A new double line scan diffusion imaging sequence (DLSDI) is presented. In DLSDI, two lines from two separate slices are acquired in each shot. As its predecessor, LSDI, DLSDI is insensitive to motion artifacts and it can be used on conventional MR scanners. In addition, DLSDI is almost twice as fast as LSDI. Preliminary results from phantom and patient studies show excellent agreement between ADC trace maps obtained with DLSDI and LSDI. The technical and the theoretical aspects of DLSDI are studied, and it is shown how the conditional random walk model can be used as an analytical tool to derive the diffusion sensitivity in the DLSDI sequence.

Key words: diffusion imaging; line scan; LSDI; stroke imaging.

INTRODUCTION

Since Moseley et al. showed that diffusion weighted MRI can detect ischemic stroke within minutes after vascular occlusion (1), water self-diffusion has become a well established contrast mechanism in MR imaging. Strong correlation between the apparent diffusion coefficient (ADC) and cerebral blood flow (CBF) has been shown in animal models of stroke (2–4) but results in humans are less conclusive. A recent study of acute stroke in humans by Sorensen et al. (5) indicates substantial differences between acute stroke in humans and acute stroke in animal models. In contrast, in a study by Warach et al. (6), it was found that diffusion-weighted images were highly accurate in identifying acute ischemic stroke and in distinguishing patients who would improve from those who would not. Therefore, further studies in humans are needed to understand the capabilities of diffusion-weighted imaging to monitor acute cerebral ischemia and predict patient outcome.

Until now, however, limited number of diffusion stroke studies have been done with humans (5–10). Diffusion imaging of humans, especially uncooperative stroke patients, has been hampered by severe motion artifacts that make evaluation of the data unreliable. With the advent of diffusion-weighted echo planar imaging (EPI) (11), motion artifacts have become much less of a problem (8); however, most MR scanners do not have EPI capabilities. Thus, it is of great interest and value to have a robust, fast, and accurate diffusion imaging technique for conventional MR scanners. With such a technique, the number of clinical sites that would have a tool for early identification and evaluation of new methods for acute stroke treatments (12) would be greatly increased.

The major challenge of diffusion imaging in humans is to minimize the influence of phase variations induced by physiological motion. In the commonly used 2D spin-warp Fourier imaging technique (13), the phase of the magnetization is used for spatial encoding. Consequentially, shot-to-shot phase variations lead to severe ghosting artifacts. Another consequence of the variable phase is that a complex function is needed to describe the magnetization as opposed to a real function that suffices to model the proton density. By acquiring the whole k-space in a single shot with multiple gradient echoes, as in single-shot EPI, these problems are eliminated, however, only at the cost of more expensive gradient hardware, somewhat limited resolution, and sensitivity to field inhomogeneities. On the other hand, in sequences that utilize multiple spin echoes, it is crucial to crush all stimulated echoes and to conjugate the signal received from every other echo in an echo train. This is because only a perfect refocusing pulse conjugates the magnetization and the stimulated echo pathways have a different phase than the primary echo pathways (14).

The line scan diffusion imaging (LSDI) sequence (15) is based on an approach that is fundamentally different from other diffusion imaging sequences. The main idea is to avoid phase encoding, because, as discussed above, it is the major source of complications in diffusion imaging. Instead, the line scan images are composed from multiple self-contained single-shot 1D magnitude profiles. Hence, although LSDI is a multishot technique, it has similar insensitivity to motion as EPI. Our initial results show that LSDI can easily be used for clinical imaging of stroke patients on conventional MR scanners with low and medium field strength and that there is an excellent agreement between LSDI and diffusion weighted EPI (16, 17).

The main disadvantage with LSDI as compared to diffusion-weighted EPI is that multisection imaging is relatively slow. To address this problem, we have developed an extension to LSDI, a double line scan diffusion imaging (DLSDI) sequence, which maintains all the robustness of LSDI but gives almost twice the acquisition speed.

In this paper, the practical and theoretical aspects of DLSDI are studied and compared with LSDI as well as few other recently introduced diffusion imaging sequences for conventional MR scanners. In addition, the diffusion sensitivity in DLSDI is derived by using a novel analytical approach, based on the conditional random walk model (18).

METHODS

The basic principles of the double line scan diffusion imaging sequence (DLSDI) are the same as of its predecessor, the LSDI sequence. Therefore, we will mainly focus on the distinct features of DLSDI and the reader is...
referred to refs. 14 and 15 for further details and relevant references.

Double Line Scan

In DLSDI, lines of two image slices are acquired simultaneously as opposed to a single line of one slice in LSDI. This is done by selecting two columns in each shot. The pulse sequence for DLSDI is shown in Fig. 1. The two slice-selective \(90^\circ\) pulses and the slice-selective \(180^\circ\) refocusing pulse produce the excitation shown in Fig. 2. With non-zero diffusion gradients, the contribution from spins outside the intersection of the \(90^\circ\) and the \(180^\circ\) pulses can be considered negligible because of lack of rephasing. Similarly, to minimize interference between spins in the two columns, crusher gradients are used to dephase one column during the readout of the other column. The timing of the readout for each of the two columns is set such, that the magnetization excited by each of the \(90^\circ\) pulses forms a spin echo during its line acquisition. Hence, the two columns acquired in each shot will have different \(T_2^*\) and diffusion weighting but no \(T_2^*\) weighting. Because all the columns in each slice have the same weighting, this does not lead to image artifacts.

The DLSDI sequence uses similar interleaving scheme as LSDI to minimize spin saturation and a “dummy” presweep to ensure uniform equilibrium magnetization in both slices. The interleave step size determines the effective repetition time, \(TR_{\text{eff}}\), i.e., how quickly the sequence sweeps through the image planes. Because the combined width of the slices produced by the two \(90^\circ\) pulses in DLSDI is larger than the width of a single slice, the minimum interleave step size is larger than in the LSDI sequence. As discussed in the next section in more details, the sequence cycles through all the specified directions and amplitudes of the diffusion weighting gradients, thereby, simultaneously acquiring all the images with various diffusion weighting. This totally eliminates all spurious echoes from spins outside the two image planes, making additional time varying crusher gradients unnecessary (15).

As shown in Fig. 2, the intersection of the slices produced by the \(90^\circ\) pulses and the \(180^\circ\) pulse produces an asymmetric point-spread function (PSF) in \(y\) and \(z\) direction. The signal-to-noise ratio (SNR) is proportional to the area of the intersection and is given by \(wh/cos(\alpha)\). From the area and the in-plane resolution in the \(y\) direction, \(w\), the effective slice thickness in the \(z\) direction is defined as \(h/cos(\alpha)\). The inclination angle, \(\alpha\), and the thickness of the excited slices, \(h\), are determined such that appropriate slice thickness and slice separation is achieved.

The area or wavenumber of the crusher gradients needs to be large enough such that the interference between the two echoes is minimal. This minimum area depends on the spatial frequencies of the object being imaged and the desired image voxel size. In fact, the echo from each column will always be contaminated with high spatial frequencies from the other column. However, with sufficiently high crusher-gradient wavenumber, \(k'\), the interference from the high spatial frequencies can be considered insignificant as compared with the low spatial frequencies of the column being acquired.

The readout bandwidth is chosen such that maximum SNR is obtained. For the first echo, the optimal bandwidth (BW) is calculated in the same way as in LSDI (15), i.e., \(BW = N_x/T_2\), where \(N_x\) denotes the resolution in the frequency encoding direction and \(T_2\) is the transverse relaxation time. For the same sensitivity to chemical shift and field inhomogeneities distortions in both slices, it is reasonable to use identical bandwidth for both echoes. Given this constraint, by using similar arguments as in ref. 15, it is easy to show that the optimal bandwidth for the second echo is given by \(BW = 3N_x/T_2\). The overall optimal bandwidth for both echoes should therefore be in the range from \(N_x/T_2\) to \(3N_x/T_2\). Hence, for brain imaging where \(T_2\) is in the range from 50 to 100 ms and \(N_x = 96\), the optimal bandwidth for DLSDI is expected to be in the range from 1 to 6 kHz.

**Diffusion Sensitivity**

The diffusion sensitivity of the slice reconstructed from the first echo is calculated by the well known Stejskal-Tanner formula (19)

\[
b_1 = b = k^2(\Delta - \delta/3)
\]
where $k$ is the wavenumber determined by the area of the diffusion gradients as

$$k = \gamma \int_{t_i}^{t_i+\Delta} G(t) \, dt$$

and $\gamma$ is the gyromagnetic ratio and $G$ is the gradient strength of the diffusion sensitising gradients. By writing the Stejskal-Tanner expression in terms of $k$, errors in Eq. [1] due to finite ramp times are negligible if $\Delta$ and $\delta$ denote the time between the beginning of the diffusion gradients and the duration of each gradient waveform, respectively (14).

The calculation of the diffusion sensitivity in the other slice reconstructed from the second echo is more complicated because of the influence of the crusher gradients. As shown in the appendix, if we ignore the slice selective gradients and the read gradient, it is given by

$$b_2 = b' + b + k'k2\Delta$$

where $b' = k'k(\Delta' - \delta'/3)$, $k' = c'G(t)\, dt$ and $G'$ denotes the amplitude of the crusher gradients. Note in Fig. 1 how the slice selected by the first slice selection pulse refocused is immediately following the RF pulse, then defocused again before the second RF pulse, to minimize cross-terms in the diffusion weighting of the second echo. Also note, that by choosing $G'$ and $G$ of opposite polarity, it is possible to make the cross-terms $k'k2\Delta$ cancel $b'$. This may however not produce sufficient isolation between the two echoes.

In our initial implementation of LSDI, we interleaved the acquisition of columns with a low non-zero $b$ factor and a high $b$ factor, for a single direction of the diffusion weighting gradients (15), thereby, simultaneously collecting diffusion-weighted and non-diffusion-weighted images. To obtain isotropic ADC trace diffusion weighting, we typically used 6 measurements, with high and low $b$ factors in three orthogonal directions, $(-1, -1, 1)$, $(1, -1, 1)$, and $(1, 1, 1)$.

Here, we extend this idea by simultaneously cycling through all the directions and amplitudes of the diffusion weighting gradients. This provides even lower gradient duty-cycle than our earlier approach and because of the increased cycle length, it fully eliminates all secondary echoes and makes the additional crusher gradients previously used in LSDI fully unnecessary.

The magnitude and the polarity of each individual crusher gradient is chosen such that the crusher-gradient vector is always in the same direction as the diffusion gradient vector. This simplifies the calculations of the diffusion sensitivity of the second echo, especially for anisotropic diffusion. By changing the direction of the crusher gradient along with the diffusion gradient, a simple expression like Eq. [3] can be used to calculate the diffusion sensitivity. The amplitude of the crusher-gradient vector is, however, always kept constant.

Finally, it should be mentioned, although it was not used in the present work, that for improved speed, four measurements can be used to measure the ADC-trace, i.e., by using low $b$ factor in one direction only. This increases the gradient duty-cycle by 13% as compared with the duty-cycle in our original six measurement approach. Similarly, the noise in the ADC trace is increased by approximately 11%, if optimal $b$ factors are used (i.e., $bD = 1$). However, by using four measurements, the noise per unit time is reduced by approximately 9%. Furthermore, it is easy to devise an interleaving scheme for LSDI/LSDLSDI, with 63, 95, 127, or 255 columns, to map the complete diffusion tensor efficiently and maintain a low gradient duty-cycle. For instance, this can be achieved by cycling the diffusion gradients through:

$$(0.0, 0.0), (1.1, 1.1), (1.0, 1.0), (0.1, 1.1), (1.0, -1), (1.0, -1), (0.1, -1).$$

**Measurements**

The DLSDI sequence described in the previous section was implemented on a 1.5T GE Signa whole body scanner (General Electric Medical Systems, Milwaukee, WI) equipped with the 5.4 operating system and standard gradient hardware with a maximum gradient strength of 1 G/cm = 0.01 T/m. Currently, the images are reconstructed on the Signa terminal by using a Unix script file and a specially written C-program, compiled for the Signa host computer, which interpolates and reorients the columns in the Signa raw-data images. The program also calculates an ADC trace map and an image with artificial diffusion weighting based on the trace map, the desired $b$-factor, and the non-diffusion-weighted images. These images can then be filmed and analyzed on the Signa terminal.

To compare the mutual accuracy of diffusion measurements in the slices reconstructed from the first and the second echo, ADC trace maps $(D = (D_x + D_y + D_z)/3)$ of a phantom containing doped water and corn oil at room temperature were calculated using Eqs. [1] and [3] for the first and the second echo, respectively. From an approximately 650 mm$^2$ region containing doped water, the mean and the standard deviation of the ADC trace were calculated. To estimate the influence from the read gradient, these measurements were repeated with different resolution in the frequency encoding direction ($x$).

To test the reproducibility of the DLSDI ADC trace maps, four sets of DLSDI images were acquired from the brain of a healthy volunteer, with minimal head restraints and no cardiac gating. The imaging parameters were the same as those in the phantom experiment. From these images, four independent ADC trace maps were calculated. For each pixel within a specified region of interest (ROI), the mean $MD = \Sigma (D_i + D_j + D_k)/3$ and the variance $\sigma_D^2 = \Sigma (D - MD)^2/3$ of the ADC are calculated.

The DLSDI sequence was tested in a clinical setting for a patient study where the diffusion imaging protocol was added to the regular scans. Minimal head restraints and no cardiac gating was used. With an RF repetition time of 150 ms and an effective repetition time of 0.9 s, 10 ADC...
trace maps were acquired in 7 min and 17 s with the DLSDI sequence. The resolution in the x-direction was set to 96 pixels and the y direction was covered by 95 columns. Other imaging parameters were identical to those used in previous experiments. Following the DLSDI scan, ADC trace maps of three selected slices were acquired using the regular LSDI sequence. In each slice, a ROI was defined in locations where no cerebrospinal fluid (CSF) is prominent. In the LSDI images, the resolution in the frequency encoding direction was 128 pixels and 127 columns were used. As in earlier studies with the LSDI sequence (15), an inclination angle of 70° was used and $h = w = 5 \text{ mm}$. The RF repetition time was 135 ms and the effective repetition time was 2.1 s.

RESULTS

The results from the phantom studies are shown in Table 1 along with the $b$ factors that were used for the measurements. The relatively low diffusion coefficient measured in this phantom is due to a fairly low room temperature (around 17°C), however, it agrees well with our previous measurements using the same phantom and the LSDI sequence (15). Notice, that for the second echo, the $b$ factor depends on the resolution because the wavenumber of the crusher gradient, $k^*$, is a function of the image resolution.

Figure 3 shows two of the four ADC trace maps that were acquired from a volunteer to estimate reproducibility. The following three regions were defined: left, right, and posterior to the ventricles. The mean of $M_D$ and $\sigma_D$ from each ROI is presented in Table 2.

The images in Fig. 4 are from the first patient study done with the DLSDI sequence. Diffusion images were acquired with the DLSDI and the LSDI sequence for comparison. As Fig. 4 shows, there are no signs of motion artifacts on the diffusion-weighted images. In Fig. 5, the LSDI and the DLSDI trace diffusion maps are compared. The results from the analysis of the regions is presented in Table 3.

DISCUSSION

The results in Table 1 demonstrate the very good agreement between ADC maps of the slice from the first echo and the second echo. In terms of accuracy, it is therefore fully justified to ignore the read and the slice-selective gradients in the calculation of Eqs. [1] and [3], for most practical purposes such as clinical stroke imaging. In a recent study on acute stroke by Sorensen et al. (5), it was found that the relative ADC of a lesion, as compared with normal tissue, was $0.48 \pm 0.12$. Therefore, the results in Table 2 indicate that the reproducibility and the precision of the DLSDI ADC maps is sufficient to distinguish regions of acute stroke from normal regions. Further studies are needed to verify this.

Our first clinical images show that DLSDI can produce multislice ADC trace maps and isotropically-diffusion-weighted images of excellent quality in very reasonable scan times. By using 4, measurements per slice, instead of 6 as in our first implementation, 10 ADC trace maps could be obtained in 5 min. Also, there is a good agreement between ADC trace maps produced with LSDI and DLSDI as Fig. 5 and Table 3 indicate. The small disagreement that is found between ROIs (Figs. 5a and 5b as well as Figs. 5c and 5f) is most likely due to partial volume effects and the fact that LSDI (15) and DLSDI have very different PSF in the y and the z direction. This difference in the PSF is most noticeable from the difference in the outline of the cerebrospinal fluid in Fig. 5c and Fig. 5f.

The speed increase of DLSDI over LSDI, which is 80% in the case shown in Fig. 4, comes at the cost of a reduced SNR in the slice constructed from the second echo, especially in tissues with short $T_2$. Therefore, the choice of readout bandwidth and resolution in the frequency encoding direction becomes even more important than in LSDI. Not only is the echo time of the second echo elongated by the duration of its readout window but also by the duration of the first readout. To maintain a similar SNR in the LSDI sequence as in the LSDI sequence, the resolution in the frequency encoding direction was set to 96 pixels as compared with 128 pixels in LSDI. The LSDI diffusion maps appear sharper than the DLSDI maps, however, as Fig. 5 shows, most details found in the LSDI maps are still visible on the DLSDI maps.

Obviously, the idea behind the DLSDI sequence can be extended such that larger number of columns is excited in each shot. However, with the gradient power limitations of most conventional MR scanners and the inherent $T_2$ decay of the signal, we do not consider it practical. Furthermore, larger interleave step size is needed as the number of columns is increased and this may set limitations on the effective repetition time. Also, the image slices that are acquired simultaneously don’t have to be adjacent to each other as shown in Fig. 2. With the correct slice thickness, slice separation, and inclination angle, it is possible to acquire simultaneously image slices that are further apart. However, because of possible spin saturation in neighboring columns, this reduces the flexibility in the selection of the inclination angle. Finally, instead of using two 90° pulses and one 180° pulse, it is also possible to design a DLSDI sequence that uses one 90° pulse and two 180° pulses. However, our current approach with DLSDI uses less RF power and was simpler to implement.

The use of crusher gradients to separate echoes has previously been used in numerous other MRI techniques such as; echo-shifted FLASH imaging (20), BURST imag-

---

**Table 1**

<table>
<thead>
<tr>
<th>Phantom Measurements</th>
<th>Frequency</th>
<th>$b_{\text{low}}$ (s/mm$^2$)</th>
<th>$b_{\text{high}}$ (s/mm$^2$)</th>
<th>$\overline{D}$ (μm$^2$/ms)</th>
<th>$\sigma_D$ (μm$^2$/ms)</th>
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<tr>
<td>First slice/echo</td>
<td>64</td>
<td>5</td>
<td>555</td>
<td>1.854</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>5</td>
<td>555</td>
<td>1.854</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>5</td>
<td>555</td>
<td>1.865</td>
<td>0.044</td>
</tr>
<tr>
<td>Second slice/echo</td>
<td>64</td>
<td>32</td>
<td>703</td>
<td>1.871</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
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<td>791</td>
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<td></td>
<td>128</td>
<td>66</td>
<td>805</td>
<td>1.872</td>
<td>0.073</td>
</tr>
</tbody>
</table>

Mean diffusion tensor trace, $\overline{D}$, and the standard deviation, $\sigma_D$, in slices reconstructed from the first and second echo. Also shown are the $b$ factors used for the measurements in each direction x, y, and z.
FIG. 3. ADC-trace maps of the first slice (left) and the second slice (right). The ROIs used for the analysis in Table 2 are highlighted.

As LSDI, DLSDI is much less sensitive to motion artifacts than other approaches for diffusion imaging on conventional scanners that use multiple shots. Many of these techniques use combination of cardiac gating (24), gradient moment nulling (25), and navigator echoes (26–28) to minimize the shot-to-shot phase variations in the pulsed gradient spin-echo (PGSE) sequence. In a recent clinical study with the navigated PGSE sequence, it is reported that only in 18 out of 32 examinations, images were of diagnostic value for all three directions of the diffusion sensitising gradients (10). As expected (27), diffusion images with the diffusion sensitivity along the phase-encoding direction were most free of motion artifacts. Also, because navigated PGSE relies heavily on cardiac gating to minimize the influence of spatially varying motion induced by cardiac action (24, 29), the number of sections that can be acquired within 15 min is between 8 and 10 (10). In a more recent implementation, that was suggested to address these limitations, two orthogonal navigators are used with an interleaved echo-planar imaging (IEPI) sequence (28). By using two navigators, the phase dispersion in both the readout and the phase-encoding direction can be estimated, allowing the diffusion sensitising gradients to be applied in all three directions. Also, the speed of IEPI gives more flexibility in choosing the number of image sections. However, positional shifts in k-space of acquired data, because of velocity-induced phase changes, can easily be on the order of a whole k-space line, especially when large b-factors are used. This can cause problems, because it is only possible to correct positional shifts that are a fraction of a line in the phase encoding direction by gridding the data to a Cartesian grid (28). In DLSDI, the PSF has a rectangular box shape in the y direction. Therefore, it is easy to show that a linear phase dispersion, equal to one k line shift, causes additional signal loss of \( \sin(\pi w/\text{FOV})/(m\pi\text{FOV}) \) (see Fig. 2). With 5-mm column width w, and 20-cm FOV, this signal loss is insignificant. The DLSDI sequence is therefore clearly much less sensitive to motion than the nav-
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FIG. 4. Images from the first patient study with DLSDI. From each section, three images are shown: with T2 weighting (left), with artificial isotropic diffusion weighting (ADWI) with a b-factor of 1000 s/mm² (middle), and an ADC-trace map (right). The left column shows the slices reconstructed from the first echo (TE = 89 ms) and the right column shows the slices from the second echo (TE = 127 ms). The total imaging time for the 10 sections was 7 min and 17 s.

In conclusion, we find that LSDI and DLSDI images compare well with diffusion images acquired with other techniques on conventional scanners. The fact that DLSDI does not require any specialized hardware, cardiac gating, shimming, or complex postprocessing makes this sequence very robust and gives it potentiality for being useful in a clinical setting. Moreover, the acquisition speed of DLSDI is fast enough to make it part of routine studies on patients that are expected to have ischemic stroke.

APPENDIX

Diffusion Sensitivity Calculation

Diffusion in a linear magnetic field gradient causes phase dispersion in the magnetization. For free diffusion, the phase dispersion can be described by a Gaussian proba-
bility distribution, $P_r$. The diffusion attenuation, $A$, is then given by

$$A = \int_{-\infty}^{\infty} \delta^2 P(\Phi) d\Phi = \exp \left[ - \frac{\sigma_\Phi^2}{2} \right] = \exp[-bD] \quad [A1]$$

It is therefore sufficient to know the variance of the phase distribution, $\sigma_\Phi^2$, to calculate the diffusion sensitivity, $b$. A very simple way to carry out such calculations is by using the conditional random walk model (18). In this model, the position of a spin, $X$, and its phase, $\Phi$, are governed by the following equations

$$X_{n+1} = X_n + x_n \quad [A2]$$

$$\Phi_{n+1} = \Phi_n + \gamma G_d(X_n + x_n/2) + \phi_n \quad [A3]$$

where $x$ and $\phi$ are independent zero mean random variables denoting change in location and phase angle due to diffusion, respectively. Their variance is given by (18)

$$\text{var}(x_n) = 2Dt_n \quad [A4]$$

$$\text{var}(\phi_n) = \gamma^2 G_d^2 D t_n^3/6 \quad [A5]$$

First, before we calculate the combined diffusion sensitivity due to the crusher gradients and the diffusion gradients (see Fig. 1), we consider only the influence of the diffusion gradient pair. Initially all spins are in phase and without loss of generality we can assume that $\Phi_0 = 0$. Then, from Eqs. [A2] and [A3], $X_3 = X_2 + x_2$ and $\Phi_3 = \gamma G_b(X_2 + x_2/2) + \phi_2$, because according to Fig. 1, we see that $t_2 = t_4 = \delta$ and $t_3 = \Delta - \delta$. Also, because of the refocusing pulse, $\Phi_4 = -\Phi_3$ and $X_4 = X_3 + x_3 + x_4$. In our notation, variables that are zero are left out, e.g., $\phi_3 = 0$. Finally, we get

$$\Phi_5 = \Phi_4 + \gamma G_b(X_4 + x_4/2) + \phi_4 \quad [A6]$$

$$= \gamma G_b(x_2/2 + x_3 + x_4) - \phi_2 + \phi_4$$

The variance of $\Phi_5$ is then easily found by using Eqs. [A4] and [A5]. However, here we don’t need to work through the details, since we know that the result is given by the well known Stejskal-Tanner formula

$$\text{var}(\Phi_5) = 2\gamma^2 G_d^2 D t_n^3(\Delta - \delta/3) \quad [A7]$$

Next, the influence of the simultaneous use of both gradient pairs can be found by repeated use of Eqs. [A2] and [A3]. A much easier way is to recognize that the total phase should equal the sum of the phase found with either $G$ or $G'$ set to zero. Therefore, we get two terms with similar structure as Eq. [A6]

$$\Phi_7 = \gamma G' \delta'(x_2/2 + x_1 + x_2 + x_3 + x_4 + x_5 + x_6/2)$$

$$+ \gamma G b(x_2/2 + x_3 + x_4)$$

$$- \phi_0 + \phi_0 - \phi_2 + \phi_4 \quad [A8]$$

Notice that the random variables $x_2$, $x_3$, and $x_4$ appear both in terms with $G$ and $G'$. Therefore, in the expression

<table>
<thead>
<tr>
<th>Image no.</th>
<th>Technique</th>
<th>TE (ms)</th>
<th>$D$ (µm²/ms)</th>
<th>$\sigma_D$ (µm²/ms)</th>
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<tr>
<td>a</td>
<td>LSDI</td>
<td>105</td>
<td>0.846</td>
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<td>DLSDI</td>
<td>127</td>
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<td>LSDI</td>
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<td>f</td>
<td>DLSDI</td>
<td>89</td>
<td>0.796</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Comparison of the diffusion measured in the ROIs on the ADC-trace maps shown in Fig. 5. The echo time of each image is also given.
for var $\{\Phi_i\}$, there will be cross-terms proportional to $G'G$. For example, var $\{x_i(G' + G/2)\} = 2D(t_2^2G'^2 + G'G + G^2/4)$. We only need to keep account of the cross-terms, since by setting either $G$ or $G'$ to zero, we know the sum of all the other terms yields the Stejskal-Tanner expression (Eq. [A7]) for each gradient pair. Hence

$$\text{var}\{\Phi_i\} = 2\gamma G^2D\delta^2(\Delta' - \delta'/3) + 2\gamma^2G'D\delta^2(\Delta - \delta/3) + \gamma^2G'G\delta^22D(t_2 + 2t_3 + t_4)$$

$$= 2D(b' + b + k'k2\Delta)$$

where $k$ is the gradient pulse wavenumber, i.e., $k = \gamma G(t)dt$, and $k'$ is defined in a similar fashion. From Eqs. [A1] and [A9] follows Eq. [3]. Similarly, if we had three gradient pairs, $G''$, $G'$, and $G$, there would be cross-terms proportional to $G''G'$, $G'G$, and $G G$. The total $b$ factor would therefore be

$$b_3 = b'' + b' + b + k'k'2\Delta' + k'k2\Delta + k'k2\Delta$$

Diffusion Sensitivity Accuracy

Here we provide analytical estimation of the influence imaging gradients have on the diffusion sensitivity and how they affect the accuracy of Eqs. [1] and [3]. A detailed analysis of cross-terms in diffusion imaging sequences can be found in Mattiello et al. [33]. However, for the present work, their analysis is unnecessarily complicated, because in the DLSDI sequence, special care has been taken to reduce the amount of cross-terms.

We start by looking at the diffusion sensitivity of the first echo, which is the same as in LSDI. In the calculation of Eq. [1], we assumed that the diffusion sensitivity of the trapezoidal gradients could be accurately determined by their area, $k$, even for significantly long ramp time, $t$. Exact calculation for trapezoidal gradients gives (14)

$$b = \gamma^2G^2\left[\delta^2(\Delta - \delta/3) + \frac{8\delta}{15}\right]$$

$$= \frac{7\delta^2}{6} + \delta^2t + t^2\Delta - 2\Delta\delta t$$

A similar expression can be found in refs. (33, 34) where $\delta$ is defined in a slightly different manner. With ramp times as long as 10% of $\delta$, the disagreement between Eqs. [A11] and [1] is less than 0.2%. The second approximation we made when calculating Eq. [1] was to ignore the influence of the slice-selective gradients and the read gradient. Because the 90° pulse slice-selective gradients leave the magnetization unmodulated and the read gradient acts on unmodulated (focused) magnetization, there is no coupling between the diffusion attenuation caused by these gradients and the main diffusion gradients or the slice selective gradients of the 180° pulse. In contrast, because the slice selective gradient of the 180° pulse acts on magnetization modulated by the diffusion gradients, there will be cross-terms between the two gradient pairs. These cross-terms can be found by using Eq. [3], if we replace $k'$ with half the area of the 180° slice selective gradient, $k_{180'}$. The total diffusion attenuation, $A$, of the first echo is therefore given by

$$A = \exp[-D(b_{90'} + \{b + b_{180'}\})]$$

$$+ 2kk_{180'}A_{180'} + b_j$$

where $A_{180'}$ is half the duration of the 180° slice selective gradient and $b_{90'}$, $b_{180'}$, and $b_j$ represent the diffusion sensitivity of the slice-selective and the read gradients, respectively. It is most important to recognize that from the terms in the exponent of Eq. [A12], only $b$ and the cross-terms $2kk_{180'}A_{180'}$ are dependent on the diffusion gradient area, $k$. The other terms are constant throughout all the measurements and the additional diffusion attenuation caused by them can be treated as irreversible $T_2$ attenuation. Hence, the read gradient and the slice-selective gradient of the 90° pulse have no effect whatsoever on the accuracy of the diffusion estimate. Therefore, we see from Eq. [A12] that by using Eq. [1], the relative error in the diffusion estimate is

$$\frac{2kk_{180'}A_{180'}}{b}$$

$$= \frac{2k_{180'}A_{180'}}{k(\Delta - \delta/3)} < \frac{3k_{180'}A_{180'}}{k\Delta} \approx \frac{3G_{180'}A_{180'}}{G\Delta^2}$$

With the imaging parameters used in DLSDI and LSDI, this error is less than 0.1%.

The accuracy of the diffusion sensitivity of the second echo in DLSDI, Eq. [3], can be analyzed in a similar way. By arguing as before, we see that the slice selective gradients of the first 90° pulse and the read gradients of the second echo will have no effect on the diffusion estimate. Similarly, there will be no cross-terms between the strong diffusion gradients and the slice-selective gradients of the second 90° pulse or the read gradient of the first echo. However, these gradients will produce cross-terms with the crusher gradients that are not all fully accounted for in Eq. [3]. By approximating the slice-selective gradient and the read gradient as two pairs of two symmetric bipolar gradients, one easily finds that the neglected cross-terms account for less than 1% of the diffusion sensitivity when the diffusion gradients are off and make insignificant contribution to the diffusion sensitivity, with the diffusion gradients on. Therefore, because the relative accuracy of the high $b$ factor is much more important in the calculation of the diffusion coefficient, ignoring these additional cross-terms in Eq. [3] has insignificant effect on the accuracy of the diffusion estimate.

Background gradients probably affect the diffusion sensitivity in DLSDI more than all the approximations that were made in deriving Eqs. [1] and [3]. As a final remark, it should be emphasized that incorrect calibration of the gradient hardware is also a likely source of error in MRI diffusion estimates. Fortunately, however, to identify acute stroke, it is the relative difference of diffusion in healthy and diseased tissue which matters.
REFERENCES


