Unprecedented Echo Times for Diffusion MRI Using Connectom Gradients, Spiral Readouts and Field Monitoring

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Summary

- Using a unique combination of the ultra-strong (300 mT/m) magnetic field gradients provided on the MAGNETOM Connectom[1] scanner, a diffusion-weighted MRI sequence with spiral EPI read-out, and a field camera to monitor and correct for deviations from prescribed *k*-space trajectories, we present high quality images with unprecedented short echo times for diffusion MRI in the living human brain
- For b = 1000 s/mm^2, the echo time is 21.7 ms
- These short echo times confer two advantages:
  - Enhanced signal to noise ratio (SNR) due to reduced T2-weighted signal loss (which makes measurement of tissue with short T2, e.g., muscle, more robust)
  - Sensitivity to species previously 'invisible' in diffusion MRI, e.g., the myelin water, opening up the possibility of measuring their diffusion properties for the first time.
- In summary, this unique combination of hardware, sequence, field monitoring and reconstruction opens up a new window into tissue microstructural properties in the living human brain.

[1] *MAGNETOM Connectom is ongoing research. All data shown are acquired using a non-commercial system under institutional review board permission. Siemens does not intend to commercialize the system.*

The challenge of diffusion MRI

The introduction of diffusion-weighted imaging [3] into the armoury of quantitative MRI techniques, has revolutionised our understanding of tissue properties *in vivo* across a wide range of organs. Characterizing the *anisotropic* diffusion of water in tissue, allows properties such as density, shape, size, and orientation of different tissue compartments to be inferred [e.g., 1, 2, 6, 9].

A successful diffusion MRI sequence has two key components:

1. The application of sufficient diffusion-weighting (through the application of magnetic field gradients for a finite duration) that makes the sequence sensitive to **microscopic** displacements.
2. A very rapid read-out of the image, to effectively 'freeze' the physiological motion (**macroscopic** displacements) that would otherwise corrupt the diffusion-weighted image.

Regarding the first point, the field of diffusion MRI has been a key driver in the development of gradient technologies, providing higher and higher gradient amplitudes [10, 19]. The amount of diffusion weighting depends on the **product** of the amplitude and duration of the gradient pulses, and thus the stronger the gradient, the less time it needs to be applied to achieve the same diffusion-weighting. Regarding the second point, by far the most prevalent read-out is echo planar imaging (EPI), introduced into diffusion MRI by Turner et al. [21] (Fig. 1).

Thus, both stronger gradients and echo-planar readouts have improved the robustness and utility of diffusion

MRI since its initial inception. However, both of these pulse components take time to play out. In the most commonly-used pulse sequence, the diffusion-weighted **spin echo**, during these times the signal is constantly being lost due to an additional mechanism, i.e., transverse (T2) relaxation. Not only does this reduce the signal to noise ratio (SNR), but it also means that the signal from species with shorter T2 will contribute much less than species with longer T2.

The motivation for myelin

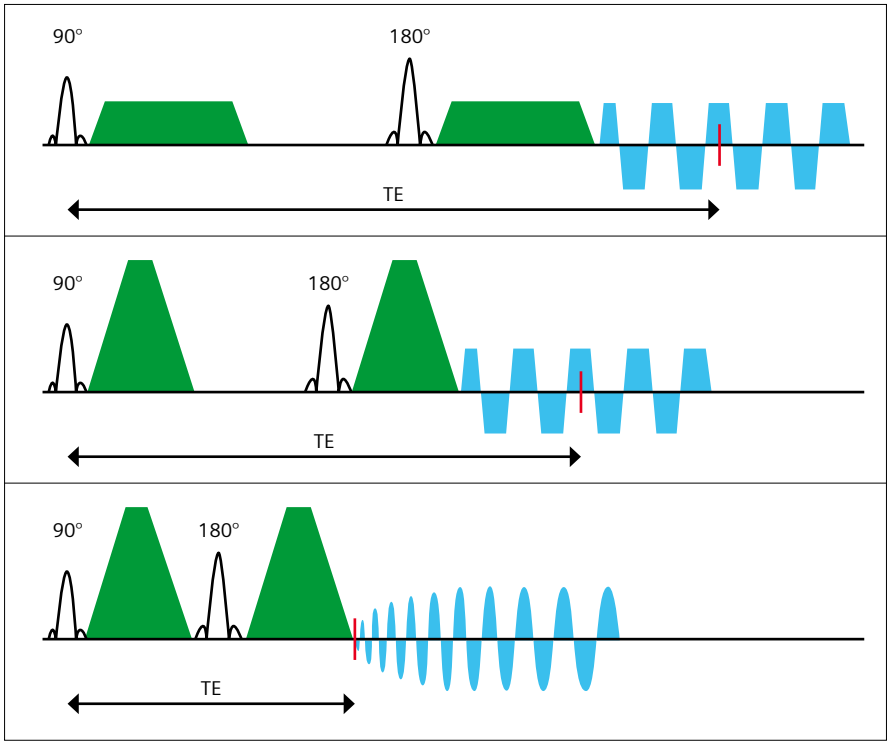
In the brain, the white matter fibres form the 'motorways' that transport packets of information between different brain regions. The white matter derives its name from the color of the myelin, a fatty layer that wraps around the axons, serving multiple functions (including speeding conduction velocity and reducing the energy requirements for signal transmission). The myelin is a key component of the white matter, and deficits in myelin have been implicated in a wide range of neurological, psychiatric, and developmental disorders, and it has thus been the focus of investigation and key-driver of a number of methodological advances in MRI, including multi-component relaxometry (looking at the water trapped between the layers of myelin, i.e. the 'myelin water' [13, 14, 22]), magnetization transfer imaging (looking at the macromolecules in the myelin *per se* [24], and quantitative susceptibility imaging [7]. However, myelin is rarely considered in diffusion MRI experiments [8]. The ultra-short T2 of the macromolecules themselves is too short (80 ms) to contribute to the spin echo signal, but also the myelin water (T2 ≤ 20 ms) for the echo times **typically** used in a diffusion-weighted spin echo sequence (TE ~80 ms), contributes around 2% of the signal (Fig. 2). Therefore, the contribution of myelin to the diffusion MRI signal in most human MRI experiments is effectively negligible.

If, however, we were able to **shorten** the echo times of the diffusion-weighted experiment to the point that the contribution from the myelin-water becomes non-negligible, the ability to quantify microstructural properties of the myelin space could offer new windows into the pathophysiology of a number of neurological and psychiatric diseases, provide earlier, differential diagnoses, and provide earlier access to treatment.

This article explores how we can achieve those shorter echo times in diffusion MRI, through manipulation of the two key components:

1. the gradient amplitude; and
2. the imaging read-out strategy.

We consider the challenges in implementation of this new approach, and the solutions we have developed to ameliorate them.



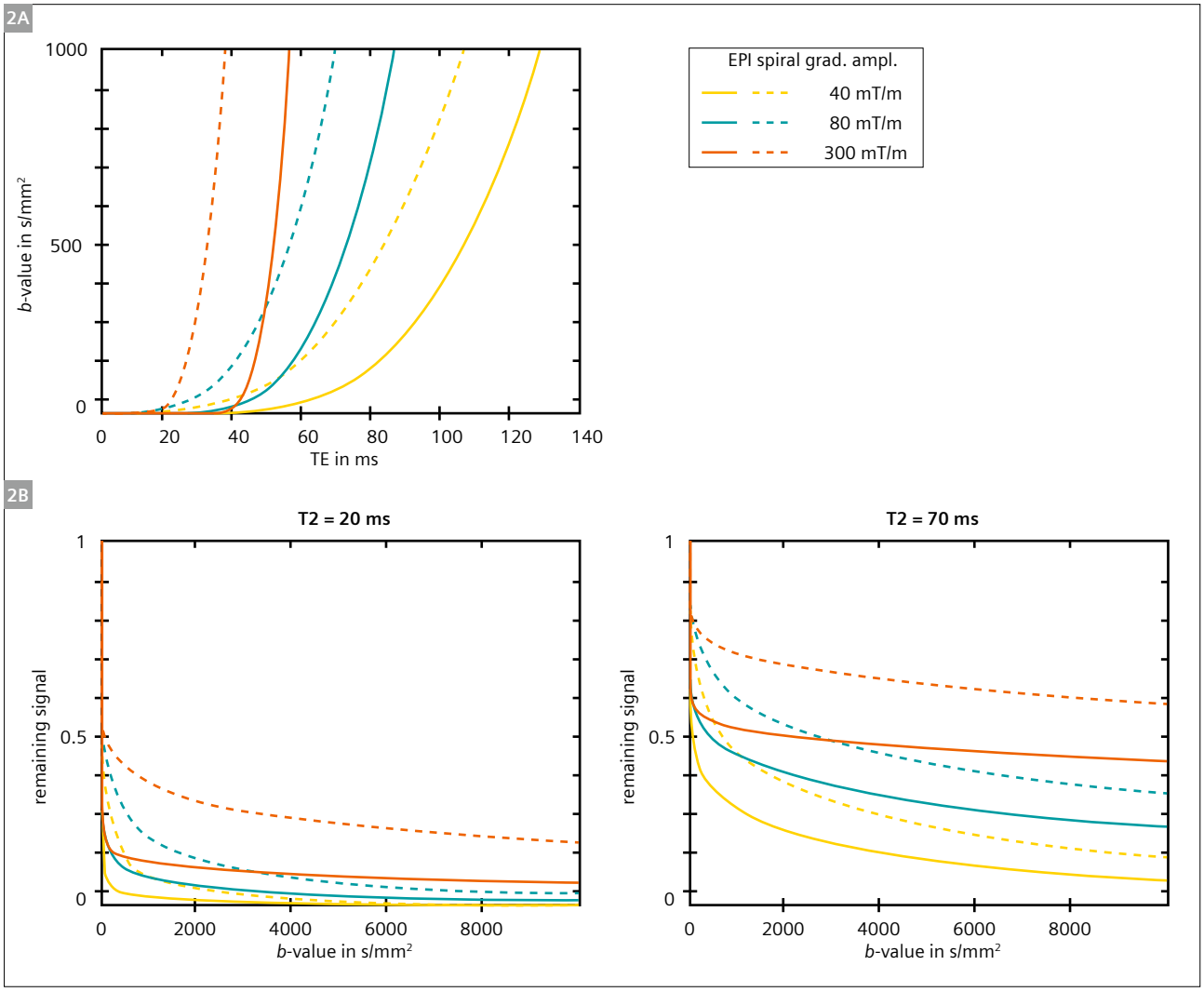
1 Sequence diagrams for different diffusion sequences. The diffusion encoding gradients are shown in green, the readout gradients are blue and the time of the spin echo is marked in red. Ultra-strong gradients and spiral readout are both needed to achieve the shortest possible echo times (TE). Top: Diffusion weighted spin echo (DWSE) sequence with echoplanar imaging (EPI) readout with normal gradient amplitude. Middle: DWSE-EPI with ultra-strong gradients. Bottom: DWSE sequence with ultra-strong gradients and spiral readout.

1. Stronger gradients to reduce the time for diffusion-encoding

The key component that reduces the diffusion-encoding time is an ultra-strong gradient system that enables stronger diffusion weightings per unit time compared to conventional gradient systems. In a typical Stejskal-Tanner experiment (Fig. 1), the amount of diffusion-weighting is determined by two factors: First, the gradient strength and duration of the diffusion-pulse (which can be expressed by q, where $q = \gamma G\delta$); and second, the duration between the diffusion-pulses during which molecular displacements take place (or the diffusion time, which can be expressed by τ, where $\tau = (\Delta - \delta/3)$). The amount of diffusion-weighting in an experiment can then be summarised by the b-value $b = q^2\tau = \gamma^2 G^2\delta^2(\Delta - \delta/3)$ [15]. From this equation, it becomes apparent that increasing the gradient-strength allows a much wider range of experiments, in that:

1. for a given b-value, a higher gradient strength allows to reduce the pulse-duration δ and the time between pulses Δ, overall shortening the time needed for diffusion-encoding. The reduction of the shortest possible TE is a direct consequence of this, and thus a wider range of TEs can be achieved;
2. for a given pulse-duration δ, a higher gradient strength provides higher q-values, and thus a wider range of q-values can be sampled;
3. for a given diffusion time, a wider range of b-values can be maintained.

While this clearly outlines the advantages of ultra-strong gradients for the usage for diffusion MRI, there are also challenges; image artifacts can become amplified or



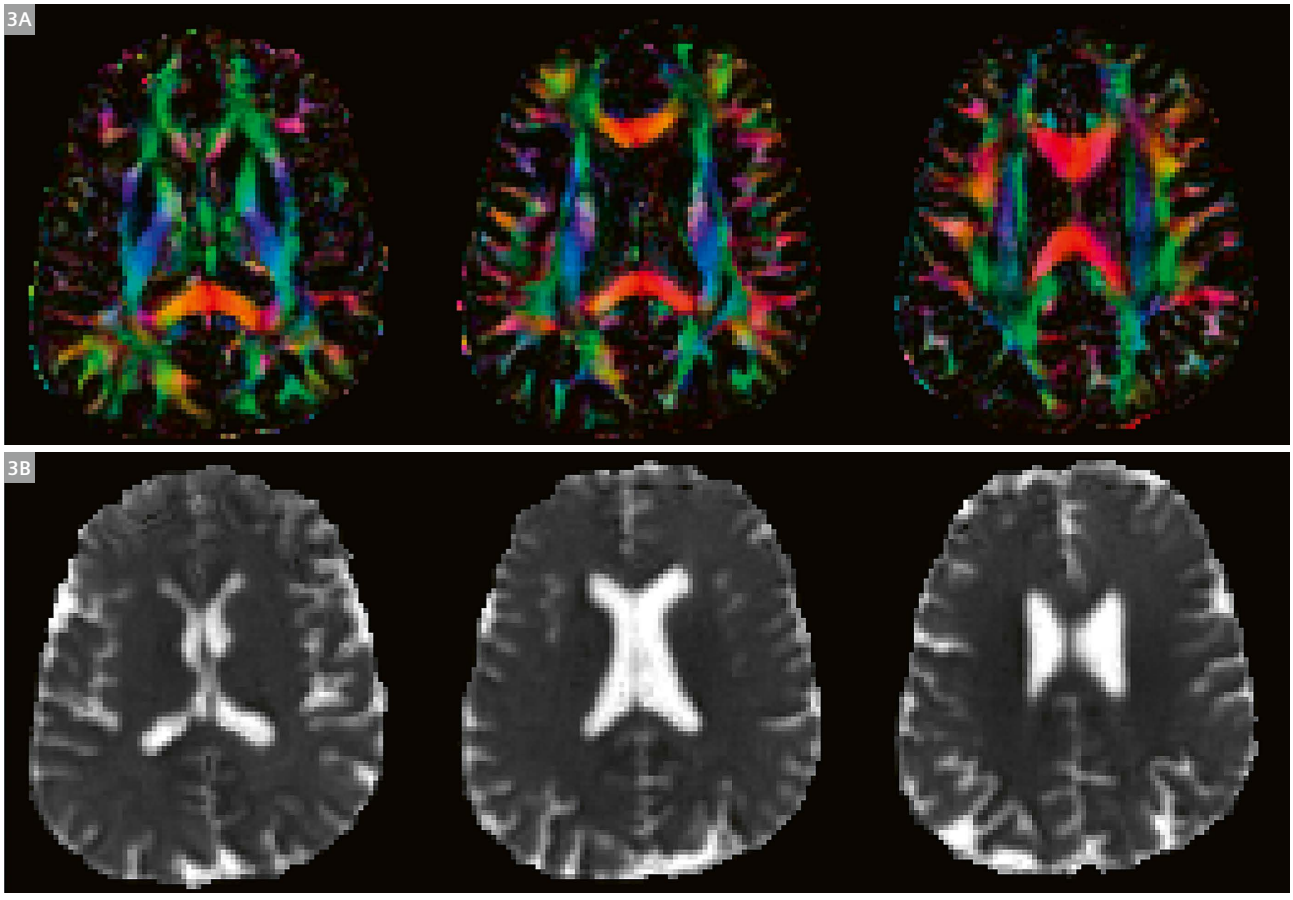
2 Relationships between b-value, echo time (TE), and T2-decay for spiral and EPI with different gradient amplitudes. For the EPI Grappa factor 2, partial fourier 6/8 and bandwidth per pixel of 2004 Hz (1536 Hz for 40 mT/m) were assumed at a resolution of 1.5 mm and FOV of 230 mm. **(2A)** Achievable b-value in given TE. **(2B)** Remaining normalized signal due to T2-decay at the shortest TE for the b-value.

additional artifacts can be observed compared to moderate gradient strengths [10, 19]. The stronger the gradient, the higher the amplitude of the long-time constant eddy currents. This will interfere with the readout gradients, which will lead to a deviation of the prescribed gradients for image readout and thus to image distortions. Achieving ultra-high gradient amplitudes furthermore comes at the cost of reducing the region over which the gradient system behaves linearly [10, 19]. In regions where the gradients exhibit nonlinearity, additional image distortions are to be expected [4, 11]. Geometrical distortions resulting from eddy currents and gradient nonlinearities are commonly corrected during post-processing; while eddy current-distortions can be ameliorated by registering the diffusion images non-rigidly, distortions from gradient nonlinearities require knowledge on the nonuniformities so that the images can be unwarped. It should be noted that eddy currents and gradient-nonlinearities distort the images in concert with B_0 inhomogeneity, and disentangling these effects is challenging.

Gradient nonlinearities additionally mean that the *b*-matrix as imposed by the diffusion gradients is spatially varying depending on the degree of nonlinearity. This means that, even when designed as such, *b*-vectors can become non-uniformly distributed over the hemisphere and *b*-values can deviate from the 'shell'. This can significantly impact diffusion measures when such deviations are not appropriately taken into account [4]. By estimating diffusion models or representations where the *b*-matrix associated with each DWI is adjusted voxel-wise, the adverse effects can be minimized at the cost of longer computation times. The situation is further exacerbated if the participant moves during the scan, as the *b*-value at a given position (after motion correction), is effectively changing over time, requiring *spatiotemporal tracking* of the *b*-matrix [17].

2. Reducing the time between diffusion encoding and *k*-space centre readout

In standard diffusion MRI, the image is read out with EPI, which traverses the *k*-space from one end to the other in parallel lines. Since the centre of *k*-space mostly determines the signal level in the final image, it is acquired at the time of the spin echo. Therefore, part of the *k*-space needs to be acquired beforehand, prolonging TE. Changing



3 Direction-encoded fractional anisotropy **(3A)** and mean diffusivity **(3B)** calculated from diffusion data acquired with TE = 21 ms and b = 1000 s/mm².

the readout trajectory to a spiral starting at the centre negates this necessity of data acquisition before the spin echo. The use of a spiral readout allows shorter TE, compared to EPI, but introduces new difficulties in the imaging process. While the typical artefacts for an EPI readout (e.g., distortions due to eddy currents or B_0 inhomogeneities, ghosting due to gradient imperfections) can be handled in image processing, the artefacts with spiral readouts are often corrected during the image reconstruction. The main sources for artefacts in spiral imaging are:

1. B_0-inhomogeneities
2. T2* decay during the readout
3. Eddy currents and other gradient imperfections leading to a mismatch between prescribed and actual gradients.
4. Gradient nonlinearities (similar to EPI)

To measure the B_0 inhomogeneities, a B_0-map can be estimated by using a multi echo gradient echo sequence. This requires a few minutes additional acquisition time but is essential to reduce blurring. If an additional image with the same timing is acquired with the body coil, they can be combined to estimate the coil sensitivities necessary for a SENSE-type reconstruction. SENSE enables the undersampling of the spiral data and thus shorter readout times leading to less T2* blurring.

The gradients during the readout were measured with a spatio-temporal field monitoring approach [5] with a commercially available field camera. Knowledge of the B_0-map and the real *k*-space trajectory were combined with the knowledge of gradient nonlinearities in a single reconstruction pipeline [16], expanding on a previously introduced approach [23].

Unprecedented echo times and opportunites they present

Bringing together the ultra strong-gradients of the Connectom and a spiral readout with a proper reconstruction pipeline enables diffusion-weighted imaging at unprecedented TE *in vivo*. For b = 1000 s/mm^2, TE = 21.7 ms (see Fig. 3). This opens up new and exciting possibilities in diffusion imaging. Obviously, by reducing the (unwanted) T2-related signal decay during the diffusion encoding, the SNR is enhanced. This can be particularly important for species where diffusion MRI is challenging, e.g., in muscle, because the T2 is short.

Beyond the enhanced SNR, such a reduction in TE opens up new opportunities for exploration of brain microstructure and physiology. For example, with this short TE it might become feasible to measure the diffusion of myelin water [20]. Another promising new avenue is to explore the new contrast mechanism of diffusion-weighted fMRI, by looking into the TE dependence [18] or acquiring gradient echo and diffusion-weighted spin echo at the same TR with only tens of milliseconds between [18]. At present, we have only explored single shot spiral-EPI readouts. Future work will explore the combined use of multi-shot, navigated interleaved acquisitions [12], and external field monitoring to provide enhanced spatial resolution, while maintaining short echo times for diffusion MRI.

Overall objective	Shorten the echo time	
	Encoding	**Readout**
Objective	Shorten diffusion-encoding time	Shorten the time between diffusion encoding and the image readout of the center of *k*-space
Method	Increase the gradient strength	Spiral readout
Challenges	• Gradient nonlinearities and eddy currents cause geometrical distortions • Gradient nonlinearities cause spatiotemporally varying *b*-matrices	Interactions of readout gradients with • gradient nonlinearities and eddy-current induced fields cause geometrical distortions • mechanical vibrations cause signal loss and geometrical distortions
Solution	Image registration to correct for geometrical distortions. Compute spatiotemporally varying *b*-matrices from gradient nonlinearity information	Use field camera measurements to derive the actual readout trajectories

Table 1: Summary of key objectives, the methods, challenges, and solutions.

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