimates from acquisitions with SENSE 3 in combination with PF = 0.6 yielded the lowest correlations with conventional measures. SAGE estimates of R_2 and R_2^* (mean $\pm$ std_p across subjects) in white and gray matter ROIs are outlined in Table 1 along with the mean percent difference from a voxel-wise comparison with MGE and MSE measures. Based on high tSNR, small std_p and mean percent difference, and higher correlations (across subjects) with conventional measures ($r_{R_2}=[0.55–0.79]$, $r_{R_2^*}=[0.47–0.71]$ in WM and $r_{R_2}=[0.26–0.59]$, $r_{R_2^*}=[0.39–0.74]$ in GM), it was determined that a SENSE factor of 2 with a PF = 0.73 (highlighted in Table 1) provided the most reliable estimates of R_2 and R_2^* from the SAGE acquisitions evaluated. Using this optimal acceleration scheme, fits to the SAGE data, over a single slice, resulted in a RMSPE of 0.12 ± 0.06 across subjects.

Fig. 3a shows example images at each SAGE echo in muscle. The SAGE decay curve from an ROI encompassing the TA and the corresponding fit can be seen in Fig. 3b. Also shown are the R_2^* (dash-dot) and R_2 (dashed) decay curves. Table 2 shows the effect of varying image acceleration on SAGE measures of R_2 and R_2^* in muscle when compared to MGE and MSE measures. The use of a smaller SENSE factor (e.g. SENSE = 2) resulted in an overestimation in relaxation rates up to 24%, while SENSE > 2 provided more accurate estimates, particularly in R_2^* . Acquisitions with SENSE = 3 and PF = 0.6 as well as SENSE = 4 and PF = 0.65 performed equally as well based on the mean percent difference and std_p reported in Table 2. For the dynamic muscle perfusion studies, a SENSE factor of 3 and PF = 0.6 was selected as the optimal acquisition due to higher mean tSNR at each echo ($\text{tSNR}_{\text{TE1-5}} = 423, 295, 150, 114, 93$).

Fig. 4a shows the SAGE signal decay curves for a region of normal appearing white matter and tumor prior to the administration of CA. Also shown are portions of the corresponding individual R_2^* (dashed lines) and R_2 decay curves (dotted lines) before and after the refocusing pulse. Note that for both tumor and white matter, the GE data points fall directly on the calculated R_2^* decay curve, while the R_2 decay curve intersects the SAGE data points at the SE (TE₅). The resulting SAGE R_2 and R_2^* curves for white matter and tumor ROIs during CA passage are displayed in Fig. 4b and 4c, respectively. Also displayed are R_2 and R_2^* time-courses calculated from single GE (TE₂) and SE (TE₅) data. As expected, only minor differences between SAGE R_2 and R_2^* and single-echo estimates were observed in white matter. The SAGE time-courses in tumor (particularly during washout), however, were quite different when compared to those from single-echo measurements, as the SAGE estimates are intrinsically corrected for T₁ effects due to CA leakage, while enhancing sensitivity to T₂^{*} effects. Additionally, the contrast-to-noise ratio (CNR), as measured from peak to baseline, in whole tumor across patients was found to be 33.9 ± 18.8 and 10.8 ± 2.1 in SAGE R_2^* and R_2 time-courses, respectively, compared to 50.3 ± 30.3 and 7.2 ± 3.7 in the single-echo estimates.

Fig. 5 demonstrates the utility of SAGE EPI for DSC perfusion imaging. Parametric maps created from R_2^* and R_2 data highlight increases in both *CBV* and *CBF* in the enhancing tumor regions. GE *CBV*, *CBF* and *MTT* in whole tumor were 4.07 ± 1.59 ml/100g, 31.53 ± 10.78 ml/100g/min, and 7.75 ± 0.39 s, respectively. SE *CBV*, *CBF* and *MTT* in tumor were 2.97 ± 0.68 ml/100g, 16.95 ± 4.13 ml/100g/min, and 10.95 ± 0.43 s, respectively. Voxel-wise measures of *mVD* (Fig. 5e) were found to predominantly vary between 2 μm –25 μm across the brain. In normal appearing white matter *mVD* was observed to be 6.6 μm across patients, while whole tumor *mVD* was 10.7 μm . In addition, voxel-wise T₁-weighted signal time-courses were extrapolated from the GE data, resulting in a mean R_1 time course for the tumor ROI (Fig. 6a). Pharmacokinetic analysis of the R_1 time courses using the standard Tofts model (Fig. 6b, c) resulted in $K^{\text{trans}} = 0.16 \pm 0.03 \text{ min}^{-1}$ and $v_e = 0.45 \pm 0.04$ in the enhancing tumor volumes across patients.

SAGE R_2^* , R_2 , and R_2' time-course data were acquired from the tibialis anterior of one male subject and one female subject before, during, and after 4 or 5 minutes, respectively, of thigh cuff-induced arterial occlusion. Relaxation rate constant time courses included similar features for both subjects: initial rapid decrease with cuff inflation; slow increase during

occlusion; rapid decrease to minimum after cuff deflation; slow return to baseline from minimum. Data from the 4 minute occlusion are presented in Fig. 7a. The R_2^* , R_2 and R_2' baseline 30s prior to cuff inflation for both subjects were 41.4 ± 1.7 , 37.5 ± 1.6 , and $3.9 \pm 0.1 \text{ s}^{-1}$. These values decreased rapidly to 37.9 ± 2.4 , 36.0 ± 0.4 , and $2.2 \pm 2.5 \text{ s}^{-1}$ with cuff inflation, then increased more slowly over the duration of occlusion to 40.7 ± 0.1 , 38.2 ± 3.0 , and $2.7 \pm 2.9 \text{ s}^{-1}$. Following cuff deflation, relaxation rate constants reached minima of 38.2 ± 0.1 , 34.7 ± 0.3 , and $3.4 \pm 0.2 \text{ s}^{-1}$ with times to minimum of $23.8 \pm 5.3 \text{ s}$. Return to baseline following occlusion required 445 ± 49.5 and $150 \pm 3.5 \text{ s}$ for R_2^* and R_2 , respectively.

SAGE R_2^* , R_2 , and R_2' time-course data were also acquired from the TA of 3 subjects before, during, and after a 10 second duration maximal voluntary isometric contraction of the dorsiflexors. Example time-course data from a subject are presented in Fig. 7b. R_2^* , R_2 and R_2' 30 s prior to each contraction were 39.1 ± 6.0 , 37.9 ± 5.6 , and $1.3 \pm 0.5 \text{ s}^{-1}$. Following the contraction, R_2^* and R_2 showed a muscle BOLD related decrease to 37.8 ± 5.7 and $36.1 \pm 5.8 \text{ s}^{-1}$ with 20.8 ± 5.2 and $17.5 \pm 6.6 \text{ s}$ times to minimum, respectively. R_2' increased following contraction to a peak of $2.2 \pm 0.4 \text{ s}^{-1}$ with a time to peak of $6.7 \pm 2.9 \text{ s}$.

Discussion

This study evaluates a multiple-echo SAGE EPI acquisition with SENSE PI developed for perfusion MRI. Regarding acquisitions in the brain, this analysis demonstrates the potential drawbacks of using large SENSE factors in the context of quantitative imaging with SAGE EPI. Consequently, the use of more conservative PI required the addition of partial Fourier acquisitions to produce TEs suitable for characterizing transverse relaxation rates in brain and muscle. It has been previously shown in the brain that the use of large SENSE factors (≥ 3) with ssEPI may lead to an increase in image artifact and noise, as observed here, when compared to other PI techniques (11,16). The present study does show that reasonable estimates of R_2 and R_2^* can be made in the brain with SENSE = 3 if PF techniques are excluded, supporting the previous use of GRAPPA ($R = 3$) with SAGE EPI (27,28,32). It should be noted, however, that these implementations, because they forgo PF imaging, may ultimately be limited to the use of longer TEs (without changing other imaging parameters). This could confound the characterization of tissues with short T_2 s, as demonstrated here in muscle, where the use of shorter TEs (with multi-echo imaging) is essential. Therefore, knowledge of the present acceleration techniques' impact on data reliability and accurate relaxation rate estimates with SAGE EPI is important when considering application across multiple tissue types.

Sequence validation was performed in healthy subjects both in the brain and skeletal muscle. The mean RMSPE for the four-parameter SAGE fit in brain and in the TA ROI were 0.12 and 0.21, respectively, which was significantly less than that observed previously by Schmiedeskamp *et al* (28). In addition, we observed a mean whole brain tSNR (tSNR > 70 at all echoes) that was larger than previously reported at 3T using SENSE EPI with similar acceleration (15,16). Moderate correlations were found between estimates of R_2 and R_2^* from SAGE acquisitions in the brain when compared to conventional multi-echo techniques. In the optimized acquisition, mean values of R_2^* differed by less than 5% from

corresponding MGE measures in the brain, while larger differences were observed in R_2 . For muscle, mean values of SAGE R_2 and R_2^* from the optimized acquisition corresponded well ($< 12\%$ difference) with estimates from conventional acquisitions (Fig. 3). Despite these differences, the mean transverse relaxation rates estimated from the optimized SAGE acquisitions fell within the range of those previously reported for brain and muscle at 3T (42,43). Aside from known effects of ssEPI imaging, differences in relaxation rate estimates from SAGE EPI may be attributed to slice profile mismatch due to non-ideal RF pulse profiles, as previously reported (28). In this regard, the value of δ in white matter across subjects was 1.09 ± 0.08 , which corresponded well to previous SAGE measurements in brain (28). The corresponding measure in muscle was observed to be larger with $\delta = 1.51 \pm 0.40$. Though the perfusion experiments implemented a fixed estimate of δ (and therefore a three-parameter fit) throughout the dynamic time course, potential errors associated with excitation and refocusing slice profile mismatch, particularly during CA bolus passage, may still need to be considered.

Brain Tumor Perfusion

The utility of fast multi-echo EPI measurements, as demonstrated with SAGE EPI, is well suited for perfusion imaging, both with and without CA administration. To this end, the work presented here further validates application of SAGE EPI in the evaluation of brain tumors. In DSC-MRI it is known that estimates of CBV , CBF and MTT can be confounded by CA extravasation, as is observed in enhancing tumors (44,45). Because traditional single-echo DSC measures can lead to underestimation of tumor CBV in this scenario, multiple-echo acquisitions have been used in their place to calculate T_1 -leakage corrected estimates of R_2^* (Fig. 4c) (18,21,46). The range of T_1 -corrected CBV , CBF and MTT estimates (Fig. 5) in this study were found to agree with published values in healthy brain and tumor (47,48). The SE-based perfusion maps (Fig. 5f–h) exhibited decreased measures of CBV (27% decrease) and CBF (47% decrease) in tumor, when compared to GE techniques. This is expected, as SE measurements are maximally sensitive to capillary-sized blood vessels. The differences in GE and SE DSC parameters closely reflect those previously observed in leakage corrected SAGE measurements in glioblastoma multiforme patients (32). In addition to traditional DSC parameters, the simultaneous measurement of R_2 and R_2^* with SAGE EPI provides sensitivity to a range of blood vessel sizes. As a byproduct of these simultaneous measurements, information about blood vessel diameter was also ascertained. The resulting estimates of mVD in healthy brain and tumor tissue were in good agreement with those observed in a previous experiment using confocal microscopy (49) and appear to be more similar to histological measurements when compared to previous vessel size imaging studies in humans (30).

In addition to correcting CA leakage effects, multiple-echo DSC acquisitions permit the extraction of T_1 -weighted signal time-courses. SAGE EPI data was used to compute R_1 time-courses in order to estimate DCE-MRI parameters K^{trans} and v_e . These data highlight both perfusion and permeability characteristics of the enhancing lesions. Simple pharmacokinetic modeling was implemented. This approach differed from that previously reported for analyzing T_1 -based time-courses acquired with SAGE EPI (32). The previous study by Schmiedeskamp *et al.* implemented a four-parameter model with abbreviated (< 2

minutes) tissue [CA] time-courses. Though the estimated parameters were used to correct DSC perfusion estimates for T_2^* leakage effects, the complexity of the model may make it more susceptible to noise propagation when compared to the more conventional Tofts' model. The use of shortened dynamic time-courses may also lead to confounded measures of v_e due to incomplete sampling of tracer washout.

Muscle Perfusion

This study presents the first evaluation and application of dynamic SAGE EPI outside of the head. Overall, the SAGE R_2^* and R_2 responses that we report here agree with reports from the literature when factors such as field strength, the muscle studied, the limited sample size, and pulse sequence are considered. For the occlusion experiments, the 7.4% increase in SAGE R_2^* during occlusion and the relative SAGE R_2^* hyperemic decrease to 90% of the baseline rate constant, after 4–5 minutes of arterial occlusion in the TA, are in very good agreement with studies using a range of cuff durations. Sanchez *et al.* (50) reported a 7.0% increase in R_2^* of the TA during 3 minutes of cuff occlusion. T_2^* data from Englund *et al.* (51), when converted to rate constants, showed an 8.7% increase in R_2^* of the soleus during occlusion and a hyperemic decrease to 87% of the baseline signal after 3 minutes of occlusion. Elder *et al.* (5) reported a 9.8% increase in R_2^* in the TA during occlusion and a decrease to approximately 95% of baseline after 5 minutes of occlusion. In contrast, Toussaint *et al.* (52) reported a 6.5% decrease in GE (TE = 60 ms) signal intensity after 5 minutes of occlusion in the soleus at 1.5T and Lebon *et al.* (53) demonstrated a 6% decrease in GE (TE = 15 ms) signal intensity of the gastrocnemius after 7 minutes of occlusion at 3T. Only a $2.2 \pm 1.0\%$ decrease in GE (TE = 4.9 ms) signal intensity was observed in the TA during 4 or 5 minutes of occlusion at 3T (data not shown). In addition, our 2.2 s^{-1} increase in SAGE R_2^* was also less than the $\sim 8 \text{ s}^{-1}$ increase during 3 minutes of occlusion and the 15 s^{-1} increase in R_2^* observed during 5 minutes of occlusion in the soleus at 3T (TE = 27.2 ms) by Donahue *et al.* (26).

The differences in relative signal intensity decrease and increase in R_2^* are likely explained first by differences in the physiological sensitivity of the echo times employed (shorter TE being less sensitive to oxygen saturation (20)), and second, by potential differences in oxygen utilization rate (54) in ischemic muscle between subject populations. Our data agrees, however, with other studies that included similarly short echo times (5,50,51). The 6.1% increase in SAGE R_2 we observed in the TA during occlusion at 3T agrees with the 4.6% increase in R_2 during occlusion that results when the data from Toussaint *et al.* (52) are adjusted for differences in field strength. This increase, however, is greater than the little to no change in R_2 of the TA reported previously by Elder *et al.* (5). Our 2.2 s^{-1} increase in R_2 is comparable with the approximately 4 s^{-1} increase in R_2 of the soleus reported by Donahue *et al.* (26) when the muscle group and possible differences in training status of the subject populations are considered.

For the muscle contraction experiments, the decrease in SAGE R_2^* of 3.3% following a 10 s isometric contraction is in good agreement with the 4.6% decrease in R_2^* following an 8 s isometric contraction of the same muscle group reported by Damon *et al.* (20). Meyer *et al.* (55) reported an average decrease in R_2^* of 0.85 s^{-1} and a time to peak of the BOLD

response of 7.9 s following 1 s isometric contractions of the TA, while we observed a 1.3 s^{-1} decrease in R_2^* for 10 s contractions and a 20.8 s time to minimum. The signal and time to peak differences are consistent, and the approximately 2 fold difference in the time and magnitude of the response is reasonable considering the potential effect of contraction duration (55) and the effect of differences in physical activity status on post-contraction changes in apparent relaxation rates (54).

The SAGE acquisition, applied in skeletal muscle during arterial occlusion and maximal isometric contractions, allows the simultaneous measurement of R_2^* and R_2 and permits a more direct calculation of R_2' , a parameter that provides a basis for image based calculation of muscle oxygen saturation (5). Compared to protocols that separately measure R_2 and R_2^* , SAGE EPI improves experimental efficiency, reduces between-test physiological variability, decreases subject burden, and reduces investigator processing time. These advantages allow many potential applications and would be most useful in the investigation of patient populations such as individuals with diabetes, peripheral vascular disease, and other conditions affecting oxygen delivery or cellular metabolism.

The SAGE EPI acquisition presented here was developed and implemented with relatively minor modifications to an existing SE ssEPI pulse sequence. Furthermore, the current sequence employed vendor-provided RF pulses, PI capabilities, and image reconstruction techniques, all of which were achieved completely on the scanner itself. In addition, SAGE EPI acquisitions with SENSE were successfully made using multiple RF coils (32 channel and 8 channel (data not shown) head coils and 8 channel knee coil). Further optimization and customization of the sequence will be necessary, as translation to higher fields (e.g. 7T) will require custom RF refocusing pulses to mitigate slice profile mismatch, SAR issues, and improve data quality. This will be important in future high-field application of SAGE EPI for functional neuro- and musculoskeletal imaging. Building on the data presented here, larger studies focused on treatment response in high-grade glioma and BOLD imaging of muscle contractions are already in progress.

Conclusion

This work presents a new implementation of a SAGE EPI acquisition using SENSE PI. Voxel-wise estimates of transverse relaxation rates from conventional multi-echo methods were used to validate SAGE EPI measurements using SENSE acceleration with partial Fourier imaging. This combination allowed reliable estimates of relaxation rates with SAGE EPI in tissues with shorter T_2 's due in part to the reduction in achievable echo times. In this regard, we presented the first application of SAGE EPI outside of the head. Simultaneous measurement of R_2^* and R_2 afforded with SAGE provided dynamic tracking of muscle R_2' during reperfusion. An optimized SAGE EPI acquisition was also used to compute simultaneous perfusion and permeability parameters in high-grade glioma patients. Overall, this study complements the previous development of SAGE EPI while further permitting application of the technique across a wider range of tissue types and MR scanner environments.

Acknowledgments

The authors thank the National Institute of Health for funding through NCI 2R25CA092043, NCI R01CA158079 (CCQ) and NIAMS 2R01 AR050101 (BMD) and the Vanderbilt Ingram Cancer Center (VICC) for funding through the Young Ambassadors Grant (CCQ). We would also like to thank Dr. Paul Moots, MD for his collaboration and our subjects for their participation.

Abbreviations

CA	contrast agent
ssEPI	single-shot echo planar imaging
PI	parallel imaging
CBV	cerebral blood volume
CBF	cerebral blood flow
MTT	mean transit time
MGE	multiple gradient-echo
MSE	multiple spin-echo
PF	partial Fourier
RMSPE	root mean squared percent error
TA	tibialis anterior
MFA	multiple flip angle
AIF	arterial input function
mVD	mean vessel diameter

References

1. Ostergaard L. Principles of cerebral perfusion imaging by bolus tracking. *J Magn Reson Imaging*. 2005; 22(6):710–717. [PubMed: 16261573]
2. Willats L, Calamante F. The 39 steps: evading error and deciphering the secrets for accurate dynamic susceptibility contrast MRI. *NMR Biomed*. 2013; 26(8):913–931. [PubMed: 22782914]
3. Christen T, Bolar DS, Zaharchuk G. Imaging brain oxygenation with MRI using blood oxygenation approaches: methods, validation, and clinical applications. *AJNR Am J Neuroradiol*. 2013; 34(6): 1113–1123. [PubMed: 22859287]
4. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America*. 1992; 89(13):5951–5955. [PubMed: 1631079]
5. Elder CP, Cook RN, Chance MA, Copenhaver EA, Damon BM. Image-based calculation of perfusion and oxyhemoglobin saturation in skeletal muscle during submaximal isometric contractions. *Magn Reson Med*. 2010; 64(3):852–861. [PubMed: 20806379]
6. Ledermann HP, Schulte AC, Heidecker HG, Aschwanden M, Jager KA, Scheffler K, Steinbrich W, Bilecen D. Blood oxygenation level-dependent magnetic resonance imaging of the skeletal muscle in patients with peripheral arterial occlusive disease. *Circulation*. 2006; 113(25):2929–2935. [PubMed: 16785340]

7. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995; 34(4):537–541. [PubMed: 8524021]
8. Newton AT, Rogers BP, Gore JC, Morgan VL. Improving measurement of functional connectivity through decreasing partial volume effects at 7 T. *NeuroImage*. 2012; 59(3):2511–2517. [PubMed: 21925611]
9. Farzaneh F, Riederer SJ, Pelc NJ. Analysis of T2 limitations and off-resonance effects on spatial resolution and artifacts in echo-planar imaging. *Magn Reson Med*. 1990; 14(1):123–139. [PubMed: 2352469]
10. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. *Magn Reson Med*. 1999; 42(5):952–962. [PubMed: 10542355]
11. Blaimer M, Breuer F, Mueller M, Heidemann RM, Griswold MA, Jakob PM. SMASH, SENSE, PILS, GRAPPA: how to choose the optimal method. *Top Magn Reson Imaging*. 2004; 15(4):223–236. [PubMed: 15548953]
12. Bammer R, Keeling SL, Augustin M, Pruessmann KP, Wolf R, Stollberger R, Hartung HP, Fazekas F. Improved diffusion-weighted single-shot echo-planar imaging (EPI) in stroke using sensitivity encoding (SENSE). *Magn Reson Med*. 2001; 46(3):548–554. [PubMed: 11550248]
13. de Zwart JA, van Gelderen P, Kellman P, Duyn JH. Application of sensitivity-encoded echo-planar imaging for blood oxygen level-dependent functional brain imaging. *Magn Reson Med*. 2002; 48(6):1011–1020. [PubMed: 12465111]
14. Preibisch C, Pilatus U, Bunke J, Hoogenraad F, Zanella F, Lanfermann H. Functional MRI using sensitivity-encoded echo planar imaging (SENSE-EPI). *NeuroImage*. 2003; 19(2 Pt 1):412–421. [PubMed: 12814590]
15. Lupo JM, Lee MC, Han ET, Cha S, Chang SM, Berger MS, Nelson SJ. Feasibility of dynamic susceptibility contrast perfusion MR imaging at 3T using a standard quadrature head coil and eight-channel phased-array coil with and without SENSE reconstruction. *J Magn Reson Imaging*. 2006; 24(3):520–529. [PubMed: 16888776]
16. Preibisch C, Wallenhorst T, Heidemann R, Zanella FE, Lanfermann H. Comparison of parallel acquisition techniques generalized autocalibrating partially parallel acquisitions (GRAPPA) and modified sensitivity encoding (mSENSE) in functional MRI (fMRI) at 3T. *J Magn Reson Imaging*. 2008; 27(3):590–598. [PubMed: 18219627]
17. Schmiedeskamp H, Newbould RD, Pisani LJ, Skare S, Glover GH, Pruessmann KP, Bammer R. Improvements in Parallel Imaging Accelerated Functional MRI Using Multiecho Echo-Planar Imaging. *Magnet Reson Med*. 2010; 63(4):959–969.
18. Vonken EJ, van Osch MJ, Bakker CJ, Viergever MA. Measurement of cerebral perfusion with dual-echo multi-slice quantitative dynamic susceptibility contrast MRI. *J Magn Reson Imaging*. 1999; 10(2):109–117. [PubMed: 10441012]
19. Newbould RD, Skare ST, Jochimsen TH, Alley MT, Moseley ME, Albers GW, Bammer R. Perfusion mapping with multiecho multishot parallel imaging EPI. *Magn Reson Med*. 2007; 58(1):70–81. [PubMed: 17659630]
20. Damon BM, Hornberger JL, Wadington MC, Lansdown DA, Kent-Braun JA. Dual gradient-echo MRI of post-contraction changes in skeletal muscle blood volume and oxygenation. *Magn Reson Med*. 2007; 57(4):670–679. [PubMed: 17390346]
21. Barbier EL, den Boer JA, Peters AR, Rozeboom AR, Sau J, Bonmartin A. A model of the dual effect of gadopentetate dimeglumine on dynamic brain MR images. *J Magn Reson Imaging*. 1999; 10(3):242–253. [PubMed: 10508283]
22. Vonken EP, van Osch MJ, Bakker CJ, Viergever MA. Simultaneous quantitative cerebral perfusion and Gd-DTPA extravasation measurement with dual-echo dynamic susceptibility contrast MRI. *Magn Reson Med*. 2000; 43(6):820–827. [PubMed: 10861876]
23. Quarles CC, Gore JC, Xu L, Yankeelov TE. Comparison of dual-echo DSC-MRI- and DCE-MRI-derived contrast agent kinetic parameters. *Magn Reson Imaging*. 2012; 30(7):944–953. [PubMed: 22617148]
24. Donahue KM, Krouwer HG, Rand SD, Pathak AP, Marszalkowski CS, Censky SC, Prost RW. Utility of simultaneously acquired gradient-echo and spin-echo cerebral blood volume and

- morphology maps in brain tumor patients. *Magn Reson Med*. 2000; 43(6):845–853. [PubMed: 10861879]
25. Schmainda KM, Rand SD, Joseph AM, Lund R, Ward BD, Pathak AP, Ulmer JL, Badrudoja MA, Krouwer HG. Characterization of a first-pass gradient-echo spin-echo method to predict brain tumor grade and angiogenesis. *AJNR Am J Neuroradiol*. 2004; 25(9):1524–1532. [PubMed: 15502131]
 26. Donahue KM, Van Kylen J, Guven S, El-Bershawi A, Luh WM, Bandettini PA, Cox RW, Hyde JS, Kissebah AH. Simultaneous gradient-echo/spin-echo EPI of graded ischemia in human skeletal muscle. *J Magn Reson Imaging*. 1998; 8(5):1106–1113. [PubMed: 9786149]
 27. Schmiedeskamp H, Straka M, Newbould RD, Zaharchuk G, Andre JB, Olivot JM, Moseley ME, Albers GW, Bammer R. Combined spin- and gradient-echo perfusion-weighted imaging. *Magn Reson Med*. 2012; 68(1):30–40. [PubMed: 22114040]
 28. Schmiedeskamp H, Straka M, Bammer R. Compensation of slice profile mismatch in combined spin- and gradient-echo echo-planar imaging pulse sequences. *Magn Reson Med*. 2012; 67(2): 378–388. [PubMed: 21858858]
 29. Tropres I, Grimault S, Vaeth A, Grillon E, Julien C, Payen JF, Lamalle L, Decorsys M. Vessel size imaging. *Magnet Reson Med*. 2001; 45(3):397–408.
 30. Kiselev VG, Strecker R, Ziyeh S, Speck O, Hennig J. Vessel size imaging in humans. *Magn Reson Med*. 2005; 53(3):553–563. [PubMed: 15723391]
 31. Pannetier N, Lemasson B, Christen T, Tachrount M, Tropres I, Farion R, Segebarth C, Remy C, Barbier EL. Vessel size index measurements in a rat model of glioma: comparison of the dynamic (Gd) and steady-state (iron-oxide) susceptibility contrast MRI approaches. *NMR Biomed*. 2012; 25(2):218–226. [PubMed: 21751270]
 32. Schmiedeskamp H, Andre JB, Straka M, Christen T, Nagpal S, Recht L, Thomas RP, Zaharchuk G, Bammer R. Simultaneous perfusion and permeability measurements using combined spin- and gradient-echo MRI. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2013; 33(5):732–743.
 33. Skinner, JT.; Robison, RK.; Quarles, C. A Single-Shot Multiple Spin- and Gradient-Echo Acquisition for Perfusion Imaging Using SENSE Acceleration and Partial k-Space Sampling. *Proc Int Soc Magn Reson Med*; Salt Lake City, Utah. 2013.
 34. Murphy K, Bodurka J, Bandettini PA. How long to scan? The relationship between fMRI temporal signal to noise ratio and necessary scan duration. *NeuroImage*. 2007; 34(2):565–574. [PubMed: 17126038]
 35. Newton, AT.; Skinner, JT.; Quarles, CC. Automatic AIF Estimation in Multi-Echo DSC-MRI of Pediatric Patients: Avoiding the Noise Floor. *Proc Int Soc Magn Reson Med*; Salt Lake City, Utah. 2013.
 36. Carroll TJ, Rowley HA, Haughton VM. Automatic calculation of the arterial input function for cerebral perfusion imaging with MR imaging. *Radiology*. 2003; 227(2):593–600. [PubMed: 12663823]
 37. Calamante F, Connelly A, van Osch MJ. Nonlinear DeltaR*2 effects in perfusion quantification using bolus-tracking MRI. *Magn Reson Med*. 2009; 61(2):486–492. [PubMed: 19161169]
 38. Kjolby BF, Ostergaard L, Kiselev VG. Theoretical model of intravascular paramagnetic tracers effect on tissue relaxation. *Magn Reson Med*. 2006; 56(1):187–197. [PubMed: 16724299]
 39. Wu O, Ostergaard L, Weisskoff RM, Benner T, Rosen BR, Sorensen AG. Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. *Magn Reson Med*. 2003; 50(1):164–174. [PubMed: 12815691]
 40. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging*. 1997; 7(1):91–101. [PubMed: 9039598]
 41. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, Larsson HB, Lee TY, Mayr NA, Parker GJ, Port RE, Taylor J, Weisskoff RM. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging*. 1999; 10(3):223–232. [PubMed: 10508281]

42. Wansapura JP, Holland SK, Dunn RS, Ball WS Jr. NMR relaxation times in the human brain at 3.0 tesla. *J Magn Reson Imaging*. 1999; 9(4):531–538. [PubMed: 10232510]
43. Gold GE, Han E, Stainsby J, Wright G, Brittain J, Beaulieu C. Musculoskeletal MRI at 3.0 T: relaxation times and image contrast. *AJR American journal of roentgenology*. 2004; 183(2):343–351. [PubMed: 15269023]
44. Boxerman JL, Schmainda KM, Weisskoff RM. Relative cerebral blood volume maps corrected for contrast agent extravasation significantly correlate with glioma tumor grade, whereas uncorrected maps do not. *AJNR Am J Neuroradiol*. 2006; 27(4):859–867. [PubMed: 16611779]
45. Quarles CC, Ward BD, Schmainda KM. Improving the reliability of obtaining tumor hemodynamic parameters in the presence of contrast agent extravasation. *Magn Reson Med*. 2005; 53(6):1307–1316. [PubMed: 15906288]
46. Paulson ES, Schmainda KM. Comparison of dynamic susceptibility-weighted contrast-enhanced MR methods: recommendations for measuring relative cerebral blood volume in brain tumors. *Radiology*. 2008; 249(2):601–613. [PubMed: 18780827]
47. Bjornerud A, Emblem KE. A fully automated method for quantitative cerebral hemodynamic analysis using DSC-MRI. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2010; 30(5):1066–1078.
48. Carroll TJ, Horowitz S, Shin W, Mouannes J, Sawlani R, Ali S, Raizer J, Futterer S. Quantification of cerebral perfusion using the “bookend technique”: an evaluation in CNS tumors. *Magn Reson Imaging*. 2008; 26(10):1352–1359. [PubMed: 18538523]
49. Cassot F, Lauwers F, Fouard C, Prohaska S, Lauwers-Cances V. A novel three-dimensional computer-assisted method for a quantitative study of microvascular networks of the human cerebral cortex. *Microcirculation*. 2006; 13(1):1–18. [PubMed: 16393942]
50. Sanchez OA, Copenhagen EA, Elder CP, Damon BM. Absence of a Significant Extravascular Contribution to the Skeletal Muscle BOLD Effect at 3 T. *Magnet Reson Med*. 2010; 64(2):527–535.
51. Englund EK, Langham MC, Li C, Rodgers ZB, Floyd TF, Mohler ER, Wehrli FW. Combined measurement of perfusion, venous oxygen saturation, and skeletal muscle T-2* during reactive hyperemia in the leg. *J Cardiovasc Magn R*. 2013:15.
52. Toussaint JF, Kwong KK, Mkpuru FO, Weisskoff RM, LaRaia PJ, Kantor HL. Perfusion changes in human skeletal muscle during reactive hyperemia measured by echo-planar imaging. *Magn Reson Med*. 1996; 35(1):62–69. [PubMed: 8771023]
53. Lebon V, Brillault-Salvat C, Bloch G, Leroy-Willig A, Carlier PG. Evidence of muscle BOLD effect revealed by simultaneous interleaved gradient-echo NMRI and myoglobin NMRS during leg ischemia. *Magnet Reson Med*. 1998; 40(4):551–558.
54. Towse TF, Slade JM, Meyer RA. Effect of physical activity on MRI-measured blood oxygen level-dependent transients in skeletal muscle after brief contractions. *Journal of applied physiology*. 2005; 99(2):715–722. [PubMed: 15802369]
55. Meyer RA, Towse TF, Reid RW, Jayaraman RC, Wiseman RW, McCully KK. BOLD MRI mapping of transient hyperemia in skeletal muscle after single contractions. *NMR Biomed*. 2004; 17(6):392–398. [PubMed: 15468084]

Figure 1.

(a–c) Example single-echo (TE_2) images from the SAGE acquisition showing the effect of increased SENSE acceleration on image quality. (d–f) G-factor maps calculated from the SAGE acquisition. (g–i) tSNR at each SAGE echo over an entire slice (mean $\pm$ std across subjects).

Figure 2.

Example voxel-wise plots of R_2 and R_2^* from SAGE and MGE/MSE acquisitions in a white matter ROI at a) SENSE=2, PF=0.6, b) SENSE = 2, PF = 0.73, c) SENSE = 3, PF = 0.6, d) SENSE = 3, PF = 1.0, e) SENSE = 4, PF = 0.6, f) SENSE = 4, PF = 1.0. Regression lines (black line) and correlation coefficients (r) are presented for both R_2 and R_2^* data.

Figure 3.
a) Example muscle images for each SAGE echo. b) SAGE signal decay data (and fits) for an ROI encompassing the TA. Also shown are portions of the corresponding individual R_2^* (dash-dot line) and R_2 decay curves (dashed line) before and after the refocusing pulse, respectively.

Figure 4.

a) SAGE signal decay data (and fits) for a region of normal appearing white matter and tumor prior to the administration of contrast agent. Also shown are portions of the corresponding individual R_2^* (dashed line) and R_2 decay curves (dotted line) before and after the refocusing pulse, respectively. b) Resulting R_2 curves from SAGE fits (solid line) and single echo analysis (dashed line) during contrast agent passage in white matter (gray) and tumor (black). c) Resulting R_2^* curves from SAGE fits (solid line) and single echo analysis (dashed line) during contrast agent passage in white matter (gray) and tumor (black).

Figure 5.

a) Post-contrast T_1 -weighted anatomical image highlighting a brainstem glioma and an additional enhancing lesion (white arrows). Parametric perfusion maps (CBV , CBF , and MTT) from R_2^* (b–d) and R_2 (f–h) data. e) Map of mean vessel diameter computed from simultaneous measurements of R_2^* and R_2 .

Figure 6.
a) Resulting R_1 time course (calculated with the addition of a T_1 map) from an ROI in tumor. The arterial input function acquired for pharmacokinetic modeling is displayed in the inset. DCE-MRI parametric maps of K^{trans} (b), and v_e (c). Arrows point to regions identified in Fig. 5.

Figure 7. SAGE R_2^* , R_2 , and R_2' time-courses from the tibialis anterior of one subject a) before, during, and after 4 minutes of cuff-induced arterial occlusion, and from a different subject b) before, during and after a 10 second duration maximal voluntary isometric contractions of the dorsiflexors.

Table 1

Group analysis of R_2 and R_2^* measures from SAGE acquisitions in brain with various SENSE and partial Fourier acceleration factors.

SENSE/PF	TE (ms)	R_2 (s ⁻¹)	R_2^* (s ⁻¹)
		mean±std _p (% diff)	mean±std _p (% diff)
White Matter			
1.5/0.6	6.6,25,51,69,87	15.46±2.09 (20.38%)	19.85±2.07 (0.43%)
2.0/0.6	5.7,19,41,54,68	16.30±2.19 (26.70%)	20.85±2.92 (5.24%)
2.0/0.73	8.3,24,50,66,82	15.95±1.49 (23.81%)	20.21±2.25 (2.04%)
2.5/0.81	8.8,23,48,62,77	16.48±1.92 (28.03%)	20.44±3.66 (3.14%)
3.0/0.6	5.2,15,33,42,51	16.72±2.20 (30.01%)	20.70±3.31 (4.94%)
3.0/1.0	9.9,25,52,66,81	16.39±1.62 (27.11%)	20.05±2.55 (1.09%)
4.0/0.6	4.8,12,29,37,44	18.26±4.92 (41.95%)	24.93±9.61 (26.14%)
4.0/1.0	9.2,21,45,57,69	16.35±2.93 (26.91%)	21.12±5.29 (6.83%)
MSE/MGE		12.88±0.70	19.83±1.63
Gray Matter			
1.5/0.6	6.6,25,51,69,87	14.34±4.90 (42.27%)	19.55±6.15 (−5.63%)
2.0/0.6	5.7,19,41,54,68	15.02±4.98 (49.47%)	20.12±8.94 (−3.68%)
2.0/0.73	8.3,24,50,66,82	14.04±2.42 (39.40%)	19.82±6.41 (−4.90%)
2.5/0.81	8.8,23,48,62,77	13.93±2.70 (37.84%)	19.71±7.84 (−5.80%)
3.0/0.6	5.2,15,33,42,51	14.10±4.24 (39.83%)	17.50±6.80 (−16.10%)
3.0/1.0	9.9,25,52,66,81	13.45±1.79 (33.13%)	18.58±7.25 (−10.30%)
4.0/0.6	4.8,12,29,37,44	13.80±5.25 (36.22%)	15.92±9.49 (−23.22%)
4.0/1.0	9.2,21,45,57,69	13.79±2.16 (37.01%)	18.22±6.52 (−12.26%)
MSE/MGE		10.20±1.33	20.79±2.53

* Optimal sequence in highlighted row.

Table 2

Group analysis of R_2 and R_2^* measures from SAGE acquisitions in muscle with various SENSE and partial Fourier acceleration factors.

SENSE/PF	TE (ms)	R_2 (s^{-1})	R_2^* (s^{-1})
		mean $\pm$ std _p (% diff)	mean $\pm$ std _p (% diff)
2.0/0.6	5.5,19,37,50,63	39.12 $\pm$ 5.72 (23.38%)	42.50 $\pm$ 6.80 (11.88%)
3.0/0.6	4.9,14,29,38,47	35.62 $\pm$ 5.25 (11.73%)	38.69 $\pm$ 6.18 (1.17%)
3.0/0.65	5.5,15,30,39,49	37.10 $\pm$ 4.62 (16.69%)	41.15 $\pm$ 5.08 (7.81%)
4.0/0.65	5.0,13,25,33,41	33.95 $\pm$ 4.78 (6.45%)	39.35 $\pm$ 6.18 (2.76%)
MSE/MGE		32.00 $\pm$ 1.99	38.28 $\pm$ 2.16

* Optimal sequence in highlighted row.