Diffusion Tensor Imaging and Fiber Tractography in the Human Brain

A dissertation submitted to the
Swiss Federal Institute of Technology Zurich
for the degree of Doctor of Natural Sciences

presented by Thomas Järmann, Dipl. Phys. ETH, Dipl. Ing. HTL
born December 7th, 1967
citizen of Röthenbach i.E. BE, Switzerland

Zürich 2005 accepted on the recommendation of
Prof. Dr. Peter Bösiger, examiner
Prof. Dr. Anton Valavanis, co-examiner
## Contents

Summary 4  
Zusammenfassung 6  
Introduction 8  
  1. SENSE-DTI at 3 Tesla 12  
  2. The Influence of SENSE on Image Properties in DTI 26  
  3. Depicting Axonal Terminations in Cortical Gray Matter 44  
  4. Advanced Fast Marching Tractography 58  
  5. Fiber Tracking in Multiple Sclerosis 74  
Conclusion and Outlook 84  
References 86  
Acknowledgements 94  
Curriculum Vitae 96
Summary

The dysfunction of the human brain’s network is responsible for a variety of diseases. Its complexity on the cognitive as well as on the structural level makes neuroscience a challenging venture.

Since the introduction of Diffusion Tensor Imaging (DTI) a decade ago, progress has been made in the non-invasive depiction of the neuronal organization. DTI allows to probe the tissue microstructure by characterizing the local mobility of water molecules in all three spatial dimensions. As an auspicious application, the so-called fiber tractography technique connects tiny, virtual brain segments in direction of the main diffusion, representing axonal pathways in three dimensions.

The key problems of DTI consist in the low signal-to-noise ratio (SNR) and the poor image quality: As it is sensitive to motion, the underlying diffusion-weighted images are preferably acquired from a single radio frequency excitation. Single-shot experiments suffer from an increased susceptibility to magnetic field inhomogeneities, leading to image distortions, and a restricted spatial resolution due to spin relaxation processes. The limited image quality affects also the performance of reconstructing fiber trajectories. Misleading pathways may result.

The present dissertation is dedicated to the development of new concepts for improving DTI and fiber tracking. With the advent of the parallel imaging technique SENSitivity Encoding (SENSE) and the initiation of high-field magnets, major advances in Magnetic Resonance Imaging have been achieved. A focus of the presented work is the implementation and investigation of SENSE-DTI at a high magnetic field strength. It is shown that the application of SENSE at 3 Tesla exploits the increased SNR of the main magnetic field while diminishing artifacts based on susceptibility variations. As a result of the reduced number of spatial encoding steps, the point spread function narrows, thus yielding data with an enhanced intrinsic spatial resolution. High-quality DTI with an in-plane resolution in the sub-millimeter range has been achieved in volunteers and patients. Furthermore, the increase of SNR resulting from the use of SENSE has been studied in detail.

The non-destructive investigation of the occipital gray matter structure is essential to bridge the gap between anatomy and function. It requires very high SNR since the cortical anisotropy is relatively poor. Therefore, a sensitive miniature phased array detector, consisting of up to five surface coils, has been developed. The dedicated setup together with an optimal parallel acquisition strategy has enabled to resolve the matrix-like structure of the gray matter. In addition, axonal trajectories have been reconstructed which penetrate the cortical ribbon, where their radial arrangement represents the vertical organization of the occipital cortex.
Fiber tractography using high-quality SENSE-DTI data provides a promising method for exploring the neuronal connectivity of the brain. It is crucial, however, to be aware of the intrinsic limitations of the technique. Standard procedures fail in brain regions where nerve bundles branch or intersect. To overcome this obstacle, an algorithm has been developed based on the Fast Marching method. Simulations as well as in-vivo results confirm the progress in reconstructing complex brain areas.

In a patient study, the sensitivity of SENSE-DTI to the disease-related characteristics in Multiple Sclerosis (MS) has been examined. Preliminary results demonstrate the ability of fiber tractography to assess changes between affected white matter tracts and the contralateral normal appearing white matter. This may have prognostic and functional implications for differentiation of the form of MS amongst clinical subgroups with consequences on planning early treatment.

In conclusion, the presented methods contribute to a better access and depiction of the brain’s neuronal architecture. This is of importance for an improved understanding of its functionality, both in physiological and pathological conditions.
Zusammenfassung

Die Funktionsstörung des neuronalen Netzwerkes im menschlichen Gehirn ist verantwortlich für eine Vielzahl von Krankheiten. Seine Komplexität auf der kognitiven, sowie auf der strukturellen Ebene stellt die Neurowissenschaften immer wieder vor große Herausforderungen.


In einer Patientenstudie wurde die Empfindlichkeit von SENSE-DTI bezüglich krankheitsspezifischen Charakteristika in Multiple Sklerose (MS) evaluiert. Erste Resultate zeigen, dass die Faserabbildungstechnik in der Lage ist, Unterschiede zwischen gesunden und betroffenen Nervenfasersystemen auszumachen. Dies könnte in Zukunft eine spezifischere Diagnose von MS in Untergruppen ermöglichen, mit der Aussicht auf eine frühzeitige, verbesserte Behandlungsplanung.

Die hier vorgestellten Methoden tragen zu einer besseren Beschreibung der neuronalen Architektur des Gehirns bei. Sie sind äusserst wertvoll für ein umfassenderes Verständnis seiner Funktionalität, sowohl im gesunden als auch im pathologischen Zustand.
Introduction

Disorders of the brain are a major cause of human long-term morbidity and mortality in industrialized countries. Improvements in the prevention and therapy of such diseases rely on early and reliable diagnosis, accurate assessment of disease severity, as well as a deeper understanding of the normo- and pathophysiology.

For many diseases, Magnetic Resonance Imaging (MRI) has proven to be a powerful technique for medical diagnoses. In today’s radiological practice, MRI has become the premier modality for visualizing anatomy and anatomical changes caused by diseases. In Switzerland, 133 MRI devices were in use at January 2003, thereof 23 in the canton Zurich (1). According to the annual report of the Institute of Neuroradiology at the University Hospital in Zurich, 5288 neuroradiological MRI examinations have been performed in 2003 (2).

However, the standard MRI procedure, based on proton density-, T1- and T2-weighting, suffers from the inability to display the inherent structure of the brain white matter. While gray matter is the tissue where information is processed, white matter serves importantly as a channel of communication, between gray matter regions and between the brain and the body. When that communication breaks down, the consequences for cognition and physiology can be severe, contributing to disorders such as Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), or Alzheimer’s disease.

The introduction of Diffusion Tensor Imaging (DTI) in the mid-nineties by Basser et al. (3) has offered a modality to go beyond anatomical imaging and to probe the tissue microstructure at a sub-voxel level. This is achieved by characterizing the local mobility of water molecules in all three spatial dimensions. The diffusion process reflects the microscopic structure of the surrounding tissue and may vary with respect to different directions in space. DTI opened a door, allowing to assess the integrity of the brain white matter in vivo non-invasively.

An important application of DTI is fiber tractography, proposed in humans by Lori et al. (4) and Poupon et al. (5), for elucidating white matter tracts. Sophisticated algorithms connect voxels along the direction of the determined fastest water diffusion, potentially representing axonal fiber pathways. Such connectivity may reveal important information about neuro-cognitive networks.

Despite its vast potential, two obstacles hamper DTI: poor image quality and low sensitivity. Different attempts have been reported, in order to progress DTI’s applicability. Multi-excitation echo-planar methods (6,7), stimulated echo sequences (8) and the line-scan tech-
Introduction

nique (9) are only a few out of a respectable list. DTI based on the single-shot echo-planar technique is the most promising derivative due to its motion insensitivity and the relatively high signal-to-noise ratio (SNR). Using this sequence, however, spatial resolution is limited and the increased susceptibility to magnetic field inhomogeneities leads to image artifacts, especially near bone / tissue interfaces and air cavities.

Among many innovations in the MR field, two recent developments stand out. The first is the advent of compact and actively shielded high-field MRI magnets. These high-field MRI systems allow for an improved signal-to-noise ratio, thus partially overcoming the sensitivity problem. The second is the development of parallel imaging techniques, such as SENSitivity Encoding (SENSE) (10), which potentially allows for reduction of artifacts, shorter acquisition time and better spatial and temporal resolutions. DTI substantially benefits from both achievements.

Also the fiber tractography technique is still impeded by several shortcomings. The adequate depiction of axons which are intersected by another neuronal system remains to be solved. The voxel-averaged quantity of DTI precludes the detection of more than one dominant fiber orientation, as it is the case in the so-called Corona Radiata, for instance. A further challenge is the spatial reconstruction of branching fiber bundles. In this case, the strategy of propagating a single trajectory in direction of the main diffusion orientation fails. Recently, Fast Marching (FM) was proposed in neuroscience by Parker and coworkers (11). The concept of the FM method can be visualized as the motion of a wave front emanating from a source. A simple example is the evolution of a wave when a pebble is thrown in a pond of still water. Adapting this idea to the brain, a virtual front is spreading from a user-defined seed point towards the cortex in direction of the underlying pathways. In contrast to sequential line propagation, FM is capable to diverge in different sub-directions simultaneously.

Objectives

The aim of the present dissertation is to improve DTI acquisition as well as to advance the reconstruction and the depiction of cerebral nerve fibers. An auxiliary target is to provide a methodological framework to assess image properties in sensitivity encoded DTI, such as the signal-to-noise ratio (SNR) and the intrinsic resolution, which is strongly coupled to the point spread function.
Outline

In Chapter 1 and 2, the parallel imaging approach is applied to DTI at a field strength of 3 Tesla. It is shown, that SENSE balances the increased susceptibility artifacts due to a high field strength and enables high quality imaging. The somewhat surprising finding that the use of SENSE (which often causes an SNR reduction) results in a gain of SNR, is explained in detail. Furthermore, the influence of SENSE on high-resolution image properties is explored. The potential profit in image quality using sensitivity encoded data is inspected. The SNR as well as the width of the point spread function as a function of SENSE acceleration is presented. The clinical usefulness of the method is demonstrated in a study with healthy volunteers and patients.

Chapter 3 utilizes the benefits of sensitivity encoded DTI and introduces a miniature detector for further boosting SNR. The dedicated phased array head coil provides the high sensitivity at the skullcap, which is required for high-resolution imaging of the brain visual cortex. To resolve the gray matter structure in the occipital lobe non-invasively is a crucial step to link the brain architecture with its function. High quality DTI images are proposed with an in-plane resolution of 0.58 x 0.58 mm². The observation of a gray matter matrix, perpendicular to the white/gray matter boarder, is discussed.

Chapter 4 is dedicated to data processing and visualization. The Fast Marching method is expanded with the capability to accomplish brain regions containing fiber intersections. In contrast to standard line propagation, the described technique utilizes the entire tensor information. The improvements are quantitative evaluated using artificial and in-vivo data.

Chapter 5 presents a patient study, in which the improved image quality of SENSE-DTI at 3 Tesla and the sophisticated data analysis incorporating fiber tractography are used to reveal changes between affected white matter tracts and normal appearing white matter in Multiple Sclerosis.
1. SENSE-DTI at 3 Tesla

Published as:
“SENSE-DTI at 3 Tesla”
Abstract

While holding vast potential, Diffusion Tensor Imaging with single-excitation protocols still faces serious challenges. Limited spatial resolution, susceptibility to magnetic field inhomogeneity and low signal-to-noise ratio (SNR) may be considered the most prominent limitations. It is demonstrated that all of these shortcomings can be effectively mitigated by the transition to parallel imaging technology and high magnetic field strength. Using the sensitivity encoding (SENSE) technique at 3 Tesla, brain DTI was performed in nine healthy volunteers. Despite enhanced field inhomogeneity, parallel acquisition permitted both controlling geometric distortions and enhancing spatial resolution up to 0.8 mm in plane. Heightened SNR requirements were met in part by high base sensitivity at 3 Tesla. A further significant increase in SNR efficiency was accomplished by SENSE acquisition, exploiting enhanced encoding speed for echo time reduction. Based on the resulting image data, high-resolution tensor mapping is demonstrated.

Introduction

Diffusion Tensor Imaging (DTI) (3,12) is a promising non-invasive method for studying white matter structure of the human brain in vivo. Based on the concept of anisotropic water diffusion across tissue, the measurement of three-dimensional (3D) diffusion properties, as described by a local diffusion tensor, allows the characterization of the axonal architecture of white matter networks. For that purpose, a 3D tracking of axonal projections, known as fiber tracking (13-17), is required. However, the low SNR and the limited spatial resolution (18-20) of the method severely impair its application. A serious resolution limit stems from the strong link between voxel size and SNR, the latter being inherently low due to diffusion weighting. Only improving the SNR of the initial diffusion-weighted (DW) images will enable better spatial resolution. Therefore, the use of high magnetic fields and the related SNR gain could considerably enhance the performance of DTI and fiber tracking.

The calculation of the local diffusion tensor requires a set of DW images, acquired with diffusion gradients applied in at least six non-collinear directions, plus a reference image without diffusion weighting. The sequence most commonly used for DTI is spin-echo single-shot EPI (SE-sshEPI). It allows for whole brain coverage in an acceptable scan time and is insensitive to bulk motion due to its speed. Critical shortcomings of sshEPI are image blurring due to T2* decay during the EPI readout interval and off-resonance effects, caused by the long EPI echo train (21,22). Both effects scale with the main magnetic field B0, making the transition to higher field strength challenging. At 3 Tesla, signal alteration and geometric distortion due to static resonance offset effects, e.g. in the vicinity of air-tissue interfaces, are a serious problem when using sshEPI-based protocols.
Recently, the potential of parallel imaging techniques, such as simultaneous acquisition of spatial harmonics (SMASH) (23) and sensitivity encoding (SENSE) (10), has been demonstrated for sshEPI in general (24), as well as for diffusion-weighted MRI (DWI) (25-27) and DTI (28) at 1.5 Tesla. Parallel imaging techniques were shown to significantly reduce EPI-related artifacts as a result of shortening the echo train by factors in the range of 2 to 4.

In this study we explore SENSE-DTI at 3 Tesla, in order to make the enhanced baseline SNR at high $B_0$ available for high quality DTI in the human brain. SENSE-DTI using SE-sshEPI at 3 Tesla is discussed with respect to intrinsic resolution limits and to susceptibility-related artifacts. It is shown that increasing the average phase encoding gradient strength with the SENSE approach mitigates these problems by a factor equal to the SENSE reduction factor. In order to estimate the resulting SNR, a formal expression for SNR as a function of the reduction factor has been derived and evaluated on the basis of experimental data. Our evaluation shows that sensitivity encoding allows the SNR yield of SE-sshEPI to be enhanced, balancing inherent SNR losses by mitigating T2 decay. Improved SNR efficiency along with reduced susceptibility to blurring and distortion are demonstrated by examples of high-resolution DTI in vivo.

**Theory**

**Enhanced Average Phase Encoding Rate**

By increasing the spacing of phase encoding steps in $k$-space, parallel imaging enhances the average rate of phase encoding during data acquisition. This reduces the deleterious effects of transverse spin relaxation (T2, incoherent dephasing) and evolution through field gradients (T2*, coherent dephasing) caused by field inhomogeneity. As a result, the sequence is made more robust against blurring and susceptibility artifacts, respectively, in the resulting image. Quantitatively the benefit can be expressed by the temporal average of the strength of the phase encoding gradient, $\overline{G_{PE}}$, which scales linearly with the SENSE reduction factor $R$. Using this quantity, the benefits of parallel acquisition with respect to spatial resolution and susceptibility artifact are readily described.

Spatial resolution in the phase encoding (PE) direction is inherently limited by transverse relaxation, which acts as a $k$-space filter. The shape and width of this filter are determined by T2, T2*, and $\overline{G_{PE}}$, the latter being a scaling factor of the filter width. In the image domain the $k$-space filtering results in loss of spatial resolution through blurring. The blurring kernel is the Fourier transform of the $k$-space filter, so its width scales inversely with $\overline{G_{PE}}$. Hence, SENSE enhances the intrinsically achievable resolution in sshEPI by a factor equal to the reduction factor. However, significant resolution improvement is only achieved when the nominal resolution approaches or exceeds the intrinsic limit, i.e. when the total readout time exceeds T2 and T2*. 
With respect to susceptibility artifacts, $G_{PE}$ characterizes the strength of phase encoding relative to the offset frequency due to local field inhomogeneity. In the reconstructed image, frequency offset results in a shift along the phase encoding direction, which leads to typical distortion, hyperintensity and blurring effects. The shift distance in the image domain scales with the ratio of the frequency offset and $G_{PE}$. Hence, parallel imaging reduces the shifts, again by a factor equal to the reduction factor, thus mitigating image degradation very effectively.

**SNR Efficiency**

According to Ref. (10), the SNR in sensitivity-encoded image data with respect to standard full Fourier encoding is given by

\[
\text{SNR}_{\text{SENSE}} = \frac{\text{SNR}_{\text{full}}}{g\sqrt{R}}. \quad [1]
\]

The square root of the reduction factor $R$ accounts for SNR decrease due to reduced data sampling, whereas the local geometry factor $g$ describes geometry-related noise enhancement inherent to sensitivity encoding (10,29). The factor $g$ depends on the individual experimental setup, characterized by the coil configuration, the slice orientation, the field-of-view (FOV) and on $R$, and is always equal to or larger than one. Note that for the comparison underlying Eq. [1], it is assumed that full and reduced Fourier encoding are equivalent in terms of relaxation effects. However, due to sequence timing constraints, a single-shot readout with full $k$-space density requires a longer echo time than the corresponding SENSE readout. It thus incurs enhanced T2 decay, for which Eq. [1] needs to be corrected as described in the following.

![Figure 1: Schematic timing of a diffusion weighted spin-echo EPI pulse sequence: RF90 and RF180 indicate the positions of the 90° excitation and the 180° echo pulse. $t_{\text{ref}}$ denotes the time interval of the EPI readout. The duration of the diffusion encoding gradients is $\delta$ and their sepa-](image)
ration is \( \Delta \). The optimal sequence timing (minimal echo time \( TE \)) is governed through the interval between RF180 and the maximal EPI echo, which is approximately the sum of \( \delta \) and \( \frac{t_{acq}}{2} \).

For maximum SNR in DW-SE-sshEPI the echo time should be minimized within the constraints set by the required \( b \)-factor. Figure 1 shows a schematic of the relevant timing parameters. Assuming rectangular gradients and negligible read-out dephasing time and RF pulse duration, the minimal echo time \( TE \) is given by the sum of half the EPI acquisition time (denoted as \( \frac{t_{acq}}{2} \)) and the duration \( \delta \) of each diffusion encoding gradient pulse (30,31):

\[
\frac{TE}{2} = \frac{t_{acq}}{2} + \delta .
\]  

The following equations are derived for sequences with full Fourier encoding. Alternatively, in the case of partial Fourier encoding the term \( \frac{t_{acq}}{2} \) in Eq. [2] is multiplied by a factor smaller than one and all equations are modified accordingly.

SENSE shortens the echo train. The difference in \( TE \) is given by:

\[
\Delta TE = TE_{SENSE} - TE_{full} = t_{acq} \left( \frac{1}{R} - 1 \right) + 2(\delta_{SENSE} - \delta_{full}) .
\]  

The term \( \delta_{SENSE} - \delta_{full} \) is small but not equal to zero, because the duration of the diffusion-encoding gradient pulse pairs has to be increased to compensate for the reduced separation in time, \( \Delta \), to accomplish a given \( b \)-factor according to the Stejskal-Tanner equation (32)

\[
b = \gamma^2 G^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right) .
\]  

The minimal echo time for a given \( b \)-factor is subject to numerous hardware constraints. Therefore, it is typically calculated by iterative optimization. In order to obtain a closed form expression for the reduction in \( TE \) as a function of \( R \), the correction term \( \delta_{SENSE} - \delta_{full} \) was determined iteratively for the hardware used in this study and the function \( c \cdot \sqrt[4]{R} - 1 \) was fitted to this data. Figure 3b shows the difference \( \delta_{SENSE} - \delta_{full} \) as a function of \( R \) for two different \( b \)-factors. The parameters \( c \) and \( n \) depend on the \( b \)-factor and the maximal gradient strength \( G \). Our analytical expression for \( \Delta TE \) thus reads

\[
\Delta TE = t_{acq} \left( \frac{1}{R} - 1 \right) + 2 \cdot c \cdot \sqrt[4]{R} - 1 .
\]  

Reducing the echo time by \( \Delta TE \) increases the signal by the factor

\[
f = \exp \left( -\frac{\Delta TE}{T2} \right) .
\]  

Using this factor to correct Eq.[1], the SNR in diffusion-weighted SE-sshEPI with SENSE can be expressed as
1. SENSE-DTI at 3 T

\[ SNR_{\text{SENSE}} = \exp\left( -\frac{t_{\text{acq}}(1/R - 1) + 2 \cdot c \cdot \sqrt{R - 1}}{T2} \right) \cdot \frac{g \sqrt{R}}{\text{SNR}_{\text{full}}} \]  

Materials & Methods

Data from nine healthy volunteers were acquired using a 3 Tesla Philips Intera whole body system (Philips Medical Systems, Best, the Netherlands) equipped with a PowerTrak 6000 gradient system (30 mT/m strength, 150 mT/m/ms ramp rate). All volunteers signed informed consent.

DTI Measurements and SENSE Reconstruction

For SENSE acquisition, an 8-element head coil array (MRI Devices Corporation, Waukesha, USA) was used. 3D gradient echo images, acquired interleaved from the body coil and the SENSE coil array (acquisition matrix = 48 \times 2, \alpha = 7^\circ, TR = 8 \text{ ms}, TE = 1.6 \text{ ms}), served as references for sensitivity calibration. The time required to collect the reference data was approximately 1.5 minutes.

The SENSE-DTI data were based on SE-sshEPI measurements. Two different SENSE-DTI protocols were used: Whole brain scans with conventional resolution (acquisition matrix = 128^2, 33 slices) and scans with enhanced in-plane resolution (acquisition matrix = 256^2, 6 slices).

Whole brain scans (FOV = 200 x 200 mm^2, 33 contiguous slices, slice thickness = 3 mm, phase encoding direction = AP, NEX = 4) with SENSE reduction factors of 1.0, 2.0, 2.5 and 3.0 (TE / TR = 103 ms / 10371 ms, 84 ms / 6390 ms, 80 ms / 5318 ms and 79 ms / 4717 ms) were carried out along six directions (-2/3 -1/3 -2/3)T (1/3 2/3 -2/3)T (-2/3 2/3 1/3)T 1/\sqrt{2}(1 1 0)T 1/\sqrt{2}(0 -1 -1)T 1/\sqrt{2}(1 0 -1)T with a b-factor of 1000 s/mm^2. This gradient scheme, standard on our system, was chosen in order to always use a minimum of two gradients simultaneously applied, so as to reduce the echo time as much as possible, while acknowledging its uneven spatial sampling. Additionally, for each slice a baseline image with minimal diffusion weighting (b < 20 s/mm^2) was acquired. In order to limit T2 decay, partial Fourier encoding of 70 % was applied. After SENSE reconstruction each slice matrix consisted of 128 x 128 voxels with a nominal resolution of 1.6 x 1.6 x 3 mm^3 (Figure 2).

For enhanced resolution the acquisition parameters were as follows: FOV = 200 x 200 mm^2, slice thickness = 3 mm, TR = 7752 s, TE = 93 ms, phase encoding direction = AP, SENSE reduction factor R = 2.4, partial Fourier encoding = 60 %. Due to memory constraints the acquisition was limited to six slices. These scans were carried out along the same six direc-
tions as for the whole brain acquisitions. Matrices of 256 x 256 voxels with an in-plane resolution of 0.8 x 0.8 mm were used for diffusion tensor calculation.

For both types of experiments, a total of 16 signal averages were collected to ensure sufficient SNR for high quality tensor mapping. In order to compensate for motion, the signal averages were grouped into four scans of four averages each, permitting registration of the groups before final averaging. The duration for one whole brain scan (33 slices) was between 2 min 21 s for \( R = 3 \) and 5 min 11 s for \( R = 1 \), leading to a total scan time (including the SENSE reference scan) in the range of 12 to 23 minutes.

Figure 2: Comparison of diffusion weighted transverse images (1.6 x 1.6 mm² in plane resolution) acquired with and without SENSE at 3 Tesla: The images in each row (a and b, c and d) have the same slice location. In the left column, images acquired without parallel imaging using an echo time of 103 ms are shown, whereas in the right column, images acquired using SENSE reduction \( R = 3 \) in anterior-posterior direction are shown. For (b) and (d), a TE of 79 ms was used.
SNR Estimation

In order to characterize the SNR behavior of SENSE SE-sshEPI relative to single-shot imaging with full-density Fourier encoding, Eq. [7] was evaluated using values for $g$ computed from geometry factor maps. The maps require that the mutual noise correlation between the receiver channels be assessed, by analysis of noise data (33). The latter were obtained by repeating the SENSE experiment without excitation. The maps themselves depend on $R$ and were derived using the noise data and coil sensitivity maps, as described in Ref. (14). Finally, Eq. [7] and the $g$ factor maps served as the basis for calculating the relative SNR at each pixel (SNR of SENSE SE-sshEPI divided by the SNR of full Fourier encoding using SE-sshEPI) in dependence on $R$ (Figure 3a).
1. **SENSE-DTI at 3 T**

Figure 3 (previous page): A: Relative SNR (SNR\text{SENSE} / SNR_{\text{full}}) in a sensitivity-encoded diffusion weighted image using a 128² acquisition matrix as a function of R: Mean and minimum SNR correspond to mean and maximum g, respectively. All curves exhibit a maximum relative SNR value determining the respective optimum R. The two curves denoted with “70 %” were obtained using partial Fourier encoding of 70 %. R = 1 with SNR = 1.0 corresponds to the acquisition without SENSE.

B: Solid lines represent $\delta_{\text{SENSE}} - \delta_{\text{full}}$ for $b = 1000$ s/mm$^2$ and $b = 400$ s/mm$^2$. Each determined for full (100 %) and partial (70 %) Fourier encoding. Dashed lines show a fit of the function $y = c(R-1)^{-\frac{1}{n}}$ with $c = 5.0$ ms / $n = 2.7$ (100 %) and $c = 3.4$ ms / $n = 2.8$ (70 %) for $b = 1000$ s /mm$^2$. For $b = 400$ s/mm$^2$ the parameters are $c = 4.0$ ms / $n = 2.8$ and $c = 2.7$ ms / $n = 2.6$, respectively.

The parameters $c$ and $n$ in Eq. [5] and [7] were assessed by a least mean square fit of the function $c \cdot R^{-\frac{1}{n}}$ to the values $\delta_{\text{SENSE}} - \delta_{\text{full}}$ for $R$ in the range between $R = 1$ and $R = 6$. $\delta_{\text{SENSE}} - \delta_{\text{full}}$ was evaluated by calculating the difference between the minimal TE for a certain $R$ and the theoretical value $t_{\text{acq}}(1/R-1)$. The minimal allowed echo time was determined through software, which calculates the optimal pulse sequences in an iterative fashion. The algorithm accounts for specific pulse lengths and finite gradient ramps. Figure 3b shows $\delta_{\text{SENSE}} - \delta_{\text{full}}$ as a function of $R$ for two different $b$-factors, as well as for full and reduced Fourier encoding. The fit related to $b = 1000$ s/mm$^2$ yields $c = 5.0$ ms / $n = 2.7$ for full k-space coverage and $c = 3.4$ ms / $n = 2.8$ for partial Fourier encoding of 70 %. For $b = 400$ s/mm$^2$ the parameters are $c = 4.0$ ms / $n = 2.8$ and $c = 2.7$ ms / $n = 2.6$, respectively. T2 of white matter at 3 Tesla was assumed to be 60 ms; $t_{\text{acq}}$ was set to 124 ms in accordance with limitations imposed by the available hardware.

**Postprocessing and Visualization**

Retrospective inter-scan motion correction was achieved using a 3D-rigid co-registration algorithm (34). Subsequently, eddy current-induced image warping was reduced with a correlation-based 2D-affine registration algorithm described in Ref. (34). An isotropic diffusion-weighted image was calculated as the geometric mean of three orthogonal diffusion-weighted images and served as a reference for the registration process. The six diffusion-weighted images and the b0-image were registered to this reference. The independent elements of the diffusion tensor were obtained on a pixel-by-pixel basis by singular value decomposition, using the DW-images and the control images with $b = 0$. After diagonalization, the eigenvalues and eigenvectors were determined and fractional anisotropy (FA) maps and color coded orientation field maps (35) were created (Figure 4).
Results

The side-by-side-comparison between regular DW SE-sshEPI and DW SENSE SE-sshEPI in Figure 2 illustrates artifact reduction as achieved with sensitivity encoding. The images acquired without SENSE (Figure 2a, c) show strong EPI-related off-resonance artifacts in the forebrain close to the frontal cavity and in the temporal lobe near the inner ear. Image blurring is observed especially in the temporal lobe and the cerebellum. As a consequence of reduced sampling density in $k$-space, these image artifacts are reduced significantly with SENSE (Figure 2b, d). Improved depiction of anatomical detail is demonstrated in Figure 2d, showing details of the brain stem.

Figure 4: Two ultra-high resolution (0.8 x 0.8 mm$^2$ in plane resolution) color-coded fractional anisotropy maps using SENSE-DTI (reduction = 2.4) at 3 Tesla: Each orientation of the axonal fibers is assigned to a color as it is illustrated at the bottom. The images clearly depict the major white matter fiber tracts. OR: optic radiation, FMJ: forceps major, FMN: forceps minor, EC: external capsule, CC: corpus callosum, CR: corona radiata and IC: posterior limb of the internal capsule.

Figure 3a shows the relative SNR ($SNR_{SENSE} / SNR_{full}$) in a sensitivity-encoded DW image using an acquisition matrix of $128^2$ points as a function of SENSE reduction. With full $k$-space coverage (no partial Fourier acquisition), the spatial mean of the relative SNR assumes its maximum of 1.68 at 2.2-fold SENSE reduction. In the regime of low $R$ the SNR generally increases as the number of sampled $k$-space profiles decreases. As $R$ increases, this trend persists only until increasing geometry factors outgrow the $T_2$ effect. As a consequence, SNR improvement occurs in the range between $R = 1.0$ and $R = 3.9$. In this range,
the mean SNR of the SENSE images exceeds that of the conventional image. Due to the inhomogeneous SNR distribution in SENSE images, one has to consider the local minimal SNR as well. The minimal relative SNR is still 1.31 for SENSE reductions of 1.6 and 2.1. Compared to the mean relative SNR the curve of the minimal relative SNR is more jagged because each value comes from a single pixel in the map, representing the local minimum. For partial Fourier encoding of 70%, the reduction of $TE$ is less than that in the previous case without partial Fourier encoding and thus the relative mean SNR is maximal 1.02 at $R = 1.4$. The range where the SNR of the SENSE image still exceeds the SNR of the conventional image decreases to an interval between $R = 1.0$ and $R = 1.8$.

Examples of ultra-high resolution ($0.8 \times 0.8$ mm$^2$ with a 256 x 256 image matrix) color coded FA maps using a SENSE reduction factor of 2.4 are shown in Figure 4. The presented maps have negligible residual aliasing artifacts and the sharp contours disclose successful image co-registration of the DW images. (FA maps are sensitive indicators of any error in spatial alignment of DW-images). Only minor distortions related to susceptibility variations were observed. Comparison with histological preparations allows identification of some of the major fiber bundles, such as the optic radiation (OR), forceps major (FMJ) and minor (FMN), the external capsule (EC), corpus callosum (CC), corona radiata (CR) and the posterior limb of the internal capsule (IC), including the descending cortical spinal tracts.

**Discussion**

As susceptibility-related artifacts scale with the main magnetic field, they appear more pronounced at 3 Tesla, preventing conventional DTI in regions close to the skull base, frontal cavity or inner ear. Parallel imaging effectively compensates for these enhanced off-resonance artifacts by shortening the EPI readout. The benefits of parallel techniques regarding artifact reduction were previously discussed for 1.5 Tesla (25-27). The present study demonstrates that the same approach permits substantial artifact suppression also at 3 Tesla. In particular, the benefits have been found sufficient to deal even with approximately doubled field inhomogeneity relative to 1.5 Tesla. Very similar effects in terms of susceptibility artifacts could be accomplished with multiple-shot EPI. However, ensuring data consistency across multiple excitations is difficult in DWI acquisition due to its pronounced motion-sensitivity. This problem can be addressed by advanced means of motion correction and elimination, such as phase navigation and cardiac triggering (36,37). Nevertheless, the relative simplicity and robustness of plain single-shot acquisition certainly make the strategy discussed in this work a promising alternative.

A large part of the increase in SNR required for reducing the voxel size has been provided by operating at 3 Tesla. Another significant contribution stems from the fact that with a shorter readout train the echo time can be reduced as well, mitigating $T2$ decay. In fact, since the option to reduce the echo time is directly attributable to parallel acquisition, the parallel approach may as well be regarded as a means of enhancing SNR in the present con-
text. This is particularly remarkable, because the inherent loss of SNR is commonly regarded as the main drawback of parallel imaging techniques. It has been found that, for a given set of sequence parameters and hardware environment, the SNR is optimal for a distinct SENSE factor. Along with choosing this factor, the sequence timing must be adjusted for actually realizing the optimum SNR gain. For acquisition matrices of 128² points, a mean SNR benefit of factors up to 1.7 has been achieved. The parameters $c$ and $n$ in Eq. [7] will vary depending on the performance of the gradient system. Using stronger gradients will decrease the parameter $c$. Similar to Figure 3b the two parameters $c$ and $n$ can be assessed for each gradient system individually, making the SNR estimation all-purpose.

The influence of the repetition time on SNR was neglected in this work. It becomes significant when the actual relaxation period of imaged tissue is in the same range as $T_1$. This will be the case for imaging of a single slice or of few slices with relatively low resolution and / or high SENSE factors. In such situations, slightly lower SENSE factors will be favored, resulting in longer TR and thus stronger baseline signal.

In all experiments the $b$-factor was fixed to $b = 1000$ s/mm². This is not optimal according to Ref. 21, since the most favorable $b$-factor for best SNR in tensor images is echo time dependent. However, optimizing the $b$-factor with varying SENSE speed up factors would complicate the SNR assessment unnecessarily.

Another aspect of using SENSE in combination with DW SE-sshEPI is the possibility to acquire data with high spatial resolution. Reducing signal decay during the readout effectively broadens the associated $k$-space filter, leading to a narrower point spread function and higher actual resolution than with conventional DTI. This has been demonstrated in Figure 4, where more detail can be appreciated in the FA color maps with enhanced resolution.

As a consequence of the spatially varying geometry factor of the SENSE procedure, minor spatial SNR inhomogeneities were encountered in the DW images. With the coil configuration used in this study a locally slightly decreased SNR in the area in the middle of the brain could be observed. This is hardly visible on the corresponding ultra-high resolution color-coded FA maps in Figure 4, because the SNR was still sufficient for multi-variate fitting of the diffusion weighted images in these locations.

No aliasing artifacts due to the SENSE unfolding procedure were observed in any DW images. The reduced acquisition time also effectively prevented image blurring and artifacts due to physiologic motion.

The 3D-rigid co-registration scheme and the subsequent signal averaging used in this study proved to be a robust retrospective processing method, effectively correcting for inter-scan bulk motion. Eddy current induced geometric distortions were reduced sufficiently with an affine co-registration algorithm, which used an isotropic diffusion-weighted reference image. The influence of geometric distortions on the reference seems to be minimal. However, since the agreement of all images involved in the computation of a tensor map is most important, small geometric distortions that all images have in common are less critical.
SENSE can be combined with partial Fourier acquisition as an additional mechanism to reduce the EPI readout duration. In all images shown in Figure 2 and 4, SENSE was successfully combined with partial Fourier reconstruction. The optimal reduction factor then shifts towards lower values, leading to less gain in SNR efficiency (Figure 3a). However, the absolute SNR still remains higher for SENSE-DTI in combination with half-Fourier reconstruction than without. The SNR benefit due to echo time reduction overcompensate the SNR loss incurred by partial $k$-space sampling. In terms of image quality DW images acquired without partial Fourier encoding show stronger susceptibility artifacts. The used coil configuration has a great influence on the SNR efficiency. An optimal coil configuration includes low noise correlation and consequently lower local $g$ values, resulting in better SNR efficiency at higher SENSE reductions. In the present work, a commercially available head coil was used.

**Conclusion**

It has been demonstrated that sensitivity encoding substantially enhances DTI in the human brain at 3 Tesla. The strength of the parallel approach is that it addresses the key shortcomings of SE-sshEPI simultaneously, while preserving its advantages, such as motion robustness. Image distortion due to $B_0$-inhomogeneity as well as intrinsic resolution limits due to $T2^*$ decay are effectively mitigated, leading to high quality data. As expected, the enhanced demand for SNR at high resolution can partly met by the high baseline sensitivity at 3 Tesla. A significant second contribution to enhanced SNR efficiency is accomplished by parallel acquisition, as shown in the present work.
2. The Influence of SENSE on Image Properties in DTI

Submitted to *Magnetic Resonance in Medicine* (2004):
“The Influence of SENSE on Image Properties in High-Resolution Single-Shot Echo-Planar DTI”
T. Jaermann, K. P. Pruessmann, A. Valavanis, S. Kollias, P. Boesiger
Abstract

Limited spatial resolution is a key obstacle to the study of brain white matter structure with Diffusion Tensor Imaging. Because of its common implementation with single excitation spin-echo echo-planar sequences, DTI’s ability to resolve small structures is strongly restricted by $T_2$ and $T_2^*$ decay, $B_0$ inhomogeneity, and limited signal-to-noise ratio (SNR). In this work the influence of sensitivity encoding (SENSE) on diffusion-weighted image properties is investigated. Computer simulations show that the point spread function becomes narrower with increasing SENSE reduction factors, $R$, enhancing the intrinsic resolution. After a brief theoretical discussion, the SNR as a function of $R$ is estimated on a pixel-by-pixel basis. The mean image SNR behavior is manifold: SENSE is capable of increasing SNR efficiency by reducing the echo time. Each SNR($R$) curve reveals a maximum whose location depends on the amount of partial Fourier encoding. The overall best SNR efficiency for an eight-element head coil array and a $b$-factor of 1000 s/mm$^2$ is achieved at $R = 2.1$ and partial Fourier encoding of 60 %. In-vivo tensor maps of volunteers and patients with an in-plane resolution of $0.78 \times 0.78$ mm$^2$ are presented demonstrating the practical implementation of the parallel approach.

Introduction

Diffusion Tensor Imaging (DTI) (3,12) has become a well established tool for the non-invasive mapping of axonal structures in the living human brain (38-40). Recently, DTI studies have been performed to explore the developing brain (41-43), ischemic brain injuries (44,45) and various demyelinating diseases (46), such as multiple sclerosis (MS) (47,48) or amyotrophic lateral sclerosis (ALS) (49). Clinical trials in common neuropsychiatric disorders using DTI revealed abnormalities in white matter microstructure (50,51). Despite these promising applications detailed investigation of the axonal integrity is seriously hampered by the resolution limits of the technique. For clinical applications a typical in-plane resolution of $2 \times 2$ mm$^2$ prohibits the detection of minor structural changes associated with brain disorders. Moreover, improved resolution in the sub-millimeter realm is of great importance for the detailed mapping of the subcortical white matter architecture and its connectivity to attain a better understanding of the normal and injured brain’s network.

Ideal would be to acquire data with high isotropic resolution, which do not introduce directional errors in fiber tracking algorithms (18) and can be easily reformatted in any plane. However, due to the strong relation between voxel size and SNR of multi-slice sequences, the voxel dimensions are commonly anisotropic, in particular larger in slice direction than in the plane.

Various techniques have been investigated to improve resolution for diffusion-weighted imaging (DWI) and DTI: Peled et al. (19) suggested the use of an image postprocessing...
method to artificially enhance the spatial resolution. Golay et al. (20) introduced cardiac-gated 3D-DTI with isotropic high resolution. The long acquisition time (compared to its multi slice analogue) and its intrinsic sensitivity to motion limited the widespread utilization in neuroscience. Fast diffusion imaging based on a segmented 3D steady-state free precession scheme (3D-SSFP) has been also proposed (52). On the basis of multi slice excitation protocols, multishot echo-planar imaging, multishot spiral acquisition and fast spin-echo (FSE or TSE) sequences have been reported. Butt et al. (53) as well as Brockstedt et al. (6) used interleaved EPI in combination with navigator echoes to correct for motion artifacts. Pipe et al. (54) published high resolution data using the self navigated FSE technique called PROPELLER. Segmented radial acquisition, a technique which is based on FSE, was shown to be immune to some types of motion artifact (55,56). Gradient echo pulse sequences, such as stimulated echo acquisition mode (STEAM), have been used without motion correction (8). Using the line-scan technique, single excitation data with high resolution were obtained (57). This method achieves reduced distortion and is insensitive to motion, but requires long data acquisition times for DTI using six diffusion directions.

Diffusion-weighted (DW) spin-echo single-shot EPI (SE-sshEPI) is the most popular DWI technique due to its motion insensitivity and relatively high SNR. Cardiac triggering or navigator echoes for motion correction are not required. Signal phase variations arising from small motions are identical for all k-space samples and vanish when the image magnitude is taken. However, with this sequence, spatial resolution is strongly restricted by $T_2$ and $T_2^*$ decay, causing blurring, and distortions related to $B_0$ inhomogeneities. Another serious limitation stems from the limited SNR in consequence of the reduced voxel size, the former being inherently low due to extensive $T_2$ decay and diffusion weighting. The use of higher magnetic fields is currently explored for overcoming these limitations. Unfortunately, the SNR benefit at higher $B_0$ is counteracted by likewise enhanced $T_2^*$ decay and inhomogeneity effects.

In view of these challenges, DTI in conjunction with parallel imaging techniques, such as SENSE (10), is currently receiving increasing attention. It has been shown that reducing the EPI train length with the parallel approach effectively mitigates both susceptibility artifacts and blurring (28,58). Thus, the enhanced baseline SNR at high $B_0$ can become available for DTI using smaller voxels, providing improved resolution for applications in the human brain.

In the present work, the influence of SENSE on image properties for pushing DTI resolution beyond the previous limitations is explored. Computer simulations are performed to investigate the point spread function (PSF) for different SENSE reduction factors. The seemingly paradoxical observation that parallel acquisition does not reduce but rather enhance SNR efficiency in SE-sshEPI with enhanced matrix size is discussed. To estimate the resulting SNR, a formal expression for SNR as a function of the reduction factor (58) is adapted and compared to an alternative approach described in (24). To provide more generally applicable results the SNR of DW images acquired using two gradient strengths (30 mT/m and 80
mT/m maximal gradient strength) is estimated. Finally, DTI’s improved image quality and its application in a clinical setting are demonstrated by examples of high-resolution data in volunteers and patients.

**Theory**

**Point Spread Function**

With SE-sshEPI, the spatial resolution in the phase encoding direction is limited by transverse relaxation. Signal attenuation by magnetization decay effectively acts as a \( k \)-space filter. The shape and width of this filter depend on \( T_2, T_2^* \), and the speed of the EPI readout. Let \( T_2^* \) account for the dephasing caused by local field inhomogeneity, 

\[
\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2^1},
\]

and \( k_y \) denote the \( k \)-space coordinate in the phase encoding direction. Then the damping factor along \( k_y \) can be formally expressed as

\[
d(k_y) = \text{rect}(k_y) \cdot \exp\left( -\frac{TE - (k_y - k_{y,\min})/v_y}{T_2} \right) \cdot \exp\left( -\frac{|k_y - k_{y,\min}|/v_y}{T_2^*} \right) \tag{2}
\]

where the rect-function reflects finite sampling of \( k \)-space within the limits \( k_{y,\min}, k_{y,\max} \),

\[
\text{rect}(k_y) = \begin{cases} 
1 & -k_{y,\min} < k_y < k_{y,\max}, \\
0 & \text{otherwise}
\end{cases} \tag{3}
\]

and \( v_y \) denotes the average \( k \)-space speed in the \( y \) direction, which is proportional to the SENSE reduction factor \( R \).

In addition to parallel acquisition, partial Fourier sampling is considered as another means of shortening the readout train. With a partial Fourier factor \( 0.5 < pF < 1 \) the lower sampling limit shifts to

\[
k_{y,\min} = -(pF - 0.5) \cdot k_{y,\max}. \tag{4}
\]

Partial Fourier acquisition requires phase-constrained image reconstruction, e.g., using the so-called homodyne approach \((59,60)\). In this method the partial \( k \)-space data is first Fourier-transformed. The image phase is then removed according to a phase estimate, which is extracted from the center of \( k \)-space. After this operation the imaginary part is discarded and the phase modulation reapplied. According to this procedure the PSF of a partial Fourier SE-sshEPI image is equal to the real part of the Fourier transform of \( d(k_y) \):

\[
\text{PSF}(y) = \Re\left\{ \mathcal{F}^{-1}\{d(k_y)\} \right\} \tag{5}
\]
SNR Efficiency

The SNR yield of a diffusion-weighted SE-sshEPI sequence depends on the sequence timing and the $T_2$ of the tissue. At the image level it also depends on the PSF, which causes local signal averaging if it is broadened. However, SNR benefits due to PSF effects do not correspond to a genuine increase in sensitivity and are hence not considered in the following analysis.

The SNR efficiency for sensitivity encoded data with a resolution of 128 x 128 points has been derived in Ref. (58). Partial Fourier sampling was not taken into account. Here, a modified term describing the SNR efficiency for high resolution partial Fourier acquired data is introduced.

A single-shot readout with a reduced number of phase encoding steps (achieved with SENSE and / or partial Fourier acquisition) requires a shorter time period than the corresponding full density $k$-space readout. According to Ref. (58), the SNR in SENSE image data with respect to standard full Fourier encoding is given by

$$SNR_{SENSE} = \exp \left( -\frac{\Delta TE}{T_2} \right) \frac{R g}{\sqrt{R}} SNR_{full}. \quad [6]$$

The local geometry factor $g$ describes geometry-related noise enhancement inherent to sensitivity encoding, whereas the square root of the reduction factor $R$ accounts for SNR decrease due to reduced data sampling. The factor $g$ is always equal to or larger than one and depends on the experimental setup. The reduced echo time $\Delta TE$ as a function of $R$ is

$$\Delta TE = t_{acq} \left( \frac{2 \cdot (pF - 0.5)}{R} - 1 \right) + 2 \cdot c \cdot \sqrt{R - 1}, \quad [7]$$

where $pF$ corresponds to the partial Fourier factor and $t_{acq}$ denotes the length of the full Fourier EPI readout with 256 x 256 sampling points. The second addend is a correction term which accounts for the increased duration of the diffusion-encoding gradient pulse pairs to accomplish a given $b$-factor when the separation in time is reduced. The parameters $c$ and $n$ depend on the $b$-factor and the maximal gradient strength.

Please note that the ratio $SNR_{SENSE}$ divided by $SNR_{full}$ of Eq. [6] estimates the relative SNR (rSNR): It describes the change in SNR using sensitivity encoded data (sometimes acquired with partial Fourier encoding) relative to a standard DW SE-sshEPI acquisition with full $k$-space density. The latter will be referred to as the “reference” in the following text.

When SENSE data are compared to partial Fourier acquired data, Eq. [6] changes to

$$SNR_{SENSE} = \sqrt{pF} \frac{\exp \left( -\frac{\Delta TE}{T_2} \right)}{g \sqrt{R}} SNR_{full}, \quad [8]$$

using a modified expression for $\Delta TE$:
\[ \Delta TE = 2 \cdot \left( pF - 0.5 \right) \cdot t_{\text{acq}} \left( \frac{1}{R} - 1 \right) + 2 \cdot c \cdot \sqrt{R - 1}. \]  

[9]

**Materials & Methods**

**PSF Simulations**

PSFs were calculated (Figure 1) by straightforward implementation of Eq. [5]. In these calculations, \( T_2 \) and \( T_2^* \) were set to 70 ms and 44 ms. These values are typical for white matter in-vivo at 3 Tesla (61).

![PSF Simulations](image)

*Figure 1: PSF in the phase encode direction for six different reduction factors. Y-axis is arbitrary; X-axis corresponds to the number of pixels. All functions were computed for partial Fourier acquisition of 60%.*

**MRI Hardware**

Imaging was performed on a clinical 3 T Philips Intera whole body systems (Philips Medical Systems, Best, the Netherlands). The scanner was equipped with two different gradient coils: gradient system A with a maximal gradient strength and slew rate of 30 mT/m and 150 mT/m/ms, gradient system B with coil characteristics of maximal 80 mT/m gradient strength and up to 200 mT/m/ms slew rate. The equipment provides an eight element head coil array (MRI Devices Corporation, Waukesha, USA) whose eight elements were con-
connected to six independent receiver channels in such a way that four elements were combined pairwise.
The images shown in Figure 6 and 8 were acquired with gradient system A, whereas the fractional anisotropy (FA) maps in Figure 7 were reconstructed from images obtained with the gradient coil B.

**SNR Estimation**

The common method of estimating SNR using a region of interest (ROI) in a signal region and a second ROI in a noise region can be unreliable whenever a phased array coil is used, because the noise contribution varies on a pixel-by-pixel basis. Therefore, the pixel-by-pixel based technique described in the “Theory” section has been used to estimate SNR. Note that this method is not based on simulations since in-vivo geometry factor maps are used. The maps were derived using coil sensitivity and noise information from in-vivo data (10,62). The required mutual noise correlation between receiver channels was assessed by the analysis of noise data. The average noise level and the local maximal noise were determined from the maps. Each of the Figures 2 – 4 shows the mean as well as the minimal SNR, corresponding to the average noise and the maximal noise in the geometry maps, respectively.
2. The Influence of SENSE on Image Properties in DTI

Figure 2: Relative SNR (SNR\text{SENSE} / SNR\text{full}) in sensitivity encoded diffusion-weighted images using 256$^2$ acquisition matrices and partial Fourier factors of 60\%, 80\% and 100\% as a function of $R$: Average (solid lines) and minimum (dashed lines) image SNR correspond to mean and maximum geometry factors $g$, respectively. The dotted lines were obtained using an 80 mT/m-gradient system. All curves correspond to a $b$-factor of 1000 s/mm$^2$. A: An image acquired with full k-space sampling ($R = 1, pF = 100\%$) served as reference (SNR\text{full}). B: Images acquired with according partial Fourier factors ($pF = 60\%, 80\% 100\%$) and $R = 1$ served as references. As illustration the g-maps of two images with $R = 2.67$ and $R = 3.20$ are shown.

The parameters $c$ and $n$ in Eq. [7] and [9] were assessed as described in (58) and are listed in Table 1. Figure 2a and 2b differ in the reference used to determine rSNR: In Figure 2a a DW image acquired with a full EPI readout ($pF = 100\%, R = 1$) served as SNR reference, whereas in Figure 2b partial Fourier acquired images ($pF = 60\%, 80\%$ and 100\%, $R = 1$) served as references. All data in Figure 2 were obtained using $b = 1000$ s/mm$^2$. To evaluate the gain in SNR for a system with 80 mT/m-gradient coils as compared to a system with 30 mT/m-coils (Figure 4) Eq. [8] was used. $\Delta T_E$ was determined through our scanner software, which calculates the optimal pulse sequences (with a minimal $T_E$) in an iterative fashion. The algorithm accounts for specific pulse lengths and finite gradient ramps. In accordance to limitations imposed by the available hardware, $t_{\text{acq}}$ was set to 462 ms for the system with 30 mT/m-gradient coils and to 452 ms for the system with a maximal gradient strength of 80 mT/m. All solid lines in Figure 4 were computed with a 6\textsuperscript{th} degree polynomial fit. $T_2$ of white matter at 3 Tesla was assumed to be 70 ms (61).
2. The Influence of SENSE on Image Properties in DTI

Figure 3: Relative SNR (SNRSENSE, pF=60% / SNR R=1, pF=60%) as a function of R: Average image SNR is depicted using 30 mT/m gradient strength (solid lines) and 80 mT/m gradient strength (dotted lines), respectively. Dashed lines correspond to the minimal image SNR for both systems. To display each maxima a region in the range between R = 1.5 and 2.5 is enlarged. The letters a, b and c are related to three different b-values.

To verify the SNR derived with Eq. [6-9] SNR was estimated using phantom experiments. According to Ref. (24) the most accurate SNR estimation method is the National Electrical Manufacturers Association (NEMA) standard method (63), where several images are acquired at a given slice. The SNR is calculated on a pixel-by-pixel basis, using the ratio of the mean intensity of a pixel over all acquired images divided by the standard deviation around that mean. Therefore, a bottle in size comparable to a human head was doped with CuSO₄ to attain a spin-spin relaxation of $T_2 = 70$ ms. The parameter $T_2$ was monitored using two gradient echo sequences with different $TE$ (FOV = 200 x 200 mm², 3 slices, slice thickness = 5 mm, $TR = 5000$ ms, $TE = 2.4 / 4.8$ ms). Six series were acquired, each consisting of 36 equal sensitivity encoded images. The DW images of each collection were obtained with the same sshEPI sequence as for the in-vivo data. For each set the reduction factor $R$ was increased starting at $R = 1$, resulting in six points in the graph of Figure 5. The SNR was computed according to the NEMA standard method. The resulting pixel wise SNR was then averaged over the object and plotted in Figure 5. The data points were interconnected using cubic spline interpolation. Compared to the interpolated curve the course of the relative SNR derived by the use of $g$-maps for $f = 60$ % and $b = 1000$ s/mm² is plotted.
2. The Influence of SENSE on Image Properties in DTI

Figure 4: SNR comparison of sensitivity encoded images acquired using an 80 mT/m-gradient coil with images acquired without SENSE using a 30 mT/m-gradient coil. Average (solid lines) and minimum (dashed lines) relative image SNR are plotted as a function of R using three different b-factors and partial Fourier encoding of 60%.

Figure 5: Comparison of two different approaches to determining the relative SNR as a function of R. Dashed line: Interpolated course of six experiments (crosses) obtained at different reduction factors. (For details refer to text). Four SNR maps each derived from a series of DW images (b = 1000 s/mm²) indicate the spatially varying SNR. Solid line: Average image rSNR approximated using geometry maps. Dotted line: Minimal image rSNR.
Subjects and Imaging Protocols

Nine healthy volunteers participated in the study. All volunteers signed informed consent. To obtain information for sensitivity calibration 3D gradient echo images acquired interleaved from the body coil and the SENSE head coil array served as references. DTI experiments were conducted using three sshEPI imaging protocols with three different SENSE reduction factors ($R = 1, 2.1, 2.4$). The comparison data showed in Figure 6 were acquired using a SENSE-SE-sshEPI sequence with the following parameters: $\text{FOV} = 200 \times 200$ mm$^2$, matrix = 256 x 256, 9 contiguous slices, slice thickness = 2.5 mm, NEX = 4. Two similar scans were performed using $R = 2.4$ ($TE = 93$ ms, $TR = 3799$ ms) and $R = 1.0$ ($TE = 140$ ms, $TR = 9628$ ms). The parameters for the two coronal FA-maps in Figure 7 were: $\text{FOV} = 200 \times 200$ mm$^2$, matrix = 256 x 256, $R = 2.4$, $TE = 65$ ms, $TR = 3475$ ms, 12 contiguous slices, slice thickness = 3.5 mm, NEX = 9. The acquisition time for the clinical sample (Figure 8) with a SENSE factor of $R = 2.1$ ($\text{FOV} = 200 \times 200$ mm$^2$, matrix = 256 x 256, $TE = 72$ ms, $TR = 2467$ ms, 8 contiguous slices, slice thickness = 4 mm, NEX = 8) was 7 min 10 sec, leading to a total scan time (including SENSE ref scan) of approximately 9 min.

For all scans partial Fourier encoding of 60 % was applied. After SENSE reconstruction each slice matrix consisted of 256 x 256 voxels with a nominal in-plane resolution of 0.78 x 0.78 mm$^2$. Diffusion weighting was carried out along six directions $(-2/3 -1/3 -2/3)^T \ (1/3 2/3 -2/3)^T \ (-2/3 2/3 1/3)^T \ \sqrt{2}(1 1 0)^T \ \sqrt{2}(0 -1 -1)^T \ \sqrt{2}(1 0 -1)^T$ with a $b$-factor of 1000 s/mm$^2$. This gradient scheme, standard on our MR system, was chosen to always use a minimum of the two gradients simultaneously applied, so as to reduce the echo time as much as possible, while acknowledging its uneven spatial sampling. Additionally, for each slice a baseline image with minimal diffusion weighting ($b < 20$ s/mm$^2$) was acquired.
2. The Influence of SENSE on Image Properties in DTI

Figure 6: Comparison of diffusion-weighted images (0.8 x 0.8 mm² in plane resolution) acquired with and without SENSE, both obtained using partial Fourier acquisition of 60%. The axial images (a) and (b) have the same slice location. (a): DW image acquired without parallel imaging (R = 1). (b): Image acquired using SENSE reduction R = 2.4 in anterior-posterior direction. (c – f): Pairs of magnified regions from image (a) and (b), respectively.

Postprocessing and Visualization

For Figures 7 and 8 eddy current-induced image warping was reduced with a correlation-based 2D-affine registration algorithm described in Ref. (64). An isotropic DW image served as a reference for the registration process. The reference was calculated as the geometric mean of three orthogonal DW images (58). The independent elements of the diffusion tensor were obtained on a pixel-by-pixel basis by singular value decomposition. After diagonalization, the eigenvalues and eigenvectors were determined and color-coded fractional anisotropy maps (35) were created. For postprocessing a custom made software package developed in C++ was used.

Results

Figure 1 illustrates different PSFs in phase encode direction for SENSE reduction factors in the range between 1 and 6. As expected, narrower PSFs are obtained using higher R-factors. For R = 2.0 the full width at half maximum (FWHM) is 1.9 pixels, compared to 3.7 pixels at
$R = 1$. This corresponds to a reduction in FWHM of 49%, whereas an increase in $R$ from 2 to 6 reduces the width by 26%.

Figures 2 to 4 show the relative SNR of DW images with a data matrix of 256 x 256 as a function of $R$. The SNR of a DW image acquired with full EPI readout ($R = 1, pF = 100\%$) served as reference in Figure 2a. For $pF = 60\%$, the maximum in average image SNR is reached at $R = 2.1$, whereas for $pF = 80\%$ the SNR curve shows its maximum at $R = 3.2$. For images acquired with a full k-space readout ($pF = 100\%$) the maximal SNR shifts to $R = 3.7$. Considering the minimal image SNR, maxima occur at $R = 1.7$ for $pF = 60\%$, $R = 2.9$ for $pF = 80\%$ and $R = 2.9$ for $pF = 100\%$. When using an 80 mT/m-gradient system, SNR increases by a factor of 1.04 at $R = 2.1$ for $pF = 60\%$.

In Figure 2b the rSNR of sensitivity encoded images as compared to the corresponding non-SENSE images using partial k-space acquisition is plotted. The specific acceleration factors $R$ to achieve maximal SNR correspond to the values in Figure 2a. The benefit in SNR for SENSE images is 49 ($pF = 100\%$), 7 ($pF = 80\%$) and 1.3 ($pF = 60\%$). In contrast to Figure 2a, the maximal SNR enhancement is largest for $pF = 100\%$.

The high rSNR values seen in Figure 2 can be explained by the significant reduction in $TE$. For example using an MR system equipped with a 30 mT/m-gradient coil the EPI readout of a 256 x 153 data matrix could be reduced from 462 ms to 277 ms, yielding a $TE$ of 138 ms for $R = 1$ and $b = 1000\ s/mm^2$. With SENSE as an additional instrument for shortening the EPI readout $TE$ can be reduced to 89 ms for $R = 3$. 

Figure 7: Two coronal high-resolution (0.8 x 0.8 mm$^2$ in plane resolution) color coded fractional anisotropy maps using SENSE-DTI (reduction = 2.4). slf: superior longitudinal fasciculus; plic: posterior limb of internal capsule; ifo: inferior fronto-occipital fasciculus; cc: cingulum; cc: corpus callosum; ctp: corticopontine tract; cst: corticospinal tract; mcp: middle cerebellar peduncle; pct: pontine crossing tract; ifo: inferior fronto-occipital fasciculus; ilf: inferior longitudinal fasciculus.
For purpose of clarification, an enlarged section of the curve with $pF = 60\%$ is shown in Figure 3. The rSNR of SENSE images acquired with three different $b$-factors using two different gradient strengths is outlined. The mean rSNR varies in the range between 1.28 and 1.32 for a system with an 80 mT/m-gradient coil and varies in the range between 1.24 and 1.28 for a 30 mT/m-coil. All maxima arise between $R = 2.0$ and $R = 2.1$. The local minimal image SNR is highest at a reduction factor of $R = 1.75$ for $b = 1000$ s/mm$^2$ for both gradient coils.

Figure 4 illustrates the rSNR characteristics of sensitivity encoded images acquired using an 80 mT/m-gradient coil as compared to partial Fourier encoded images ($pF = 60\%$) acquired without SENSE on a 30 mT/m-gradient system. Three different $b$-factors between 500 s/mm$^2$ and 1500 s/mm$^2$ were evaluated. Using a stronger gradient coil (without applying SENSE, $R = 1$) improves SNR efficiency by a factor of 1.32 for $b = 500$ s/mm$^2$, 1.43 for $b = 1000$ s/mm$^2$ and 1.55 for $b = 1500$ s/mm$^2$. The average image SNR improves maximal in the range between 1.76 and 1.97 for SENSE acquisition at $R = 2.1$. Independent of the maximal gradient strength and the $b$-factor the rSNR-maxima of a 256$^2$-image obtained with $pF = 60\%$ are located at $R = 2.1$. Compared to 30 mT/m-gradients, the mean image SNR efficiency increases to up to a factor of 1.54 when using a maximal gradient strength of 80 mT/m and no SENSE is applied ($R = 1$). With the same $b$-value but $R = 2.1$ the echo time is reduced from 138 ms to 72 ms, increasing mean rSNR by a factor of 1.9.

Figure 8: Coronal high resolution FA maps of a patient suffering from an arteriovenous malformation (AVM). The examples were acquired using a clinical protocol during 7 minutes 10 seconds. In order to enhance the depiction of the lesion its boarders are highlighted with a yel-
A second approach was used for verifying the approximations according to Eq. [6–9]. The results of both methods are given in Figure 5: The relative SNR rises to an interpolated factor of 1.38 at $R = 1.9$ for the alternative method, whereas the maximum derived by the use of g-maps is 1.25 at $R = 2.1$. This corresponds to a difference of 10.4 % in rSNR level and a shift of the maximum by -9.5 %.

The side-by-side-comparison between DW SE-sshEPI and DW SENSE SE-sshEPI in Figure 6 demonstrates the improved image quality when using SENSE. EPI-related distortions due to susceptibility variations and image blurring are reduced significantly. The enlarged sections from the image obtained without SENSE suffer from strong blurring in phase encode direction. The sections c and d (acquired with $R = 2.4$) reveal reduced blurring. The enhanced depiction of anatomical detail can be appreciated. Image 6b exhibits a hyperintense artifact spread over the posterior part of the occipital lobe caused by an off-resonance effect.

Figure 7 and 8 show examples of high resolution color coded FA maps. The images illustrate minimal residual distortions, yielding an excellent depiction of white and gray matter gross anatomy. In a clinical case of a patient with an AVM, image quality is still high enough to provide details of the pathology (Figure 8). Due to the prolonged EPI readout the images of Figure 8 are more distorted compared to Figure 7, e.g. at the right side of the cerebellum. All images are free from motion artifacts and the sharp contours reveal successful image co-registration of the DW images.

Discussion

DTI based on single excitation protocols is severely restricted in its spatial resolution by off-resonance artifacts, relaxation effects and poor SNR. The latter being inherently low due to small voxel size, diffusion weighting and $T_2$ decay. The utility of parallel imaging for reducing susceptibility artifacts in DW-SE-sshEPI has been discussed previously (26,28,58). In this study we have shown that SENSE diminishes the limits set by relaxation effects as well as SNR constraints and allows DTI with increased resolution.

The PSF becomes narrower with increasing $k$-space velocity in the phase encode direction (which is proportional to $R$). In this regard the largest possible value for $R$ would be the most favorable. Large $R$-factors are suboptimal, however, in terms of SNR. In the regime of low $R$ the SNR($R$) curves generally increase as the number of sampled $k$-space profiles decreases. As $R$ increases, this trend persists only until increasing geometry factors outweigh the $T_2$ effect. As a consequence, SNR optima can be found between $R$ values of 2.0 and 3.7, depending on the amount of partial Fourier encoding. The gain in SNR (compared to the SNR of an image acquired with full Fourier encoding) is highest for DW images acquired with partial Fourier encoding of 60 % and a reduction factor of $R = 2.1$. This can be ex-
plained by the vast reduction in $TE$ when SENSE is applied in conjunction with half Fourier acquisition. The SNR gain for partial Fourier acquired images even without SENSE ($R = 1$) is still remarkable. Therefore, application of partial Fourier acquisition is advisable as a tool to reduce $TE$ and increase SNR for DW-SE-sshEPI. An increased maximal gradient strength reduces the duration of the two bipolar diffusion encoding gradients within the constraints set by the required $b$-factor. Stronger gradients can be regarded as a further tool to shorten the echo time and therefore boost SNR.

Note that these suggestions hold for the mean image SNR. In contrast, the minimal image SNR reaches its maximum at lower $R$-values. Then, SNR characteristics strongly depend on the image geometry and on the direction of phase encoding. For example, in Figure 2b the minimal image SNR (dashed lines) drops considerably between $R = 2.6$ and $R = 3.2$. This drop is due to a local increase of the $g$-value in the center of the image where the two fold-over artifacts (caused by the reduced sampling density of SENSE) start to overlap as $R$ increases.

Relaxation imposes a limit on the total number of echoes that can be acquired. In general, for high resolution imaging based on sshEPI protocols the reduction of the long readout is substantial. Long readouts diminish image quality by severe $T_2$ and $T_2^*$ decay, causing blurring, low signal and distortions related to $B_0$ inhomogeneities. SENSE in combination with partial Fourier acquisition is a very effective way to achieve short EPI readouts.

However, it has to be taken into account that the proposed SNR approximations depend on other factors as well. For instance the coil configuration has a great influence on SNR efficiency. An optimal coil configuration includes low noise correlation and consequently low local $g$ values, resulting in better SNR efficiency at high SENSE reduction factors. The influence of the repetition time on SNR was neglected in this study. It becomes significant only when the actual relaxation period of imaged tissue is in the same range as $T_1$. Equation 6 and 8 depend on the relaxation parameter $T_2$. Although the brain consists of a variety of tissues with a spectrum of relaxation parameters, $T_2$ was chosen in accordance with the average value of white matter at 3 Tesla (61). Changing this parameter leads to a scaling of the rSNR curves without qualitatively changing their course or the location of their maxima.

The validation using the NEMA standard method seems to confirm the SNR evaluation. Both methods differ maximal 11 % in amplitude. A possible explanation for this incongruity could be a difference in object geometry as well as an insufficient agreement of the relaxation characteristics. The optimal acceleration factor with respect to SNR differs by 0.2 or approximately 10 %. The alternative approach is accurate but time consuming and therefore not feasible for acquiring in-vivo data.

For the images shown in Figure 6 and 7 a SENSE factor of $R = 2.4$ was chosen. This is a compromise between high SNR and a narrow PSF. At $R = 2.4$ the SNR is 4 % lower than the maximum at 2.1, at the same time the PSF is reduced by approximately 10 %. Therefore, an increase in SENSE acceleration from 2.1 to 2.4 seems to be profitable. A significant reduction in the width of the PSF can be observed especially in the range between $R = 1$ and $R$
The resulting good image quality of the SENSE images can be appreciated in Figure 6 and 7. Coronal images acquired with EPI-based sequences often suffer from strong susceptibility artifacts close to the temporal lobe or the cerebellum. The high resolution maps in Figure 7 demonstrate the excellent image quality when combining SENSE with partial Fourier acquisition – even in a coronal plane.

Given the limited imaging time available in clinical situations, time efficiency is very relevant. The clinical examples provided in Figure 8 were scanned with a 7 minutes protocol, without ECG triggering or navigator phase correction. The disease model that is presently investigated and has been used as an example to demonstrate the technical improvements in the present study is intracranial arteriovenous malformations (AVM). In these patients, conventional MRI sequences provide excellent anatomical detail for the relation of the lesion with the brain parenchyma. Magnetic resonance angiography also reveals the vascular dynamics of the AVM. DTI has not yet assumed a definitive role in the diagnostic evaluation of AVMs. However, with its ability to provide in-vivo mapping of the organization of deep tissues, it is a promising research tool that affords non-invasive data about the direct effect of these lesions into the adjacent white matter tracts and also potential secondary effects (i.e. Wallerian degeneration) resulting from involvement of the overlying cortex. It has been already demonstrated that DTI is more sensitive to damage produced secondary to Wallerian degeneration than T2-weighted MRI (100% vs. 50% sensitivity, respectively) (65). By adding this technique to the diagnostic battery of test available to the specialties that deal with this kind of vascular pathologies, DTI can have an important role in treatment planning for the endovascular surgeon, the neurosurgeon and the radiation therapist.

When performing studies with a resolution in the sub millimeter realm brain motion during the cardiac cycle might have to be considered. Ref. (66) reported a peak brain displacement in the range of 0.1 – 0.5 mm for all the structures except the cerebellar tonsils, which had greater displacements (0.4 mm). As a consequence, future DTI-studies with an increased resolution comparable to the range of pulsatile brain displacement might require ECG triggering.

Pulse sequences descendant from single-shot techniques, such as multi-shot EPI, spiral imaging and FSE could accomplish similar improvements on image resolutions. They are insensitive to motion artifacts when the readout time (~100 ms) is short compared to the time scale of bulk motion (~1 s). However, ensuring data consistency across multiple excitations is difficult in DWI acquisition. Those sequences require motion correction such as phase navigation. Nevertheless, the simplicity and robustness of plain single excitation acquisition make the discussed strategy a promising alternative to MR imaging using multiple-shot techniques.
Conclusion

In this work the influence of SENSE on image properties such as the PSF and SNR has been evaluated for DTI based on single excitation echo-planar protocols. The parallel approach narrows the PSF in the phase-encode direction and improves SNR efficiency by reducing the echo time, as suggested by estimation of the SNR behavior. While preserving the advantages of sshEPI, SENSE-DTI allows diffusion mapping with high resolution in the submillimeter range and minimal susceptibility artifacts. A suitable compromise between SNR and PSF is provided for two different gradient systems. The presented patient results show the potential of DTI in conjunction with SENSE in a clinical setting, permitting detailed depictions of diffusion anisotropy. The performance of SENSE-DTI will likely benefit from increasing the number of coil channels since higher reduction factors are achievable (narrower PSF, less distortions related to susceptibility variations) and a further increase in image SNR is expected.
3. Depicting Axonal Terminations in Cortical Gray Matter

For submission to *Proceedings of the National Academy of Sciences*:
“Non-Destructive Depiction of Axonal Terminations in Cortical Gray Matter Using Focused SENSE Diffusion Tensor MRI”
Abstract

A better understanding of the living human brain requires precise knowledge of neuronal connections between cortical and subcortical neuronal populations. Until now the depiction of axonal fibers to its origin in the cortical gray matter has been impeded due to the lack of adequate non-invasive methods. In this work, a high-resolution diffusion tensor imaging technique is used to reveal the microscopic axonal organization at the intracortical level non-destructively in the human visual cortex. A sensitive miniature phased array detector in combination with parallel magnetic resonance imaging at 3 Tesla permits the acquisition of in-vivo tensor maps of the occipital lobe with a sub-millimeter pixel resolution of $0.58 \times 0.58$ mm$^2$. The axonal trajectories reconstructed from the diffusion data penetrate into the cortical ribbon where their radial arrangement perpendicular to the cortical surface may represent the vertical organization of the white matter in the cortex. This is consistent with the known microstructural organization of the cerebral cortex. Diffusion tensor imaging with comparable resolution has previously been achievable only in small-bore animal scanners at field strengths more than triple that used in this study. The benefits and current limitations of the method and its underlying model are also discussed.

Introduction

The development of neuroimaging techniques (particularly PET and fMRI) has permitted the direct merging of anatomical and functional information of the human brain to design maps relating function with location (67). This combination has enabled the identification of specific cortical areas that respond selectively to various aspects of cognitive and sensorimotor processing. However, regionally specific effects depend not only on a classification based on anatomy, but also to connections among areas (68). Visualization of communication pathways between cortical and subcortical neuronal populations on an individual basis is a necessary step for understanding anatomical connectivity.

Connectivity has been extensively studied in the non-human primate brain using various degenerative methods (69,70) and tracing experiments (71-75). However, the human brain remains poorly investigated due to the lack of methods for measuring neural connections non-destructively. A non-invasive method that appears promising for the investigation of the neuronal network in the living human brain is Diffusion Tensor Imaging (DTI) (3,12). This technique is unique in that it provides structural information at the microscopic scale by allowing the examination of the anisotropic nature of diffusion within the observed tissue. It is based on the measurement of the three-dimensional (3D) water diffusion properties, as described by a local diffusion tensor, thus permitting the characterization of the directive organization of human brain tissue. Parameters associated with the diffusion tensor, such as the fractional anisotropy (FA) (12,76), give an indication of the degree of tissue organiza-
3. Depicting Axonal Terminations in Cortical Gray Matter

By measuring the molecular diffusion of water along neural pathways, DTI techniques have been widely applied for determining the orientation of fiber tracks in the white matter of the human brain (see Refs. (77) and (78) for review). Line propagation algorithms, for instance, reconstruct fiber trajectories throughout the brain by tracking the direction of fastest diffusion from a grid of seed points (14,17,79). Major fiber tracts in the white matter have been successfully imaged using this reconstruction strategy (39,40,80). This in-vivo technique shows great potential to clarify the structural basis of human brain cortical interactions in a non-destructive manner.

However, a full exploration of human brain connectivity requires that fiber tracts be reconstructed and followed to their intracortical neuronal origin, preferably with the single-neuron accuracy achieved by invasive tracer techniques in non-human primates. Whereas in white matter axonal membranes and myelination modulate the degree of anisotropic water diffusion (81), gray matter has a relatively low anisotropy. Cortical gray matter anisotropy results from an organized microstructure, where the size of “periodic structures”, i.e. axons and dendrites that give rise to the diffusion anisotropy, is much smaller than in white matter. Directional diffusion properties are associated with a significant component of parallel interconnecting fibers both within and between cortical layers. Conversely, the cell bodies of cortical neurons produce quasi-isotropic water diffusion. Measurements of FA in major white matter bundles thus reveal values of up to 0.8, whereas the FA of cortical gray matter is approximately 0.2 (82). A value of 1 is associated with purely anisotropic diffusion and a value of zero with isotropic diffusion. The resulting diffusion tensor appears either more isotropic, without fully reflecting the microscopic anisotropy, or it contains a set of diffusion directions that preclude the extraction of a single specific preferred direction. Resolving intravoxel heterogeneity can be achieved either by increasing the spatial resolution (thus diminishing the size of the voxel), or by developing strategies (e.g., modeling of the diffusion process in the neural tissue) that are able to resolve multiple intravoxel fiber directions (83,84).

Distinct anisotropy has been found in the Apparent Diffusion Coefficient (ADC) of the cortical and subcortical gray matter of the mouse brain (85). The major diffusivity within the cortex pointed radially outward in a coronal image slice. This is in agreement with the direction of the pyramidal cells in the rat cortex, which extend from the basal ganglia out towards the brain surface. The radial organization of the cortex has also been demonstrated using DTI in the human fetal cerebrum at 26 weeks of gestational age before the appearance of a prominent laminar organization that characterizes the adult cortex (86). Recently, Ronen et al. have published preliminary results of fiber tracking in the cat visual cortex (87), where multidirectional diffusion MRI data were decomposed into fast and slow diffusion tensors using a biexponential model. Fiber trajectories were generated from the slow diffusion tensor. It was found that its anisotropy was higher than that measured by conventional DTI, while reflecting a similar directionality. This model may extract information about the diffusion characteristics of water in various compartments, such as the extra- and intracellular
space, but it is not able to overcome volume averaging effects. Q-ball imaging (QBI) (84), a modeling strategy that can resolve intravoxel heterogeneity, has been used to reconstruct the complex arrangement of human white matter fibers at the cortical surface (88). The fiber architecture at the cortical margin was depicted with an in-plane voxel resolution of 2.8 × 2.8 mm². QBI is model-independent and therefore highly appropriate for diffusion imaging of complex tissue. However, to determine whether the reported surface-normal diffusion component originates from gray matter, it is important to perform QBI with sufficient spatial resolution to resolve purely gray matter voxels. All of the previous studies pursuing fiber tracking within the cortex have emphasized that image resolution is of outmost importance for the extraction of anisotropy data for fiber tractography.

High spatial resolution can only be achieved with a high signal-to-noise ratio (SNR). The voxel size and SNR are strongly linked, the latter being inherently lower in diffusion measurements than in conventional imaging due to the effects of diffusion weighting. To overcome this obstacle, the use of receiver coils with very high sensitivities and a high main magnetic field are required. Increased local sensitivities at cortical level can be provided by miniature surface coils. Covering a large section of the brain with multiple miniature coils also permits the application of parallel imaging techniques.

The benefits of the Sensitivity Encoding (SENSE) (10) parallel imaging technique was demonstrated in combination with DTI (58). SENSE was shown to improve image quality by mitigating effectively both susceptibility artifacts and blurring. By reducing blurring, SENSE conferred DTI an increased intrinsic resolution.

In the present work, a miniature coil array is utilized for SENSE-DTI to achieve detailed visualization of the visual cortex in vivo. This area was identified as the ideal location to investigate cortical gray matter using DTI since it is anatomically well understood, and its stimulation is relatively straightforward when BOLD-fMRI is incorporated in future studies. The experimental setup extends resolution beyond previous limitations, thus enabling 3D reconstruction of fiber tracks at the intracortical level.

Materials & Methods

Subjects and MRI Hardware

DTI data were acquired from 6 healthy volunteers using a 3 T Philips Intera whole-body MRI scanner (Philips Medical Systems, Best, the Netherlands) equipped with a Quasar Dual gradient system. It provides a maximal gradient strength of 80 mT/m and a slew rate of up to 200 mT/m/s.
Depicting Axonal Terminations in Cortical Gray Matter

Figure 1: Single miniature coil and surface coil array. a: Miniature coil. The loop dimension is 35 × 70 mm. b: Surface coil array consisting of three elements. Each coil was wrapped with foam and shrinkable tubing. The coil configuration was fixed on an arced plate of 200 mm diameter made of Plexiglas. In comparison to the setup a regular pen.

Coil Setup

To achieve the SNR required for high-resolution DTI of the cortical ribbon suitable for an in-vivo human study, a dedicated receive-only radiofrequency coil array was developed. The dimensions of each element were chosen to maximize signal strength. To achieve the required penetration depth and field of view, the shape of each coil loop was chosen to be a 35 mm × 70 mm rectangle (Figure 1a). Each rectangular loop was connected to a high-impedance, low-noise preamplifier through a matching network to minimize the effects of inductive coupling (89), and attain favorable noise figure (90), respectively. The array in its final form is assembled by placing several such coils on an arced acrylic plate whose 10 cm radius of curvature permitted a comfortable fit to the occiput of the volunteer’s head (Figure 1b). Depending on the desired lateral field of view (FOV) either three or five coils were used.
The coils’ noise performance was evaluated by imaging a five liter aqueous phantom having approximately the shape of a parallelepiped with dimensions 130 mm × 180 mm × 250 mm and conductivity similar to that of soft tissue. Three coils were placed adjacent to each other so that a space of ~1 mm separated the long sides of the loops. Spin echo images were acquired and SNR was averaged along a line 120 mm long, parallel to the row along which the coils were arranged, to smoothen spatial variations of the signal in that direction. The spacing between the coil array and the phantom was then varied between 5 and 13 mm to create different loading conditions (Figure 2).

**Imaging Protocol**

\( R = 2.4 \)-fold SENSE reduction was applied in the LR-direction using a diffusion-weighted (DW) single-shot spin-echo echo planar imaging (sshSE-EPI) scheme (matrix = 256 × 256, FOV = 150 × 150 mm\(^2\), 5 slices, thickness = 2.5 mm, \( TE = 67 \) ms, \( TR = 2140 \) ms, partial Fourier acquisition = 60 %). The effective in-plane resolution achieved was 0.58 × 0.58 mm\(^2\) (Figure 3). Diffusion weighting with a \( b \)-factor of 1400 s/mm\(^2\) was carried out along 15 icosahedrally distributed directions (91), complemented by one scan with \( b = 0 \). In order to compensate for motion, the signal averages were grouped into two scans of 12 averages each, permitting registration of the groups before final averaging. The duration for one scan was 12 minutes, leading to a total scan time (including the SENSE reference scan) of 26 minutes.
3. Depicting Axonal Terminations in Cortical Gray Matter

Figure 3: High resolution (580 × 580 µm² in plane) diffusion-weighted images of the occipital lobe. The images were obtained with the minia-
ture coil array consisting of five coils using 2.4-fold SENSE accelera-
tion. The diffusion weighting was b = 1400 s/mm².

Postprocessing and Visualization

After SENSE reconstruction, retrospective interscan motion correction was performed using a 3D rigid co-registration algorithm. Subsequently, eddy-current-induced image warping was removed with an affine registration algorithm (64) and the diffusion tensor’s elements were derived by singular value decomposition. In contrast to Ref. (87), where the cat visual cortex was investigated using a biexponential diffusion model, data were fitted to a single-
compartment diffusion model. After diagonalization, the eigenvalues and eigenvectors were determined and color-coded diffusion orientation maps were created (Figure 4b). Each arrow is parallel to the tensor’s largest eigenvector and its length is proportional to the local
FA value. The fiber trajectories in Figure 4c were reconstructed using standard line propagation based on the FACT algorithm (13). The rectangular seed area was placed in the white matter close to the white/gray matter junction, covering approximately 20 voxels. From each voxel five trajectories were launched in both directions. The algorithm terminated when a certain lower limit FA value was reached. A value of FA = 0.1 was chosen in order to trace the structure within the gray matter. In addition to the advantages of parallel imaging with respect to artifacts and blurring, the tractography approach enabled to “trace” fiber tracts to specific cortical neuronal populations. Postprocessing was performed using a dedicated software package developed in C++.
3. Depicting Axonal Terminations in Cortical Gray Matter

Figure 4: Magnified sulcus visualized with three different methods. 

- **a:** Diffusion weighted image of the occipital lobe using a coil array consisting of three coils. 
- **b:** Color-coded main diffusion vectors superimposed on T2-weighted (b = 0) image. 
- **c:** Reconstructed trajectories representing nerve fibers. The seed area was located anterior to the sulcus. 

Figure b and c reflect the same (magnified) sulcus as shown in a.

**Results**

According to Figure 2 the SNR does not vary appreciably with the coil-phantom spacing but is only a function of the distance between the coil and imaging voxel. This indicates that sample noise is a minor contribution to the overall noise, which is to be expected given the coils’ limited field of view. The SNR at the object’s surface is four times higher than at 35
3. Depicting Axonal Terminations in Cortical Gray Matter

mm depth, assuming a gap of 5 mm between coil and object to accommodate a layer of foam insulation. A depth of 35 mm corresponds to the width of the miniature coil, which is nominally taken to be its viewing depth.

Figure 3 demonstrates DTI data acquired with a detector array consisting of five miniature coils. A T2-weighted image ($b = 0$) as well as two sensitivity encoded base DW examples obtained with different diffusion encoding directions are presented. The data are free of residual SENSE aliasing artifacts and reveal only minor distortions related to susceptibility variations. The images demonstrate an excellent distinction between gray and white matter. All images are hyperintense at the anterior border due to the restricted penetration depth of the coils. While conventional images are shaded where coil sensitivity is reduced, the SENSE procedure balances the sensitivity inhomogeneity of the coil array, which leads to an increase in the signal where the coil’s sensitivity is low. Those areas are, as expected, noisier than regions nearer to the surface coils. According to Figure 2, a penetration depth of 30 mm reduces the SNR to 28 % of the value at the surface of the head. Due to the high base sensitivity of the surface coils the SNR at 30 mm is still sufficient for depicting anatomical details with high spatial resolution and contrast.

The base DW images of the reconstructions shown in Figure 4 were obtained with an array consisting of three miniature coils. The rectangle of Figure 4a illustrates an area of $32 \times 22$ mm$^2$, which is enlarged in Figure 4b and 4c. Looking at the main diffusion directions represented by the color-coded arrows (Fig. 4b), the gray/white matter junction is clearly identifiable by the sharp change in orientation of the diffusion vectors. The anisotropy in the cerebrospinal fluid within the subarachnoid space (hyperintense on the T2-weighted background image) is low and thus the displayed diffusion orientations appear random. A mean anisotropy of $FA = 0.25 \pm 0.08$ was determined for the gray matter in the occipital sulcus after manual segmentation. The anisotropy of the surrounding white matter tissue is $FA = 0.62 \pm 0.07$. The fibers reconstructed from the high-resolution DTI data displayed in Figure 4c can be followed to the gray/white matter junction where they visibly bend as they penetrate into the cortical ribbon. Their intracortical radial arrangement perpendicular to the cortical surface may represent the vertical organization of the white matter in the visual cortex. This is consistent with the microscopic organization of the intracortical white matter connections, which are aligned orthogonally to the cortical layers.

Discussion

The parallel imaging approach relies on the sensitivity distribution of phased array coils. For optimal performance, both SNR and the spatial uniqueness of the individual coil sensitivity profiles are important. The latter can be quantified by the geometry factor (10). The sensitivity distribution of the miniature coil phased array is sufficiently distinct to permit low geometry factors, and hence to assist an artifact-free encoding process, also for increased acceleration factors. No unfolding artifacts are visible in the images, even though a 2.4-fold
SENSE acceleration was performed in conjunction with only three coils. The robustness of the setup potentially allows for even higher SENSE factors close to the upper limit which coincides with the number of coil elements in the array.

When combined with parallel imaging, this setup facilitates the use of single-excitation echo-planar protocols for DTI. Such protocols are insensitive to motion and easy to apply. Image distortions due to susceptibility variations can be reduced by parallel imaging (58).

A fundamental advantage of the multi-channel miniature coils is that they provide very high SNR at the surface, which is required for high-resolution imaging of the cortex. High quality DTI images were obtained with an in-plane resolution of $0.58 \times 0.58$ mm$^2$. This is comparable to the resolution ($0.39 \times 0.39$ mm$^2$ in plane) achieved for the same purpose in the cat visual cortex at 9.4 T (87), a considerable result given the large difference in size between cat and human brain and the more than 3-fold increase in static field strength. Sensitivity, and hence resolution, is an increasing function of main magnetic field strength, and a decreasing function of object size. The application of SENSE contributes to achieving such a high SNR by reducing the sampling density and therefore shortening the echo-planar readout and the echo time (58). Furthermore, it narrows the point spread function, thus enhancing the intrinsic image resolution.

Fractional anisotropy in the cortical gray matter has been reported to be in the range of 0.09 to 0.24 (82,92,93), depending on the location in the cortex, the acquisition technique, the SNR of the underlying images and the age of the subjects. Compared to FA in white matter (e.g., callosal white matter, $FA = 0.81 \pm 0.03$ (92)), the gray matter anisotropy measured in the occipital sulcus is lower. The small amount of anisotropy present in cortical regions does however indicate that at least one spatial direction is prominent in the matrix of neuronal tissue. The high SNR achievable with the miniature coil array allows resolving the vertical alignment of specific neuronal cells in the cortical gray matter, as demonstrated in Figure 4.

Similar findings were reported in the cat visual cortex (87) by Ronen et al. who used a two-compartment model to decompose the data into a slow- and fast-component diffusion tensor. Fibers generated based on the slow diffusion tensor appeared to follow the vertical fibers in gray matter. The choice of such a biexponential diffusion model, also used by others (94,95), and whether this model successfully separates the intracellular and extracellular space, is still highly controversial. It is suggested that a biexponential model may be more suitable to describe the diffusion properties in gray matter because of its potential to separate both the isotropic (cell bodies, glia) and the anisotropic (axons, dendrites) intracellular diffusion components, as well as the extracellular components. The considerable microscopic heterogeneity present in the cerebral cortex makes it difficult to isolate the effect of each of those structures on the diffusion tensor. In comparison to the biexponential model, the $b$-value used in the presented study probed the “fast” diffusion component, which is associated with extracellular water.

Diffusion data based on a tensor description, whether derived from a mono- or multiexponential model, is described at each spatial location by three orthogonal vectors. However,
the complex matrix-like structure of cortical gray matter may not be characterized appropriately by such a simple model. High angular resolution diffusion imaging (HARDI), such as diffusion spectrum imaging (96,97) and q-ball imaging (84), could provide more sophisticated models to characterize the complex structure. While HARDI methods have been applied to white matter structures they have not been employed yet to investigate the neuronal architecture of gray matter. Unfortunately, data acquisition is very time consuming and therefore feasibility is still limited for in-vivo human studies.

A relatively small number of DTI slices is sufficient to visualize the fine distribution of individual axons at the intracortical level, even though the resolution achieved in this experiment (0.58 × 0.58 mm² in plane) must still be improved. The discrete columnar pattern of axon terminations in the human visual cortex was demonstrated. It is readily seen that the DTI-generated fibers penetrate the gray matter at the gray/white matter junction in a manner consistent with structures that may be identified as the vertical connections in cortical gray matter. They are aligned perpendicular to the cortical surface. The observed anisotropy presumably reflects a degree of microscopic geometrical order within the cortical tissue. It is generally agreed that the axonal cytoskeleton of neurofilaments and microtubules as well as intact membranes are the primary determinant of anisotropic water diffusion in neural fibers such as brain or spinal cord white matter (81). The anisotropy pattern observed is consistent with the microstructural organization of the cerebral cortex even though it contains only few ordered bundles of axons. The adult cerebral cortex is believed to operate as an ensemble of functionally-linked radial columns (98). However, this organization is obscured in adult cerebrum by the predominance of laminar organization. The cortex is organized horizontally in six laminas and vertically into groups of synaptically linked cells across the horizontal laminas. The basic unit of the mature neocortex is the minicolumn, a narrow chain of neurons extending vertically across the cellular layers II-VI (99). The minicolumn is located perpendicular to the pial surface, which contains all the major neural cell phenotypes. Those cells are interconnected in the vertical dimension. The general pattern of cortical connectivity linking neurons across cortical layers has been described by Lorente De No back in 1938 (100). Columnar organization has been described in a wide range of mammalian brains and in every cortical area examined in detail. This organization would account for a high anisotropy in the cortex, which is not observed in diffusion measurements. The reason is that during embryonic development (approximately 36 weeks gestational age), a sequence of cellular events during neuronal maturation results in microstructural changes with the formation of local circuits. These changes in microstructure disrupt the initially more pronounced columnar organization, resulting in relatively low water diffusion anisotropy.

It is known both from degeneration studies (101,102) and studies using axonal transport techniques (103,104) that widespread intrinsic cortical connections cover large regions within the cortical area from which they originate. Individual cortical neurons are capable of forming projections of extraordinary richness and extent. For instance, individual neurons in the cat primary visual cortex have been found to communicate over surprisingly long dis-
stances horizontally (up to 4 mm), in directions parallel to the cortical surface (105). Also, histologically stained sections of adult human cerebral cortex demonstrate bands of neural processes oriented parallel or orthogonal to the brain surface in different cortical areas.

**Conclusion**

In this report it has been demonstrated that a high-resolution DTI technique, in combination with computer algorithms for reconstruction of the anatomical data, can reveal the microscopic axonal organization at the intracortical level in a non-destructive manner in vivo for the human brain. Intracortical tracking and, potentially, quantification of individual white matter connections is a first essential step for understanding the structural anatomy of cortical organization. The high level of resolution in the occipital lobe attained in the presented study has been achieved by the use of a miniature phased array detector in conjunction with parallel MR imaging. It is anticipated that with improved resolution, more connectivity patterns in gray matter will be detected. The combination of these techniques with methods revealing the functional activity of clusters of cortical neurons may help us to understand how human brains generate and control behavior.
4. Advanced Fast Marching Tractography

Submitted to *Neuroimage* (2005):
“Resolving Fiber Crossing Using Advanced Fast Marching Tractography Based on Diffusion Tensor Imaging”
P. Staempfli, T. Jaermann, G. R. Crelier, S. Kollias, A. Valavanis, P. Boesiger
Abstract

Magnetic resonance diffusion tensor tractography is a powerful tool for the non-invasive depiction of the white matter architecture in the human brain. However, due to limitations in the underlying tensor model, the technique is often unable to reconstruct correct nerve trajectories in heterogeneous fiber arrangements, such as axonal crossings. A novel tractography method based on fast marching (FM) is proposed which is capable of resolving fiber crossings and also permits trajectories to branch. It detects heterogeneous fiber arrangements by incorporating information from the entire diffusion tensor. The FM speed function is adapted to the local tensor characteristics, allowing in particular to maintain the front evolution direction in crossing situations. In addition, the FM’s discretization error is reduced by increasing the number of considered possible front evolution directions. The performance of the technique is demonstrated using artificial data and in the healthy human brain. Comparisons with standard FM tractography and conventional line propagation algorithms show that in the presence of interfering structures, the proposed method is more accurate in reconstructing trajectories. The in-vivo results illustrate that the elucidated major white matter pathways are consistent with known anatomy and that multiple crossings and tract branching are handled correctly.

Introduction

One of the requirements for understanding brain function, both in physiological and pathological condition, is the knowledge of the architectonical organization inside the brain’s white matter. The technique of Diffusion Tensor Imaging (DTI) (106,107) promises to deliver the required information in humans and in vivo. DTI allows to measure and to describe the three dimensional (3D) water diffusion properties across tissue by a local diffusion tensor on a voxel-by-voxel basis. For each voxel with a distinct fiber alignment, the tensor’s principle eigenvector corresponds to the direction of the main diffusivity. All three orthogonal eigenvectors, weighted by the corresponding eigenvalues, span the diffusion ellipsoid which can be regarded as a 3D-visualization of the diffusion distribution within a single voxel.

A further advancement of DTI is the 3D-tracking of axonal projections, known as fiber tracking (see review articles (108-111)). This technique allows to reconstruct cerebral nerve bundles in the white matter. Fiber tractography based on DTI provides a potential method for exploring the connectivity network of the brain. It is essential, however, to be aware of the limitations of this procedure. Jones et al. (112) showed that each calculated principle diffusion eigenvector is associated with an uncertainty, due to e.g. partial volume effects. Note that the typical in-plane resolution is approximately 2 x 2 mm², which is several orders of magnitude larger than the diameter of a single nerve fiber. Thus, due to DTI’s voxel aver-
aged quantity, the principle eigenvector does not necessarily correspond to the main fiber direction, particularly when bundles intersect, branch or merge. Barrick et al. (113,114) observed tensor field singularities in such regions which results in an indistinct main diffusion direction. Consequently misleading fiber pathways may be reconstructed if the tracking algorithm incorporates only the principle eigenvector for determining the propagation direction. This has been identified as one of the main problems for fiber tracking based on DTI data (115-119). Another problem stems from the image noise inherent to each MR acquisition procedure, deviating the directions of the principal eigenvectors (114,120,121).

Different approaches have been proposed so far in order to solve these problems. One of the most promising for line propagation algorithms is the tensor deflection method (122,123). It uses the entire information carried by the diffusion tensor to estimate the trajectory. When the diffusion distribution within the voxel of interest is planar, suggesting inhomogeneous fiber alignment, the propagation direction is determined by the superposition of the first and second eigenvector. Another approach uses a diffusion metric based on the diffusion ellipsoid’s shape, differentiating between prolate, oblate and spherical fiber distributions (123-125). Depending on that measure, the propagation direction is calculated by a weighted sum of all three diffusion eigenvectors.

In contrast to line propagation algorithms, the level set (126) and fast marching (FM) (127) techniques are based on evolving a 3D-wave front through a volume of interest. Parker et al. proposed a FM algorithm (128) adapted to DTI data. Its reliability was verified in the macaque brain (128,129). The front evolution is controlled by the speed function $v$, which direction and speed depends on the diffusion tensor. The FM method can be visualized as the motion of a wave front emanating from a source. This concept permits trajectories to diverge and merge. Another benefit is the access to a voxel based connectivity metric (128) which represents the probability of the corresponding voxel to be connected to a seed area. This metric can be used to color-code the reconstructed fiber bundle corresponding to its likelihood or can serve as threshold criteria to abort fiber reconstruction.

Until now, only FM algorithms have been suggested which consider solely the principle eigenvector. As a result, wrong fiber pathways may be reconstructed in regions where the principle eigenvector does not describe adequately the main fiber direction (e.g. in crossing situations). Another intrinsic property of the FM method is its discrete front evolution, meaning that the possible propagation directions are limited by the number of neighboring voxels. The limitation of 26 possible directions may cause discretization errors. Tournier et al. (130) suggested an adaptive evolution grid to overcome this obstacle. However, their algorithm is not able to resolve fiber crossing.

In this study, an advanced implementation of FM is proposed. Combining the advantages of classical FM and of the tensor deflection approach, it is hypothesized that the proposed algorithm can resolve correct pathways in brain regions where fiber systems intersect. To this end, the algorithm takes into account the entire information contained by the diffusion tensor. Furthermore, it should allow to reduce the discretization error originating from the finite
number of evolution directions. The performance of the proposed algorithm is measured and compared with existing algorithms both in artificial diffusion data modeling fiber crossing and branching and \textit{in vivo} with healthy volunteers in well known anatomical structures.

\section*{Methods}

\subsection*{The Fast Marching algorithm}

The standard FM algorithm described in \cite{128} starts from a manually defined seed area. From the start region a wave front propagates through the 3D-volume. During iteration the voxels are subdivided into three groups: “front voxels” at the inner boarder of the spreading cloud, voxels in the \textit{narrow band} (members of the adjacent outer shell) and the “outside voxels” (see Fig. 1). In each iteration step the front expands from an \textit{origin} front voxel at location \(r'\) to a narrow band \textit{destination} voxel at position \(r\). The enlargement of the front, i.e. the transition from \(r'\) to \(r\), is characterized by a speed function \(v\). In \cite{128} two speed functions were proposed. The one retained for the model used in this study reads as follows:

\begin{equation}
 v(r) = \frac{1}{1 - \min\left(\|e_1(r) \cdot n(r)\|, \|e_i(r') \cdot n(r)\|, \|e_j(r) \cdot e_j(r')\|\right)} \label{eq:1}
\end{equation}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Front propagation depicted schematically in 2D. The voxels are partitioned into three groups: dark grey voxels represent the spreading cloud, containing the front voxels at the inner border of the evolving wave. The narrow band voxels are colored in light grey and the outside voxels are shown in white.}
\end{figure}

The transition velocity \(v\) depends on the diffusion tensor’s first eigenvectors at the origin, \(e_i(r')\), and at the adjacent destination voxel, \(e_j(r)\), as well as on the vector \(n(r)\). The unit vector \(n(r)\) describes the front dispersion direction at \(r\) and thus is always orthogonal to the front. The scalar product terms in the speed function give a measure for the alignment of the three vectors to each other. The speed function is governed by the vector pair with the largest included angle. Thus the maximal front evolution velocity from \(r'\) to \(r\) occurs when all three vectors are co-linear to each other and decays to one if one vector pair is orthogonal. For each voxel in the narrow band, the arrival time \(t_r\) is updated by the quotient of the distance \(|r - r'|\) and the front velocity \(v\):
4. Advanced Fast Marching Tractography

\[ t_r = t_{r'} + \frac{|r - r'|}{v} \]  \[2\]

For each iteration step the destination voxel of the narrow band with the earliest arrival time is included into the front. To prevent wave expansion into gray matter or cerebral spinal fluid, a minimal fractional anisotropy (FA) is required for each voxel to be included into the front.

**The Advanced Fast Marching Algorithm: Resolving Fiber Intersections**

Brain regions with fiber intersections are characterized by an oblate diffusion ellipsoid. Due to the lack of a single pronounced diffusion direction in such areas it is insufficient to describe the arrangement of the intra voxel axons only by the tensor’s first eigenvector. Therefore, the proposed advanced FM method accounts for the diffusion ellipsoid’s shape, which reflects the type of fiber arrangement within the voxel of interest. Then, depending on the local combination of ellipsoids, different speed functions are applied. Additionally, an increased number of potential front expansion directions are considered in each iteration step in order to reduce the discretization error.

**Speed Functions**

In contrast to the work of Parker et al. (128), the vector \( n \) of Eq. [1] in this study is defined as the front propagation direction \( n = r - r' \). This allows to reduce the discretization error as described in the section Additional front expansion directions.

To classify the diffusion ellipsoid’s shape, the metric proposed by Westin et al. (123,131) is utilized. The metric describes the shape by a superposition of three parameters, \( c_l, c_p \) and \( c_s \). The parameter \( c_l \) is a measure for the prolate (linear) fraction of the ellipsoid, \( c_p \) for the oblate (planar) fraction, and \( c_s \) for the spherical fraction. In the proposed method the prolate measure \( c_l \) is used to separate the shape spectrum in two classes. Above a threshold \( tc_l \), the shape of the ellipsoid is considered prolate, corresponding to a situation where axons highly correlate with the tensor’s first eigenvector. Below the threshold the shape is considered oblate (planar), indicating fiber crossing or branching. Based on theoretical experiments a threshold of \( tc_l = 0.27 \) was chosen. Depending on the classification of two adjacent voxels a different speed function is assigned for front propagation. Four different transition situations A-D can occur (Fig. 2).
Figure 2: Classification of two adjacent voxels: a) prolate-prolate tensor, b) prolate-oblate tensor, c) oblate-prolate tensor, d) oblate-oblate tensor. Vector $n$ corresponds to the front propagation direction, $r$ to the origin voxel inside the front and $r'$ to the destination voxel inside the narrow band.

Situations A and B both describe a front transition starting from a voxel containing a prolate diffusion ellipsoid. The velocity function [3] assigned to case A is defined similar to Eq. [1], with the difference that the terms in the denominator are squared. The squared terms cause an increase in the angular sensitivity.

$$v_1 = \frac{1}{1 - \min(|e_3(r) \cdot n|^2, |e_3(r') \cdot n|^2, |e_i(r) \cdot e_i(r')|^2)}$$  \[3\]

The velocity function [4] assigned to case B is expressed with a function similar to Eq. [3]. However, since the diffusion at $r$ is characterized by a plane, the alignment is measured relative to the plane. Hence the unit vector $e_3(r)$ is used which characterizes the diffusion plane and is orthogonal to it. The term $1 - |e_3(r) \cdot n|$ is then a measure of the co-linearity of the evolution direction and the local diffusion plane. Accordingly, the term $1 - |e_3(r) \cdot e_3(r')|$ quantifies co-linearity between the linear diffusion direction at $r'$ and the diffusion plane at $r$. Since these two terms are considered to represent less confident information about the possible diffusion path than the third, unchanged term $|e_i(r') \cdot n|^2$, they enter the final speed function with less angle sensitivity and thus are not squared:

$$v_2 = \frac{1}{1 - \min((1 - |e_3(r) \cdot n|), |e_3(r') \cdot n|^2, (1 - |e_3(r) \cdot e_3(r')|)))}$$  \[4\]

In situation C the front evolution speed function [5] is applied:

$$v_3 = \frac{1}{1 - \min(|e_i(r) \cdot n|^2, (1 - |e_3(r') \cdot n|), (1 - |e_i(r) \cdot e_3(r')|), |n \cdot n_{old}|)}$$  \[5\]

In analogy to the previous situations, $v_3$ consists of three terms which take into account the angles between the vectors $e_i$ ($e_3$ in case of planar diffusion) and $n$. The incorporation of $|n \cdot n_{old}|$ provides a “memory” for the front entrance direction at $r'$ in previous iterations. It penalizes propagation directions that would represent a change in the front evolution direction. As in Eq. [4], the term containing the most reliable orientation is squared.

In the last case, D, diffusion in both, origin as well as destination voxel, is characterized by an oblate ellipsoid. In this case, the transition is described by speed function [6]:

$$v_4 = \frac{1}{1 - \min(|e_i(r) \cdot n|^2, (1 - |e_3(r') \cdot n|), (1 - |e_i(r) \cdot e_3(r')|), |n \cdot n_{old}|)}$$  \[6\]
In contrast to case C, diffusion in the destination voxel is planar. Therefore, \(1 - \|e_1(r) \cdot e_3(r')\|\) is replaced with \(\|e_3(r) \cdot e_3(r')\|\). The “memory” term \(n \cdot n_{old}\) is squared due to the idea that in crossing situations the trajectory’s bending energy should be minimal. It causes a reduction in velocity if directional changes occur.

**Additional Front Expansion Directions**

Since FM is performed in a discrete voxel grid, the number of possible propagation directions is limited to 26. To determine the next front member from the center of the origin voxel causes discretization errors (Fig. 3). In the proposed advanced FM implementation the thickness of the narrow band is enlarged, thus considering for each iteration step an increased number of possible front propagation directions. This effectively reduces the discretization error (see Fig. 4 for a schematic two dimensional (2D) depiction).

For the propagation in one of the additional directions, the implementation includes all voxels into the front which are intersected by the vector \(n\). They are assigned to the same arrival time as the destination voxel at \(r\).

**Reconstruction of Trajectories and the ‘Connectivity Metric’**

Trajectories are reconstructed by connecting voxels in direction of the inverse front evolution direction. To adjust the number of trajectories the connectivity metric \(\Phi_1\) proposed in (128) was used (Eq. [7]). This metric is adequate with respect to the used model because it involves information of the whole diffusion tensor.

\[
\Phi_1(\gamma) = \min_{\tau} v(\gamma(\tau)).
\]

Figure 3: Discretization error. Light grey arrows and diffusion ellipsoids indicate the global course of the fiber structure. Black line denotes fibers reconstructed by a continuous tracking algorithm. Dashed black line shows the reconstructed FM trajectory. Discretization error corresponds to the dark grey arrows.

It is defined for any putative pathway, \(\gamma\), as the minimal speed \(v\) along a particular path. The metric corresponds to the likelihood that any given path is representative for a true anatomical connection. By setting a threshold for \(\Phi_1\), the most “likely” pathways can be extracted.
In contrast to Ref. (128) where trajectories were smoothened using a gradient descent method, a spline interpolation is performed along each trajectory.

**Artificial Data**

Artificial diffusion data were created using the following geometric parameters: 128 x 128 x 46 voxels, in-plane resolution = 1.56 x 1.56 mm, slice thickness = 2 mm. Each voxel consisted of three orthogonal vectors representing the tensor’s eigenvectors. The vectors together with the corresponding eigenvalues were used to model each voxel’s diffusion properties.

The artificial data consisted of two intersecting cylinders whose positions, inner and outer radii as well as the slopes of the first eigenvectors were adjustable (Fig. 5). With these data, different crossing, kissing and branching situations with arbitrary intersection angles were imitated. In crossing areas the tensor’s first and second eigenvalues were assumed to be equal (123). Note that by superimposing the two cylinders the principle eigenvectors in the crossing region do point in direction of the vector sum of the principal eigenvectors of both cylinders. As a consequence the diffusion ellipsoids are planar shaped in those areas, in contrast to linear shaped ellipsoids in regions without fiber intersection (Fig. 5).
4. Advanced Fast Marching Tractography

Figure 5: Left side: Artificial data consisting of two intersecting cylinders. Right side: zoomed view of the modeled crossing area, illustrating oblate diffusion ellipsoids (black) in the intersection area and prolate shaped ellipsoids (grey) elsewhere.

In-vivo Data

Data from 18 healthy volunteers were acquired using a 3 T whole body system (Philips Medical Systems, Best, the Netherlands) equipped with 80mT/m/ms gradient coils and a 8-element receive head coil array (MRI Devices Corp., Waukesha, USA). Partial Fourier acquisition of 60% was applied in a diffusion-weighted single-shot spin-echo EPI sequence. The geometric parameters were chosen equivalent to the artificial data: FOV = 200 x 200 mm², matrix = 128 x 128, 46 contiguous slices, slice thickness = 2.0 mm. 2.1-fold sensitivity encoding (SENSE) (10) was applied in order to reduce susceptibility artifacts and to enhance image quality (132,133). Diffusion weighting with a maximal $b$-factor of 1000 s/mm² was carried out along 15 icosahedral directions (91), complemented by one scan with $b = 0$. A total of 2 averages were obtained, resulting in a net scan time of 18 min 17 s.

Figure 6: Comparison test between standard (left side) and advanced
(right side) FM algorithm. Each cylinder consisted of a concentric vector field. Reconstructed fibers are shown in blue. Possible front propagation directions are indicated by the yellow arrows. The red rectangle marks the tracking seed area.

Data Preprocessing

Eddy current-induced image warping was reduced with a correlation-based 3D-affine registration algorithm (134) which registered the diffusion-weighted data to the \( b_0 \)-image. The independent elements of the diffusion tensor were obtained on a voxel-by-voxel basis using singular value decomposition. After diagonalization of the diffusion tensor, the eigenvalues and eigenvectors were determined.

Comparison Tests Using Artificial Data

An artificial cylinder was composed consisting of a concentric vector field. First, the effects of the additional front propagation directions were explored. From a seed area at the left side of the cylinder trajectories were reconstructed using standard and advanced FM (Fig. 6). Further, with the use of intersecting 3D cylinders, two elementary fiber arrangements were tested: fiber crossing and branching. Those arrangements were modeled by varying the distance between the cylinder’s center as well as the slope of the vector field with respect to the long axis of the cylinders. An attempt to resolve each of the virtual fiber architectures was carried out with each of the following three algorithms: the FACT algorithm (109), the standard FM algorithm, and the proposed advanced FM algorithm (Fig. 7).
4. Advanced Fast Marching Tractography

Figure 7: Evaluation of artificial crossing and branching situations. Columns from left to right: FACT algorithm (a, d, g), standard FM (b, e, h) and advanced FM algorithm (c, f, i). First row: 90° crossing situation in which the slope of the first eigenvectors of both cylinders are defined orthogonal to the cylinder’s long axis. Second row: branching situation. Third row: 90° intersection. The directions of the eigenvectors inside the right cylinder are parallel to the cylinder’s main axis. The red rectangle indicates the start region. Resulting fibers are shown in blue.

Validation Using in-vivo Data

DTI data were obtained using the sequence described in the “in-vivo data” section and three target fiber structures were chosen. One of them was the Cingulum, a well-marked fiber bundle passing longitudinally in the white matter of the cingulate gyrus. Seed areas were placed in a coronal slice covering its cross section (Fig. 8). To test the performance in regions with known fiber intersection, the corticospinal projection system and the commissural system of the Corpus Callosum (CC) was selected. The latter penetrates the Corona Radiata, an area where the radiation of the CC and axons of the corticospinal projection system intersect. For reconstructing the corticospinal tracts the seed area was placed in the brain stem (Fig. 9). The commissural system was reconstructed using a seed area in a sagittal slice covering the center of the CC (Fig 10).
4. Advanced Fast Marching Tractography

Results

Figure 6 shows a comparison of circular trajectories using the standard FM algorithm and the advanced FM algorithm incorporating additional front expansion directions. While the standard FM trajectories are of low quality due to discretization errors, the trajectories reconstructed using advanced propagation capabilities appreciate more uniform contours. They are in better agreement with the concentric arrangement of the principal eigenvectors.

Figure 9: Reconstructed trajectories of the corticospinal pathway. a: FACT algorithm, b: standard FM algorithm and c: advanced FM algorithm. The pathways were seeded in the brainstem. Left and right tracts were reconstructed independently. Fibers are directionally color coded as in Figure 8.

The results obtained in the artificial data are presented in Figure 7. Conventional line propagation (FACT algorithm), standard and advanced FM tractography were compared. In the
composition with two orthogonal intersecting cylinders (top row), the advanced FM algorithm reconstructed the circular trajectories of the left cylinder continuously. In the intersecting region the interfering cylinder did not effect a deviation of the trajectories. In contrast, the pathways of the FACT and the standard FM algorithm were deviated into the second cylinder. In the second situation (middle row), the differences between reconstructions of the standard and the advanced FM were minimal. Both algorithms were able to reconstruct bifurcating trajectories. The “fibers” of the FACT algorithm were deviated into the right cylinder. The arrangement exhibits the advantage of algorithms based on the FM technique: they allow trajectories to bifurcate. The third configuration (bottom row) reveals deviated trajectories when processed using the FACT algorithm. In the crossing area (intersection of both cylinders) the stream lines were diverted by 90° in the orthogonal through-plane direction (Fig. 7g). The standard FM trajectories did not penetrate the intersection. Due to a strong deceleration of the wave in the junction the front continued propagating into parallel slices. The advanced FM algorithm reconstructed concentric trajectories which were not deviated by the crossing zone.

Figure 10: Depictions of color-coded commissural fibers overlaid on coronal FA maps. The same color-coding was used as described in Figure 8. From left to right: FACT algorithm (a), standard FM algorithm (b) and advanced FM algorithm (c). The seed area was defined in a sagittal plane as the segmented cross section of the Corpus Callosum.

Figure 8 – 10 illustrate comparisons using in-vivo data. The results in Figure 8 demonstrate the ability of all three algorithms to reconstruct the Cingulum, a structure with relatively well defined boarders and with few fiber intersections. Compared to FACT and standard FM algorithms, advanced FM tractography reveals bundles running from the cingulate gyrus to the cortex. Regarding the corticospinal tracts of the projection system (Fig. 9) each algorithm exposes similar fibers. The white matter pathways of the advanced FM algorithm diverge at the superior end of the tracts. The estimates of the radiating CC (Fig. 10) show the diversity of the three algorithms. The pathways of the advanced FM algorithm penetrate large parts of the hemisphere, which is in better agreement with anatomical reality. In comparison, the trajectories of the FACT and the standard FM algorithm were deviated in the area of the Corona Radiata, where the commissural system intersects the pyramidal tracts.
Discussion

An in-vivo verification of fiber mapping algorithms faces serious challenges. The knowledge of the anatomy beyond the gross fiber pathways is absent and the voxel resolution is restricted. A resolution and specificity comparable to the one of tracer and histological staining techniques would be required for a reliable validation. However, the strong invasive nature of these techniques prohibits an in-vivo appliance. For these reasons, the properties of the presented technique were studied using artificial data, modeling fiber crossing and branching. In a subsidiary step, the depiction of three main fiber pathways was analyzed.

Based on artificial data, the advanced FM algorithm reconstructed pathways most accurately. Trajectories could be tracked through regions with heterogeneous “fiber” arrangements. The FACT and the standard FM algorithm failed to reconstruct closed circular pathways when a second structure interfered. In contrast to the presented method, they determine propagation by only the tensor’s first eigenvector, which may result in erroneous fiber pathways. When multiple fiber directions overlay (as modeled by the intersecting cylinders), the diffusion tensor’s averaged quantity impedes a correct depiction of the underlying fiber structure. Then, diffusion is no longer characterized by a single vector along the ellipsoid’s long axis, but the multiple directions of a plane. Note that in planar ellipsoids the first eigenvector can be located in the plane arbitrarily with respect to the fiber orientation. In Figure 7a, b and d the trajectories were deviated into the adjacent cylinder. The reason is that the direction of the planar shaped first eigenvectors in the intersection region contained a strong horizontal component caused by the mathematical superimposition of the diffusion tensors. Compared to line propagation algorithms, FM tractography benefits from its intrinsic characteristic of allowing trajectory branching, as can be observed in Figures 7 e, and f. The propagating wave is split in the intersection area into two fronts, which follow both cylinders “simultaneously”. This characteristic is of importance for in-vivo reconstructions, since large fiber bundles bifurcate all along to smaller structures.

Reconstructions of the Cingulum, the motor pathway and the radiation of the CC in the healthy brain have been presented in Figure 8 – 10. The localization and course of the pathways identified using advanced FM tractography are consistent with known anatomy. Both standard and advanced FM tractography were able to elucidate branching fibers of the motor pathway as well as of the radiating CC. The fiber divergence of the projection and the commissural system is one of the tractography quality criterions. Fiber crossings in the Corona Radiata often prohibit the penetration of trajectories and thus hinder fibers to diverge. The reason is that DTI provides information concerning the average orientation of fibers at the voxel level and if this volume-averaged information is used to reconstruct a pathway, either false positives or an abortion of the tracking process may be observed. As Figure 9c and 10c demonstrate, the advanced FM algorithm is able to continue through such regions and follow the “correct” pathways. However, to allow for a detailed validation concerning the reliability and reproducibility of reconstructing fiber pathways additional studies are required.
The core of the presented algorithm is its capability to detect fiber crossings and to proceed accordingly. The precondition for a successful detection is the appropriate classification of the diffusion ellipsoids into subclasses. In the presented implementation this is accomplished by dividing the shape metric into two realms. The estimation of a suitable threshold is challenging and to some extent empirical. The attempt to avoid any discrete value by introducing a linearly weighted sum of the four speed functions achieved, however, poor in-vivo results.

The used model is based on four different situations. The assigned speed functions are symmetrical in regard to “entrance” term, “exit” term and “memory” term. The “entrance” term, for instance, is of importance when entering a voxel classified as “heterogeneous fiber arrangement”. It ensures that front evolution will occur most rapidly in the same direction as the front entered the voxel. As demonstrated in Figure 7, this strategy impedes a deviation from the origin direction, which may be caused by the interfering structure. Utilizing a linear “memory” term causes the trajectory to proceed in a straight line. Future work could incorporate higher order “memory” terms in order to allow curvatures.

DTI has the significant limitation in that it can only resolve single fiber orientations within each imaging voxel due to the constraints of the tensor model. In contrast, intravoxel fiber crossing can be resolved using techniques based on higher order descriptions of the diffusion properties, such as angular diffusion imaging and spectral decomposition methods (83,88,135-137). Using q-space imaging, for instance, the microscopic diffusion function has been measured directly and investigators have found that in regions of fiber crossing the diffusion function possesses significant multimodal structure (88). However, acquiring such data is very time consuming and the achievable spatial resolution is limited. In future a combination of DTI and higher order techniques could potentially contribute to resolve the neuronal architecture of the brain.

The results in this study show that the introduced additional front expansion directions allow a reduction of discretization effects. Nevertheless, a certain inaccuracy remains due to the discrete underlying voxel grid (Fig. 6). The number of front propagation directions was increased but is still limited. The discrete nature of front evolution is an intrinsic drawback of FM. An adaptive continuous FM technique, analogues to the method described in (130), could further mitigate the discretization error. Also increasing artificially the grid resolution by interpolating the data could enhance the results. Note that algorithms based on line propagation, as e.g. FACT, overcome this obstacle by continuous line integration.

The quality of the in-vivo data has a significant impact on the precision of reconstructed trajectories (114,121). The signal-to-noise ratio (SNR) and the absence of image artifacts are important factors. Since noise is always present in DTI data, an uncertainty in the orientation of the eigenvector remains (112). The uncertainty degrades the output of any tractography method, causing errors that will increase with distance from the start point. To obtain high quality in-vivo data with sufficient SNR, a high magnetic field, 3 Tesla in particular, and parallel imaging (SENSitivity Encoding, (10)) was employed. It has been shown that
DTI in conjunction with SENSE effectively mitigates both susceptibility artifacts and blurring (132,133).

In conclusion, the proposed advanced FM tractography algorithm was able to resolve fiber pathways in regions where fiber systems intersect. This was demonstrated both in artificial data and in-vivo in the human brain. Gross fiber pathways, such as the Cingulum, the pyramidal tracts and the radiation of CC, could be depicted in-vivo and were in enhanced agreement with known anatomy. The key part of the advanced FM algorithm is its ability to detect voxels containing heterogeneous fiber arrangement and to apply an according speed function. The technique is based on the level set method and thus allows trajectories to bifurcate. However, a validation based on the neural histoarchitecture and an elaboration of a “gold-standard” remains an inalienable requirement for the assessment of any DTI-based tractography technique.
5. Fiber Tracking in Multiple Sclerosis

Adapted from *Proceedings of the Swiss Society of MS* (2004):
“Preliminary Results of Multiple Sclerosis-Induced Changes in White Matter Fasciculi Revealed by Diffusion Tensor Tractography”
Abstract

For diagnosis and treatment planning of patients suffering from Multiple Sclerosis (MS) it is essential to assess in-vivo its heterogeneous pathological hallmarks in order to classify the phenotype of MS. The aim of the presented study was to evaluate the ability of the fiber tractography technique to reveal pathological changes of white matter tracts in comparison to the normal appearing white matter. Conventional Magnetic Resonance Imaging (MRI) as well as Diffusion Tensor Imaging has been performed in 14 patients with clinically definite MS and in 8 healthy volunteers. After creating fractional anisotropy maps, three-dimensional fiber trajectories have been reconstructed from seed areas which delineated a lesion and from mirrored seed grids located in the contra-lateral hemisphere. The mean fractional anisotropy accumulated along the mapped fibers (mFA) and the total fiber volume have been computed. Preliminary results show a visual difference between trajectories of the lesion side and the healthy side. Fractional anisotropy is significantly lower in the lesion compared to the contra-lateral region. The average mFA of the affected tracts is $0.40 \pm 0.07$ compared to the corresponding average mFA of $0.42 \pm 0.07$ in the contra-lateral side. The tractography technique provides additional information to conventional MRI and permits a more comprehensive anatomical study of the disease.

Introduction

In light of the heterogeneous clinical course of Multiple Sclerosis (MS), it has become the rule to categorize MS as relapsing-remitting (RRMS), secondary progressive (SPMS) or primary progressive (PPMS). In terms of pathological changes, MS lesions show heterogeneous hallmarks: inflammation, demyelination, gliosis, axonal loss and remyelination. The predominance of one or another process can contribute to phenotypic differences between MS patient groups. However, these differences are not apparent in conventional Magnetic Resonance Imaging (MRI) examinations. Although conventional MRI has proven to be sensitive for detecting certain types of lesions and their changes over time, it suffers from an imperfect correlation to the clinical disability.

Recently, it has been shown that Diffusion Tensor Imaging (DTI) (3) is very sensitive to disease-related pathological processes (138,139) and may even distinguish different MS subgroups of disease (140). DTI is a non-invasive technique for measuring the movement of water molecules. In fluid-filled spaces, the diffusivity of water is equal in all directions. In vivo, the diffusivity is lower than in pure water due to the influence of cell membranes and organelles. Furthermore, the mobility of water molecules is not the same in all directions, due to the presence of tissue components such as cell membranes and myelin fibers. If these components are arranged in a way that the water diffusion in a specific direction is restricted, the displacement of water becomes directionally preferential (anisotropic). In white
matter (WM) the organization of the axons into parallel bundles, for example, causes water to diffuse preferentially along the direction of the axons rather than across them. The fiber tractography technique connects each voxel in direction of the fastest water diffusion, depicting virtual nerve fibers. Several authors have used the tractography technique to study the three-dimensional architecture of WM tracts in healthy volunteers (13,39,48). The maps generated correspond with known anatomy (39,48). However, until now the anatomical assignment of lesions to particular WM tracts in MS imaging studies has been unspecified. Furthermore, it remains unclear what influence specific MS lesions have on WM fasciculi and if such disease-related change can be assessed by DTI.

The aim of this study is to clarify whether or not DTI fiber tracking has the capacity to reveal changes between affected WM tracts and normal appearing white matter (NAWM) in RRMS, SPMS and PPMS. As a long-term objective one would like to use the tractography technique to classify pathological findings in clinical subgroups.

Materials & Methods

Subjects and Image Protocol

Fourteen patients (8 women, 6 men) with clinically definite MS and 8 healthy volunteers (5 women, 3 men) participated in the study. The mean age of the patients was 34 (range 22 – 64), whereas the mean age of the volunteers was 30 (range 22 – 40). All patients and volunteers signed informed consent and ethic committee approval was obtained. Conventional T2-weighted images (T2WI), T1-weighted images (T1WI), Fluid attenuation inversion recovery (FLAIR) images and DTI data were acquired using a 3 Tesla whole body system (Philips Medical Systems, Best, the Netherlands) equipped with 80 mT/m, 100 mT/m/ms gradient coils and a 6 channel receive head coil array. For DTI a SENSE (10) reduction factor \( R = 2.1 \) was used in conjunction with a single-shot spin-echo echo planar imaging scheme (matrix = 96 x 96, FOV = 200 x 200 x 105mm, 44 slices, slice thickness = 3 mm, TE = 71 ms, TR = 7751 ms). Diffusion-weighting was carried out along six directions using \( b = 1000 \) s/mm\(^2\), complemented by one scan with \( b = 0 \).
5. Fiber Tracking in Multiple Sclerosis

Figure 1: T1- (a) and T2-weighted (b) images of a female RRMS patient. L1: lesion 1 in the left corona radiate. L2: lesion 2 of the left parietal WM. H1, H2: Corresponding contra-lateral ROIs.

Data Processing

Processing of the DTI data involved calculating the diffusion tensor elements, eigenvectors, apparent diffusion coefficient (ADC) and fractional anisotropy (FA) on a voxel-by-voxel basis. For patients, lesions were segmented as region of interest (ROI) on the T2WI and mirrored in the contra-lateral correspondent NAWM (Figure 1). FA values were determined in both the lesion ROIs as well as in the contra-lateral NAWM ROIs and compared to the corresponding FA values in healthy volunteers (Figure 2).

Lesions with diameter > 5mm were used as seed areas for fiber tracking. Trajectories were reconstructed using Fiber Assignment by Continuous Tracking (FACT) (5). The algorithm aborted processing of individual trajectory when an FA threshold of $T_{FA} = 0.15$ was undershot. The reconstructed fibers were visually inspected as well as analyzed quantitatively by the use of the mean FA values accumulated along the reconstructed trajectories (mFA) and the volume of the fibers. The fiber volume (depiction rate) was defined as the total volume of all DTI voxels which were intersected by at least one trajectory. Examples of recon-

Figure 2: Mean FA of all hypointense lesions compared to the mean FA of the corresponding contra-lateral side and in healthy subjects. Error bars represent the standard deviation.
5. Fiber Tracking in Multiple Sclerosis

Reconstructed fibers of three different patients are illustrated in Figure 3 – 5. The derived mFA values were compared with the values of the identical topography and size, seeded in the contra-lateral correspondent NAWM (Figure 6). As controls, ROIs were bilaterally defined in frontal cingulum, forceps minor, major and corona radiate of healthy controls. To compare mFA of “affected” fasciculi with mFA of fibers located in the corresponding contra-lateral side, the average mFA of all lesions was computed (Figures 7). Color-coded maps were also generated showing the main direction of any anisotropic tissue in accordance with a standard color-coding scheme. Fiber tracking, distortion correction and analysis have been performed using a dedicated software written in C++.

![Figure 3: Reconstructed fibers of the seed areas depicted in Figure 1, overlaid onto coronal T2-weighted images. (a) Lesion 1: focally reduced depiction rate. (b) Lesion 2: global reduction of the depiction rate.](image)

**Results**

10 clinically definite relapsing-remitting (RR), 2 secondary progressive (SP), and 2 primary progressive (PP) MS patients were analyzed.
57 MS-lesions were assessed. 50 lesions were supratentorially and 7 infratentorially located. 19 lesions were enhancing. 37 lesions were hypointense on T1WI. 3 lesions showed perifocal edema, 2 lesions had a diameter larger than 2.5 cm. The location of the most frequent supratentorial lesions in the WM fibers were: corona radiata, corpus callosum, forceps major, cingulum. The location of the most frequent infratentorial lesions in the WM fibers were: ponto-cerebellar, cortico-spinal, cortico-nuclear tracts. Mean FA of all hypointense lesions was $0.24 \pm 0.11$, compared to a mean FA of $0.43 \pm 0.14$ in the contra-lateral side and a mean FA of $0.44 \pm 0.11$ in healthy volunteers.
5. Fiber Tracking in Multiple Sclerosis

Figure 5: T2-weighted (a), FA map (b) and tractogram (c) of a female 31 year old patient with new diagnose of MS and with a lesion bigger than 2.5 cm in the right centrum semiovale. The lesion is mild non-homogeneous enhancing. L1 marks the lesion. Figure b shows a reduction of FA in the lesion (arrow). Figure c illustrates a tractogram of the tilted brain volume. The arrow denotes interrupted trajectories in the lesion side.

The tractography showed no qualitative differences of fibers in enhancing and in non-enhancing lesions. The volumes of the reconstructed fibers (depiction rate) were reduced in 30 hypointense lesions compared to the NAWM side, while there was no significant change of the depiction rate assessed in the isointense T1WI lesions. For lesions bigger than 15 mm a focal reduction of the fiber volume was observed. A displacement of fibers was observed in lesions surrounded by edema. In SP patients there was focal and diffuse reduction in the depiction of fibers. The cingulum was tracked in 3 normal subjects and in 5 patients. A consistent rarefaction of fibers was observed in patients both with and without isolated lesions located in the cingulum. As Figure 6 and 7 show there is a small difference in the average mFA. On the lesion side average mFA is $0.40 \pm 0.07$ compared to the corresponding average mFA of $0.42 \pm 0.07$ in the contra-lateral side.
5. Fiber Tracking in Multiple Sclerosis

Figure 6: Examples of mean FA accumulated along fibers (mFA). Each pair represents the mFA of the reconstructed “affected” fibers (light gray) and the mFA of the “healthy” contra-lateral fibers (dark gray). 15 out of 54 lesions are displayed. The error bars correspond to the standard deviation.

Figure 7: Average mFA over all “affected” fibers of all patients (light gray) compared to the average mFA in the corresponding contra-lateral side (dark gray). In total the average mFA of 54 lesions was derived.

Discussion and Conclusion

These preliminary results suggest that DTI fiber tracking shows changes of WM tracts in different types of MS lesions compared to the correspondent NAWM. The differences in tracking results likely reflect variations in FA values and seem to provide supplementary information to the known observed changes in signal intensity on T1WI. There is however little difference in the average FA accumulated along the tracts compared to the contra-lateral values. It remains to be proven whether this is a significant and reproducible finding. A decrease in mFA could be explained with a reduction of diffusion anisotropy in the
plaque and a demyelination of the affected WM tracts. In presence of demyelinated tracts
water diffusion is less anisotropic, resulting in a decreased FA measure. Differences be-
tween reconstructed trajectories of the lesion side and the contra-lateral side could be clearly
observed by visual inspection. Thus, the tractograms assessed by SENSE-DTI allow a more
comprehensive anatomical study of the disease. However, quantification is difficult. The
used mFA measure and the depiction rate quantity are two potential metrics. In addition to
quantitative measures derived from two-dimensional diffusion maps, the three-dimensional
information garnered from diffusion tractography can provide identification of regional ab-
normalities and structural changes related to axonal disruption. This analysis may also pro-
vide early evidence of remyelination.

The proposed quantitative intra-subject analysis should be extended to clinical MS sub-
groups and the anatomical assignment of MS lesions should be applied in a wider patient
population for additional characterization of the different subgroups. Future implementa-
tions of DTI and fiber tractography in the evaluation of MS patients will likely involve a
combination of approaches. A standardized MRI examination could be performed from
which a variety of indices could be obtained, including the apparent diffusion coefficient
(ADC), FA, mFA and the fiber volume. Additionally, the tractography procedure could be
combined with other emerging techniques such as functional MRI, which may provide a
means of identifying loss of connectivity in cortical areas, as well as for determining the
underlying integrity of the axonal pathways.
Conclusion and Outlook

Diffusion Tensor Imaging (DTI) is a promising technique in neuroscience, which provides non-destructively unique information about the white matter architecture of the brain. With the introduction of axonal reconstruction strategies DTI has become more and more popular over the last few years. Nevertheless, on its way to clinical routine the technique still faces serious challenges. The present dissertation has been focused on the improvement of image acquisition as well as on the design of advanced fiber mapping procedures to enhance the potential of DTI.

Sensitivity Encoding (SENSE) has proved to be enormously beneficial for DTI acquisition. Despite enhanced field inhomogeneity at higher field strengths, parallel acquisition permits both controlling susceptibility-related geometric distortions and enhancing spatial resolution (chapters 1 and 2). Computer simulations as well as experiments have shown that the point spread function (PSF) becomes narrower with increasing SENSE acceleration factors, enhancing the intrinsic resolution. In terms of signal-to-noise ratio (SNR), a significant increase in efficiency can be achieved by SENSE acquisition, exploiting higher encoding speed for echo time reduction. This is noteworthy because in principle parallel imaging incurs loss of SNR efficiency. It has been shown that SNR can be optimized by choosing an appropriate SENSE acceleration factor.

In the near future, MR scanners with a main magnetic field of 7 T and 32 receiver channels will become available. SENSE-DTI is likely to benefit from both. An increased number of receiver channels makes it possible to apply dedicated head phased array coils with superior noise performance (141). Thus, higher acceleration factors may be achievable, resulting in narrower PSFs and less susceptibility artifacts. Further, with a higher main magnetic field strength increased image SNR is expected. However, at shorter electromagnetic wavelength, wave interference becomes a challenging effect (142).

The theoretical and practical concepts of SENSE-DTI developed in chapter 1 and 2 have been applied in combination with a high-sensitivity miniature coil array for revealing the microscopic fiber organization at the intracortical level of the occipital lobe (chapter 3). Cortical tracking and, potentially, quantification of individual connections are essential steps for understanding the structural neuroanatomy. It is anticipated that with increased field strength, spatial resolution will be further improved. Nevertheless, DTI on a whole-body system can never provide the single-neuron accuracy achieved by invasive tracer techniques. Instead, it benefits from its non-destructiveness, which is required to overcome the lack of non-invasive methods for measuring neural connections in vivo.

The Fast Marching DTI tractography method described in chapter 4 is capable of resolving fiber pathways in regions where neuronal systems intersect. This is a valuable contribution to elucidate the neuronal network of the brain. However, the tracking technique is con-
strained by the tensor model, which can only resolve a single diffusion ellipsoid within each imaging voxel. Future work could extend the presented method in combining DTI tractography with a model-independent technique, such as $q$-ball tractography (84). Depending on the complexity of the underlying diffusion process, the diffusion data would then be reconstructed on a voxel-by-voxel basis using either the simple tensor model or the more sophisticated $q$-ball model.

The patient study presented in chapter 5 has demonstrated that fiber tractography based on SENSE-DTI data allows the assessment of white matter changes in Multiple Sclerosis. Preliminary results show a visual difference between reconstructed three-dimensional fiber trajectories of the lesion side and the healthy side. Mean diffusion anisotropy accumulated along each fiber and the total fiber volume have been defined to quantify the dissimilarities. Although tractography is a potent tool for depicting estimates of white matter fasciculi, quantification is demanding due to inter-subject variability and the absence of appropriate probabilistic metrics. Recently, tracking studies have been presented which analyze statistically patient groups using normalized neuroarchitecture (143-145). This could be an appropriate approach for sophisticated patient studies in this context. Furthermore, one should keep in mind that reconstructed trajectories are virtual and reflect real neuronal fiber tracts only with a certain likelihood. Reliability and accuracy of different fiber mapping strategies remain key topics for future research.
References

References


Acknowledgements

I would like to thank everyone who has supported me during the last years. Many colleagues and friends have contributed to this work in one way or another. My special thanks go to...

Prof. P. Bösiger, for providing excellent research conditions and his keen sense to employ the right people.

Prof. A. Valavanis, for his faith in my work, his scientific approach and his efforts in examining this thesis.

PD S.S Kollias, for his enthusiastic cooperation, his countless anatomy lesions and for having always time for me.

Prof. K. Prüssmann, for sharing his intelligence with me. (He is the only person I know, who is able to discuss concentrated after working two days and nights in a row.)

Dr. D. Meier and U. Sturzenegger, for maintenance of excellent scanning facilities and their extraordinary support which resulted in a trip to Hawaii.

Dr. G. Crelier, for his efforts in teaching me how to think scientific.

Dr. R. Lüchinger, for his endless computer support (also at 11 pm.)

Philipp, for writing millions of lines C++ code.

Hendrik and Nicola, for revising my abstracts and manuscripts.

Moe, for fruitful discussions on our jogging laps, not only about MRI.

Andreas and Florian, for sharing many intensive and creative days in the alps.

My past and present colleagues, Trabi, Jeff, Oliver W., Markus W., Xavier, Malex, Michi H., Ulrike, Salome, Michi S., Conny, Anke, Reto, Christof, Christoph, Martin, Urs, Marco L., Stephan, Jonas, Mike, Basti, Peter S., Jurek, Andrea, Rolf, Thomas L., Marco P. and Michael W.
Corinne, Joëlle and my parents, for believing in me, their support and their interest in my work.
Curriculum Vitae

I was born on December 7th 1967 in Arbon TG, as the second son of Katharina and Hugo Järmann. After primary and secondary school, I attended an apprenticeship as “Elektronikmechaniker” at Gebr. Bühler AG in Amriswil TG and Uzwil SG. From 1988 to 1991, I studied “Elektronik, Mess- und Regeltechnik“ at the Neu-Technikum Buchs NTB, where I graduated as “Dipl. Ingenieur HTL”. Subsequently, I worked until 1994 as development engineer at Optronic AG in Goldach SG.

In autumn 1994 I started my studies in physics at the ETH Zürich and at the TU Wien. After one year industrial research experience at Leica AG in Heerbrugg SG, I graduated in 2000 with the diploma thesis “Event-related functional MRI” at the Institute for Biomedical Engineering, ETH & Uni Zürich. This work was supervised by Prof. Dr. P. Bösiger and Dr. G. Crelier.

In summer 2000 I joined the group of Prof. Dr. P. Bösiger as a PhD research assistant.