Published in final edited form as:

Magn Reson Med. 2017 March ; 77(3): 1124–1133. doi:10.1002/mrm.26197.

Robust Diffusion Tensor Imaging by Spatiotemporal Encoding: Principles and *In Vivo* Demonstrations

Eddy Solomon¹, Gilad Liberman¹, Noam Nissan^{1,2}, and Lucio Frydman^{1,*}

¹Department of Chemical Physics, Weizmann Institute of Science, 76100 Rehovot, Israel

²Department of Biological Regulation, Weizmann Institute of Science, 76100 Rehovot, Israel

Abstract

Purpose—Evaluate the usefulness of single-shot and interleaved spatiotemporally-encoded (SPEN) methods to perform diffusion tensor imaging (DTI) under various pre-clinical and clinical settings.

Methods—A formalism for analyzing SPEN DTI data is presented, tailored to account for the spatially-dependent *b*-matrix weightings introduced by the sequence's use of swept pulses acting while in the presence of field gradients.

Results—With its *b*-matrix calculations suitably accounted for, SPEN's ability to deliver faithful DTI measurements is corroborated on phantoms, *ex vivo* and *in vivo* animal and human studies. For both *ex vivo* and *in vivo* investigations, SPEN data proved less sensitive to distortions arising from eddy currents than conventional single-shot alternatives.

Conclusion—The robustness of SPEN-based sequences vis-à-vis field instabilities and heterogeneities, enables the implementation of DTI experiments with good sensitivity and resolution even in challenging environments like lactating breasts.

Keywords

diffusion-tensor imaging - DTI; spatiotemporal encoding - SPEN; b-value calculations; brain DTI; breast DTI

Introduction

MRI is commonly used to measure water's diffusivity throughout opaque matter. In anisotropic tissues molecules tend to diffuse more freely along the principal axis of fibers than in the perpendicular plane (1). To characterize such anisotropic molecular motions, diffusion-sensitizing gradients are applied along multiple directions; from the water's resulting signal attenuation, an effective second-rank diffusion tensor $\mathbf{D} = \{D_{ij}\}_{i,j=x,y,z}$ can be mapped (2–4). Estimating such tensor requires accounting for the effects of the imaging and diffusion-sensitizing gradients into a so-called *b*-matrix that summarizes their action, and whose elements $\mathbf{b} = \{b_{ij}\}_{i,j=x,y,z}$ need to be calculated for every particular pulse sequence used (3,5–7). A diffusion tensor can then be extracted on the basis of

*Corresponding author. Fax: +972 8 9344123. lucio.frydman@weizmann.ac.il.

$S(\mathbf{b})/S(0) = \exp \left[-\sum_{i,j} (b_{ij} D_{ij}) \right]$ (2–4), where $S(\mathbf{b})$ and $S(0)$ are signal intensities with and without the diffusion-sensitizing gradients. When incorporated into MRI measurements these calculations lead to a variety of Diffusion Tensor Imaging (DTI) modalities (4,8,9), of widespread use in preclinical and clinical tractography (10–14). Since all DTI-based modalities aim to represent the effects introduced by random molecular displacements spanning sub-mm ranges, tissue motions happening on similar length-scales can harm their performance. Therefore, single-shot imaging techniques that overcome potential motion artifacts, have played a key role in enabling the acquisition of reliable *in-vivo* diffusion data (15,16). In most cases, and foremost in clinical applications, spin-echo echo planar imaging (SE EPI) is the method of choice for performing these rapid, diffusion-monitoring scans. Still, SE EPI is prone to artifacts such as geometric distortions and ghosting, as it is inherently sensitive to field and chemical shift heterogeneities (17,18). These artifacts tend to affect principally the experiment's low-bandwidth direction, and become especially noticeable at higher fields (19). Numerous strategies have been proposed to overcome these limitations, including replacing the single shot methodology with a small number of interleaved shots (20,21); spiral sampling schemes redistributing artifacts more evenly along the two imaged dimensions (22–24); and parallel acquisition strategies reducing EPI's otherwise long acquisition time (25,26). All of these can improve diffusion imaging (27–32), yet these methods are still challenged by certain blurring artifacts resulting from hardware imbalances and/or motion between shots (20,33–37).

Recently, attention has been elicited by the diffusion-monitoring capabilities of an alternative single shot method, derived from spatiotemporal encoding (SPEN) principles (38,39). SPEN provides a number of potential advantages, thanks to its reliance on a direct image acquisition that is not bound by k -space Nyquist sampling criteria. This enables the use of stronger gradients along the low-bandwidth dimension, overcoming image distortions arising from B_0 -inhomogeneities and heterogeneous chemical environments (40–42). Augmenting this ability to reduce distortions is SPEN's ability to deliver images under so-called “full-refocusing” conditions (43,44), where each spin packet experiences a full spin echo from the time being excited until the time its signal is acquired. This leads to images that are nearly T_2^* -free. The potential of various SPEN imaging forms in both single/interleaved-shot and single/parallel-receive acquisition modes (45–47), has been demonstrated in a number of applications including BOLD (48–52) and isotropic diffusivity (53–55) studies. The present study describes the use of SPEN within a DTI framework, requiring a calculation of the $\mathbf{b}$ -matrix elements that will ensure a reliable DTI analysis. With a theoretical description of these elements at hand, we explore the capabilities of DTI SPEN in a number of imaging modalities, both in preclinical and human settings.

Methods

Theoretical Background

The effects of diffusion are here described by the Bloch-Torrey equations (56), and incorporate a conventional Stejskal/Tanner pulsed-gradient-spin-echo (PGSE) block (57) subjecting spins to a pair of magnetic field gradients G_d acting for a duration δ each and

separated by a diffusion-sensitizing time Δ . While in PGSE b values are nominally

$b_{PGSE} = \gamma^2 G_d^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right)$, DTI sequences will include imaging gradients that lead to diffusion weightings of their own. This is particularly true for the single-shot SPEN sequences, which in addition to purging, crushing, slice-selecting and read-out gradients, include a relatively prolonged spatiotemporal encoding process occurring in the presence of gradients (Figure 1). These multiple gradients interact with the diffusion-sensitizing ones leading to cross-terms that weight into the b -matrix.

Three SPEN sequences were here adapted for DTI. One includes a 90° chirped pulse that, acting in unison with an encoding gradient G_e , progressively excites spins throughout the sample (58,59). PGSE was integrated into this sequence by flanking both sides of the central 180° spin echo pulse with identical G_d 's (Figure 1A). A second sequence (Figure 1B) incorporated an adiabatic 180° encoding pulse; an initial slice-selective pulse and a hard 180° pulse at the conclusion of the acquisition, render this sequence suitable for multi-slice imaging. Diffusion gradients were integrated in this multi-slice implementation by a bipolar block, inserted during a $T_d/2$ delay timed to accommodate the full-refocusing conditions. The third sequence (Figure 1C) involved a 2D spatial/spatial pulse (60–62), imparting an encoding akin to that described for the 90° chirped pulse sequence but affecting only a single slice. This enabled its use in multislice acquisitions, while enjoying a lower specific absorption rate (SAR) than its 180° -based counterparts. All these sequences operated in a so-called “hybrid” mode, involving conventional k -space readout (along X) and slice-selection (along Z), in addition to their use of SPEN along the low-bandwidth (Y) dimension. All images thus arose from Fourier transforming the data along k_x and applying a super-resolution (SR) reconstruction (43,51,63) along the SPEN axis. SR enables one to apply weaker encoding gradients, contributing to lowering the overall SAR and decreasing the cross-terms arising between G_e and G_d .

As a result of SPEN's non-uniform spatial evolution, a number of distinct features arise upon using it for diffusion mapping. Most evident among these, and deriving from SPEN's asymmetric use of gradients together with excitation/refocusing swept pulses, is the appearance of spatially dependent $G_d \times G_e$ cross-terms in both the diagonal and off-diagonal elements of the b -matrix (55). These can be accounted by adapting the Karlicek-Lowe formalism (57,64,65), according to which the combined effect of all gradients throughout

the sequence is given by $b(t) = \gamma^2 \cdot \int_0^t K^2(t') dt'$, where $K(t') = \gamma \int_0^{t'} G(t'') dt''$ is a wavenumber summarizing the action of all gradients up to a particular time t' . This description is suitable as long as the local dephasing undergone by the spins is linear and independent of the spins' absolute positions. In SPEN, however, the use of frequency swept pulses while under the action of a gradient means that spin dephasing is neither linear in space nor independent of position. This can be accounted by re-expressing the K -wavenumber in terms of a local spatial dispersion K^{local} experienced by the spins' rotating-frame evolution phases –which will eventually be the quantity that random displacements will monitor (66). K^{local} arises if expanding these phases in proximity to an arbitrary position r_0 , as

$$\phi(t, r_0 + \delta r) = \phi(t, r_0) + \frac{d\phi(t, r_0)}{dr} \delta r + O(\delta r^2) \approx \phi(t, r_0) + K^{local}(t, r_0) \delta r \quad [1]$$

This leads to a diffusion-driven attenuation function

$$\frac{S[\mathbf{b}(t), r_o]}{S[0, r_o]} = \exp \left[- \sum_{i,j} D_{ij}(r_o) \cdot b_{ij}(t, r_o) \right] \quad [2]$$

where now

$$b_{i,j}(t) = \gamma^2 \cdot \int_0^t \left[K_i^{local}(t') \cdot K_j^{local}(t') \right] dt' \quad [3]$$

depends on a local phase derivative $\left\{ K_k^{local}(t') = \frac{d\phi(t', r_o)}{dk} \right\}_{k=x,y,z}$. For a general DTI case involving 3D diffusion weightings, the effective calculation needed to obtain the SPEN-based $\mathbf{b}$ -tensor becomes:

$$b_{ij}(t, r_o) = \gamma^2 \int_0^t \left[\left(\frac{d\phi(t', r_o)}{dx} \right)^2 + \left(\frac{d\phi(t', r_o)}{dy} \right)^2 + \left(\frac{d\phi(t', r_o)}{dz} \right)^2 + \left(\frac{d\phi(t', r_o)}{dx} \right) \left(\frac{d\phi(t', r_o)}{dy} \right) + \left(\frac{d\phi(t', r_o)}{dx} \right) \left(\frac{d\phi(t', r_o)}{dz} \right) + \left(\frac{d\phi(t', r_o)}{dy} \right) \left(\frac{d\phi(t', r_o)}{dz} \right) \right] dt' \quad [4]$$

where

$$\phi(t, r_o) = \phi_{enc}(r_o) + \phi_{acq}(t, r_o) \quad [5]$$

describes the dynamic evolution phase imparted by the excitation and acquisition for any r_o position in the sample.

Phantom, animal and human scans

To evaluate the usefulness of SPEN DTI analyses and the accuracy of the proposed methods, a number of tests were carried out. These included CuSO₄-doped isotropic water samples, *ex vivo* spinal cord and brain measurements (not all of which are here shown), *in vivo* rodent mappings and breast DTI scans of healthy volunteers. *Ex-vivo* specimens included formalin-fixed swine spinal cords and rat brains obtained from healthy animals, washed twice and left overnight in phosphate buffer, and studied within 10mm tubes filled with Fluorinert® at

25±1°C. Additionally, *in vivo* experiments approved by the Institutional Animal Care and use Committee of the Weizmann Institute, were executed on adult mice. These were anesthetized with 1–2% Isoflurane in O₂, placed into the magnet using a nose and tooth-bar, and their body temperatures were maintained at 37 °C using a water circulation system. Finally, DTI SPEN scans of lactating breasts were run on healthy volunteers, after receiving signed consents and approval by the Internal Review Board of the Wolfson Medical Center (Holon, Israel).

Scanners, pulse sequences and data processing

Phantom and rodents experiments were performed on an Agilent DD2[®] 7T/110mm pre-clinical horizontal magnet (Agilent Technologies, Santa Clara, CA) using a quadrature-coil probe. To achieve the best *in-vivo* results, first and second order shims were adjusted using FASTMAP (67), resulting in a water linewidth of 36 Hz for a 5 x 6 x 7 mm³ voxel in the center of the brain. DTI SPEN pulse sequences were programmed and compared with similarly structured and timed SE EPI-based diffusion experiments, all running within Agilent's VNMRJ 3.2 software environment. Also run in these tests were spin-echo multi-shot (SEMS) and fast spin echo (FSE) diffusion-weighted sequences provided by the scanners. The parameters of the multi- and single-shot scans are summarized in the corresponding figure captions. Additionally, human breast DTI SPEN experiments were programmed and acquired at 3T on a Siemens TrioTIM[®] scanner (Erlangen, Germany), using a 4-channels bilateral breast receiver coil (Siemens) and the sequence shown in Figure 1C based on a 2D 90° chirped pulse (60,61). Scouting images included T2-weighted FSE scans.

This study compared SPEN and SE EPI DTI results, from experiments including both single- and interleaved multi-shot acquisitions. The interleaved multi-shot feature was applied for both methods along the low-bandwidth (phase- or SPEN-encoded) axes, and involved repeating N_{shot} scans differing by the addition of a gradient-driven displacement (K_{shot}). This methodology has been extensively described for EPI (21,32) and scanner-supplied sequences were used for these acquisitions; for the interleaved SPEN DTI experiments, sequences were written and images processed as described by Schmidt *et al* (47). DTI measurements were performed by incorporating diffusion-sensitizing gradient as illustrated in Figure 1, along six (68), twenty (69) or twenty one (70) different orientations. Explicit calculations for the *b*-matrix elements were carried out according to Eqs. 4 and 5, by programming scripts accounting for all gradient and pulse waveforms. Diffusion tensors were then derived from the measured signals by an inversion procedure $D_{ij} = \text{inv}\langle b(t, r_0) \rangle_{ij} \cdot S[b(t, r_0)]$, carried out in a pixel-by pixel manner. Parametric maps were generated from these diffusion tensors, including apparent diffusion coefficient (ADC) maps, fractional anisotropy (FA) and color-coded FA maps (71) reconstructed according to

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \lambda_{mean})^2 + (\lambda_2 - \lambda_{mean})^2 + (\lambda_3 - \lambda_{mean})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}, \text{ where } \lambda_1, \lambda_2, \lambda_3 \text{ are the eigenvalues and } \lambda_{mean} \text{ is the mean value of the diffusion tensor.}$$

Maps were also derived based on the eigenvectors' orientations. Both *b*-matrix calculations and DTI processing were programmed in MATLAB[®] (The MathWorks, Inc., Natick, MA); these macros are available

from the authors upon request. Image registration between the diffusion weighted images was accomplished by the SPM software package's rigid body registration module (72).

Results

SPEN DTI: Basic validations

Figure 2 shows diffusion tensor profiles arising if one ignores (Figures 2A, 2C) or includes (Figures 2B, 2D) the explicit effects of the SPEN imaging gradients in the $\mathbf{b}$ -matrix calculation. For the water sample in question these measurements should yield identical $\lambda_1, \lambda_2, \lambda_3$ eigenvalues, constant throughout the single z -slice selected in the sample tube. This is clearly not the outcome if SPEN gradients are ignored. The errors in the estimated eigenvalues are less pronounced when implementing 180° -based encodings than their 90° counterparts, yet discrepancies still emerge among the three eigenvalues. The distortions arising if ignoring the SPEN gradients are most evident along the SPEN-encoded axis (Fig. 2A), scattering these eigenvalues between 1.5 and $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$. By contrast, maps taking into account the imaging and diffusion gradient cross-terms (Fig. 2B) provide uniform and accurate eigenvalue maps, with the λ s scattering around the average diffusion value $D = 2.2 \times 10^{-3} \text{ mm}^2/\text{s}$ by $\pm 0.05 \times 10^{-3} \text{ mm}^2/\text{s}$. The Supporting Information Figure S1 illustrates another aspect of these effects, with maps of the $\{b_{ij}\}$ -values adopted by the different in-plane elements, in the absence of diffusion-sensitizing gradients.

Ex vivo DTI measurements

Figure 3 compares maps obtained from various sequences on an *ex vivo* rat brain, displayed as color-coded FA maps. SEMS DW images (Fig. 3A) and their corresponding FA maps (color-coded in Fig. 3B) were used as references; DTI results based on multi-slice SPEN and on SE EPI are shown in Figures 3C and 3D, respectively. All of these images were collected at 7T –the latter two employing data interleaving procedures, capable of reducing echo times by combining multiple shots. Data interleaving was carried out in a referenceless manner for SPEN (47), while for SE EPI we used scanner-supplied four-shot interleaving routines. Both of these experiments evidenced comparable results in one-sixth of the SEMS DTI scan time, and showed fine orientational brain details such as the corpus callosum (Figure 3E) and cerebral cortex. All three pulse sequences clearly succeed in tracking the white matter fibers in these regions; corresponding FA maps for the same slices can be found in Figure S2 of the Supporting Information.

Fast diffusion imaging can be challenged by eddy-current artifacts, particularly when involving strong readout and strong diffusion-sensitizing gradients (67,73). Figure 4 illustrates this feature for DTI pulse sequences using relatively short diffusion timings ($\delta = 3 \text{ ms}$, $\tau = 11 \text{ ms}$) yet relatively high b_{PGSE} values (1200 s/mm^2). Under these conditions, the diffusion gradient amplitude reached 43.2 G/cm (out of a nominal maximum for our system of 100 G/cm). *Ex-vivo* coronal rat DTI maps for SEMS (Fig. 4B) and SPEN (Fig. 4C) show similar anatomical information under these conditions; for SE EPI, by contrast, the FA maps were clearly distorted by the effects of eddy current interferences (Fig. 4D). These effects were consistent in all experiments and could not be avoided unless extending either δ or τ , at the expense of longer echo times.

In Vivo DTI validations

In vivo experiments were conducted on adult mice. Whereas SPEN afforded acceptable brain DTI data using similar diffusion-sensitizing delays as in the *ex vivo* cases just presented, eddy-current artifacts prevented—at least in our system and using a single spin-echoed G_d pair—the acquisition of *in vivo* data based on SE EPI. To avoid these artifacts had to be nearly doubled, from 11 to 20 ms. Upon doing so, similar FA maps were achieved for SPEN and SE EPI, under comparable timings and similar resolutions (Figure 5). Clear anatomical details and nearly no motional artifacts, despite the absence of respiratory gating, were then observed for both data sets.

As a final example, we present diffusion properties measured for a human lactating breast. The new SPEN pulse sequence shown in Fig. 1C was used in these studies, as this still endows spins with the desired quadratic encoding along the Y-axis yet excited a single Z-slice, without the SAR penalties associated to the use of frequency-swept 180° pulses. Figure 6 summarizes the resulting measurements, analyzed under the assumption of axially symmetric diffusion tensors. The λ_1 -map (Fig. 6A), with a total average value $2.3 \pm 0.6 \times 10^{-3} \text{ mm}^2/\text{s}$ over both breasts, represents the fastest diffusion component; the slower $\lambda_2 = \lambda_3$ components (Fig. 6B) average only $1.8 \pm 0.6 \times 10^{-3} \text{ mm}^2/\text{s}$. Figure 6C presents the average of the three eigenvalues; also illustrative is to explore the FA map of the lactating breast (Fig. 6D). This is remarkably isotropic towards the center of the organ, where the central milk ducts are widely distended, but increases in anisotropy towards the breasts' peripheral regions, where the ducts become smaller and thus radial diffusivity more restricted. The fold-free nature of the SPEN experiment also allows one to zoom into a single breast or a region of thereof; a vector map representation of the ensuing principal diffusion eigenvectors (represented by the blue arrows in Fig. 6E) shows an alignment of the λ 's along the anterior-posterior axis, reflecting the structure of milk ducts heading from the base of the breast toward the nipple. SPEN's robustness to field inhomogeneities can thus be exploited to take a closer look on this phenomenon towards the nipple of the breast—a region challenged by air/tissue interface problems.

Discussion and Conclusions

SPEN variants have been explored in recent years as potential alternatives to EPI—particularly in the context of overcoming B_0 -inhomogeneities or dealing with heterogeneous environments (52,54,74–76). These features are again evidenced here, for DTI studies. This application required extending a formalism that was previously presented for evaluating isotropic diffusion, to the calculation of the $\mathbf{b}$ -matrices arising in DTI. A quantitative description of these weighting elements is important, as the SPEN gradients together with their cross terms with the diffusion gradients, can lead to significant corruptions in the diffusion maps unless suitably accounted for. With the aid of this formalism, validation studies showed that equally good diffusion tensor images and FA parametric maps, could be recorded using single-shot or interleaved SPEN and SE EPI counterparts. Upon shortening the diffusion times and increasing the diffusion-sensitizing gradients, DTI SPEN showed a substantially higher immunity to eddy currents than its EPI counterpart. These benefits proved most remarkable under *in vivo* conditions—where SE-EPI failed to yield sensible

DTI information upon using short (15 ms) times. When relaxing these conditions and reverting to interleaved multi-shot modes, both SPEN and SE EPI demonstrated good DTI performance. As an example of SPEN DTI's nimbleness we examined the diffusion properties of human lactating breast, an organ which although usually examined with dynamic contrast enhancement, cannot be probed in this manner during pregnancy and lactation. In such instances the non-invasive nature of diffusion MRI becomes particularly favorable (77). DTI SPEN had no difficulty to distinguish the facile and restricted diffusing directions in lactating breasts, with FA maps revealing that while a significant amount of bulk fluid experiences free isotropy in the center of the organ, ductal restrictions are reflected by the eigenvectors maps. When examined closely, a directionality of those milk ducts heading towards the nipple was also noticeable. Further efforts are in progress to test more sophisticated SPEN implementations, as well as applications in challenging regions that are known to suffer from chemical and susceptibility heterogeneities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Noam Shemesh and Tangi Roussel for their assistance in this study; the professional help of Dr. Nava Nevo (Veterinary Services, Weizmann Institute), Dr. Sagit Shushan (Wolfson Medical Center) and the Weizmann MRI team (Edna Furman-Haran, Fanny Attar and Nachum Stern) is also gratefully acknowledged. Financial support from the Israel Science Foundation grant 795/13, the EU through ERC-2014-PoC grant # 633888, the Kimmel Institute for Magnetic Resonance and the generosity of the Perlman Family Foundation, are also acknowledged.

Abbreviations

ADC	Apparent Diffusion Coefficient
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EPI	Echo Planar Imaging
FOV	Field of View
ROI	region of interest
SAR	specific absorption rates
SE	Spin Echo
SPEN	spatio-temporal encoding
TSE	Turbo Spin Echo

References

1. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med*. 2000; 44(4):625–632. [PubMed: 11025519]

2. Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. *NMR Biomed.* 2002; 15(7–8):456–467. [PubMed: 12489095]
3. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J.* 1994; 66(1):259–267. [PubMed: 8130344]
4. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H. Diffusion tensor imaging: Concepts and applications. *J Magn Reson.* 2001; 13(4):534–546.
5. Mattiello J, Basser PJ, LeBihan D. The b matrix in diffusion tensor echo-planar imaging. *Magn Reson Med.* 1997; 37(2):292–300. [PubMed: 9001155]
6. Neeman M, Freyer JP, Sillerud LO. Pulsed-Gradient Spin-Echo Diffusion Studies in NMR Imaging - Effects of the Imaging Gradients on the Determination of Diffusion-Coefficients. *J Magn Reson.* 1990; 90(2):303–312.
7. Price WS, Kuchel PW. Effect of Nonrectangular Field Gradient Pulses in the Stejskal and Tanner (Diffusion) Pulse Sequence. *J Magn Reson.* 1991; 94(1):133–139.
8. Tuch DS. Q-ball imaging. *Magn Reson Med.* 2004; 52(6):1358–1372. [PubMed: 15562495]
9. Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magn Reson Med.* 2002; 48(4):577–582. [PubMed: 12353272]
10. De Santis S, Barazany D, Jones DK, Assaf Y. Resolving relaxometry and diffusion properties within the same voxel in the presence of crossing fibres by combining inversion recovery and diffusion-weighted acquisitions. *Magn Reson Med.* 2015
11. Ugurbil K, Xu J, Auerbach EJ, Moeller S, Vu AT, Duarte-Carvajalino JM, Lenglet C, Wu X, Schmitter S, Van de Moortele PF, Strupp J, et al. Pushing spatial and temporal resolution for functional and diffusion MRI in the Human Connectome Project. *Neuroimage.* 2013; 80:80–104. [PubMed: 23702417]
12. Colon-Perez LM, King M, Parekh M, Boutzoukas A, Carmona E, Couret M, Klassen R, Mareci TH, Carney PR. High-field Magn Reson Imaging of the human temporal lobe. *Neuroimage.* 2015; 9:58–68. [PubMed: 26413472]
13. Wood ET, Ercan AE, Branzoli F, Webb A, Sati P, Reich DS, Ronen I. Reproducibility and optimization of in vivo human diffusion-weighted MRS of the corpus callosum at 3 T and 7 T. *NMR Biomed.* 2015; 28(8):976–987. [PubMed: 26084563]
14. Chabert S, Molko N, Cointepas Y, Le Roux P, Le Bihan D. Diffusion tensor imaging of the human optic nerve using a non-CPMG fast spin echo sequence. *J Magn Reson Imaging.* 2005; 22(2):307–310. [PubMed: 16028249]
15. Norris DG, Driesel W. Online motion correction for diffusion-weighted imaging using navigator echoes: Application to RARE imaging without sensitivity loss. *Magn Reson Med.* 2001; 45(5): 729–733. [PubMed: 11323797]
16. Nunes RG, Jezzard P, Behrens TE, Clare S. Self-navigated multishot echo-planar pulse sequence for high-resolution diffusion-weighted imaging. *Magn Reson Med.* 2005; 53(6):1474–1478. [PubMed: 15906309]
17. Bernstein, MA., King, KF., Zhou, XJ. Handbook of MRI pulse sequences. Vol. xxii. Burlington, MA ; London: Elsevier Academic; 2004. p. 1017
18. 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]
19. Abduljalil AM, Kangarlou A, Yu Y, Robitaille PM. Macroscopic susceptibility in ultra high field MRI. II: acquisition of spin echo images from the human head. *J Comput Assist Tomogr.* 1999; 23(6):842–844. [PubMed: 10589556]
20. Reeder SB, Atalar E, Bolster BD Jr, McVeigh ER. Quantification and reduction of ghosting artifacts in interleaved echo-planar imaging. *Magn Reson Med.* 1997; 38(3):429–439. [PubMed: 9339445]
21. Butts K, Riederer SJ, Ehman RL, Thompson RM, Jack CR. Interleaved echo planar imaging on a standard MRI system. *Magn Reson Med.* 1994; 31(1):67–72. [PubMed: 8121272]
22. Tsai CM, Nishimura DG. Reduced aliasing artifacts using variable-density k-space sampling trajectories. *Magn Reson Med.* 2000; 43(3):452–458. [PubMed: 10725889]

23. Wiczorowski M. Spiral sampling as a fast way of data acquisition in surface topography. *Int J Mach Tool Manu.* 2001; 41(13–14):2017–2022.
24. Meyer CH, Hu BS, Nishimura DG, Macovski A. Fast spiral coronary artery imaging. *Magn Reson Med.* 1992; 28(2):202–213. [PubMed: 1461123]
25. 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. *Magn Reson Med.* 2010; 63(4):959–969. [PubMed: 20373397]
26. Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, Kiefer B, Haase A. Generalized autocalibrating partially parallel acquisitions (GRAPPA). *Magn Reson Med.* 2002; 47(6):1202–1210. [PubMed: 12111967]
27. Shi X, Ma X, Wu W, Huang F, Yuan C, Guo H. Parallel imaging and compressed sensing combined framework for accelerating high-resolution diffusion tensor imaging using inter-image correlation. *Magn Reson Med.* 2015; 73(5):1775–1785. [PubMed: 24824404]
28. Mukherjee P, Chung SW, Berman JI, Hess CP, Henry RG. Diffusion tensor MR imaging and fiber tractography: technical considerations. *AJNR Am J Neuroradiol.* 2008; 29(5):843–852. [PubMed: 18339719]
29. Ellingson BM, Sulaiman O, Kurpad SN. High-resolution in vivo diffusion tensor imaging of the injured cat spinal cord using self-navigated, interleaved, variable-density spiral acquisition (SNAILS-DTI). *Magn Reson Imaging.* 2010; 28(9):1353–1360. [PubMed: 20797830]
30. van de Looij Y, Kunz N, Huppi P, Gruetter R, Sizonenko S. Diffusion Tensor Echo Planar Imaging Using Surface Coil Transceiver with a Semiadiabatic RF Pulse Sequence at 14.1T. *Magn Reson Med.* 2011; 65(3):732–737. [PubMed: 20939068]
31. Li TQ, Kim DH, Moseley ME. High-resolution diffusion-weighted imaging with interleaved variable-density spiral acquisitions. *J Magn Reson imaging : JMRI.* 2005; 21(4):468–475. [PubMed: 15779030]
32. Bogner W, Pinker-Domenig K, Bickel H, Chmelik M, Weber M, Helbich TH, Trattinig S, Gruber S. Readout-segmented Echo-planar Imaging Improves the Diagnostic Performance of Diffusion-weighted MR Breast Examinations at 3.0 T. *Radiology.* 2012; 263(1):64–76. [PubMed: 22438442]
33. Anderson AW, Gore JC. Analysis and correction of motion artifacts in diffusion weighted imaging. *Magn Reson Med.* 1994; 32(3):379–387. [PubMed: 7984070]
34. Banerjee S, Beatty PJ, Zhang JZ, Shankaranarayanan A. Parallel and partial Fourier imaging with prospective motion correction. *Magn Reson Med.* 2013; 69(2):421–433. [PubMed: 22488750]
35. Chen NK, Guidon A, Chang HC, Song AW. A robust multi-shot scan strategy for high-resolution diffusion weighted MRI enabled by multiplexed sensitivity-encoding (MUSE). *Neuroimage.* 2013; 72:41–47. [PubMed: 23370063]
36. O'Halloran RL, Holdsworth S, Aksoy M, Bammer R. Model for the correction of motion-induced phase errors in multishot diffusion-weighted-MRI of the head: are cardiac-motion-induced phase errors reproducible from beat-to-beat? *Magn Reson Med.* 2012; 68(2):430–440. [PubMed: 22213138]
37. Tam LK, Galiana G, Stockmann JP, Tagare H, Peters DC, Constable RT. Pseudo-random center placement O-space imaging for improved incoherence compressed sensing parallel MRI. *Magn Reson Med.* 2015; 73(6):2212–2224. [PubMed: 25042143]
38. Frydman L, Lupulescu A, Scherf T. Principles and features of single-scan two-dimensional NMR spectroscopy. *J Am Chem Soc.* 2003; 125(30):9204–9217. [PubMed: 15369377]
39. Frydman L, Scherf T, Lupulescu A. The acquisition of multidimensional NMR spectra within a single scan. *Proc Natl Acad Sci U S A.* 2002; 99(25):15858–15862. [PubMed: 12461169]
40. Ben-Eliezer N, Shrot Y, Frydman L. High-definition, single-scan 2D MRI in inhomogeneous fields using spatial encoding methods. *Magn Reson Imaging.* 2009; 28(1):77–86. [PubMed: 19608367]
41. Ben-Eliezer N, Solomon E, Harel E, Nevo N, Frydman L. Fully refocused multi-shot spatiotemporally encoded MRI: robust imaging in the presence of metallic implants. *MAGMA.* 2012; 25(6):433–442. [PubMed: 22743822]
42. Tal A, Frydman L. Spatial encoding and the single-scan acquisition of high definition MR images in inhomogeneous fields. *J Magn Reson.* 2006; 182(2):179–194. [PubMed: 16843690]

43. Ben-Eliezer N, Irani M, Frydman L. Super-resolved spatially encoded single-scan 2D MRI. *Magn Reson Med*. 2010; 63(6):1594–1600. [PubMed: 20512863]
44. Tal A, Frydman L. Single-scan multidimensional magnetic resonance. *Prog Nucl Magn Reson Spectrosc*. 2010; 57(3):241–292. [PubMed: 20667401]
45. Idiyatullin D, Corum CA, Garwood M. Multi-Band-SWIFT. *J Magn Reson*. 2015; 251:19–25. [PubMed: 25557859]
46. Schmidt R, Baishya B, Ben-Eliezer N, Seginer A, Frydman L. Super-resolved parallel MRI by spatiotemporal encoding. *Magn Reson Imaging*. 2014; 32(1):60–70. [PubMed: 24120293]
47. Schmidt R, Seginer A, Frydman L. Interleaved multishot imaging by spatiotemporal encoding: A fast, self-referenced method for high-definition diffusion and functional MRI. *Magn Reson Med*. 2015
48. Airaksinen AM, Niskanen JP, Chamberlain R, Huttunen JK, Nissinen J, Garwood M, Pitkanen A, Grohn O. Simultaneous fMRI and local field potential measurements during epileptic seizures in medetomidine-sedated rats using raser pulse sequence. *Magn Reson Med*. 2010; 64(4):1191–1199. [PubMed: 20725933]
49. Ben-Eliezer N, Goerke U, Ugurbil K, Frydman L. Functional MRI using super-resolved spatiotemporal encoding. *Magn Reson Imaging*. 2012; 30(10):1401–1408. [PubMed: 22789843]
50. Chen L, Bao L, Li J, Cai S, Cai C, Chen Z. An aliasing artifacts reducing approach with random undersampling for spatiotemporally encoded single-shot MRI. *J Magn Reson*. 2013; 237:115–124. [PubMed: 24184712]
51. Chen Y, Li J, Qu X, Chen L, Cai C, Cai S, Zhong J, Chen Z. Partial Fourier transform reconstruction for single-shot MRI with linear frequency-swept excitation. *Magn Reson Med*. 2013; 69(5):1326–1336. [PubMed: 22706702]
52. Ciobanu L, Solomon E, Pyatigorskaya N, Roussel T, Le Bihan D, Frydman L. fMRI contrast at high and ultrahigh magnetic fields: Insight from complementary methods. *Neuroimage*. 2015; 113:37–43. [PubMed: 25795340]
53. Solomon E, Avni R, Hadas R, Raz T, Garbow JR, Bendel P, Frydman L, Neeman M. Major mouse placental compartments revealed by diffusion-weighted MRI, contrast-enhanced MRI, and fluorescence imaging. *Proc Natl Acad Sci U S A*. 2014; 111(28):10353–10358. [PubMed: 24969421]
54. Solomon E, Nissan N, Furman-Haran E, Seginer A, Shapiro-Feinberg M, Degani H, Frydman L. Overcoming limitations in diffusion-weighted MRI of breast by spatio-temporal encoding. *Magn Reson Med*. 2015; 73(6):2163–2173. [PubMed: 25045867]
55. Solomon E, Shemesh N, Frydman L. Diffusion weighted MRI by spatiotemporal encoding: analytical description and in vivo validations. *J Magn Reson*. 2013; 232:76–86. [PubMed: 23562003]
56. Torrey HC. Bloch Equations with Diffusion Terms. *Physical Review*. 1956; 104(3)
57. Stejskal EO, Tanner JE. Spin Diffusion Measurements: Spin Echoes in the Presence of a Time-Dependent Field Gradient. *Journal of Chemical Physics*. 1965; 42(1):288–292.
58. Kunz D. Use of Frequency-Modulated Radiofrequency Pulses in Mr Imaging Experiments. *Magn Reson Med*. 1986; 3(3):377–384. [PubMed: 3724417]
59. Pipe JG. Spatial Encoding and Reconstruction in Mri with Quadratic Phase Profiles. *Magn Reson Med*. 1995; 33(1):24–33. [PubMed: 7891532]
60. Ben-Eliezer N, Frydman L. Spatiotemporal encoding as a robust basis for fast three-dimensional in vivo MRI. *NMR Biomed*. 2011; 24(10):1191–1201. [PubMed: 21360603]
61. Dumez JN, Frydman L. Multidimensional excitation pulses based on spatiotemporal encoding concepts. *J Magn Reson*. 2013; 226:22–34. [PubMed: 23202845]
62. Pauly J, Nishimura D, Macovski A. A k-space analysis of small-tip-angle excitation. 1989. *J Magn Reson*. 2011; 213(2):544–557. [PubMed: 22152370]
63. Cai C, Dong J, Cai S, Li J, Chen Y, Bao L, Chen Z. An efficient de-convolution reconstruction method for spatiotemporal-encoding single-scan 2D MRI. *J Magn Reson*. 2013; 228:136–147. [PubMed: 23433507]
64. Callaghan, PT. Principles of nuclear magnetic resonance microscopy. Vol. xvii. Clarendon Press; Oxford: 1993. p. 492p., 494 col. plates p

65. Karlicek RF, Lowe IJ. Modified Pulsed Gradient Technique for Measuring Diffusion in the Presence of Large Background Gradients. *J Magn Reson.* 1980; 37(1):75–91.
66. Shrot Y, Frydman L. The effects of molecular diffusion in ultrafast two-dimensional nuclear magnetic resonance. *J Chem Phys.* 2008; 128(16):164513. [PubMed: 18447465]
67. Gruetter R, Tkac I. Field mapping without reference scan using asymmetric echo-planar techniques. *Magn Reson Med.* 2000; 43(2):319–323. [PubMed: 10680699]
68. Giannelli M, Cosottini M, Michelassi MC, Lazzarotti G, Belmonte G, Bartolozzi C, Lazzeri M. Dependence of brain DTI maps of fractional anisotropy and mean diffusivity on the number of diffusion weighting directions. *J Appl Clin Med Phys.* 2010; 11(1):2927.
69. Jones DK, Horsfield MA, Simmons A. Optimal strategies for measuring diffusion in anisotropic systems by Magn Reson Imaging. *Magn Reson Med.* 1999; 42(3):515–525. [PubMed: 10467296]
70. Ozarslan E, Mareci TH. Generalized diffusion tensor imaging and analytical relationships between diffusion tensor imaging and high angular resolution diffusion imaging. *Magn Reson Med.* 2003; 50(5):955–965. [PubMed: 14587006]
71. Roberts TP, Schwartz ES. Principles and implementation of diffusion-weighted and diffusion tensor imaging. *Pediatr Radiol.* 2007; 37(8):739–748. [PubMed: 17598100]
72. Collignon A, Maes F, Delaere D, Vandermeulen D, Suetens P, Marchal G. Automated multi-modality image registration based on information theory. *Comp Imag Vis.* 1995; 3:263–274.
73. 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]
74. Leftin A, Rosenberg JT, Solomon E, Bejarano F, Grant SC, Frydman L. Ultrafast In Vivo Diffusion Imaging of Stroke at 21.1 T by Spatiotemporal Encoding. *Magn Reson Med.* 2015; 73(4):1483–1489. [PubMed: 24845125]
75. Schmidt R, Frydman L. Alleviating artifacts in 1H MRI thermometry by single scan spatiotemporal encoding. *MAGMA.* 2013; 26(5):477–490. [PubMed: 23443884]
76. Goerke U, Garwood M, Ugurbil K. Functional Magn Reson Imaging using RASER. *Neuroimage.* 2011; 54(1):350–360. [PubMed: 20699123]
77. Ayyappan AP, Kulkarni S, Crystal P. Pregnancy-associated breast cancer: spectrum of imaging appearances. *Br J Radiol.* 2010; 83(990):529–534. [PubMed: 20335428]

Figure 1.

SPEN pulse sequences assessed in DTI experiments. RF pulse manipulations include a chirped-90 pulse followed by a single-slice refocusing 180 pulse (A), a chirped-180 multi-slice approach (B), and a slice-selective 2D pulse imparting a 90° chirped-like evolution (60,61) (C). Diffusion-sensitizing gradients (indicated by stepped gray gradients) are symmetrically located on both sides of a central refocusing pulse in A and C, and placed in a pre-encoding $T_a/2$ delay required by B to reach full-refocusing conditions (47). The RF/ADC line displays the pulses and signal acquisitions; G_e , encoding gradient; G_d , diffusion-weighting gradients; G_{ss} , slice-selective gradient; G_{pr} , purge gradients; G_{cr} , crusher gradients; G_a , acquisition gradients; K_{shot} , step gradient for interleaved multi-shot mode; T_e , encoding time; T_a , acquisition time; N_{pe} , number of loops encoding the low-bandwidth (SPEN) dimensions; N_{sl} , number of slices; N_{shot} , number of shots, when implemented in a segmented, reference-less acquisition mode (47). All loop indices are indicated on the inside of their corresponding brackets.

Figure 2.

Effects of SPEN on λ_1 , λ_2 and λ_3 diffusion maps, collected for a water sample using single-shot 90° chirped (top panels) and a 180° chirped (lower panels) pulse sequences. (A, C) are maps that ignored the SPEN imaging gradients and pulses; (B, D) accounted for these effects in the $\mathbf{b}$ -matrix. 1D profiles illustrate cross-sections taken for the λ -maps along the SPEN dimensions at the dashed white lines. Diffusion-oriented parameters included $\delta = 3$ ms, $\tau = 14$ ms, nominal $|b_{\text{PGSE}}|$ -value = 500 s/mm² with a diffusion gradient strength of 24.4 G/cm and 6 directions. Scanning parameters: TR = 8 s, cubic FOV = 20 × 20 mm², resolution = 0.29 × 0.29 mm² on a 3 mm slice, number of averages = 3. Gradient and timing values for the 90° chirped pulse SPEN experiments: TE = 17–59 ms (depending on the position of the spins), $T_e = T_a = 21$ ms, $G_e = 1$ G/cm, $G_a = 3.75$ G/cm. 180° chirped pulse SPEN parameters: TE = 35–56 ms, $T_{\text{SS}} = 2$ ms, $T_e = T_a/2 = 10.5$ ms, $G_e = 1$ G/cm, $G_a = 3.75$ G/cm.

Figure 3.

Interleaved DTI sagittal slices collected on an *ex-vivo* rat brain based on 21 diffusion-weighting directions. (A) SEMS DW magnitude images serving as anatomical reference, with their corresponding color-coded FA maps in (B) showing the eigenvectors' main orientation in each pixel, with red, blue, and green defining a 3D coordinate space. Color-coded FA maps of SPEN DTI (C) arising from a multi-slice 180° chirped sequence, and for SE EPI (D). Shown in (E) are magnified corpus callosum DTI results overlaid on two anatomical regions: a posterior one including the splenium (orange framed) and an anterior that includes the genu (red frame), including color-coded FA map and their corresponding anisotropy vector maps acquired by each of the three methods respectively. Diffusion parameters for (B-C) were $\delta = 6$ ms, $\Delta = 20$ ms, b_{PGSE} -value = 1100 s/mm² with a diffusion gradient strength of 15.0 G/cm and 21 directions. Scanning parameters of (A-B) were TR=5sec, FOV = 25x20 mm² (PE x RO), resolution = 0.13x0.1 mm² on a 0.8 mm slice, number of averages = 4. Total scan duration = 64 min per diffusion direction. (C-D) data were collected using 4 interleaved shots, TR=5sec, FOV = 25x20 mm² (PE x RO), nominal resolution = 0.125 x 0.156 mm² on a 0.8 mm slice, number of averages = 30 (for SE-EPI, 32 averages). Total scan duration = 10 min per diffusion direction. Additional scanning parameters for multi-slice 180° SPEN (C): TE=54-88 ms, T_{SS}=2 ms, T_e=T_a/2=16.8 ms, G_e=0.36 G/cm, G_a=2.8 G/cm. For SE-EPI (D): TE=55 ms, T_{SS}=T₁₈₀=4ms, T_a=32ms.

Figure 4.

Eddy-current effects with short diffusion timing described by magnitude images and color-coded FA maps; rows correspond to SEMS (A, B), SPEN (C) and SE EPI (D). Diffusion parameters were $\delta = 3$ ms, $\Delta = 11$ ms, b_{PGSE} -value=1200 s/mm² with a diffusion gradient strength of 43.2 G/cm and 21 directions. Scanning parameters for (A-B): TR=5sec, FOV = 20x20 mm² (PE x RO), resolution = 0.1x0.1 mm² on a 0.8 mm slice, number of averages = 4. Total scan duration = 64 min per diffusion direction. (C-D): Four interleaved shots, TR=5sec, cubic FOV = 20x20 mm² (PE x RO), nominal resolution = 0.1x0.156 mm² on a 0.8 mm slice, number of averages = 30 for SPEN, 32 for SE-EPI. Total scan duration = 10 min per diffusion direction. Additional scanning parameters: For DTI SPEN: 180°-chirped encoding with TE=35-68 ms, 2 ms slice-selective excitation, $T_e = T_a/2 = 16.8$ ms, $G_e = 0.42$ G/cm, $G_a = 3.52$ G/cm. For SE-EPI: TE=50 ms, $T_{SS} = T_{180}/2 = 2$ ms, $T_a = 32$ ms.

Figure 5.

In-vivo multi-slice mouse brain DTI results based on 21 diffusion-sensitizing directions. Magnitude images and color-coded FA maps arising from (A) 180° chirped DTI-SPEN and (B) SE EPI DTI acquisitions. Diffusion parameters included $\delta = 3$ ms, $\Delta = 20$ ms, b -value = 900 s/mm² with a diffusion gradient strength of 27.1 G/cm and 21 directions. Scanning parameters for (A) and (B) included 4 interleaved shots, TR = 3.6 sec, FOV = 20 x 20 mm² (PE x RO), nominal resolution = 0.13 x 0.16 mm² on a 1.0 mm slice, number of averages = 16, 3.8 min total scan duration per diffusion direction. Additional scanning parameters for the 180° chirped DTI-SPEN: TE = 47-75 ms, T₉₀ = 2 ms, T₁₈₀ = T_a/2 = 13.4 ms, G_e = 0.44 G/cm, G_a = 3.7 G/cm. For SE-EPI (D): TE = 42 ms, 2 * T₉₀ = T₁₈₀ = 4 ms, T_a = 25 ms.

Figure 6.

2D SPEN DTI of a human lactating breast. (A) Diffusion maps of the principal component λ_1 . (B) Idem for $(\lambda_2 + \lambda_3)/2$. (C) Isotropic ADC map. (D) FA map. All these maps are shown overlaid on the corresponding T_2 -weighted anatomical MR images (F). (E) Vector map of the principal diffusion eigenvectors represented by blue arrows pointing from the base of the breast toward the nipple, together with a graphically zoomed window from the center of the breast. Diffusion parameters are $\delta = 23$ ms, $\Delta = 49$ ms, $b_{PGSE\text{-value}} = 400$ s/mm² with a diffusion gradient strength of 1.6 G/cm and 20 directions. Scanning parameters: TR=5.5sec, FOV = 139x260 mm² (PE x RO), nominal resolution = 2.2x2.2 mm² on a 2.5 mm slice. Additional scanning parameters for 2D SPEN DTI: TE=72-200 ms, 2D chirped pulse $T_{90}=T_a=64$ ms, $G_e=0.011$ G/cm, $G_a=0.0041$ G/cm.