

Feasibility of diffusion tensor and morphologic imaging of peripheral nerves at 7 tesla

Abstract

Objectives: To describe the development of morphologic and diffusion tensor imaging (DTI) sequences of peripheral nerves at 7T, using carpal tunnel syndrome (CTS) as a model system of focal nerve injury.

Materials and Methods: Morphologic images were acquired at 7T using a balanced steady-state free precession sequence. DTI was performed using single-shot echo-planar imaging (ss-EPI) and readout-segmented EPI (rs-EPI) sequences. Different acquisition and post-processing methods were compared to describe the optimal analysis pipeline. MRI parameters including cross-sectional areas, signal intensity, fractional anisotropy as well as mean, axial and radial diffusivity were compared between patients with CTS (n=8) and healthy controls (n=6) using analyses of covariance corrected for age (significance set at $p<0.05$). Pearson's correlations with Bonferroni correction were used to determine association of MRI parameters with clinical measures (significance set at $p<0.01$).

Results: The 7T acquisitions with high in-plane resolution (0.2x0.2mm) afforded detailed morphologic resolution of peripheral nerve fascicles. For DTI, ss-EPI was more efficient than rs-EPI in terms of signal-to-noise ratio per unit scan time. Distortion artefacts were pronounced, but could be corrected during post-processing. Registration of FA maps to the morphologic images was successful. The developed

imaging and analysis pipeline identified lower median nerve fractional anisotropy (pisiform bone 0.37 (SD 0.10)) and higher radial diffusivity (1.08 (0.20)) in patients with CTS compared to healthy controls (0.53 (0.06) and 0.78 (0.11) respectively, $p < 0.047$). Fractional anisotropy and radial diffusivity strongly correlated with patients' symptoms ($r = -0.866$ and 0.866 respectively, $p = 0.005$).

Conclusions: Our data demonstrate the feasibility of morphologic and diffusion peripheral nerve imaging at 7T. Fractional anisotropy and radial diffusivity were found to be correlates of symptom severity.

Keywords: diffusion tensor imaging, 7 tesla, structural imaging, peripheral nerve, carpal tunnel syndrome, peripheral neuropathy, fractional anisotropy, radial diffusivity, ultra-high field strength, magnetic resonance imaging

Introduction

Peripheral nerve imaging, also referred to as magnetic resonance neurography (1), represents a growing area in magnetic resonance imaging (2). Most methodologies have concentrated on enhancing neural signal in morphologic sequences. Over the past decade, diffusion tensor imaging (DTI) and its ability to provide information about neural microstructure has gained increasing interest in the field of peripheral nerve imaging (3). However, magnetic resonance imaging of peripheral nerves remains challenging mostly due to the thin nature of these structures. Technical advances and particularly the availability of higher field strength have significantly improved visualisation of peripheral nerves. Recently, morphologic peripheral nerve imaging has been performed at 7 tesla (7T) (4-7), which substantially enhances the signal-to-noise ratio (SNR) and therefore the achievable spatial resolution, thus improving anatomical depiction of peripheral nerves. In contrast to morphologic sequences, most human peripheral nerve DTI has been implemented at lower field strength, with the exception of one recent attempt at 7T in three healthy participants (4). Studies performed in the central nervous system suggest that imaging at 7T may improve diagnostic accuracy to detect neural pathology (8), something that bears even more importance when imaging comparably thin peripheral nerves.

The purpose of this study is therefore to describe the development, strengths and limitations of morphologic and diffusion tensor imaging (DTI) sequences of peripheral nerves at 7T, using carpal tunnel syndrome (CTS) as a model system of focal nerve injury. Correlations of MRI parameters with electrodiagnostic parameters and symptom severity will be established.

Material and Methods

This prospective study (December 2014-December 2016) was approved by the national ethics committee and all participants gave written informed consent. Magnetic resonance imaging was performed on a 7T whole-body MR system (MAGNETOM, Siemens Healthcare, Erlangen, Germany, 70mT/m) with a dedicated 16-channel transmit-receive wrist array-coil (RAPID Biomedical, Germany). Six healthy participants volunteered for wrist scanning (3 females, mean age 30.3 years (SD 7.11)). Eight patients with electrodiagnostically confirmed CTS (9) were recruited from hand surgery departments (4 females, mean age 55.3 years (SD 11.5)). Participants with evidence of neuropathies other than CTS (e.g., ulnar neuropathy, cervical radiculopathy) or with MRI contraindications were excluded. Participants were positioned prone with the scanned hand above their head ("superman" position). This position optimally places the wrist in the isocentre of the magnet, but is often associated with discomfort. We therefore limited the acquisition time to a maximum of 30 minutes, which was tolerated by all participants.

Clinical parameters

Standard electrodiagnostic tests were performed as previously described (10) including median sensory and motor amplitudes and conduction velocities. Patients' symptom severity was established with the Boston symptom scale (see Appendix Table 1 for clinical severity of patients with CTS).

Morphologic scans

3D balanced Steady-State Free Precession (SSFP) images were acquired using a multiple-acquisition phase-cycled technique, where two constituent phase-cycled

images (variation of phase of radiofrequency pulses) were combined using root sum of squares to mitigate the banding artefacts characteristic of balanced SSFP imaging (11). In-plane resolution was 0.2x0.2 mm and slice thickness was 0.4 mm (see Table 1 for scan parameters).

Nerve cross-sectional areas (CSA) and normalised signal intensity (SI) of the median and ulnar nerves were quantified at the level of the radioulnar joint, pisiform and hamate bone by manually outlining the nerves (by AS). Due to its division into small branches, the CSAs for the ulnar nerve were not determined at the hamate level. For SI, the average pixel intensity within the CSAs over 3 adjacent slices was divided by the average grey level of the pronator quadratus or hypothenar muscle (12).

Diffusion imaging

Data acquisition

We compared two methods of k-space sampling: single-shot echo-planar imaging (ss-EPI) (13) and readout-segmented EPI (rs-EPI) (14). rs-EPI has successfully been used at 3T for imaging of the mandibular nerve with a 64-channel head-neck coil (15), and has the advantage of shorter echo-spacing and echo train durations, thereby reducing susceptibility-induced distortion and T2* blurring (16). However, rs-EPI requires longer scan times than ss-EPI. To stay within tolerable scan times, the rs-EPI acquisition was limited to one repetition of 12 directions with one $b=0$ s/mm² image, whereas five repetitions of 12 directions with five $b=0$ weighted images interleaved were acquired for ss-EPI. Diffusion weighting of $b=1000$ s/mm² was used for both sequences. Comparison of acquisitions with 5x12 directions versus 1x60 directions showed that 12 directions were sufficient to obtain comparable FA values

(Appendix Figure 1). The repetition of fewer directions increases the chances of obtaining at least one complete direction set should a scan be interrupted. The phase-encode direction was right-left and was reversed by 180 degrees for a second acquisition to allow for susceptibility-induced distortion correction during post-processing. All scan parameters are summarised in Table 1.

DTI post-processing

Data were post-processed using FMRIBs software library (FSL) (17), which is a freely available library of MRI analysis tools. Previous work has shown that different software packages provide modest to substantial intra- and intertester reliability when analysing DTI data (18). From the two acquisitions with opposing phase encode blips, which are distorted in opposite directions along the phase-encoding axis, the susceptibility-induced off-resonance field was estimated using the TOPUP tool (19) as implemented in FSL (20). Subsequently, the EDDY tool was applied to correct for eddy-current-induced distortions and rigid-body movement (21). We quantified the correction of distortion artefacts as the mean correlations of reversed phase-encoded acquisitions at each slice in healthy participants before and after TOPUP. SNR and SNR efficiency ($\frac{SNR}{\sqrt{\text{acquisition time}}}$) within the median nerve were determined for both ss-EPI and rs-EPI acquisitions from the first b=0 image, using a difference method on the two distortion-corrected reversed phase encode images (22).

We then used DTIFIT (21) to create fractional anisotropy (FA) maps and FMRIBs Linear Image Registration Tool FLIRT (23) to register the diffusion images with the morphologic images (linear registration, 6 degrees of freedom, correlation ratio cost

function). Registration success was visually judged (by AS) by overlapping the morphologic images and registered FA maps and grading the alignment of the median nerve in the two images at the level of the pisiform bone (perfect, partial or no alignment). Estimates of median and ulnar nerve FA as well as median nerve mean diffusivity (MD), axial (AD) and radial diffusivity (RD) were obtained using regions of interest (ROI, average of three slices) at the three wrist levels. All quantification was performed by an investigator with 7 years experience in MRI research (AS). To determine intertester reliability, a second rater with less than one year of experience in MRI interpretation also performed the ROI analysis for all DTI measures in the middle of the carpal tunnel (pisiform bone).

Statistical analysis

Statistical analysis was performed with SPSS version 24 (IBM). The success of distortion correction was evaluated with paired t-tests on the mean correlation between the reversed phase-encode images, before and after TOPUP correction.

Intertester reliability of DTI measurements was determined for all DTI measures using intraclass correlation coefficients (ICC 3,2). As diffusion measures are age-dependent (24) and our sample was not matched for age, we used analyses of covariance corrected for age to compare all MRI parameters between healthy participants and CTS patients (significance $p < 0.05$). For DTI, ROIs with signal loss were excluded from the analysis.

Pearson's correlations with Bonferroni correction (5 comparisons: $p < 0.01$) were used to determine associations of MRI parameters in the middle of the tunnel (pisiform

bone) with clinical parameters (Boston symptom score, median sensory nerve action potential amplitude and conduction velocity, median distal motor latency and compound motor action potential amplitude) in patients with CTS.

Results

7T produces high resolution morphologic images

Figure 1 demonstrates the high in-plane resolution and banding artefact correction achievable with the morphologic 7T sequences. Median and ulnar nerves were imaged with a high level of morphologic detail, with visualisation of fascicles as well as clear boundaries of the nerves and tendons (Figure 1B).

Quantification revealed that the CSA of the median nerve was larger in patients with CTS at the hamate bone ($p=0.020$, Table 2A). There was a trend towards increased SI in patients with CTS compared to healthy participants at the pisiform bone ($p=0.066$), which reached significance at the level of the hamate bone ($p<0.0001$). SI and CSA of the ulnar nerve were comparable between groups at all levels ($p>0.201$).

DTI images at 7T are distorted but can be corrected with TOPUP

Distortion artefacts were pronounced, especially at bone-bone interfaces at the level of the carpal bones (Figure 2 A and B). This was apparent by low correlations of reversed phase-encoded acquisitions (mean $r=0.44$ (SD 0.05), Figure 2 C). TOPUP achieved substantial distortion correction (Figure 2A and B, mean $r=0.90$ (SD 0.01) after TOPUP, $p<0.0001$, Figure 2C). EDDY correction was also found to be crucial in aligning the diffusion-weighted images, which are distorted differentially as a result of changing the diffusion gradient directions (Appendix Figure 2).

The rs-EPI images provided reduced image distortion compared to ss-EPI images as demonstrated by a direct comparison in the same participant during the same session (mean correlation rs-EPI $r=0.62$ vs ss-EPI $r=0.47$, Figure 2A, B). Following TOPUP correction, the slice-wise correlation was comparable between ss-EPI and rs-EPI ($r=0.91$ vs 0.92 , Figure 2D).

Whereas SNR was comparable between ss-EPI (5.36) and rs-EPI acquisitions (4.07), SNR efficiency was a factor two lower than rs-EPI acquisitions (1.01 versus 2.24 in ss-EPI) due to longer scan time per image. This lower SNR efficiency offset the benefits of reduced artefacts in the rs-EPI data.

Registration of DTI to morphologic scans is successful at 7T

Despite the significant distortion artefacts in 7T EPI data, FLIRT was capable of achieving an accurate registration of the distortion-corrected diffusion images with the morphologic images for both the median (Figure 3A and B) and ulnar nerve (Figure 3C and D). This was apparent by perfect alignment of the median nerve in morphologic scans and FA maps in 12 participants and partial alignment in two participants.

Fractional anisotropy maps clearly delineate the peripheral nerves at 7T

On FA maps, the median nerve could be distinguished from surrounding structures as a hyper-intense line (Figure 4A and B). Measuring FA at the three wrist levels revealed comparable values across rs- and ss-EPI sequences (ss-EPI pisiform: 0.55; rs-EPI 0.59). In accordance with the lower SNR efficiency, standard deviations within ROIs were consistently higher in rs-EPI (0.032) compared to ss-EPI acquisitions (0.019). In addition to the lower FA variability, the median nerve was more clearly

separated from its surrounding structures in the ss-EPI acquisitions (Figure 4A and B).

Whereas most distortions could be effectively corrected, severe distortions caused focal signal loss, which could not be corrected in some participants (n=1/6 healthy, n=3/8 patients, Figure 5). However, this signal loss remained localised to the radioulnar joint.

7T imaging detects altered diffusion parameters in patients with CTS

Intertester reliability was good to excellent for all DTI parameters (ICC 3,2 (95% confidence intervals): FA 0.955 (0.860-0.986), MD 0.867 (0.586-0.957), raD 0.885 (0.641-0.963), axD 0.919 (0.721-0.971) $p < 0.0001$).

There was a significant decrease in FA of the median nerve at all wrist levels in patients with CTS compared to healthy controls ($p < 0.047$; Figure 6A). The ulnar nerve, which is unaffected in CTS, demonstrated comparable FA ($p > 0.248$, Figure 6B). Whereas MD and AD were comparable between groups ($p > 0.188$), RD was significantly higher at the pisiform and hamate bone in patients with CTS ($p < 0.031$, Table 2B).

Diffusion values correlate with patients' symptoms

FA and RD ($r = -0.866$ and 0.866 respectively, $p = 0.005$), but not AD ($p = 0.413$) strongly correlated with symptom severity (Figure 6C). None of the diffusion ($p > 0.177$) or morphologic parameters ($p > 0.020$) correlated with electrodiagnostic test parameters after Bonferroni correction. Electrodiagnostic test parameters did not correlate with symptom severity ($p > 0.365$).

Discussion

Our data demonstrate the feasibility and challenges of morphologic and diffusion peripheral nerve imaging at 7T. In our data, diffusion but not morphologic parameters correlate with symptom severity in patients with CTS.

Anatomical imaging of peripheral nerves has been previously attempted at 7T (4-6, 25). Our SSFP sequence with T2/T1 contrast allowed us to achieve an approximately four times smaller voxel volume (0.2x0.2mm, 0.4mm slice thickness) than previously reported for pure T2-weighted sequences at 7T (e.g., 0.39x0.36mm, 0.4mm slice thickness) (4). At this high resolution, it was possible to visualise single fascicles within the median nerve and small branches of peripheral nerves (e.g., superficial radial nerve) as well as other structures within the carpal tunnel such as the flexor tendons and their sheaths. Such highly-resolved images might be of diagnostic value for neuropathies affecting inaccessible small diameter nerve trunks (e.g., radiculopathy, thoracic outlet syndrome). Whereas SSFP sequences reveal fine anatomical details of different structures within relatively short scan times, they are not specifically optimised for neural tissues such as classical MR neurography sequences (e.g., spin echo acquisitions with fat saturation). Future work at 7T could explore the feasibility of increasing SSFP T2 contrast with T2 preparation pulses (26) and the addition of fat suppression (27) to optimise neural contrast.

The identified increased CSA and SI at the level of the hamate bone in patients with CTS are in agreement with data collected at lower field strength (28). The non-significant trend at more proximal wrist levels is most likely attributed to the small sample of this technical development.

Whereas DTI of peripheral nerves has been performed at lower field strength (e.g., 29, 30-32) and has been suggested to outperform the diagnostic accuracy of morphologic imaging alone (32), this is the first 7T DTI study in a patient population. As expected, the 7T acquisitions come with several challenges. First, distortion artefacts worsen with increasing field strength. We were able to successfully correct the majority of distortion artefacts caused by B0 inhomogeneity and eddy-currents. Distortion artefacts caused by tissue specific parameters (e.g., susceptibility differences, chemical shift) may have led to exacerbated distortions at the level of the carpal tunnel, where the anatomy is highly complex. Unfortunately, these led to un-correctable signal loss in the FA maps in a minority of participants. Signal loss was not encountered more proximal or distal of the tunnel, suggesting that EPI-based peripheral nerve imaging at 7T is more reliable in less anatomically complex regions.

Another challenge of DTI is the quality of the EPI images (low spatial resolution and artefacts), which can make it difficult to confidently outline specific structures on diffusion maps. The successful registration of morphologic and diffusion images achieved here will ensure correct structure identification. Due to some remaining blurring in the phase encode direction, the peripheral nerves are slightly wider on the axial diffusion images compared to the morphologic images. In the sagittal plane however, where distortion artefacts are much less pronounced, the peripheral nerves in the morphologic images and FA maps almost perfectly aligned. To minimise partial volume effects, we recommend outlining an ROI within the peripheral nerves in FA maps, then confirming a correct alignment in the morphologic images.

Long scan durations are a further challenge in DTI, which can be exacerbated at 7T due to the higher specific absorption rate (SAR). The use of a local radiofrequency transmit coil permitting higher SAR limits enabled us to develop protocols with an acceptable scan duration for clinical use. The advantages of the ss-EPI sequences (higher SNR efficiency leading to better delineation of the nerves in FA maps in a shorter scan time) outweighed the reduced distortions in rs-EPI images.

Recent developments such as simultaneous multi-slice (SMS) imaging (15, 16, 33) and a reduced number of readout segments with partial Fourier reconstruction (34) have previously been used to accelerate rs-EPI of peripheral nerves and the brain at 3T and have recently been optimized for the brain at 7T with low-SAR PINS RF pulses (35). These methods could be used in future studies to increase the SNR efficiency of rs-EPI and shorten the scan times.

We found a reduction in FA of the median but not ulnar nerve in patients with CTS. In addition, median RD increased but AD did not change. The pattern identified here is similar to recent DTI studies at lower field strength in patients with CTS (24, 36, 37) or other peripheral neuropathies (31, 38, 39). Reduced FA and increased RD are also the predominant findings in experimental nerve injury models, where they correlate with histological markers of axon and myelin degeneration (40-42), or the presence of inflammation-induced oedema (43). In humans, correlation of diffusion parameters with electrodiagnostic parameters thought to reflect axonal damage or demyelination reveal conflicting outcomes (24, 44, 45). This may be attributed to the limited ability of electrodiagnostic tests to differentiate axonal from myelin damage (46, 47) as well as their inability to determine changes in small fibres (C and A δ), which are affected early in CTS (10). Importantly, intraneural oedema, which is likely

present in entrapment neuropathies such as CTS (48) and can influence DTI parameters (43), cannot be depicted with electrodiagnostic tests. Here, MRI parameters did not correlate with electrodiagnostic measures. However, FA and RD strongly correlated with symptom severity. Peripheral nerve FA has previously been found to correlate with symptoms in patients with CTS (49) and lumbar radiculopathy (50). Those results and our findings suggest that FA and RD are imaging correlates for symptom severity in patients with entrapment neuropathies. This is of specific relevance in CTS, where the diagnostic 'gold standard' (electrodiagnostic testing) shows no or at best only a modest correlation with patients' symptoms (51).

Although our main outcome measures were significant due to the large effect sizes, the findings in this preliminary report are based on a relatively small proof-of concept sample. Future work will have to determine optimal diagnostic cut-off values of DTI parameters as previously reported at lower field strength (24). Importantly, the here reported diffusion and morphologic parameters at 7T in healthy participants and patients with CTS will provide important baseline measurements for future studies in larger patient populations of different aetiologies.

In conclusion, our data demonstrate the feasibility of morphologic and diffusion peripheral nerve imaging at 7T field strength. DTI at 7T suffers from EPI artefacts, which our results suggest are largely correctable in post-processing. The strong correlation with the Boston symptom scale suggests a role for FA and RD as imaging correlates for symptom severity.

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Table 1: Scan parameters

	SSFP	ss-EPI	rs-EPI
Repetition time (TR)	7.43 ms	3300ms	4000ms
Echo time (TE)	3.11 ms	60ms	57ms
Flip angle (FA)	20 degrees	90 degrees	90 degrees
Field of view (FoV)	100 mm	192mm	192mm
Dimensionality	3D	2D	2D
Slice thickness	0.4mm	1.5mm	1.5mm
Number of slices	288	32	32
In plane resolution	0.2x0.2mm	1.5 x1.5mm	1.5 x1.5mm
Number of readout segments	NA	NA	7
Echo spacing	NA	0.83ms	0.32ms
δ Diffusion time	NA	14.7ms	14.7ms
Δ Diffusion time	NA	15.7ms	15.7ms
Fat suppression	Water excitation fast	Fat saturation	Fat saturation
Parallel acquisition technique (PAT)	2	2	2
Bandwidth	349 Hz/Px	1346Hz/Px	849 Hz/Px
Number of gradient directions	NA	12	12
Number of signal averages	NA	1	5
Scan time single phase-encode blip (right-left or left-right)	NA	4:01	6:66
Total scan time (min)	8:42	8:02	13:32

PAT was applied with the mentioned acceleration factor using a generalized auto-calibrating partially parallel acquisition (GRAPPA).

Table 2: (A) Signal intensity and cross-sectional area of median and ulnar nerves in patients with CTS and healthy controls.

(B) Mean, axial and radial diffusivity values of the median nerve.

Data are shown as mean (SD), p-values represent the age corrected group analyses.

	Healthy	CTS	p-value
(A) Morphologic parameters			
Signal intensity			
Median nerve			
Radioulnar joint	0.91 (0.18)	0.94 (0.12)	0.342
Pisiform bone	0.87 (0.17)	1.04 (0.22)	0.066
Hamate bone	0.87 (0.47)	1.36 (0.28)	<0.0001
Ulnar nerve			
Radioulnar joint	0.86 (0.11)	1.02 (0.04)	0.201
Pisiform bone	1.04 (0.24)	1.25 (0.14)	0.249
Hamate bone	1.19 (0.29)	1.15 (0.16)	0.205
Cross sectional area			
Median nerve			
Radioulnar joint	9.40 (1.70)	11.38 (3.80)	0.901
Pisiform bone	8.23 (0.95)	16.02 (5.51)	0.534
Hamate bone	8.58 (0.70)	14.04 (4.09)	0.020
Ulnar nerve			
Radioulnar joint	5.63 (0.50)	5.66 (1.87)	0.608
Pisiform bone	6.27 (1.40)	6.52 (1.55)	0.475
(B) Diffusion parameters median nerve			
Mean diffusivity			
Radioulnar joint	0.95 (0.10)	0.98 (0.38)	0.929
Pisiform bone	1.18 (0.07)	1.39 (0.16)	0.194
Hamate bone	1.24 (0.03)	1.47 (0.19)	0.278
Axial diffusivity			
Radioulnar joint	1.64 (0.20)	1.48 (0.53)	0.741
Pisiform bone	2.00 (0.09)	1.99 (0.12)	0.893
Hamate bone	2.05 (0.10)	2.04 (0.24)	0.188
Radial diffusivity			
Radioulnar joint	0.60 (0.06)	0.73 (0.32)	0.889
Pisiform bone	0.78 (0.11)	1.08 (0.20)	0.031
Hamate bone	0.84 (0.07)	1.19 (0.19)	0.029

Appendix Table 1: Clinical characteristics of patients with CTS

Mean Boston symptom questionnaire (SD)	2.92 (0.63)
Electrodiagnostic test severity (n)	
very mild	2
mild	0
moderate	3
severe	1
very severe	2
extremely severe	0

Electrodiagnostic test severity graded according to Bland

Figure captions:

Figure 1

T2-weighted 3D balanced Steady-State Free Precession (SSFP) images of the wrist acquired at 7T. (A) Reduction of banding artefacts in the SSFP images. The panels show transaxial SSFP images through the wrist acquired with and without phase cycling with clearly visible banding artefacts. The combined sum of square image largely eliminates banding artefacts, despite the severity in the two original images. (B) Combined SSFP images. Panels show the median nerve (arrow) at the level of the radioulnar joint (left), pisiform bone (middle) and hook of hamate (right). The high spatial resolution of the 7T images allows high visibility of morphologic details such as the differentiation of fascicles within the median nerve (zoomed insets). The 7T morphologic sequences also allow visualisation of the ulnar nerve (filled arrowhead) and the superficial radial nerve (empty arrowhead) at the wrist. The peripheral nerves are isointense with muscle (asterisk).

Figure 2A and B

Diffusion imaging at 7T induces significant distortion, which can be corrected by combining acquisitions with reversed EPI phase-encoding blips. (A) shows frontal plane slices of morphologic, unweighted right-left phase encode blip, unweighted left-right phase encode blip and the combination of unweighted opposing blips (TOPUP) for the ss-EPI acquisition. The red lines show the edges of the morphologic scan overlaid onto the diffusion images. There is extensive distortion, which can be substantially mitigated with TOPUP correction. (B) shows the rs-EPI acquisition,

which reduces distortions and achieves a more anatomically faithful image after TOPUP correction, in comparison with ss-EPI images.

Figure 2C and D

Slice-wise correlation between reversed phase-encode blips $b=0$ acquisitions (RL right-left; LR left-right). (C) Before TOPUP (red), correlations between reversed phase encode acquisitions are low, indicating substantial distortions at 7T. TOPUP (blue) successfully corrects the distortions and increases the correlations. (D) Correlations between uncorrected blip reversed acquisitions (red) within the same scan session were higher for rs-EPI compared to ss-EPI sequences, but could largely be corrected with TOPUP (blue).

Figure 3A and B

Registration of the unweighted ($b=0$) images and fractional anisotropy (FA) maps to the morphologic images was successful at 7T in the transaxial plane (A), which is commonly used for diagnostic purposes, as well as sagittal planes (B). The median nerve is delineated in red on the morphologic images at the level of the pisiform bone (asterisk). Registration reveals good alignment with the hyperintense median nerve structure on the unweighted $b=0$ images. The median nerve is also clearly indicated by a region of elevated signal in the FA maps, with accurate registration to the morphologic image. Insets show magnifications of the outlined nerve. Due to the left-right phase encode direction, distortion artefacts are more apparent in the transaxial images (A) compared to the sagittal images (B). However, registration remains accurate.

Figure 3C and D

Fractional anisotropy (FA) maps of the ulnar nerve at the wrist are successfully depicted. (C) transaxial and (D) sagittal sections of the wrist demonstrating successful registration of the ulnar nerve (red outline) on the T2-weighted image (left) with the FA map (right).

Figure 4A and B

The median nerve is clearly delineated in fractional anisotropy (FA) maps at 7T. (A) shows sagittal slices of morphologic, unweighted $b=0$ and FA maps at 7T acquired with rs-EPI sequences and (B) ss-EPI sequences. The extraneural variability in the FA values is higher with the rs-EPI compared to ss-EPI sequences. The arrows depict the level of the radioulnar joint, pisiform bone and hook of hamate, where FA within regions of interests of the median nerve were compared.

Figure 5

Whereas the distortions at 7T could be effectively corrected in most participants, the bone-bone interfaces at the level of the carpal bones induced significant distortions in some participants. These severe distortions could not be corrected by TOPUP, leading to focal signal loss in TOPUP-processed ss-EPI images and subsequent FA map reconstruction (arrows, sagittal slices).

Figure 6A and B

(A) Median nerve fractional anisotropy (FA) at 7T is lower in patients with CTS (open red symbols) than healthy participants (blue filled symbols). FA of the median nerve

is shown at the level of the radioulnar joint ($p=0.016$), the pisiform ($p=0.047$) and the hamate bone ($p=0.001$). (B) FA of the ulnar nerve is comparable at the different wrist levels between patients with CTS (red) and healthy controls (blue, all $p>0.248$).

Figure 6C

Fractional anisotropy (FA) negatively correlates with symptom severity as measured with the Boston symptom questionnaire ($p=0.005$). Radial diffusivity positively correlates with symptom severity in patients with CTS ($p=0.005$). No correlations of axial diffusivity with patients' symptoms was apparent ($p=0.413$).

Appendix Figure 1:

The number of diffusion directions does not affect fractional anisotropy (FA) maps. In a single healthy subject, the effect of using different numbers of directions was evaluated by comparing the image quality of ss-EPI images acquired with 5 averages of 12 directions or 1 average of 60 directions. (A) The median nerve is clearly delineated in the sagittal FA maps of both 5x12 directions and 1x60 directions acquired with ss-EPI sequences. (B) FA values and their standard deviations within a ROI are comparable among the acquisitions with different numbers of directions.

Appendix Figure 2:

Performance of different eddy-current correction tools. We used two methods to correct for eddy current induced distortions and rigid body movement: EDDY and EDDY_CORRECT, which are available in FMRIB's Diffusion Toolbox (21).

EDDY_CORRECT

EDDY_CORRECT applies a linear registration (12 degrees of freedom) of all volumes to a reference volume (e.g. the initial $b=0$ volume), but often performs poorly when trying to correct high resolution data that were acquired with strong and fast switching gradients (52). The images were first distortion corrected using TOPUP and EDDY_CORRECT was subsequently applied.

EDDY

EDDY is a new tool that simultaneously models the effects of diffusion eddy currents and movements on the image (52) and has been shown to be superior to EDDY_CORRECT for correction of eddy current distortions (53). Susceptibility-induced distortions were also corrected during the EDDY processing by supplying the previously calculated TOPUP parameters.

In order to check the performance of these two tools, single slice cross sections (1-D profiles) were taken from all TOPUP-processed diffusion weighted images along the phase encode direction. These 1-D profiles of the 60 different diffusion directions were juxtaposed for the EDDY and EDDY_CORRECT processed images.

Post processing with these two tools demonstrated superiority of EDDY compared to EDDY_CORRECT in reducing eddy current induced distortions. The image on the left (Appendix Figure 2) shows the mean of all diffusion weighted images with the eddy current distortions along the phase-encode direction (left right, frontal slice). The images on the right represent cross sectional images taken at the red dotted line of the left image with all diffusion directions stacked from top to bottom (white arrow). Correction with EDDY better reduces the left-right distortion artefacts as apparent by a narrower band of diffusion signal through all diffusion directions (blue arrows showing same distance in EDDY_CORRECT and EDDY with better alignment of different diffusion directions in EDDY).