SUSCEPTIBILITY EFFECTS IN ULTRA-HIGH FIELD 
MAGNETIC RESONANCE IMAGING OF THE HUMAN BRAIN

DISSERTATION

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* * * * *

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ABSTRACT

In magnetic resonance imaging (MRI), susceptibility differences between deoxygenated blood or iron and surrounding tissue induce mesoscopic static magnetic field ($B_0$) inhomogeneities that provide a valuable contrast mechanism for imaging of the vasculature, functional MRI, and assessment of iron content. On the other hand, susceptibility differences at air/tissue interfaces induce macroscopic $B_0$ inhomogeneities resulting in image artifacts. Ultra-high field ($\geq 7$ tesla) MRI benefits from an enhanced susceptibility contrast, but also suffers from more severe susceptibility artifacts. The development of methods to reduce such artifacts while maintaining susceptibility contrast is the objective of this research. Development of susceptibility artifact correction methods requires knowledge of the macroscopic susceptibility effects, which can be quantified by mapping $B_0$, whereas optimization of methods sensitive to susceptibility contrast requires understanding of the mesoscopic susceptibility effects, which can be characterized by relaxation time measurements.

We first developed various methods for $B_0$ numerical simulations and experimental mapping. Our simulations showed that air/tissue interfaces at the shoulders induce substantial $B_0$ inhomogeneities in the brain, and that tilting the head
backwards can significantly reduce some of these inhomogeneities. We used the $B_0$ simulations and experimental mapping as well as radiofrequency magnetic field ($B_1$) mapping to correlate the $B_0$ and $B_1$ inhomogeneity with the artifacts observed on images of the human brain acquired at 8 T. We then evaluated different susceptibility artifact correction methods at ultra-high field strength using $B_0$ maps, including passive shimming, post-processing, and gradient compensation, and found the latter to be the most effective. Finally, we developed various methods for $T_2$ and $T_2^*$ relaxation time measurements at ultra-high field strength that are faster and less sensitive to $B_0$ and/or $B_1$ inhomogeneity than existing methods, and demonstrated these advantages in phantom and human studies. New findings obtained in this work will be used to improve ultra-high field MRI of the human brain, particularly for imaging of the venous microvasculature and assessment of iron content.
Dedicated to my parents
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<tr>
<td>1D</td>
<td>one-dimensional</td>
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<tr>
<td>2D</td>
<td>two-dimensional</td>
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<tr>
<td>3D</td>
<td>three-dimensional</td>
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<td>4D</td>
<td>four-dimensional</td>
</tr>
<tr>
<td>ASE</td>
<td>asymmetric SE</td>
</tr>
<tr>
<td>bmGESEPI</td>
<td>blipped mGESEPI</td>
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<tr>
<td>BOLD</td>
<td>blood oxygen level-dependent</td>
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<tr>
<td>BW</td>
<td>bandwidth</td>
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<tr>
<td>CPMG</td>
<td>Carr-Purcell-Meiboom-Gill</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<td>EPI</td>
<td>echo planar imaging</td>
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<td>FID</td>
<td>free induction decay</td>
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<tr>
<td>fMRI</td>
<td>functional MRI</td>
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<tr>
<td>FOV</td>
<td>field-of-view</td>
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<tr>
<td>GE</td>
<td>gradient echo</td>
</tr>
<tr>
<td>GESEPI</td>
<td>gradient echo slice excitation profile imaging</td>
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<tr>
<td>GESFIDE</td>
<td>gradient echo sampling of the FID and echo</td>
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<tr>
<td>GESSE</td>
<td>gradient echo sampling of the spin echo</td>
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<tr>
<td>GM</td>
<td>gray matter</td>
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<tr>
<td>mGESEPI</td>
<td>multi GESEPI</td>
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<tr>
<td>MIP</td>
<td>maximum intensity projection</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MTX</td>
<td>matrix size</td>
</tr>
<tr>
<td>NEX</td>
<td>number of excitations</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>RF</td>
<td>radiofrequency</td>
</tr>
<tr>
<td>ROI</td>
<td>region-of-interest</td>
</tr>
<tr>
<td>SE</td>
<td>spin echo</td>
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<tr>
<td>SNR</td>
<td>signal-to-noise ratio</td>
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<tr>
<td>SSQ</td>
<td>square root of the sum of squares</td>
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<tr>
<td>ST</td>
<td>slice thickness</td>
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<tr>
<td>TE</td>
<td>echo time</td>
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<tr>
<td>TEM</td>
<td>transverse electromagnetic</td>
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<tr>
<td>TR</td>
<td>repetition time</td>
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<td>white matter</td>
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CHAPTER 1

INTRODUCTION

1.1 Background and Significance

Magnetic resonance imaging (MRI) is a medical imaging technique that uses a static magnetic field $B_0$, a radiofrequency (RF) magnetic field $B_1$, and magnetic field gradients to produce images of the human body [1, 2]. In most applications, the signal comes from hydrogen nuclei, i.e., protons, and depends on many factors, including proton density $\rho$, longitudinal and transverse relaxation times $T_1$ and $T_2$, which characterize a material’s microscopic magnetic properties (i.e., on the atomic scale), as well as magnetic susceptibility $\chi$, which characterizes a material’s tendency to distort a surrounding magnetic field. This produces a different signal for different materials, thus generating an image contrast.

Soft tissues in the human body, consisting predominantly of water, are diamagnetic ($\chi < 0$) and have relatively similar susceptibility values. However, certain materials, such as paramagnetic ($\chi > 0$) deoxyhemoglobin in venous blood, tissue iron, air, and contrast agents, as well as ferromagnetic ($\chi \gg 1$) implants, have a significantly different susceptibility than the surrounding tissues and thus induce pronounced susceptibility effects, which can be either beneficial or harmful.
On the beneficial side, susceptibility differences between deoxygenated blood and surrounding tissue induce mesoscopic $B_0$ inhomogeneities with a random or high-order spatial variation within a voxel (i.e., on the order of 100 nm to 10 $\mu$m) that produce an image contrast dependent on the number of small vessels and the blood oxygenation level. This so-called blood oxygen level-dependent (BOLD) effect is an extremely valuable contrast mechanism used for depiction of the venous vasculature as well as functional MRI (fMRI) of brain activation. Similarly, tissue iron produces an image contrast that can potentially be used to quantify tissue iron content in various neurodegenerative diseases.

On the other hand, susceptibility differences at air/tissue interfaces induce macroscopic $B_0$ inhomogeneities with a low-order spatial variation across a voxel (i.e., on the order of 1 mm or larger) that result in image artifacts, specifically geometric distortions in gradient echo (GE) and spin echo (SE) imaging, as well as signal loss due to intravoxel dephasing in GE imaging.

While over 20,000 clinical MRI scanners existing worldwide typically operate at a magnetic field strength of 1.5 tesla (T), an ever increasing number of scanners are being developed that operate at high field strength ($\geq 3$ T) or even ultra-high field strength ($\geq 7$ T). Among those is the worldwide unique 8 T MRI scanner at The Ohio State University, which currently represents the highest magnetic field strength for a human whole-body MRI scanner.

This trend towards higher field strength is driven by the fact that high field MRI, and more particularly ultra-high field MRI, offers many advantages over MRI at lower field strength. The main advantage is an increased signal-to-noise ratio (SNR), allowing imaging at a higher spatial resolution and/or with shorter acquisition times. Furthermore, since susceptibility effects become more pronounced
at higher field strength, ultra-high field MRI benefits from an enhanced susceptibility contrast, making it more sensitive for imaging of the venous vasculature, BOLD fMRI, and assessment of tissue iron content. Its potential has been clearly demonstrated for high resolution imaging of the brain microvasculature [3, 4] and fMRI [5]. However, this also implies that ultra-high field MRI suffers from more severe susceptibility artifacts, which can significantly degrade image quality and hamper these applications.

1.2 Objective

The development of methods to reduce susceptibility artifacts while optimizing susceptibility contrast is therefore of paramount importance to take full advantage of the potential offered by ultra-high field MRI. Development and assessment of susceptibility artifact correction methods require knowledge of the macroscopic susceptibility effects, which can be quantified by mapping the static magnetic field $B_0$. In addition, optimization of methods sensitive to susceptibility contrast requires understanding of the mesoscopic susceptibility effects, which can be characterized by measuring $T_2'$ and $T_2^*$ relaxation times.

Existing susceptibility artifact correction methods have primarily been developed for fMRI applications at low field strength. These methods need to be adapted and new ones developed for high resolution imaging at ultra-high field strength. Relaxation times depend on the magnetic field strength and are typically measured from a series of images acquired with different timing parameters. These measurements are affected by susceptibility artifacts and need to be optimized for ultra-high field MRI as well. The development of such dedicated methods for $B_0$
mapping, susceptibility artifact correction, and relaxation time measurement at ultra-high field strength is therefore the objective of this research.

The newly developed methods will be useful for both fundamental research and clinical applications. They will result in a better understanding of susceptibility contrast, which is an important contrast mechanism at ultra-high field strength, unlike at lower field strength where image contrast is dominated by proton density as well as $T_1$ and $T_2$ relaxation times. New findings will be used to improve imaging of the venous microvasculature and for assessment of tissue iron content in the human brain.

1.3 Outline of the Dissertation

This dissertation is organized as follows. In chapter 2, different methods for numerical simulations (section 2.1) and experimental mapping (section 2.2) of the static magnetic field are described, as well as their application for correlation with image artifacts and development of susceptibility artifact correction methods (section 2.3).

In chapter 3, various susceptibility artifact correction methods are presented, including passive shimming using ferroshims (section 3.1), post-processing using non-Fourier reconstruction (section 3.2), as well as gradient compensation using three-dimensional (3D) z-shim (section 3.3) and Gradient Echo Slice Excitation Profile Imaging (GESEPI) (section 3.4).

In chapter 4, different relaxation time measurement methods are described, including two methods for $T_2^*$ relaxation time measurement with $B_0$ inhomogeneity compensation (multi GESEPI (mGESEPI) and blipped mGESEPI (bmGESEPI))
(section 4.1), as well as two methods for $T_2$, $T'_2$, and/or $T_2^*$ relaxation time measurement insensitive to $B_1$ and/or $B_0$ inhomogeneity (Gradient Echo Sampling of the Free Induction Decay and Echo (GESFIDE) (section 4.2) and Gradient Echo Sampling of the Spin Echo (GESSE) (section 4.3)).

Finally, in chapter 5, the main findings are summarized (section 5.1) and directions for future work are suggested (section 5.2).
CHAPTER 2

STATIC MAGNETIC FIELD MAPPING

2.1 Numerical Simulations

2.1.1 Introduction

The development of susceptibility artifact correction methods requires knowledge of the susceptibility-induced magnetic field inhomogeneities. While a variety of experimental techniques can be used to map the static magnetic field $B_0$ (see section 2.2), numerical simulations offer a promising alternative. Especially at ultra-high field strength, experimental mapping techniques may be limited because they are impeded by other sources of artifacts such as $B_1$ inhomogeneity, signal loss due to complete intravoxel dephasing in regions with large $B_0$ inhomogeneity, and/or subject physiological motion. On the other hand, numerical simulations are not affected by such problems and are more flexible.

Susceptibility-induced magnetic fields have been numerically modelled by several investigators. Bhagwandien et al. [6, 7, 8] developed a finite difference method for computing the static magnetic field for arbitrary two-dimensional (2D) or 3D magnetic susceptibility distributions, and used it on two-component (air and wa-
ter) models of the head, the chest, and the hand. Li et al. used a commercial finite element algorithm to compute the magnetic field for 2D or 3D two-component wire frame models of a human head [9, 10] and upper body [11], with a fairly coarse description of the air spaces. More recently, Yang et al. [12] described preliminary work with a modified version of Bhagwandien’s algorithm using two 3D multi-component head models (including air, fat, water, bone, blood, white matter (WM), and gray matter (GM)) derived from either the Visible Human data or MRI data. This work is very promising, however the Visible Human data can provide geometric information for only one specific subject. On the other hand, MRI data can be acquired for different subjects, but does not allow differentiating air from cortical bone, thus limiting the models near the nasal cavity, sphenoid sinus, and temporal bones.

As an alternative to prior work, we generated 3D susceptibility distributions from computed tomography (CT) images covering the head, neck, and thorax of a healthy volunteer, and used a modified version of Bhagwandien’s algorithm to compute the static magnetic field [13]. We first tested the accuracy of our algorithm by comparing the simulations with the analytical solution for the magnetic field in a sphere. We then evaluated how the magnetic field in the head was affected by air/tissue interfaces at the shoulders and in the lungs, and tested if tilting the head backwards could reduce some of the susceptibility artifacts.

For completeness, other methods for numerical simulations of susceptibility-induced magnetic fields that have been published since this work are also briefly reviewed below. Jenkinson et al. [14] developed a perturbation method to compute the magnetic field to the first order, which is appropriate for most MRI applications and can be implemented as a simple convolution, allowing efficient
calculations. A head model was derived from registered MRI data (for soft tissues) and CT data (for bone) from two different subjects. Collins et al. [15] extended the work by Yang et al. [12]. Marques et al. [16] developed a method that instead of directly calculating the magnetic field generated by a distribution of dipoles in a medium, which is a complex non-local function representing the sum of the fields generated by each dipole, performs the calculation in the Fourier domain (i.e., in k-space) where this expression becomes a simple local expression, thus allowing fast calculations. Salomir et al. [17] used a first order perturbation approach to Maxwell’s magnetostatic equations to obtain a direct relationship between the susceptibility distribution and the magnetic field perturbation, and applied a Fourier transform technique for solving partial derivative equations to achieve fast calculations.

2.1.2 Methods

**Generation of the Magnetic Permeability Distributions**

Two sets of CT images were acquired on a healthy 51-year-old male volunteer. The first set of images covered the head, neck, thorax, and abdomen, whereas the second one covered the head, neck, and shoulders, with the head tilted backwards by 35°. The images were acquired with a General Electric Highspeed CT scanner using a field-of-view (FOV) of 45.5 cm, a matrix size (MTX) of 512×512, as well as 427 and 181 slices of 2 mm thickness for the first and second data sets respectively. The images were resized to match the slice thickness, resulting in 3D data sets with an isotropic resolution of (2 mm)³. Example images from the first data set are shown in Fig. 2.1a–e.
Figure 2.1: (See figure on next page.) Axial CT images of the head (a), thorax (b), and abdomen (c) of a healthy volunteer, as well as coronal (d) and midsagittal (e) reformatted images of this data set. The solid and dashed arrows point to the planum sphenoidale and upper clivus respectively. The CT images were segmented and assigned appropriate values of relative magnetic permeability. The resulting permeability distributions are shown in (f–j) with air in black, fat in green, nonfat soft tissue in red, and bone in yellow.
Figure 2.1: See caption on previous page.
A threshold-based segmentation of these CT data sets was feasible and resulted in four masks for each data set corresponding to air, fat, nonfat soft tissue, and bone. Histograms and signal intensity profiles were used to determine the following threshold levels: -300 H.U. (Houndsfield Units) for air/fat, -50 H.U. for fat/nonfat soft tissue, and 250 H.U. for nonfat soft tissue/bone. Magnetic susceptibility values $\chi$ given in the literature ($\chi_{\text{air}} = 0.4 \cdot 10^{-6}$, $\chi_{\text{fat}} = -7.5 \cdot 10^{-6}$, $\chi_{\text{nonfat soft tissue}} = -9.5 \cdot 10^{-6}$, and $\chi_{\text{bone}} = -9.0 \cdot 10^{-6}$ [7, 10]) were converted to relative magnetic permeability values as $\mu_r = 1 + \chi$, which were then assigned to the corresponding masks (see Fig. 2.1f–j).

In order to study separately the influence of air/tissue interfaces at the shoulders and those in the lungs on the magnetic field in the head, three models were generated from the data set with the head upright. They consisted of the permeability distribution of the head and the neck (head model), the head, neck, and shoulders (head/shoulders model), as well as the head, neck, and thorax (head/thorax model). Furthermore, in order to study the influence of the head orientation, a fourth model was generated from the data set with the tilted head, and consisted of the permeability distribution of the head, neck, and shoulders (tilted head/shoulders model).

Similarly, magnetic permeability distributions were also generated for a phantom consisting of a 5 mm diameter air-filled tube surrounded by a 44 mM CuSO$_4$ solution ($\chi = -8.1 \cdot 10^{-6}$ [18]) at a resolution of $(1\,\text{mm})^3$, as well as the head, neck, and shoulders of an 84-year-old female postmortem human subject at a resolution of $(2\,\text{mm})^3$. In the remainder of section 2.1, only the results for the healthy volunteer are shown and discussed; those for the phantom and postmortem human subject can be found in section 2.2.3.
**Computation of the Magnetic Field**

The computation of the static magnetic field from the permeability distributions was carried out using a modified version of the finite difference method developed by Bhagwandien *et al.* [7]. This method is based on the Laplace equation:

$$\vec{\nabla}[\mu_r(x, y, z)\vec{\nabla}\Phi(x, y, z)] = 0,$$  \hspace{1cm} (2.1)

where $\Phi(x, y, z)$ is the magnetic scalar potential. This equation can be derived from Maxwell’s equations in a macroscopic linear medium with no charges and no currents in the steady state. Since the permeability distribution $\mu_r(x, y, z)$ is known, Eq. (2.1) can be solved for $\Phi(x, y, z)$. The $z$ component of the molecular magnetic field can then be computed as follows:

$$B_0(x, y, z) = -\mu_0 \left[ \frac{\mu_r(x, y, z) + 2}{3} \right] \frac{\partial\Phi(x, y, z)}{\partial z},$$  \hspace{1cm} (2.2)

where $\mu_0 = 4\pi 10^{-7}$ H/m is the magnetic permeability in vacuum and $\hat{z}$ is the direction of the static magnetic field in vacuum in the absence of any sample ($B_{0,\text{vacuum}}$). The Lorentz correction [1, 19, 20], which takes into account the demagnetizing field due to all neighboring spins, has been included in Eq. (2.2).

In order to obtain a value independent of $B_{0,\text{vacuum}}$, the field is expressed as the normalized magnetic field deviation from the applied field, *i.e.*, the magnetic field in air in the absence of any sample ($B_{0,\text{air}} = B_{0,\text{vacuum}} \mu_{r,\text{air}}$):

$$\Delta B_0(x, y, z) = \frac{B_0(x, y, z) - B_{0,\text{air}}}{B_{0,\text{air}}}. \hspace{1cm} (2.3)$$
The 3D problem in Eq. (2.1) is extended to a four-dimensional (4D) one with an iteration variable \( \tau \), and Eq. (2.1) is defined as the equilibrium state of the following iterative problem [7]:

\[
C \frac{d\Phi(x, y, z; \tau)}{d\tau} = \nabla \left[ \mu_r(x, y, z; \tau) \nabla \Phi(x, y, z; \tau) \right],
\]

where \( C \) is a constant and \( d\tau = 1 \). This problem has a convergent solution with \( \lim_{\tau \to \infty} \Phi(x, y, z; \tau) = \Phi(x, y, z) \). Denoting a voxel at position \((x, y, z)\) by the index (0) and its six neighboring voxels (namely \((x \pm dx, y, z)\), \((x, y \pm dy, z)\), and \((x, y, z \pm dz)\), where \( dx, dy, \) and \( dz \) is the spatial resolution in the \( \hat{x}, \hat{y}, \) and \( \hat{z} \) direction, respectively) by the indices (1) to (6), the magnetic scalar potential at that voxel can be iteratively computed as follows [7]:

\[
\Phi(0; \tau) = \sum_{i=1}^{6} D(i)\Phi(i; \tau - 1) + D(7)\Phi(0; \tau - 2),
\]

where

\[
D(i) = \frac{2B(i)}{2 - B(7)} \quad (i = 1, \ldots, 6)
\]

\[
D(7) = \frac{2 + B(7)}{2 - B(7)}
\]

\[
B(i) = \frac{2\mu_r(i)\mu_0}{(\mu_r(i) + \mu_0)Cd\lambda dy} \quad (i = 1, \ldots, 6)
\]

\[
B(7) = -\sum_{i=1}^{6} B(i).
\]

In other words, the potential at a given voxel and at a given iteration step is computed as a linear combination of the potential at each of the six neighboring voxels from the previous iteration step and the potential at that voxel from two
iteration steps before, where the coefficients of the linear combination are functions of the permeability distribution.

This iterative algorithm requires suitable boundary conditions. Specifically, the permeability distribution of the sample must be surrounded by a buffer region of uniform permeability \( i.e., \) containing only air, which must be large enough so that the influence of the sample on the magnetic scalar potential at its outside boundaries can be neglected. Bhagwandien \textit{et al.}\ [7] used a buffer size that is a multiple of the size of the sample. For an elongated sample (such as a human body), this results in a larger buffer region along the long axis of the sample. To reduce this effect, we generate the buffer by adding a buffer region that has the same thickness along each direction \( \pm \hat{x}, \pm \hat{y}, \) and \( \pm \hat{z} \) around the sample. This buffer is characterized by a “buffer thickness,” defined as the smallest distance between the sample and the outside boundaries of the buffer along any direction \( \hat{x}, \hat{y}, \) or \( \hat{z} \) (see Table 2.1).

For the first step of the iteration, a magnetic scalar potential uniform in \( \hat{x} \) and \( \hat{y}, \) and linear in \( \hat{z} \) is used as an initial value:

\[
\Phi(x, y, z; 0) = \Phi(x, y, z; 1) = -\frac{B_{0, \text{vacuum}}}{\mu_0} z. \tag{2.10}
\]

The origin is not important since the magnetic scalar potential is defined with an arbitrary additive constant. The iteration stops when the steady state is reached, as defined by the following criterion:

\[
\max_{(x, y, z) \in \text{sample}} [\varepsilon(x, y, z; \tau)] < 10^{-10}, \tag{2.11}
\]
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</tbody>
</table>

**Table 2.1**: Parameters used in the multiresolution implementation of the algorithm for the computation of the magnetic field.
where
\[
\epsilon(x, y, z; \tau) = \frac{|\Phi(x, y, z; \tau) - \Phi(x, y, z; \tau - 1)|}{\max_{(x,y,z) \in \text{sample}} |\Phi(x, y, z; 0)|}
\] (2.12)
is the normalized absolute difference between the potential at the current iteration step and the potential at the previous iteration step. The maximum is taken only over voxels inside the sample, otherwise the largest difference would occur at the outside boundaries of the buffer and would therefore be dependent on the size of the buffer. This stop criterion thus controls the maximum absolute difference inside the sample, unlike the one used by Bhagwandien et al. [8], which is based on the sum of the minimal square difference over the whole volume. The threshold value used in Eq. (2.11) was determined by comparing numerical simulations with the analytical solution for the magnetic field in a sphere (see below). This algorithm is unconditionally stable [7]. The constant $C$ determines the speed of convergence and its optimal value is found by trial and error.

The algorithm was implemented in Matlab and executed on an SGI Origin 2000 with a memory limit of 1 GB and a computation time limit of 10 hours. The advantage of using Matlab is the ability to perform very fast matrix operations, however at the expense of large memory requirements. Due to the computer memory limitation, the computation for the head/thorax model, which is the largest one, could only be carried out at a resolution of $(4 \text{ mm})^3$. Therefore, the computations for all four models were carried out at that resolution to allow direct comparisons between the different models.

Furthermore, in order to reduce the computation time, a multi-resolution approach was used [7] (see Fig. 2.2 and Table 2.1). For the first step, the multi-resolution implementation starts with a low resolution version of the permeability
distribution of the sample. This distribution is then surrounded by an air-filled buffer region with a given buffer thickness. The iterative algorithm is then run using this extended permeability distribution, a linear estimate for the initial magnetic scalar potential (see Eq. (2.10)), and an appropriate constant $C$. For the second step, the result of this iteration is interpolated to a higher resolution and the iterative algorithm is run again, now using this potential as the initial value and a higher resolution version of the permeability distribution. The constant $C$ is adjusted as needed. This procedure is repeated until the final resolution is reached. After the last step, the partial derivative of $\Phi(x,y,z)$ with respect to $z$ is computed and multiplied by $-\mu_0[\mu_r(x,y,z)+2]/3$ to yield $B_0(x,y,z)$ (see Eq. (2.2)). Because of computer memory limitations, the multiresolution approach used by Bhagwandien et al. [7] was modified. The buffer thickness was reduced as the resolution was increased in order to limit the total matrix size of the permeability distribution (see Table 2.1).

**Validation of the Algorithm**

The algorithm was validated with a sphere model, for which an analytical solution for the magnetic field is available [7]:

$$B_{0,\text{ana}}^\text{ext}(x,y,z) = \begin{cases} 
B_{0,\text{vacuum}} \left(1 + \frac{\chi_{\text{ext}}}{3}\right), & r < R \\
B_{0,\text{vacuum}} \left[1 + \frac{\chi_{\text{ext}}}{3} + \frac{(\chi_{\text{ext}} - \chi_{\text{int}})R^3(x^2+y^2-2z^2)}{3(x^2+y^2+z^2)^{\frac{3}{2}}}\right], & r > R
\end{cases} \tag{2.13}$$

where $\chi_{\text{int}}$ and $\chi_{\text{ext}}$ are the magnetic susceptibility values inside and outside the sphere respectively, $r = \sqrt{x^2+y^2+z^2}$, and $R$ is the radius of the sphere. The Lorentz correction has been taken into account in Eq. (2.13). The following param-
Figure 2.2: Schematic diagram of the multiresolution implementation of the algorithm for the computation of the magnetic field. Ovals represent parameters, whereas rectangles represent computation steps.
eters were chosen for similarity with the head model: $\chi_{\text{int}} = \chi_{\text{water}} = -9.1 \cdot 10^{-6}$ \cite{10}, $\chi_{\text{ext}} = \chi_{\text{air}}$, $R = 128$ mm, and a resolution of $(4 \text{ mm})^3$.

The accuracy of the algorithm was evaluated by computing the normalized difference between the magnetic field obtained from the numerical simulation and from the analytical solution:

$$\delta_B(x, y, z) = \frac{B_0(x, y, z) - B_0^{\text{ann}}(x, y, z)}{B_{0,\text{air}}}.$$  (2.14)

Simulations using different threshold values for the stop criterion (see Eq. (2.11)) as well as different resolutions and buffer thicknesses were carried out to determine the optimal parameters.

2.1.3 Results

Validation of the Algorithm with the Sphere Model

Images and plots of the error $\delta_B$ (see Eq. (2.14)) for the sphere model computed using different buffer thicknesses are shown in Fig. 2.3. Fig. 2.3a,b clearly show that a buffer thickness of 112 mm does not give sufficiently accurate results. When the buffer thickness is increased to 128 mm (Fig. 2.3c,d), the error $\delta_B$ inside the sphere decreases to $-0.033$ ppm. The error at the interface is substantially larger, but can be attributed to the discretization inherent in the numerical simulations. Simulations carried out at a higher resolution confirmed that this is indeed the case, as the error at the interface becomes smaller. When the buffer thickness is further increased to 144 mm (Fig. 2.3e,f), the error $\delta_B$ inside the sphere decreases to $-0.025$ ppm. As expected, the error at the interface does not decrease, since it is related to the resolution. Thus optimizing the accuracy of the algorithm
involves a trade-off between buffer size and spatial resolution, because the total matrix size of the permeability distributions is limited by the available computer memory.

As such, the computation for the head/thorax model, which is the largest one, could only be carried out with a buffer thickness of 128 mm. This value was therefore chosen for all four models to allow direct comparisons between the different models. While simulations with the sphere model showed that this buffer thickness gives overall accurate results, the lack of spatial resolution may introduce some errors, especially near tightly curved air/tissue interfaces, but these errors appear to be limited to a thin layer from the interface (see Fig. 2.3c,d). Nevertheless, increased spatial resolution is ultimately desirable.

**Head Model at (4 mm)$^3$ vs. (2 mm)$^3$**

To further investigate to what extent the limited spatial resolution affects the accuracy of the simulations, we computed and compared the magnetic field for the head model at a resolution of (4 mm)$^3$ and (2 mm)$^3$. These computations were carried out using a buffer thickness of 48 mm at the final resolution in both cases (see Table 2.1, steps 1-2-3' and 1-2-3-4 respectively). Although simulations with the sphere model showed that this buffer thickness is too small to avoid errors, it is the maximum value achievable at a resolution of (2 mm)$^3$ due to computer memory limitations. However, since the computations at both resolutions were carried out using the same buffer thickness, we expect errors related to the buffer to be identical, so that a comparison between the two computations allows evaluation of the influence of spatial resolution near tightly curved air spaces in the
**Figure 2.3:** Results for the sphere model showing images of the error $\delta_B$ [ppm] in the $x$-$z$ plane passing through the center of the sphere (a,c,e) and plots of this error along a diameter parallel to $\hat{x}$ and $\hat{z}$ (b,d,f) computed using a buffer thickness of 112 mm (a,b), 128 mm (c,d), and 144 mm (e,f) at the final resolution. The blue regions inside the sphere in (a) indicate large differences between the numerical simulation and the analytical solution. Note that the results have been cropped for ease of comparison, thus not showing the actual buffer used for the computations, and that only the error inside the sphere is shown. Because of the symmetry, results along the $\hat{y}$ axis are identical to those along the $\hat{x}$ axis.
Figure 2.4: Midsagittal (a), coronal (b), and axial (c) images of the normalized difference between the magnetic field at a resolution of (4 mm)$^3$ and (2 mm)$^3$, \(i.e., (B_{0,4\text{mm}}^\text{mm} - B_{0,2\text{mm}}^\text{mm}) / B_{0,\text{air}} \text{[ppm]}\), for the head model computed using the same buffer thickness of 48 mm at the final resolution.

sphenoid sinus and temporal bones. Images of the normalized difference between the magnetic field at a resolution of (4 mm)$^3$ and (2 mm)$^3$ are shown in Fig. 2.4.

As expected, there are differences near the sphenoid sinus (Fig. 2.4a,c) and temporal bones (Fig. 2.4b,c), as well as in the nasal cavity and the neck. In these regions, the complex geometry of the air spaces is better defined with a higher spatial resolution, thus resulting in a more precise magnetic field for the computation at (2 mm)$^3$. However, it is important to note that there are no significant differences in the brain. Therefore, although increased spatial resolution of the model is important near tightly curved air spaces, it does not add significantly to the assessment of the overall magnetic field in the brain.
Comparison Between the Head, Head/Shoulders, and Head/Thorax Models

Contour plots of the magnetic field deviation $\Delta B_0$ computed for the head, head/shoulders, head/thorax, and tilted head/shoulders models are shown in Fig. 2.5. Regions with a high density of contour lines correspond to large magnetic field inhomogeneities. To better visualize the $B_0$ inhomogeneities, the magnetic field gradients along each direction $\partial B_0/\partial x$, $\partial B_0/\partial y$, and $\partial B_0/\partial z$ were also computed. Images of $\partial B_0/\partial z$ computed for all four models are shown in Fig. 2.6, images of $\partial B_0/\partial x$ and $\partial B_0/\partial y$ computed for the head/shoulders model are shown in Fig. 2.7, and 3D views of all three gradients computed for the head/shoulders and tilted head/shoulders models are shown in Fig. 2.8.

Figs. 2.5 to 2.8 show that in most regions of the brain, magnetic field changes are moderate and vary fairly slowly with location, decreasing from anterior to posterior and from superior to inferior. Noteworthy exceptions are the regions near the frontal sinus, superior to the planum sphenoidale of the sphenoid sinus, posterior to the upper clivus, near the temporal bones and air-filled mastoids, as well as in the inferior frontal and temporal lobes. Considerable $B_0$ inhomogeneities are also observed in the nasal cavity, the mouth, and the neck. Substantial $B_0$ variations outside the head have no influence on image quality, but may cause problems when fiduciary markers are placed in these regions, e.g., for surgical planning or for registration of multimodality data [8].

A comparison between the head model and the head/shoulders model shows that the magnetic field perturbations near the cut-off region of the head model (i.e., below the neck) are artifactual (Figs. 2.5 and 2.6). More importantly, in-
Figure 2.5: (See figure on next page.) Midsagittal (a,d,g,j), coronal (b,e,h,k), and axial (c,f,i,l) contour plots of the magnetic field deviation $\Delta B_0$ [ppm] for the head (a–c), head/shoulders (d–f), head/thorax (g–i), and tilted head/shoulders (j–l) models. The results for the tilted head/shoulders model have been rotated forwards for ease of comparison. The solid and dashed arrows point to the planum sphenoidale and upper clivus respectively. The contour lines are 0.5 ppm apart.
Figure 2.5: See caption on previous page.
Figure 2.6: (See figure on next page.) Midsagittal (a,d,g,j), coronal (b,e,h,k), and axial (c,f,i,l) sections of the magnetic field gradient $\partial B_0/\partial z$ (inferior/superior) [ppm/cm] for the head (a–c), head/shoulders (d–f), head/thorax (g–i), and tilted head/shoulders (j–l) models. The results for the head/shoulders, head/thorax, and tilted head/shoulders models have been cropped and those for the tilted head/shoulders model have been rotated forwards for ease of comparison. The planes shown are the same as those shown in Fig. 2.5. The solid and dashed arrows point to the planum sphenoidale and upper clivus respectively.
Figure 2.6: See caption on previous page.
Figure 2.7: Midsagittal (a,d), coronal (b,e), and axial (c,f) sections of the magnetic field gradients $\partial B_0/\partial x$ (left/right) (a–c) and $\partial B_0/\partial y$ (anterior/posterior) (d–f) [ppm/cm] for the head/shoulders model. The results have been cropped for ease of comparison. The planes shown are the same as those shown in Figs. 2.5 and 2.6.
Figure 2.8: Three-dimensional views of the magnetic field gradients $\partial B_0/\partial x$ (left/right) (a,d), $\partial B_0/\partial y$ (anterior/posterior) (b,e), and $\partial B_0/\partial z$ (inferior/superior) (c,f) [ppm/cm] for the head/shoulders (a–c) and tilted head/shoulders (d–f) models. The results for both models have been cropped and those for the tilted head/shoulders model have been rotated forwards for ease of comparison. The cut planes shown are the same as those shown in Figs. 2.5 to 2.7. The solid and dashed arrows point to the planum sphenoidale and upper clivus respectively.
clusion of the shoulders for the numerical simulations introduces substantial $B_0$ inhomogeneities in the occipital lobes, the cerebellum, and the neck (Figs. 2.5a–f and 2.6a–f). The resulting magnetic field gradient $\partial B_0/\partial z$ is 0.21 ppm/cm at the occipito-temporal junction. This may be attributed to the fact that the air/tissue interfaces at the shoulders are nearly orthogonal to $B_0$. These results clearly show the necessity for including more distant anatomy, namely at least the neck and the shoulders, for accurate numerical simulations of susceptibility-induced magnetic fields in the head, and that if a trade-off between spatial resolution and inclusion of a larger anatomical region has to be made because of computer memory limitations, this trade-off should be made at the expense of resolution.

A comparison between the head/shoulders model and the head/thorax model shows that the air/tissue interfaces in the lungs further increase the $B_0$ inhomogeneity in the occipital lobes, the cerebellum, and the neck (Figs. 2.5d–i and 2.6d–i). The resulting magnetic field gradient $\partial B_0/\partial z$ increases from 0.21 to 0.23 ppm/cm at the occipito-temporal junction. These effects appear to be substantially less pronounced than those due to the air/tissue interfaces at the shoulders. One reason for this may be that the air/tissue interfaces in the lungs are curved, whereas those at the shoulders are nearly orthogonal to $B_0$. Another reason may be that the lungs are further away from the brain than the shoulders. It should be noted that since the CT data used for the numerical simulations were acquired over multiple respiratory cycles, and thus represent a static average of the chest position, these results do not yet allow drawing any conclusions regarding respiratory effects in fMRI.
Comparison Between the Head/Shoulders and Tilted Head/Shoulders Models

A comparison between the head/shoulders model and the tilted head/shoulders model (Figs. 2.5d–f,j–l, 2.6d–f,j–l, and 2.8) shows that tilting the head backwards significantly reduces the $B_0$ inhomogeneity in the region superior to the planum sphenoidale. This may be explained by the fact that when the head is upright, the air/tissue interface at the planum sphenoidale is almost orthogonal to $B_0$, thus resulting in strong magnetic field gradients, whereas when the head is tilted backwards (by 35° in our case), the angle between this air/tissue interface and $B_0$ is reduced, resulting in weaker magnetic field gradients. Our numerical simulations thus confirm the experimental findings by Heberlein et al. [21].

In addition, it should be noted that when the head is tilted backwards, the $B_0$ inhomogeneity increases in the region posterior to the upper clivus, slightly decreases near the frontal sinus, and does not change around the temporal bones. More importantly, tilting the head backwards significantly reduces the $B_0$ inhomogeneity in the occipital lobes and the cerebellum. The resulting magnetic field gradient $\partial B_0 / \partial z$ decreases from 0.21 to 0.09 ppm/cm at the occipito-temporal junction. This improvement may be explained by the fact that the position of the tilted head is changed relative to the shoulders, such that the occipital lobes and the cerebellum are less affected by the susceptibility effects induced by the air/tissue interfaces at the shoulders.
2.1.4 Discussion

Previous studies used finite difference [6, 7, 12] and finite element [9, 10, 11] methods to compute susceptibility-induced magnetic fields. Several models were generated to define the spatial distribution of air and tissues, including two-component (air and water) wire frame models coarsely approximating air spaces in the head [9, 10] and upper body [11], two- or multi-component models of the head [6, 7, 12], the chest, and the hand [8] generated by segmentation of MR images, as well as a multi-component model of the head and shoulders generated from the Visible Human data [12].

Unlike in previous studies, we used CT images to generate multi-component models of the head and upper body, and a finite element algorithm to compute the susceptibility-induced magnetic field. CT images can be easily segmented to generate magnetic permeability distributions for air, fat, nonfat soft tissue, and bone. As such, they offer a major advantage over MR images, from which air and bone cannot be differentiated. The most pronounced susceptibility differences occur at air/tissue interfaces and, as expected, our numerical simulations showed substantial $B_0$ inhomogeneities in regions where air and bone are in close proximity and have complex spatial distributions, such as near the frontal and sphenoid sinuses, the temporal bones, as well as in the nasal cavity and the neck. Therefore, unambiguous delineation of the air spaces is critical for the computation of susceptibility-induced magnetic fields in these regions.

On the other hand, CT images are less sensitive than MR images for distinguishing various soft tissues. Susceptibility differences between soft tissues are more subtle, and unlike susceptibility differences at air/tissue interfaces, are not
known to lead to pronounced image artifacts. However, they are very important for generating image contrast, and computing magnetic field changes due to susceptibility differences between different tissues may be of interest for a better understanding of contrast mechanisms. Using the Visible Human data as input for numerical simulations of susceptibility-induced magnetic fields has the advantage that air and bone, as well as different soft tissues, can be clearly delineated. On the other hand, these data are unique and provide geometric information only for a single subject. With our method, it would be feasible to use CT data acquired for routine diagnostic examinations, as long as a sufficiently large anatomical region is covered, since the resolution and CT image quality requirements are not particularly stringent for this application. Such data could be used to compute susceptibility-induced magnetic fields for a range of head geometries, and serve as a basis for the development of susceptibility artifact correction methods.

Our simulations allow drawing conclusions about two approaches for susceptibility artifact reduction, namely slice orientation and subject positioning. First, in 2D imaging, the slice thickness is typically larger than the in-plane resolution, so that the $B_0$ inhomogeneity is the most severe in the slice direction. Thus evaluation of the magnetic field gradients along all three directions allows determining an optimal acquisition plane for a given region of the brain. For example, for the head/shoulders model, the gradient along $\hat{x}$ in the region superior to the planum sphenoidale (Figs. 2.7a and 2.8a) is much smaller than the gradients along $\hat{y}$ and $\hat{z}$ (Figs. 2.6d, 2.7d, and 2.8b,c), making sagittal slices preferable to coronal or axial slices for this region of the brain. Similarly, the gradients along $\hat{x}$ and $\hat{y}$ in the occipital lobes and cerebellum (Fig. 2.7) are smaller than the gradient along $\hat{z}$ (Fig. 2.6d–f), making sagittal or coronal slices preferable to axial slices.
Second, our study confirmed the experimental finding by Heberlein et al. [21] that tilting the head backwards can significantly reduce the $B_0$ inhomogeneity in the region superior to the planum sphenoidale (Figs. 2.5j, 2.6j, and 2.8f). However, the observed improvement may be highly dependent on the subject’s air space anatomy. For example, the subject shown here had an air/tissue interface extending to the most posterior recess of the sphenoid sinus, resulting in larger $B_0$ inhomogeneities near the upper clivus. In addition, our study showed that tilting the head backwards can significantly reduce the $B_0$ inhomogeneities in the occipital lobes and cerebellum (Figs. 2.5j,k and 2.6j,k). More recently, Tyszka et al. [22] extended the experimental work of Heberlein et al. from 2D single-slice to 3D $B_0$ mapping of the whole brain for three head pitch angles, and also found that increased head pitch improves the $B_0$ homogeneity in the inferior frontal lobes, but introduces inhomogeneities in the lateral and superior regions of the frontal and temporal lobes.

The ultimate objective of this work is to use numerically computed magnetic fields for the assessment and optimization of various susceptibility artifact correction methods (see section 2.3.4 and chapter 3). The two examples described above show that numerical simulations are useful in this context, because they are not affected by other sources of artifacts such as $B_1$ inhomogeneity prevalent at ultra-high field strength, signal loss due to complete intravoxel dephasing in regions with high $B_0$ inhomogeneity, or subject physiological motion, and thus allow susceptibility effects to be studied in isolation.

Last but not least, our numerical simulations based on more realistic anatomical models than the simple geometric approximations used in prior studies [23] may allow gaining a better understanding of respiratory artifacts in fMRI. Sev-
eral authors have suggested that such artifacts are caused by bulk susceptibility changes during respiration due to movement of the chest and diaphragm and/or variations in the oxygen concentration. While there is clear evidence that fMRI studies are contaminated by respiratory artifacts, there are still some discrepancies between experimental findings [24, 25, 26] and simulations based on simple geometric models [23]. Numerical simulations based on more realistic anatomical models during inhalation and exhalation would allow a more detailed assessment, and since changing the susceptibility value for different oxygenation levels in the lungs is trivial with simulations, it would be possible to better distinguish effects due to changes in shape due to movement of the chest and diaphragm from effects due to changes in oxygenation. However, it should be noted that respiratory-induced $B_0$ fluctuations measured experimentally have been found to be as small as 0.01 ppm [24], whereas the accuracy of our computations is currently only about 0.03 ppm due to computer memory limitations. An improved implementation of the algorithm, allowing use of a larger buffer size, increased spatial resolution, and inclusion of yet larger anatomical regions, is therefore mandatory for this application.

Marques et al. [16] recently showed preliminary work using numerical simulations (see section 2.1.1) to compute the $B_0$ changes in the head due to movement of the lungs and chest cavity during respiration. Abdominal breathing was simulated by extending the bottom of the lungs, whereas thoracic breathing was simulated by expanding the lungs anteriorly and laterally. The results were found to be in relatively good agreement with previous studies, although some discrepancies might be attributed to the lack of variation in oxygen concentration.
2.2 Experimental Techniques

2.2.1 Introduction

$B_0$ Mapping

$B_0$ numerical simulations have the advantage of not being affected by noise and artifacts due to $B_1$ inhomogeneity, signal loss due to intravoxel dephasing, and/or subject physiological motion. However, experimental mapping techniques are eventually required for the development and assessment of susceptibility artifact correction methods that require subject-specific $B_0$ maps. A large number of experimental $B_0$ mapping methods have been proposed in the literature and are reviewed below.

The majority of these methods are based on phase images. The simplest one assumes that the phase of a GE image is directly proportional to $B_0$:

$$\phi(x, y, z) = -\gamma B_0(x, y, z) \text{TE}, \quad (2.15)$$

where $\gamma$ is the gyromagnetic ratio and TE the echo time, so that a $B_0$ map can be obtained directly from a single phase image [27]. However, additional phase shifts $\phi_0$ can arise due to flow, eddy currents, coil nonlinearities, or RF penetration, in which case Eq. (2.15) becomes:

$$\phi(x, y, z) = \phi_0(x, y, z) - \gamma B_0(x, y, z) \text{TE}. \quad (2.16)$$

By acquiring two echoes at different TEs and subtracting the phase images, this $\phi_0$ term cancels out:

$$\Delta \phi(x, y, z) = -\gamma B_0(x, y, z) \Delta \text{TE}, \quad (2.17)$$
so that a $B_0$ map can be computed as follows:

$$B_0(x, y, z) = \frac{\Delta \phi(x, y, z)}{\gamma \Delta T E}. \quad (2.18)$$

This is the basis of phase difference methods. The simplest one of such methods consists in using two GE sequences, which can be either 2D multislice [28, 29, 21, 30, 31] or 3D [32, 33, 34, 35], with different TEs. To make the method insensitive to eddy currents, some authors suggested to use $TE \gg \Delta T E$ [31], shift the phase encoding and readout rephaser gradients by $\Delta T E$ for the second acquisition to ensure that eddy current effects are the same at both TEs, and not use a crusher gradient in the slice direction so that the resulting eddy current does not influence the next acquisition [29].

Jesmanowicz et al. [36] developed a method based on two multislice two-shot echo-planar imaging (EPI) sequences with different TEs, which is faster than conventional GE methods but is affected by geometric distortions. Similarly, Kim et al. [37] used two multislice single-shot spiral GE sequences with different TEs.

Phase difference methods can potentially be affected by chemical shift artifacts of lipids, and several methods have been proposed to suppress these artifacts. Webb et al. [32] used a spectral-spatial excitation pulse with Gaussian spectral selection and approximately rectangular spatial selection to suppress the lipid signal, but this method requires a relatively homogeneous field. Alternatively, other authors [28, 38] chose $\Delta T E = 2\pi/(\sigma \gamma B_0)$, where $\sigma$ is the chemical shift between water and fat, in order to alias the water and fat signals.

An alternative to phase difference methods is spectroscopic imaging, where the spectrum of each pixel or voxel is obtained either through volume selective
methods or through 3D [39] or 4D [40] Fourier transform methods. Spectroscopic imaging is relatively immune to chemical shift artifacts of lipids, because the lipid signals can be explicitly excluded from the spectrum. The drawback is an excessive acquisition time for in vivo applications. Tropp et al. [41] developed two methods based on a free induction decay (FID) or a SE acquisition, where the resonance frequency, and therefore $B_0$, is given by the location of the water peak in the spectrum at each pixel. Similarly, Ericsson et al. [39] developed a 3D Fourier transform multi-echo GE sequence that yields water and fat images, as well as $B_0$ and $T_2^*$ maps. The $B_0$ map is computed from the location of the water peak, the water and fat images from the integrals of the water and fat peaks respectively, and the $T_2^*$ map from the width of the water peak. This method is insensitive to excitation imperfections, $B_1$ inhomogeneity, and steady state effects. In any case, it should be noted that chemical shift artifacts are not problematic in the brain because of the very low lipid signal and concentration of metabolites [42]. As such, the majority of $B_0$ mapping techniques for brain applications are based on phase difference methods rather than spectroscopic imaging.

Several phase difference methods have been developed that are based on multi-echo sequences and allow acquisition of a $B_0$ map with a single scan [43, 38, 22]. Such methods offer significant advantages over those based on two single-echo acquisitions by allowing a two-fold reduction in acquisition time and avoiding misregistrations due to subject physiological motion that may occur between successive acquisitions. However, there is a lower limit for $\Delta$TE, and eddy current effects are different for each echo [31].

Kanayama et al. [38] used a 3D three-echo GE sequence with readout gradients of alternating polarity. However, only the first and third echoes were used
for computation of the $B_0$ map. Although the first and second echoes could also be used, thus allowing a shorter $\Delta TE$, their opposing trajectories along the readout direction in k-space would lead to different geometric distortions caused by macroscopic $B_0$ inhomogeneities, resulting in misregistration errors.

Alternatively, Wen et al. [43] used a 3D double-echo GE sequence with readout gradients of same polarity and a readout rephaser/dephaser gradient in between. The duration of this gradient can be minimized to obtain a shorter $\Delta TE$ than in the previous method. A phase rewinder gradient is used to maintain a steady state, and a spoiler gradient is added in the slice direction. The readout gradients are symmetric with respect to the midpoint between the two echoes and have a zero time integral between the two echoes to ensure that motion-related phase shifts are the same in both echoes and do not affect the $B_0$ map.

Nayak et al. [44] developed a projection reconstruction method that inherently oversamples low spatial frequencies to obtain a $B_0$ map. Interleaved spokes are acquired at two different TEs. The full k-space is used to reconstruct a high resolution anatomical image, whereas the central k-space is used to reconstruct two low resolution images with different TEs, from which a $B_0$ map is computed. This map is then used to correct for off-resonance effects in the anatomical image.

A similar method has been developed by Roopchansingh et al. [26] for simultaneous acquisition of GE EPI anatomical images and a $B_0$ map. It uses a modified EPI trajectory that scans the center of k-space twice. An initial jump in k-space allows the line acquisition to be reordered so that there is a temporal delay between successive acquisitions of the same line. Again, a high resolution image is reconstructed from the full k-space, whereas a $B_0$ map with a lower resolution in the phase-encoding direction is reconstructed from the central k-space. This
map is then used to correct for geometric distortions in the anatomical images. Since the $B_0$ map is generated from the same data as the anatomical images, it is registered and does not suffer from errors due to subject motion or from different geometric distortions that can result from using different sequences.

Phase difference methods are not limited to GE sequences. Several authors [45, 46, 47] developed a method that uses a SE sequence and an asymmetric SE (ASE) sequence with identical parameters, except that in the ASE sequence, the 180° RF pulse is shifted from TE/2 by a delay $\Delta/2$, so that the echo is shifted from TE by a delay $\Delta$, and the spins are not completely rephased at TE. The resulting phase difference between the SE and ASE sequences is used to compute a $B_0$ map. To reduce the acquisition time, Prammer et al. [45] modified a Carr-Purcell SE sequence by shifting the third 180° pulse by $\Delta/2$, thus making the third echo an ASE, and used the phase difference between the first and third echoes to compute a $B_0$ map.

Yeung et al. [48] extended the Dixon technique for chemical imaging by using two two-echo Carr-Purcell-Meiboom-Gill (CPMG) SE sequences. In the first one, the interecho spacing is chosen such that water and fat are in phase at both echoes (echoes 1 and 2). In the second one, the two 180° RF pulses are shifted by $\Delta/2 = \pi/(2\sigma\gamma B_0)$ and $3\Delta/2$ respectively, so that water and fat are out of phase at the first echo (echo 3) and in phase at the second echo (echo 4). A $B_0$ map is computed from the phase difference between echoes 2 and 4. True water and fat images are then obtained from the complex sum and difference of echoes 1 and 3, which have first been phase corrected using the $B_0$ map.

Similarly, several authors extended the two-point Dixon technique and echo-time-encoding technique [49, 50, 40] into a so-called three-point Dixon technique
or echo-time-encoded chemical-shift imaging technique [52] that yields a $B_0$ map as well as true water and fat images. This method uses three SE/ASE sequences with the 180° RF pulse shifted by $-\Delta/2$, $0$, and $\Delta/2$, where $\Delta/2 = \pi/(2\sigma\gamma B_0)$, i.e., it uses three echo-time-encoding steps.

Phase difference methods are not limited to single-echo or two-echo sequences. Several authors [53, 54] developed a method for simultaneous $T_2^*$ and $B_0$ mapping using a multi-echo GE sequence. The $T_2^*$ and $B_0$ maps are computed using pixel-by-pixel linear regression of the magnitude and phase time course respectively:

\begin{align}
S(x, y, z, \text{TE}_n) &= S_0(x, y, z) \exp[-\text{TE}_n/T_2^*(x, y, z)] \\
\phi(x, y, z, \text{TE}_n) &= \phi_0(x, y, z) - \gamma B_0(x, y, z) \text{TE}_n .
\end{align}

Lee et al. [55] developed a similar method using an extended rosette acquisition, in which a rosette trajectory is extended to acquire k-space multiple times. A sliding window is then used to select one full shot of data and reconstruct a time sequence of images with different TEs, from which $B_0$ and $T_2^*$ maps are computed. Eggers et al. [56] developed a radial multi-echo GE method that inherently oversamples the central k-space to derive $B_0$ and $T_2^*$ maps, which are both used to correct for off-resonance and relaxation artifacts. Bowen et al. [57] also used a 2D multi-echo GE sequence, but computed the $B_0$ map by taking the Fourier transform of the complex signal along the echo train for each pixel and finding the location of the peak in the Fourier spectrum.

Klassen et al. [58] developed a 3D multi-echo GE method with automatic compensation for hardware timing errors, gradient propagation delays, gradient imbalance, and eddy currents. These effects cause k-space shifts that result in
phase ramps in the reconstructed images and therefore artifacts in the $B_0$ map. By acquiring two echo trains with opposite gradient polarity, the equal but opposite k-space shifts due to hardware timing errors and short time constant eddy currents can be canceled by averaging the phase images. Gradient imbalance causes increasing k-space shifts in an echo train that result in a phase gradient in the readout direction. By spacing echoes non-linearly, this phase ramp can be separated from the phase shift due to the $B_0$ variations. The frequent switching of the readout gradient results in long time constant eddy currents that cause a magnetic field gradient in the readout direction. By acquiring reference readout profiles without phase encoding before any pulse and after acquisition, the steady state magnetic field gradient caused by the sequence can be determined and removed. Steady state pulses are used to drive the eddy currents and magnetization into steady state. Finally, gradient spoiling is used only in the readout direction to minimize magnetic field gradients along the phase encode directions, and RF spoiling is used to compensate for this lack of gradient spoiling.

Some $B_0$ mapping methods have been developed specifically for active shimming and measure the field only at a limited number of points. These include a stimulated echo volume-selective spectroscopy sequence [59] as well as the so-called fast, automatic shimming technique by mapping along projections (FASTMAP) developed by Gruetter [60, 61] and its EPI version called FAST(EST)MAP [62] that uses an asymmetric EPI readout gradient train and an adiabatic low flip angle excitation to achieve subsecond acquisition times.

Finally, a few $B_0$ mapping methods are based on neither phase difference nor spectroscopic imaging. Wendt et al. [63] developed a method based on a $90^\circ - \tau_1 - 90^\circ - \tau_2$–acquisition sequence. Spins that precess an odd multiple of $\pi$
radians during $\tau_1$ are not affected by the $90^\circ - \tau_1 - 90^\circ - \tau_2$ preamble, whereas those that precess an even multiple of $\pi$ radians experience a net $180^\circ$ flip angle. Spins of intermediate frequency experience intermediate flip angles and dephase during $\tau_2$, so that the distribution of longitudinal magnetization at the end of the preamble is a function of the spatial distribution of the resonance frequency, i.e. the local $B_0$ field. The resonance frequency of each pixel is phase encoded by acquiring a series of images with different $\tau_1$ values and recovered by Fourier transform in the precessional frequency direction. Since the encoding is done without gradients and separately from spatial location, this method is not affected by flow or motion effects. However, it has two drawbacks: a long acquisition time and the fact that the nonselective preparation pulses (to minimize $\tau_1$ and avoid stimulated echoes) restrict it to be single slice.

Weisskoff et al. [64] developed a similar method that uses a pair of $45^\circ$ RF pulses instead of $90^\circ$ pulses. Spins that precess an odd multiple of $\pi$ radians during $\tau_1$ are not affected by the preamble and give no signal, whereas those that precess an even multiple of $\pi$ radians experience a net $90^\circ$ flip angle and result in a maximum SE signal. For spins of intermediate frequency, the signal follows a periodic dependence on $B_0$. A typical image thus consists of a series of light and dark bands, with a spacing between dark bands of $1/\tau_1$. This method is relatively insensitive to $B_1$ inhomogeneity and $T_2$ relaxation, which affect the amplitude of the signal but leaves the band spacing unaffected.

Mugler et al. [65] developed a method that uses a $90^\circ$ RF pulse followed by a refocusing pulse $\alpha$. The echo is therefore the sum of a GE and a SE, both generated by the $90^\circ$ pulse. (The GE generated by the $\alpha$ pulse is eliminated by spoiling.) Local $B_0$ variations generate relative phase shifts between the GE and SE, which
result in intensity variations in the magnitude image. The 0°-component of the
\( \alpha \) pulse, which produces the GE, is proportional to \( \cos^2(\alpha/2) \), whereas its 180°-component, which produces the SE, is proportional to \( \sin^2(\alpha/2) \). The choice of \( \alpha \) thus determines the relative contribution of the GE and SE signals, and therefore
the amplitude of the intensity variations, which are the largest for \( \alpha = 90° \).

Mosher et al. [66] developed a so-called Double-DANTE Tagging method that
uses a DANTE (delay alternating with nutations for tailored excitation) pulse
train in the presence of a frequency-encoding gradient to irradiate a grid pattern
of thin planes or "tags" in the sample. Following tag placement, the sample is
imaged and the tagged regions appear as dark lines, which are shifted according
to the magnitude and direction of the local \( B_0 \) field.

**Phase Unwrapping**

In all \( B_0 \) experimental mapping methods based on phase images, the problem
of phase unwrapping needs to be addressed. Since the phase is obtained from a
discrete Fourier transform, it can only be determined to within modulo 2\( \pi \) and is
said to be wrapped or aliased. This value is known as the principal value [67] and
is usually contained in the range \([-\pi, \pi)\]. Eq. (2.17) should therefore be replaced
by:

\[
\Delta \phi(x, y, z) = -\gamma B_0(x, y, z) \Delta \text{TE} \mod 2\pi. \quad (2.21)
\]

To avoid phase wrapping, some authors (e.g., [29]) restrict \( \Delta \text{TE} \) to be smaller
than \( \pi/\gamma B_0 \), which reduces the dynamic range and sensitivity of the technique,
but can be acceptable for some applications where the \( B_0 \) variations are relatively
small. Alternatively, if the phase variation is sufficiently smooth, it is possible
to use neighborhood information to detect phase discontinuities due to wrapping and restore a smooth phase across the discontinuities by adding or subtracting $2\pi$. This reconstruction of the actual phase from the wrapped phase is called phase unwrapping. More specifically, a necessary and sufficient condition for the phase to be unwrappable, known as the phase unwrapping condition, is that the phase difference between adjacent pixels is less than $\pi$ [68, 69].

In MRI, the following problems make phase unwrapping not so simple. First, it is highly sensitive to errors that can occur in regions with low SNR where the unwrapping condition may be violated. Such errors can propagate into regions with high SNR and lead to failure of the unwrapping process. Second, the regions outside the boundaries of the object have no signal, so that the wrapped phase in these regions is meaningless information that cannot be used for estimating the true phase. Finally, there may be multiple objects within the FOV and no signal to unwrap the phase between them.

A large number of phase unwrapping algorithms have been developed, not only for $B_0$ mapping, but also for various applications such as susceptibility and chemical shift mapping, blood flow measurement, temperature mapping, as well as many other applications in other fields than MRI. Some of these algorithms are reviewed below.

In so-called region growing algorithms, the phase of an object is unwrapped by choosing a reference pixel and unwrapping from this pixel along a path that covers the object. One problem with such algorithms is that when the path reaches a pixel where the unwrapping condition is violated, all pixels that are unwrapped from that pixel will be in error. Hedley et al. [69] developed an algorithm that first identifies all pixels where the unwrapping condition is violated, and does not
include them in the unwrapping path. Their phase is estimated only at the end to prevent the propagation of artifacts. These pixels are identified using the property that unwrapping is path independent in a noise-free map, so that the sum of the phase differences around any closed loop within an object must be zero. If it is not zero, in which case it will be a multiple of $2\pi$, the unwrapping condition has been violated at least once in the loop. These pixels around which there is a nonzero sum are referred to as poles [67, 70]. All poles are thus identified by calculating the sum of the phase differences around all $2 \times 2$ loops contained within the object. The phase is unwrapped vertically as far as possible in both directions from the starting point, then horizontally from all points unwrapped in the last pass, and so on. Finally, the phase at the poles is estimated by determining the number of multiples of $2\pi$ to be added to unwrap the pixel from each adjacent unwrapped pixel, and selecting the most frequently occurring value.

In so-called boundary following algorithms, the modulo $2\pi$ boundary is located and an appropriate multiple of $2\pi$ is added to maintain phase continuity. In the algorithm developed by Axel et al. [68], a region-of-interest (ROI) is first demarcated and, starting at one of its corners, the initial pixel is assigned a true phase. Making multiple passes over the ROI, the phase of each pixel is assigned as correct if it is within $\pm \pi$ of the mean of all nearest neighbors that have already been unwrapped, and it is so marked. Discontinuities due to phase wrapping produce isolated regions with unmarked boundaries. In subsequent passes over the ROI, offsets of $\pm \pi$ are applied at these discontinuities to produce the best fit smooth variation of phase. One shortcoming of such algorithms is that following phase wrapping boundaries becomes difficult in regions where the phase information is unreliable or where phase wrapping is rapid, such as near air/tissue interfaces.
Ching et al. [71] developed an algorithm that estimates the unwrapped phase along any row of data using a second-order Taylor series expansion. The zeroth-, first-, and second-order terms are computed from the phase of the one, two, or three previous adjacent pixels whose phase has been unwrapped, respectively. This estimate need only be accurate to within $\pm \pi$ of the continuous true phase and is therefore largely immune to error propagation. An initial point is chosen from a region where the phase can be assumed to vary slowly.

Song et al. [72] developed an algorithm that first estimates the phase gradient by wrapping the gradient of the original phase image. The problem is then to obtain the absolute phase given this estimate. The least-squares solution to this problem is shown to be a solution of the Poisson equation, which can be solved efficiently. This method is truly multi-dimensional, unlike previous ones that merely applied one-dimensional (1D) algorithms over 2D images, with the limitation that noise can cause the result to be dependent on the chosen path.

Liang et al. [73] developed a model-based algorithm in which the unwrapped phase function is represented by the sum of a polynomial and a residual function. By introducing such a model, the phase unwrapping problem is converted to a parameter estimation problem, which can be easily solved. The model parameters, i.e., the polynomial coefficients and residual function, are noniteratively computed from the original complex data and the phase derivatives. The extention of this algorithm to higher dimensions is straightforward. However, one of its limitations lies in the polynomial model used. If the model is accurate, the residual function will be at the noise level. On the other hand, if the phase variations deviate significantly from a polynomial, the algorithm will fail to unwrap the phase completely, because the residual function will not be in the principal value range.
Wang et al. [74] developed a method based on a three-point Dixon technique, for which the phase behavior of the water and fat in-phase images is known and can be used to deduce the phase wrapping by a simple consistency check of these two phases. This method thus uses a pixel-by-pixel comparison of water and fat in-phase images instead of just comparing adjacent pixels in the same image, as in most other methods. Therefore any errors that may occur in one part of the image will not propagate throughout the whole image.

Cusack et al. [70] developed a robust 3D phase unwrapping algorithm, in which the phase is initially unwrapped in less noisy regions. The magnitude images can be used to ascertain the amount of noise as a function of space. Alternatively, all poles in the map are first identified as in [69] (see above), then a diffuse field is generated around each pole, and these are summed to form an estimator of the noise at each voxel that is used to guide the unwrapping.

Many of the existing phase unwrapping algorithms were written to deal with 2D slices. Generalizing such methods to 3D can lead to unacceptably slow algorithms (with some exceptions [70]) because it requires that phase unwrapping be performed in multiple directions. Furthermore, a 2D phase unwrapping method applied slice-by-slice can leave phase wraps in the through-slice direction. In MRI applications, phase maps are often 3D and it is important to take into account the 3D nature and constraints of the problem. Jenkinson [75] developed a fast, robust, and fully automated algorithm for unwrapping multi-dimensional phase maps. It uses a region-merging approach to optimize a cost function that penalizes phase differences across boundaries.

Ying et al. [76] developed a 2D phase unwrapping algorithm that models the true phase as a Gaussian Markov random field. Specifically, the true phase of
a pixel is assumed to be close to that of its neighbors with high probability. By using a statistical model, this algorithm is more robust to additive Gaussian noise.

2.2.2 Methods

After having reviewed and compared the advantages and limitations of the various existing $B_0$ experimental mapping methods (see section 2.2.1), we developed two phase difference methods based on a 2D multislice ASE sequence and a 3D dual-echo GE sequence respectively, and implemented them on the 8 T human whole-body MRI system [77].

In the 2D ASE method, two ASE sequences are acquired with the 180° RF pulse shifted from TE/2 by a delay $\Delta_1/2$ and $\Delta_2/2$ respectively (see Fig. 2.9). A pair of crusher gradients is added to correct for imperfect 180° pulses, phase rewinder and slice spoiler gradients are used, and two sets of interleaved slices are acquired to cover a 3D volume while avoiding crosstalk. The delay $\Delta_1$ is chosen equal to $2\pi/(\sigma \gamma B_0)$ (= 0.9 ms at 8 T) and $\Delta_2$ equal to an integer multiple of $\Delta_1$ to avoid chemical shift artifacts. A value of $\Delta_2 = 2\Delta_1$ was found to provide sufficient sensitivity while minimizing phase aliasing. Values of $\Delta_2$ equal to half-integer multiples of $\Delta_1$ were also tested, but were not found to cause significant chemical shift artifacts in the brain.

In the 3D GE method, a 3D dual-echo GE sequence is acquired with readout gradients of same polarity (see Fig. 2.10). Phase rewinder and readout spoiler gradients are used, and phase encoding in the slice direction is oversampled by 50% to reduce slice aliasing. The pulse sequence was optimized as described below to obtain the shortest TEs and $\Delta$TE achievable, and thus minimize signal loss and phase aliasing due to intravoxel dephasing.
Figure 2.9: Two-dimensional multislice ASE pulse sequence for $B_0$ mapping. The 180° RF pulse is shifted from TE/2 by a delay $\Delta/2$, so that the echo is shifted from TE by $\Delta$.

One way to reduce TE is to shorten the RF pulse, which can be done either by keeping the same pulse shape and using a shorter duration, by truncating the pulse, or with a combination of both. In the first case, the trade-off is a higher bandwidth and RF power requirement, which, in the case of low flip angle GE sequences, becomes a limitation only for very short pulse durations. In the second case, the bandwidth and RF power requirement are identical, but the trade-off is a worse slice profile. Nevertheless, since TE is defined as starting from the center of the mainlobe of the RF pulse, it is possible to use asymmetric RF pulses (i.e., with a longer duration before than after the center of the mainlobe) [78] to reduce
Figure 2.10: Three-dimensional dual-echo GE pulse sequence for $B_0$ mapping. A short asymmetric RF pulse and minimum gradient ramp times and durations are used to achieve the shortest TEs and $\Delta$TE. Both echoes are acquired with readout gradients of same polarity to avoid errors due to opposite geometric distortions, intravoxel dephasing, eddy currents, and gradient imbalance.
TE while maintaining the same bandwidth and RF power requirement, as well as a reasonable slice profile.

A sinc\textsuperscript{3}/1 RF pulse \textit{(i.e.,} with three sidelobes preceding and one following the mainlobe) was therefore implemented on the 8 T MRI system. Both numerical simulations of the Bloch equations and experimental imaging of a homogeneous phantom were performed with various pulse shapes of identical bandwidth, including a 0.5 ms sinc\textsuperscript{1}/1 pulse\textsuperscript{1}, a 0.75 ms sinc\textsuperscript{3}/1 pulse, and a 1 ms sinc\textsuperscript{3}/3 pulse, and showed that the sinc\textsuperscript{1}/1 pulse had a worse slice profile than the sinc\textsuperscript{3}/3 pulse, as expected, but that the sinc\textsuperscript{3}/1 pulse only had a slightly worse slice profile than the sinc\textsuperscript{3}/3 pulse.

Similarly, since TE is defined as ending at the center of the acquisition window, asymmetric echoes could be used to further reduce the TEs. However, this was found to result in increased artifacts.

To reduce both the TEs and \(\Delta\)TE, a smaller matrix size and/or higher bandwidth could be used, however at the expense of resolution and SNR. An alternative solution is to use the shortest gradient durations and ramp times achievable with the maximum gradient strength and slew rate of the system. The pulse sequence was therefore programmed to use these optimal values whenever possible, rather than the default fixed values.

To reduce \(\Delta\)TE, the second echo could be acquired with a readout gradient of opposite polarity. However, this results in misregistration errors due to opposite geometric distortions, intravoxel dephasing, and eddy current effects (see section 2.2.1). In addition, the 8 T MRI system is affected by gradient imbalance, which

\textsuperscript{1}In ParaVision, a sinc\textsuperscript{2} pulse corresponds to a sinc\textsuperscript{1}/1 pulse, a sinc\textsuperscript{3} pulse to a sinc\textsuperscript{2}/2 pulse, and a sinc\textsuperscript{4} pulse to a sinc\textsuperscript{3}/3 pulse.
results in offsets along the frequency direction in the reconstructed phase images that can exceed several pixels. Nevertheless, this problem could in principle be corrected for, either by post-processing or by adding appropriate gradient offsets in the pulse sequence.

The 2D ASE and 3D GE methods were implemented and compared for their advantages and limitations at ultra-high field strength, with the expectation that the 2D ASE method has the advantage of being less affected by signal loss and phase aliasing due to intravoxel dephasing, whereas the 3D GE method has the advantage of requiring a shorter acquisition time and lower RF power, as well as being less sensitive to $B_1$ inhomogeneity.

Several of the phase unwrapping algorithms described in section 2.2.1 were implemented and tested. The model-based algorithm developed by Liang et al. [73] was implemented with a third-order polynomial, but failed in regions with rapid $B_0$ variations such as near air/tissue interfaces, as expected. Other algorithms were tested, but could not provide satisfactory results either, so we combined different features from separate algorithms (e.g., comparison with the mean phase of all neighboring voxels [68] and spiral path [71]) to generate the following algorithm.

For both the 2D ASE and 3D GE methods, the phase images from both echoes are first subtracted by complex division (i.e., by computing the phase of the ratio of the complex images) to preserve the phase aliasing. Regions with no signal are excluded using a mask obtained by thresholding the magnitude images. This phase difference is then corrected for the frequency offset in the slice direction and unwrapped slice-by-slice following a spiral path starting at the center of the image. The unwrapping is done by comparing the phase of each voxel to the mean phase of all neighboring voxels whose phase has not been unwrapped yet, and adding or
subtracting $2\pi$ depending on whether the difference is smaller than $-\pi$ or larger than $\pi$, respectively. Note that except for the first slice, neighboring voxels from the previous unwrapped slice are also included in the computation of the mean, so that the algorithm is not simply a 2D algorithm applied slice-by-slice, but does take into account the 3D nature of the problem to avoid leaving phase wraps in the slice direction.

Finally, a $B_0$ map is obtained by dividing the unwrapped phase images by $-\gamma(\Delta_2 - \Delta_1)$ for the 2D ASE method or $\gamma\Delta_\text{TE}$ for the 3D GE method. An unknown constant offset from the real $B_0$ field may still exist, but cancels out if maps of the $B_0$ gradient along $\hat{x}$, $\hat{y}$, and $\hat{z}$ are computed to allow better visualization of the $B_0$ inhomogeneities.

Both 2D ASE and 3D GE methods were tested on a phantom containing an air-filled tube orthogonal to $B_0$ surrounded by a CuSO$_4$ solution, as well as a postmortem human subject (84-year-old female) and a healthy volunteer (52-year-old male) who gave informed consent to the experimental protocol approved by our Institutional Review Board. These experimental measurements were also compared with numerical simulations performed on the same sample and subjects using a finite difference method and magnetic permeability distributions obtained from CT images (see section 2.1.2).

The $B_0$ inhomogeneities due to the magnet were first minimized by shimming on a large bottle containing mineral oil, and no additional shimming was applied on the phantom or subjects to preserve the susceptibility-induced $B_0$ inhomogeneities. The acquisition parameters are shown in Table 2.2.
<table>
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<th></th>
<th>phantom study</th>
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**Table 2.2:** Acquisition parameters for the 2D ASE and 3D GE $B_0$ mapping methods for the phantom and human studies.

### 2.2.3 Results and Discussion

Maps of $\partial B_0/\partial x$ and/or $\partial B_0/\partial y$ of the phantom (Fig. 2.11) as well as the post-mortem (Fig. 2.12) and *in vivo* (Fig. 2.13) human brains show excellent agreement between both experimental methods and the numerical simulations. Similar patterns of $B_0$ inhomogeneities are observed around the air-filled tube for the phantom study (Fig. 2.11), as well as in the inferior frontal lobes just superior to the planum sphenoidale (Figs. 2.12 and 2.13) and in the inferior temporal lobes near the mastoid and middle ear air spaces (Fig. 2.13) for the human studies.
Figure 2.11: Coronal maps of the magnetic field gradient \( \partial B_0 / \partial x \) (\( \hat{x} = \text{left}/\text{right} \)) [ppm/cm] of the phantom obtained using numerical simulations (a) as well as the 2D ASE (b) and 3D GE (c) experimental mapping methods. The air-filled tube is orthogonal to the plane of the figure.

As expected, the experimental measurements are affected by noise and artifacts due to \( B_1 \) inhomogeneity and flow. The severe \( B_1 \) inhomogeneity prevalent at ultra-high field strength leads to substantial variations of the flip angles across the images, resulting in regions of low signal intensity in the temporal and occipital lobes (Figs. 2.12a,b and 2.13a,b) (see section 2.3). These regions of low SNR and thus large phase variation appear as artifacts in the \( B_0 \) gradient maps (Figs. 2.12d,e,g,h and 2.13d,e,g,h). As expected, the 2D ASE method is more sensitive to \( B_1 \) inhomogeneity than the 3D GE method, particularly in the \textit{in vivo} study. At the brainstem level, the 2D ASE method is also affected by artifacts due to blood and/or cerebrospinal fluid (CSF) flow (Fig. 2.13a,d,g), unlike the 3D GE method (Fig. 2.13b,e,h). The 3D GE method does not appear to be limited by
Figure 2.12: Axial 2D ASE (a) and 3D GE (b) magnitude images of the brain of a postmortem human subject and corresponding maps of the magnetic field gradients $\partial B_0/\partial x$ (c–e, $\hat{x} =$ left/right) and $\partial B_0/\partial y$ (f–h, $\hat{y} =$ anterior/posterior) [ppm/cm] obtained using numerical simulations (c,f) as well as the 2D ASE (d,g) and 3D GE (e,h) experimental mapping methods.
Figure 2.13: Axial 2D ASE (a) and 3D GE (b) magnitude images of the brain of a healthy volunteer and corresponding maps of the magnetic field gradients $\partial B_0/\partial x$ (c–e, $\hat{x} =$ left/right) and $\partial B_0/\partial y$ (f–h, $\hat{y} =$ anterior/posterior) [ppm/cm] obtained using numerical simulations (c,f) as well as the 2D ASE (d,g) and 3D GE (e,h) experimental mapping methods.
excessive signal loss or phase aliasing due to intravoxel dephasing near air/tissue interfaces.

In conclusion, the 3D GE method generally performs better than the 2D ASE method, since it is significantly faster, requires less RF power, is less sensitive to $B_1$ inhomogeneity and less affected by flow artifacts, and is not limited by excessive signal loss or phase aliasing.
2.3 Application of $B_0$ Mapping for Correlation with Image Artifacts and Development of Susceptibility Artifact Correction Methods

2.3.1 Introduction

As described in chapter 1, ultra-high field MRI offers many advantages over MRI at clinical field strengths up to 3 T, particularly an increased SNR, allowing higher spatial resolution and/or faster imaging, a greater spectral dispersion, as well as an enhanced sensitivity to magnetic susceptibility. However, it also suffers from more severe $B_0$ (see sections 2.1.3 and 2.2.3) and $B_1$ [79] inhomogeneity. Susceptibility differences at tissue interfaces, most prominently air/tissue interfaces, cause macroscopic $B_0$ inhomogeneities that result in image artifacts. Moreover, severe $B_1$ inhomogeneity leads to substantial variations of the flip angle and receive sensitivity throughout the image volume, resulting in variable SNR and image contrast. In addition, $B_0$ inhomogeneity may also alter the effective flip angle [1, p. 47].

Overall, both $B_0$ and $B_1$ inhomogeneity result in regional signal variation and signal loss, and it is often not intuitive whether $B_0$ or $B_1$ effects are dominant. To characterize these effects, representative GE and SE images of in vivo and postmortem human brains were acquired at 8 T. The $B_0$ and $B_1$ inhomogeneity were experimentally mapped and/or numerically simulated, and correlated with the observed image artifacts [80]. This knowledge is expected to ultimately help devise better strategies for correction of image artifacts due to $B_0$ and $B_1$ inhomogeneity seen at ultra-high field strength, and more particularly susceptibility artifact correction methods.
2.3.2 Methods

The studies were performed on the 8 T human whole-body MRI system. The images were acquired using a transverse electromagnetic (TEM) RF head coil [81] with 16 struts and 4 excitation ports that was individually tuned for each study. We studied a total of 15 postmortem unembalmed human subjects (7 male and 8 female, 57 to 85 years old) with various pathologies and 12 healthy volunteers (7 male and 5 female, 20 to 53 years old) who gave informed consent to the experimental protocol approved by our Institutional Review Board. Postmortem studies were carried out initially to develop the acquisition protocols. Representative cases of these in vivo and postmortem studies were evaluated.

Because of the substantial flip angle variability prevalent at ultra-high field strength, we defined a “nominal” flip angle as the average flip angle in a 1 cm$^3$ region of interest, typically located in the hippocampus or the central cingulate gyrus. The transmit power level resulting in a nominal flip angle of 90° was first determined using a voxel-selective stimulated echo pulse sequence with an 8 ms sinc RF pulse. This value was then used together with the calibration of the RF amplifier as a reference to set the transmit power level corresponding to a specified nominal flip angle in subsequent acquisitions.

High resolution GE images were typically acquired with the following parameters: 8 ms sinc RF pulse, TR 600 ms, TE 12 ms, nominal flip angle 23° or 48°, BW 50 kHz, FOV 18×18 cm$^2$, MTX 1024×512, ST 2 mm, and number of excitation (NEX) 1. A series of axial, coronal, and sagittal images were acquired with the number of slices and slice gap adjusted to allow acquisition of representative images throughout the brain. High resolution SE images were typically acquired
with TR 1500 ms, TE 70 ms, nominal flip angle $90^\circ/180^\circ$, MTX $512\times256$ (in vivo) or $512\times384$ (postmortem), ST 3 mm, NEX 1 (in vivo) or 2 (postmortem), and otherwise identical parameters.

To quantify the $B_0$ inhomogeneity, a $B_0$ map was experimentally measured using a 3D dual-echo GE pulse sequence (see section 2.2.2). The following parameters were used: 0.5 ms sinc RF pulse, TR 20 ms, TE 1.2 and 3.0 ms, nominal flip angle $10^\circ$, BW 100 kHz, FOV $18\times18\times18$ cm$^3$, MTX $96\times96\times96$ (resulting in an isotropic resolution of $(1.9 \text{ mm})^3$), axial acquisition plane, NEX 1, and 50% oversampling of the slice encoding to reduce slice aliasing. In addition, for two of the subjects, the $B_0$ field was also numerically simulated at a resolution of $(4 \text{ mm})^3$ using a finite difference method and magnetic susceptibility distributions obtained by segmentation of CT images of the head, neck, and thorax (see section 2.1.2). For both the experimental measurements and the numerical simulations, maps of the $B_0$ gradient along $\hat{x}$, $\hat{y}$, and $\hat{z}$ were computed to better visualize the $B_0$ gradient in the slice direction, which contributes the most to susceptibility artifacts in 2D imaging (see section 2.1.4).

To quantify the $B_1$ inhomogeneity, maps of the local flip angle and receive sensitivity were experimentally measured as follows. Two series of low resolution GE images were acquired with TR $\gg T_1$ and nominal flip angles of $\alpha_0$ and $2\alpha_0$, in which case the signal intensity at pixel $(x,y)$ can be expressed as:

$$S_\alpha(x,y) = \rho(x,y) \ r(x,y) \ \sin[\alpha(x,y)]$$ \hspace{1cm} (2.22)

and

$$S_{2\alpha}(x,y) = \rho(x,y) \ r(x,y) \ \sin[2\alpha(x,y)]$$ \hspace{1cm} (2.23)
respectively, where $\rho$ is the proton density, $r$ the local receive sensitivity, and $\alpha$ the local flip angle. A flip angle map can be computed from the signal intensity ratio of the two series of images as follows [82]:

$$\alpha(x, y) = \cos^{-1}\left(\frac{S_{2\alpha}(x, y)}{2S_{\alpha}(x, y)}\right).$$  \hspace{1cm} (2.24)

Then a map of the product of the proton density and the receive sensitivity can be computed from the flip angle map using Eq. (2.22):

$$\rho(x, y) r(x, y) = \frac{S_\alpha(x, y)}{\sin[\alpha(x, y)]}.$$ \hspace{1cm} (2.25)

Finally, a measure of the receive sensitivity can be generated from this map by low-pass filtering with a 16×16 boxcar filter, and normalizing between 0 and 100%.

For this $B_1$ mapping, the following parameters were used: 8 ms sinc RF pulse, TR 4000 ms (in vivo) or 5000 ms (postmortem), TE 7 ms, BW 50 kHz, FOV 18×18 cm$^2$, MTX 256×64 (in vivo) or 256×128 (postmortem), ST 3 mm, slice gap 1 mm, axial or coronal acquisition plane, and NEX 1. Nominal flip angles of 60° and 120° were used since they produce maximal signal spread, and therefore most accurate flip angle measurements.

The flip angle and receive sensitivity maps were interpolated and reformatted to yield maps corresponding to the axial, coronal, and sagittal GE and SE images. In addition, to facilitate direct visual correlation between these maps and the anatomical images, contour lines were generated from these maps (at 60°, 90°, and 120° for the flip angle and at 25%, 50%, and 75% for the receive sensitivity) and superimposed on the corresponding SE images.
2.3.3 Results

Signal Variation and Signal Loss due to $B_0$ and $B_1$ Inhomogeneity

Fig. 2.14 shows in vivo axial GE and SE images as well as the corresponding maps of the flip angle, receive sensitivity, and experimental $B_0$ gradient in the slice direction. On the GE image, a central region of signal loss is seen in the inferior frontal lobes superior to the planum sphenoidale and corresponds to a region of high $B_0$ inhomogeneity ($-0.4$ ppm/cm along the slice direction as compared to 0.2 ppm/cm in most other regions of the brain). There is also a surrounding large region of increased signal with loss of detail. In addition, severe banding artifacts are seen in that region as well as near the frontal sinus. Artifacts due to $B_0$ inhomogeneity also affect axial GE images in the regions just superior to the temporal bones (not shown), whereas SE images are significantly less affected. On both the GE and SE images, regions of signal loss are seen in the left posterior and right frontal lobes and correspond to regions with low flip angle and/or receive sensitivity. Signal loss due to $B_1$ inhomogeneity is more severe on the SE image than the GE image.

Fig. 2.15 shows in vivo midsagittal GE and SE images as well as the corresponding maps of the flip angle, receive sensitivity, experimental and numerical $B_0$ gradient in the slice direction. Note the excellent depiction of vasculature in the interhemispheric fissure on both GE and SE images. On the GE image, regions of signal loss and banding artifacts are seen in the inferior frontal lobes superior to the sphenoid sinus and posterior to the frontal sinus, and are due to $B_0$ inhomogeneity. However, these susceptibility artifacts are not as severe as on the axial image (Fig. 2.14a). This is because the $B_0$ gradient in the left/right direction is
Figure 2.14: (See figure on next page.) Axial high resolution GE (TR/TE 600/12 ms, nominal flip angle 23°, MTX 1024×384) (a) and SE (TR/TE 1500/40 ms, nominal flip angles 90°/180°, MTX 256×256) (b) images of a healthy 32-year-old male through the inferior frontal lobes. While both GE and SE images provide excellent depiction of anatomical structures in some regions (e.g., the vascular and microvascular branches, putamen, globus pallidus, and splenium of the corpus callosum), other regions are completely degraded by signal loss. On the SE image, the signal intensity in GM is higher than that in WM (solid arrow). The SE image shows some chemical shift artifacts (dashed arrow, frequency encode direction anterior/posterior). The corresponding flip angle and receive sensitivity distributions (in degrees and % respectively) are shown as color maps (c,d) as well as contour lines superimposed on the SE image (e,f) to facilitate direct visual correlation. In the left posterior cortex, both flip angle and receive sensitivity are very low, accounting for the low overall signal. Note some right/left asymmetry between the flip angle and receive sensitivity maps in the central and anterior regions. The corresponding map of the experimental $B_0$ gradient along the slice direction (superior/inferior, in ppm/cm) (g) shows severe $B_0$ inhomogeneity in the central inferior frontal region due to the sinuses below, accounting for the signal loss seen in that region on the GE image but not the SE image.
Figure 2.14: See caption on previous page.
not as large as the $B_0$ gradient in the inferior/superior direction. Imaging in the sagittal plane thus allows reduction of susceptibility artifacts in this region. Regions of signal loss are also seen in the occipital lobe and cerebellum on both GE and SE images, as well as in the parietal lobe on the SE image, and correspond to regions with low flip angle and/or receive sensitivity.

Fig. 2.16 shows postmortem midsagittal GE and SE images as well as the corresponding maps of the flip angle, receive sensitivity, and experimental $B_0$ gradient in the slice direction. Again, there is a good correlation between regions of signal loss and the measured $B_0$ and $B_1$ inhomogeneity. In this particular case, the region with the largest flip angles and receive sensitivity coincides with the lateral ventricles, thus giving the rest of the brain a fairly homogeneous appearance on the GE image. Note the exquisite anatomical detail seen in the posterior fossa. Furthermore, both veins and arteries appear dark in this postmortem study because of the increased deoxyhemoglobin as compared to in vivo studies. Conversely to the GE image, the SE image shows a central dark area in the region with the largest flip angles. In this region, flip angles are much larger than the optimal 90°/180° and the spins are “overflipped,” thus causing the signal void. Due to $B_0$ inhomogeneity, the margin of the inferior anterior cranial fossa is better seen on the SE image than the GE image, and the clivus and soft palate are visible on the SE image but not the GE image. Note the difference in $B_0$ and $B_1$ inhomogeneity between Figs. 2.15 and 2.16 due to differences in the subjects’ anatomy and head tilt (see section 2.1).

Fig. 2.17 shows in vivo coronal GE and SE images and the corresponding maps of the flip angle, receive sensitivity, experimental and numerical $B_0$ gradient in the slice direction. On the GE image, regions of signal loss in the inferior
Figure 2.15: (See figure on next page.) Midsagittal high resolution GE (TR/TE 600/12 ms, nominal flip angle 23°, MTX 1024×512) (a) and SE (TR/TE 1500/70 ms, nominal flip angles 90°/180°, MTX 512×256) (b) images of a healthy 53-year-old male. Both GE and SE images provide excellent depiction of the vasculature and the more anterior brain anatomy, particularly the most anterior portion of the posterior fossa. However, there is severe signal loss in the posterior portions of the supra and infra tentorial compartments. On the GE image, signal loss is also seen in the inferior frontal lobes, whereas the SE image better shows the optic nerve (yellow solid arrow) as well as the CSF just superior to the planum sphenoidale (yellow dashed arrow). The SE image is markedly distorted by CSF flow artifacts. The corresponding flip angle and receive sensitivity distributions (in degrees and % respectively) are shown as color maps (c,d) as well as contour lines superimposed on the SE image (e,f). Variability in local flip angle and receive sensitivity account for the signal loss in the posterior region as well as the excellent depiction of the brainstem. Note that the receive sensitivity map is contaminated by residual proton density weighting, especially in the ventricles (black arrow). The corresponding maps of the experimental (g) and numerical (h) $B_0$ gradient along the slice direction (right/left, in ppm/cm) show minimal $B_0$ inhomogeneity throughout the brain, although the experimental map shows some variability due to noise in the experimental data. In contrast to Fig. 2.14, the $B_0$ variations are smaller and the associated susceptibility artifacts less severe.
Figure 2.15: See caption on previous page.
Figure 2.16: (See figure on next page.) Midsagittal high resolution GE (TR/TE 600/12 ms, nominal flip angle 48°, MTX 1024×512) (a) and SE (TR/TE 1500/50 ms, nominal flip angles 90°/180°, MTX 256×256) (b) images of a post-mortem unembalmed 57-year-old female with Huntington's disease. The GE image shows exquisite depiction of vascular and brain anatomy. On the other hand, the SE image better shows the region adjacent to the planum sphenoidale, clivus (yellow solid arrow), and soft palate (yellow dashed arrow), which are all more severely affected by signal loss on the GE image. Regions with low signal correspond to regions of high $B_0$ and/or $B_1$ inhomogeneity, as seen on the flip angle and receive sensitivity distributions (in degrees and % respectively) shown as color maps (c,d) and as contour lines superimposed on the SE image (e,f), as well as the map of the experimental $B_0$ gradient in the slice direction (right/left, in ppm/cm) (g). Note that the depicted flip angle and receive sensitivity maps in the central region are incorrect. The true flip angle exceeds 180° in that region, leading to a signal void in the SE image (see text). Also note that the receive sensitivity map is contaminated by residual proton density weighting, especially in the ventricles (black arrow). The greatest $B_0$ inhomogeneity is observed near the planum sphenoidale.
Figure 2.16: See caption on previous page.
temporal lobes near the mastoid and middle ear air spaces are due to both $B_0$ and $B_1$ inhomogeneity, as shown by the $B_0$ gradient maps as well as the flip angle and receive sensitivity maps. Again, signal loss due to $B_1$ inhomogeneity is more severe on the SE image than the GE image, and, in this particular case, affects the right side to a greater extent than the left. The combination of all these effects leads to particularly low SNR in these regions.

**Image contrast**

As was previously reported [3], GE images provide excellent depiction of the vasculature. For in vivo studies, the veins appear dark due to the BOLD effect (Figs. 2.14a, 2.15a, and 2.17a), whereas for postmortem studies, both arteries and veins appear dark because of the increase in deoxyhemoglobin [83] (Fig. 2.16a).

CSF has the highest signal intensity on GE images, followed by GM and WM, attesting to the predominant proton density contrast resulting from the choice of acquisition parameters. Such contrast combined with high spatial resolution can lead to excellent delineation of the anatomy (*e.g.*, in the cerebellum (Fig. 2.16a)), provided flip angles are not too low. Due to $T_2^*$ effects, structures with high iron content have the lowest signal intensity with excellent delineation from the surrounding brain (*e.g.*, the red nuclei and substantia nigra (Fig. 2.17a)). Vascular structures are sometimes seen on SE images, but are generally not as well depicted as on GE images. On SE images with TE < 50 ms, the signal intensity in GM is higher than that in WM (Fig. 2.14b), whereas this contrast is inverted for TE > 70 ms (Fig. 2.17b). This behavior is different from the familiar appearance seen on $T_2$-weighted images acquired at 1.5 T and was observed in a number of in vivo and postmortem studies [84, 85].

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Figure 2.17: (See figure on next page.) *In vivo* coronal high resolution GE (TR/TE 600/12 ms, nominal flip angle 23°, MTX 1024×512) (a) and SE (TR/TE 1500/70 ms, nominal flip angles 90°/180°, MTX 512×256) (b) images of the same subject depicted in Fig. 2.15. On the SE image, the signal intensity in GM is lower than that in WM (yellow arrow). The SE image also shows chemical shift artifacts with the fat scalp displaced inferiorly over the skull, as well as flow artifacts from the CSF in the preponite cistern. The corresponding flip angle and receive sensitivity distributions (in degrees and % respectively) are shown as color maps (c,d) as well as contour lines superimposed on the SE image (e,f). The flip angles and receive sensitivity are very low in the lateral inferior temporal lobes, leading to very poor image quality in these regions. Note that there are spatial differences between the flip angle and receive sensitivity distributions (black dashed arrows). Also note that the receive sensitivity map is contaminated by residual proton density weighting, especially in the ventricles (black solid arrow). The corresponding experimental (g) and numerical (h) maps of the \( B_0 \) gradient along the slice direction (anterior/posterior, in ppm/cm) have a good correlation and show severe \( B_0 \) inhomogeneity in the inferior temporal lobes. Without \( B_1 \) mapping, one might assume that the signal loss in that region is entirely due to \( B_0 \) inhomogeneity from air spaces in the mastoid and middle ear. However, concurrent \( B_0 \) and \( B_1 \) mapping show that both \( B_0 \) and \( B_1 \) inhomogeneity contribute to the signal loss.
Figure 2.17: See caption on previous page.
**Other Artifacts**

The *in vivo* images, particularly the SE images, are also affected by severe artifacts in the phase encode direction resulting from pulsating CSF flow. These artifacts are most prominent at the posterior fossa level (Figs. 2.15b and 2.17b). Further studies are needed to evaluate the effectiveness of flow compensation methods. Chemical shift artifacts are also more pronounced in SE images, misplacing the signal from the scalp in the frequency encode direction posteriorly (Fig. 2.14b) or inferiorly (Figs. 2.15b, 2.16b, and 2.17b). In GE images, fat/water intravoxel dephasing nulls the fat signal, thus avoiding pronounced chemical shift artifacts.

**Accuracy of $B_0$ and $B_1$ Mapping**

Unlike numerical simulations, experimental $B_0$ mapping is affected by noise and artifacts due to $B_1$ inhomogeneity (*i.e.*, low flip angle and/or receive sensitivity), motion, and signal loss due to intravoxel dephasing in regions with high $B_0$ inhomogeneity (although to a lesser extent than the depicted GE images due to the short TE used for the $B_0$ mapping). Although there is generally a good agreement between the experimental and numerical $B_0$ gradient maps (Figs. 2.15g,h and 2.17g,h), some discrepancies may be attributed to these problems. Furthermore, differences in head orientation between the MR images used for the experimental mapping and the CT images used for the numerical simulations may cause differences in the field maps (see section 2.1).

The method used to acquire flip angle maps from two series of images with nominal flip angles of $\alpha_0$ and $2\alpha_0$ is theoretically accurate for local flip angles $\alpha$ ranging between 0° and 180°. However, in practice, low image SNR prevents
accurate computation of flip angles close to 0° or 180°. Examples of problems with low flip angles are seen in the posterior cerebral hemispheres on axial images (Fig. 2.14c) and in the inferior temporal lobes on coronal images (Fig. 2.17c). If the local flip angle exceeds 180°, this method can no longer determine the correct flip angle (Fig. 2.16c). Finally, flip angle maps may become inaccurate in regions with high $B_0$ inhomogeneity (e.g., superior to the sphenoid sinus (Fig. 2.14c)). Such errors in the local flip angle measurement propagate into the receive sensitivity maps. Furthermore, the latter are contaminated by residual proton density weighting, especially in large anatomical structures such as the ventricles. Nevertheless, overall patterns of receive sensitivity can be assessed and show differences with the flip angle distributions. Finally, while the flip angle and receive sensitivity patterns are similar among subjects (Figs. 2.15 and 2.16), differences arise from variable subject anatomy and/or RF coil tuning.

2.3.4 Discussion

The examples shown here clearly demonstrate that ultra-high field MRI is plagued by substantial signal variation and signal loss. Correlation between $B_0$ and $B_1$ mapping and the routine magnitude images shows that these effects can be fully explained by $B_0$ and/or $B_1$ inhomogeneity. Because there are different sources of signal variation, $B_0$ and $B_1$ mapping add confidence and give important insights to the interpretation of the magnitude images well beyond what is possible from assessing signal variations alone. For example, signal loss in the lateral inferior temporal lobes is due to both $B_0$ and $B_1$ inhomogeneity (Fig. 2.17). Without $B_1$ mapping, one might assume that the signal loss is only due to $B_0$ inhomogeneity.
**$B_0$ Inhomogeneity Effects**

As expected, severe signal loss due to $B_0$ inhomogeneity is seen on GE images. The regions affected are relatively restricted to the vicinity of air/tissue interfaces (approximately within 1 cm) and are most prominent in the inferior frontal and temporal lobes, as predicted by the experimental and numerical $B_0$ gradient maps. These artifacts are more severe than what is routinely observed at lower field strength. For example, the effects of the skullbase air spaces extend well into the brain. Susceptibility artifacts can be somewhat reduced by optimal selection of the acquisition plane (see section 2.1.4). This may be an essential strategy at ultra-high field strength, even though it limits certain regions to be evaluated using only certain acquisition planes. On the other hand, SE images are significantly less affected by signal loss due to $B_0$ inhomogeneity than GE images, but the effect is still more severe than what is seen on SE images acquired at lower field strength. For example, on Fig. 2.16, the central nasal cavity structures are not seen at all on both the SE and GE images. Signal misregistration and geometric distortions may occur in both GE and SE imaging, and such artifacts may be present in the images shown here, but are not very obvious without direct comparison to images acquired at lower field strength or using different modalities such as CT.

In addition to causing signal loss and geometric distortions, $B_0$ inhomogeneity also influences the effective excitation field [1, p. 47]:

$$B_{\text{eff}} = \sqrt{B_1^2 + \Delta B_0^2}, \quad (2.26)$$

and thus the effective flip angle. In Eq. (2.26), $\Delta B_0$ represents the relative static magnetic field with respect to the field produced by the magnet. For the 8 ms
sinc RF pulses used in this work, a 90° flip angle corresponds to a field strength $B_1$ of 4 mT. Experimental and numerical $B_0$ maps show that the magnitude of $\Delta B_0$ is smaller than 0.5 ppm or 4 mT in most regions of the brain, but can reach up to 3 ppm or 24 mT in the vicinity of air/tissue interfaces, therefore significantly altering the effective flip angle and exaggerating the signal loss and banding artifacts in these regions.

$B_1$ **Inhomogeneity Effects**

While susceptibility artifacts occur predominantly in GE images and are mostly restricted to the vicinity of air/tissue interfaces, both GE and SE images show substantial signal variability due to $B_1$ inhomogeneity. Regions of low signal correspond to regions with low flip angles and/or receive sensitivity. The flip angle and receive sensitivity maps show non-intuitive complex 3D spatial distributions. There are notable differences between subjects depending on the subject’s anatomy (i.e., the spatial distribution of tissues with different dielectric and conductive properties), the RF coil design, as well as the coil tuning, but the overall patterns are relatively similar. Furthermore, the experimental maps are similar to numerical simulations based on realistic head models [86], and differences between the flip angle and receive sensitivity maps follow numerical simulations of the clockwise and counter-clockwise rotating components of the $B_1$ field [87, 88].

SE images are more severely affected by signal loss due to $B_1$ inhomogeneity than GE images. This is because the signal intensity in SE images (for $TR \simeq T_1$) is given by:

$$S(x,y) = \rho(x,y) r(x,y) \sin^3[\alpha(x,y)] \left[1 - E_1(x,y)\right] E_2(x,y), \quad (2.27)$$
where

\[ E_1(x, y) = \exp[-TR/T_1(x, y)] \]  

\[ E_2(x, y) = \exp[-TE/T_2(x, y)] \]  

where the signal intensity in GE images is given by:

\[ S(x, y) = \rho(x, y) r(x, y) \sin[\alpha(x, y)] \frac{1 - E_1(x, y)}{1 - \cos[\alpha(x, y)]} E_1(x, y) E_2^*(x, y), \]  

where

\[ E_2^*(x, y) = \exp[-TE/T_2^*(x, y)] . \]  

Furthermore, GE images were acquired with nominal flip angles at or below the Ernst angle where the signal curve (Eq. (2.30)) is fairly flat, so that the GE signal intensity does not vary strongly with flip angle, except in regions with very small flip angles (< 10°). In the examples shown here, local flip angles range from 0° to 30° (Figs. 2.14a, 2.15a, and 2.17a) and 20° to 90° (Fig. 2.16a), whereas the Ernst angle is 46° and 50° for GM and WM respectively, assuming TR = 600 ms and \( T_1 = 1650 \) and 1345 ms respectively [89]. Conversely, the SE signal intensity not only decreases in regions with small flip angles, but also in regions with flip angles larger than 90°/180° where the spins are overflipped (Fig. 2.16b).

The predicted signal variability with flip angle correlates well with measured image SNR. For example, on the postmortem sagittal GE image acquired with TR/TE 600/12 ms and a nominal flip angle of 48° (Fig. 2.14a), we selected one region in the parietal lobe and one region in the occipital lobe where the true flip angles are 57° and 25° respectively, and the receive sensitivity are 50% and 49%. On the corresponding SE image acquired with nominal flip angles of 90°/180°
<table>
<thead>
<tr>
<th></th>
<th>GE image</th>
<th>SE image</th>
<th></th>
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<td>measured SNR</td>
<td>calculated signal intensity</td>
<td>measured SNR</td>
</tr>
<tr>
<td>GM/WM ratio</td>
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<td>37.4/30.7</td>
<td>0.21/0.18</td>
<td>18.7/15.7</td>
</tr>
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<td>(parietal lobe)</td>
<td>= 1.17</td>
<td>= 1.22</td>
<td>= 1.15</td>
<td>= 1.19</td>
</tr>
<tr>
<td>GM/WM ratio</td>
<td>0.13/0.12</td>
<td>20.1/19.0</td>
<td>0.087/0.089</td>
<td>11.6/12.1</td>
</tr>
<tr>
<td>(occipital lobe)</td>
<td>= 1.14</td>
<td>= 1.06</td>
<td>= 0.98</td>
<td>= 0.95</td>
</tr>
</tbody>
</table>

**Table 2.3:** Comparison between calculated signal intensity ratios and measured SNR ratios for GM/WM regions in the parietal and occipital lobes on corresponding GE and SE images.

(Fig. 2.16b), the true flip angles are 107°/214° and 47°/94° respectively. From these values, we calculated the signal intensity ratios for GM/WM in these two regions using Eq. (2.27) for the SE image and Eq. (2.30) for the GE image. We assumed a proton density of 0.80 and 0.65 for GM and WM respectively. We neglected the $T_2$ and $T_2^*$ terms for this estimation, even though $T_2$ and $T_2^*$ effects contribute to image contrast. The results are shown in Table 2.3 and correlate well with the measured SNR ratios for GM/WM in the same regions. SNR variability with flip angle and receive sensitivity is similar on the *in vivo* images. Note, however, that SNR differences also scale with voxel size, matrix size, receiver bandwidth, and NEX, as usual, and that in vivo SNR may be further decreased by motion.
Application of $B_0$ and $B_1$ Mapping for the Development of $B_0$ and $B_1$ Inhomogeneity Correction Methods

The discussion above demonstrates the utility of $B_0$ and $B_1$ mapping for the assessment of image artifacts in ultra-high field MRI of the human brain. Because of the severity of signal and contrast variability, correction methods for both $B_0$ and $B_1$ inhomogeneity are needed to fully take advantage of the increased SNR available at ultra-high field strength.

A variety of susceptibility artifact correction methods have been proposed, including gradient compensation or z-shim techniques [90, 91, 92, 93], tailored RF pulses [94], active [61, 95] and passive [96, 46] shimming, and post-processing [97, 98, 99]. Implementation and optimization of all of these methods require knowledge of the $B_0$ field. $B_0$ numerical simulations and experimental mapping both have advantages and limitations and are therefore complementary. Numerical simulations have the advantage of being more flexible and unaffected by noise and artifacts due to $B_1$ inhomogeneity (i.e., low flip angle and/or receive sensitivity), motion, or intravoxel dephasing. On the other hand, experimental $B_0$ mapping is fast and can provide more detailed information for a specific experimental case (i.e., same subject anatomy, RF coil tuning, etc.).

Consequently, numerical $B_0$ maps will likely play an important role in the conceptual evaluation of susceptibility artifact correction methods, as well as the development of those methods that do not rely on specific $B_0$ maps such as gradient compensation or passive shimming, whereas experimental $B_0$ maps will likely be required for the development of other methods such as post-processing. Numerical simulations will be especially useful for the assessment of active and passive
shimming, because they allow shim coil configurations and currents, as well as passive shim configurations and materials, to be arbitrarily selected and optimized. Similarly, numerical simulations allow easy evaluation of a variety of shapes and materials for extending the passive diamagnetic shimming method proposed by Wilson et al. [46]. Direct experimental measurement of the static magnetic field would be comparatively laborious and uncomfortable for subjects.

Experimental $B_1$ mapping requiring a long TR (i.e., TR $\gg T_1$) is too slow for clinical applications. However, knowledge of the overall 3D characteristics of the $B_1$ field helps select optimal flip angles. For example, if a pathology is suspected in the temporal lobe, the nominal flip angle can be determined using a voxel-selective stimulated echo pulse sequence with the voxel placed in that region. On the other hand, $B_1$ mapping is crucial for the understanding of $B_1$ inhomogeneity patterns and for quantitative studies such as $T_1$ and $T_2$ measurements [89, 100, 101]. Experimental $B_1$ mapping will also play an important role in ultra-high field RF coil design and for studying the effects of coil tuning. Methods for correction of $B_1$ inhomogeneity include simulations of TEM coils with multi-port RF excitation using numerically optimized amplitudes and phases to achieve more homogeneous excitation profiles [86]. Another approach involves the use of tailored RF pulses for suppression of $B_1$ inhomogeneity [102, 103]. Both methods will require knowledge of the $B_1$ transmit and receive field.

In conclusion, artifacts due to both $B_0$ and $B_1$ inhomogeneity are severe in ultra-high field MRI, and experimental and/or numerical mapping of the $B_0$ and $B_1$ inhomogeneity is important in identifying their origin. The problems due to severe $B_0$ and $B_1$ inhomogeneity described here can be limited by focusing on localized studies. This approach has been very successfully employed in localized
spectroscopy [104] and fMRI in the occipital lobe [5]. However, if ultra-high field MRI is to become useful for a broad range of biomedical applications including survey exams covering most of the head structures in one exam, correction methods for $B_0$ and $B_1$ inhomogeneity need to be developed. Detailed characterization of the effects of $B_0$ and $B_1$ inhomogeneity is an important first step in that direction. The application of $B_0$ mapping for development and assessment of susceptibility artifact correction methods is discussed in chapter 3.
CHAPTER 3

SUSCEPTIBILITY ARTIFACT CORRECTION

3.1 Passive Shimming Using Ferroshims

3.1.1 Introduction

A variety of susceptibility artifact correction methods have been proposed in the literature, including but not limited to shimming, post-processing, and gradient compensation methods. In this chapter, we explore some of these methods for susceptibility artifact correction at ultra-high field strength, starting with passive shimming using ferroshims.

Shimming refers to the process of correcting for $B_0$ inhomogeneities by superimposing additional static magnetic fields to the main field produced by the magnet. It can be classified into two categories, active and passive shimming, depending on how these magnetic fields are produced. Active shimming uses a set of coils built the MRI scanner and designed such that each coil generates a magnetic field corresponding to a spherical harmonic (i.e., $x$, $y$, $z$, $x^2 - y^2$, $2xy$, $z^2$, $zx$, $zy$, etc.) up to a certain order. On the other hand, passive shimming uses small pieces of ferromagnetic material called ferroshims appropriately positioned in the
bore of the magnet. Both types of shimming typically involve measuring the $B_0$ field at a number of points, numerically computing the appropriate currents for the shim coils or position of the ferroshims, and iterating this process as needed until the desired level of $B_0$ homogeneity is reached.

While shimming is initially performed to correct for the small $B_0$ inhomogeneities due to magnet imperfection, it can also be applied to reduce susceptibility artifacts induced by a sample or subject. However, this is a much more difficult problem because the magnetic field produced by the magnet is relatively homogeneous with smooth spatial variations, whereas the susceptibility-induced $B_0$ inhomogeneities in a subject can be very large with rapid spatial variations, especially near air/tissue interfaces and/or at ultra-high field strength (see chapter 2). In fact, it has been shown that high order shims are required to shim a human head, and that some of the large and rapidly varying susceptibility-induced $B_0$ inhomogeneities can typically not be corrected for using conventional shimming techniques [95, 96].

Jesmanowicz et al. [96] proposed an interesting alternative. Based on an experimentally acquired $B_0$ map of the subject, a ferroshim insert is generated by overprinting rectangles with various density of copier toner, which was found to be magnetic, and placed on the inner surface of the gradient coil around the subject’s head. As compared to conventional passive shimming methods, this approach has the advantage of being safer and easier to implement, and, more importantly, offers the possibility of generating subject-specific ferroshim inserts. In this section, we numerically evaluate the effectiveness of this method for susceptibility artifact correction at ultra-high field strength. However, because a detailed algorithm for the computation of the ferroshim parameters was not available, we developed a
method based on the one used by Belov et al. [105] for conventional passive shim-ming, and used $B_0$ maps obtained by numerical simulations for different head models (see section 2.1).

### 3.1.2 Methods

The ferroshims are assumed to be iron strips positioned along $\hat{z}$ (i.e., parallel to $B_0$) on a cylinder of radius $\rho_{\text{shim}}$ and length $Z$, evenly spaced along its azimuth and length. Their position can be expressed in cylindrical coordinates as $(\rho_{\text{shim}}, \theta_{\text{shim}}, z_{\text{shim}})$, where

\begin{align}
\theta_{\text{shim}} &= 0, \frac{2\pi}{N_\theta}, \frac{4\pi}{N_\theta}, \ldots, \frac{(N_\theta - 1)2\pi}{N_\theta} \quad (3.1) \\
Z_{\text{shim}} &= \frac{Z}{2}, -\frac{Z}{2} + \frac{Z}{N_z}, -\frac{Z}{2} + \frac{2Z}{N_z}, \ldots, -\frac{Z}{2} + \frac{(N_z - 1)Z}{N_z} \quad (3.2)
\end{align}

The cylinder corresponds to the inner surface of the gradient coil of the 8 T MRI system (i.e., $\rho_{\text{shim}} = 189.5$ mm and $Z = 40$ cm) and the parameters $N_\theta$ and $N_z$ are chosen equal to 8 and 5 respectively, resulting in 40 ferroshims.

These ferroshims are considered as independent dipoles and are assumed to have a small cross-section. In this case, the magnetic field at a position $(\rho, \theta, z)$ produced by the ferroshim $(\rho_{\text{shim}}, \theta_{\text{shim}}, z_{\text{shim}})$ can be assumed to be linear with the ferroshim cross-section $A$, with a coefficient given by:

\begin{align}
\frac{B_{\text{sat}}(\hat{z}_{\text{shim}} - z)}{4\pi [(\hat{z}_{\text{shim}} - z)^2 + \rho_{\text{shim}}^2 + \rho^2 - 2 \rho \rho_{\text{shim}} \rho \cos(\theta - \theta_{\text{shim}})]^{3/2}}, \quad (3.3)
\end{align}

where $B_{\text{sat}} = 2.15$ T is the saturation induction of the ferroshims. Denoting the coordinates of each point $(\rho, \theta, z)$ by $i$, and the coordinates of each ferroshim
(\rho_{\text{shim}}, \theta_{\text{shim}}, z_{\text{shim}}) by \( j \), so that

\[
\sum_i \equiv \sum_p \sum_\theta \sum_z \quad \text{and} \quad \sum_j \equiv \sum_{i \theta_{\text{shim}}} \sum_{z_{\text{shim}}},
\] (3.4)

the magnetic field at position \( i \) produced by all ferroshims is equal to

\[
\sum_j a_{ij} A_j,
\] (3.5)

where the coefficients \( a_{ij} \) are given in (3.3).

The ferroshim cross-sections \( A_j \) are computed using a regularized least squares algorithm, which tries to minimize the following functional:

\[
M = \sum_i \left[ (B_i - B_{\text{ref}}) - \sum_j a_{ij} A_j \right]^2 + \alpha \sum_j A_j^2, \quad (3.6)
\]

where \( B_i \) is the magnetic field at position \( i \), \( B_{\text{ref}} \) a reference magnetic field, and \( \alpha \) the regularization parameter. Unlike in conventional passive shimming where the \( B_0 \) field is experimentally measured at a limited number of points in an empty magnet, we use the full 3D \( B_0 \) field obtained by numerical simulations (see section 2.1) for a head model, a tilted head model, and a head/thorax model at a resolution of (4 mm)\(^3\). The head and head/thorax models are similar to those described in section 2.1.2, whereas the tilted head model consisted of the head model numerically tilted backwards by 30°. Note that the Lorentz correction (see section 2.1.2) was not taken into account for the computation of the magnetic field; however this is not expected to affect the conclusions obtained in this study.

To shim an empty magnet, \( B_{\text{ref}} \) should be chosen equal to \( B_{0,\text{air}} \), whereas to shim a sample or subject, it should be chosen equal to the average magnetic field in the region of interest (in our case, the brain). This choice is however
not critical for the computation of the ferroshim cross-sections because it only adds a constant term to all ferroshims that can be subtracted afterwards. The regularization parameter $\alpha$ determines the maximum cross-section allowed. Larger values result in smaller cross-sections, however at the expense of a less effective shimming. With the parameters used in this study, a value of 1000 results in cross-sections on the order of 1 mm$^2$.

The functional $M$ is minimized if the following conditions are satisfied:

$$\frac{\partial M}{\partial A_k} = 2 \sum_i \left[ (B_i - B_{\text{ref}}) - \sum_j a_{ij} A_j \right] (-a_{ik}) + 2\alpha \sum_j A_j \delta_{jk} = 0 \quad \forall k , \quad (3.7)$$

where $\delta_{jk} = 1$ if $j = k$ and 0 otherwise. Rearranging the terms yields the following system of linear equations:

$$\sum_j \left( \sum_i a_{ij} a_{ik} + \alpha \delta_{jk} \right) A_j = \sum_i (B_i - B_{\text{ref}}) a_{ik} \quad \forall k , \quad (3.8)$$

which can be expressed in a matrix form and solved as follows:

$$XA = Y \quad (3.9)$$

$$A = X^{-1}Y . \quad (3.10)$$

The algorithm can result in positive or negative ferroshim cross-sections. In the latter case, the polarity of the ferroshim is simply reversed. The sum $\sum_i$ is not computed over the full 3D data set, but only over a cylinder parallel to $\hat{z}$ of radius large enough to include the whole head but smaller than $\rho_{\text{shim}}$ to avoid including regions too close to the ferroshims, where large $B_0$ inhomogeneities can occur.
Unlike in conventional passive shimming where the objective is to shim an empty magnet, our objective is to shim a human head at ultra-high field strength, which is affected by large and rapidly varying $B_0$ inhomogeneities. As discussed in the introduction, it is very difficult to achieve a global shimming of the whole head. Instead, local shimming over a smaller ROI (e.g., the brain) could be substantially more effective. However, simply restricting the computation of the sum $\sum_i$ over such an ROI alone might result in large $B_0$ inhomogeneities outside of the ROI. To overcome this problem, different weights $w_i$ can be assigned inside and outside the ROI, so that Eq. (3.6) becomes a weighted least squares:

$$M = \sum_i w_i^2 \left[ (B_i - B_{\text{ref}}) - \sum_j a_{ij} A_j \right]^2 + \alpha \sum_j A_j^2 . \quad (3.11)$$

Once the ferroshim cross-sections have been determined, the magnetic field at position $i$ can be computed as follows:

$$B_{\text{shimmed},i} = B_i - \sum_j a_{ij} A_j . \quad (3.12)$$

The $B_0$ homogeneity before and after shimming can be quantified by computing the following mean square errors:

$$\delta_{\text{before}} = \frac{1}{B_{0,\text{air}}} \sqrt{\frac{1}{4N} \sum_i (B_i - B_{\text{ref}})^2} \quad (3.13)$$

$$\delta_{\text{after}} = \frac{1}{B_{0,\text{air}}} \sqrt{\frac{1}{4N} \sum_i (B_{\text{shimmed},i} - B_{\text{shimmed,ref}})^2} , \quad (3.14)$$

where $N$ is the number of points in the sum $\sum_i$ and $B_{\text{shimmed,ref}}$ is the average magnetic field in the brain after shimming.
<table>
<thead>
<tr>
<th>head model</th>
<th>whole head</th>
<th>brain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta_{\text{before}}$</td>
<td>$\delta_{\text{after}}$</td>
</tr>
<tr>
<td></td>
<td>[ppm]</td>
<td>[ppm]</td>
</tr>
<tr>
<td>- global shimming</td>
<td>2.98</td>
<td>2.79</td>
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<td>- local shimming</td>
<td>2.98</td>
<td>3.09</td>
</tr>
<tr>
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<td></td>
<td></td>
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<tr>
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<tr>
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<td></td>
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<tr>
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<td>1.75</td>
</tr>
<tr>
<td>- local shimming</td>
<td>2.88</td>
<td>3.07</td>
</tr>
</tbody>
</table>

**Table 3.1:** Mean square errors of the magnetic field in the whole head and in the brain before and after global or local shimming for the different models.

### 3.1.3 Results and Discussion

The mean square errors of the magnetic field in the whole head and in the brain before and after global or local shimming for the different models are shown in Table 3.1. Note that the mean square error in the brain was computed over the same ROI as the one used for the local shimming.

For all three models, global shimming resulted in a slight improvement of the $B_0$ homogeneity over the whole head, but significantly decreased the homogeneity in the brain alone. This can be explained by the fact that there are substantial $B_0$ inhomogeneities outside of the brain, especially in the nasal cavity, the mouth, and
the neck (see section 2.1.3), and that the algorithm tries to improve the overall homogeneity. On the other hand, local shimming of the brain resulted in an improvement of the $B_0$ homogeneity in that region without significantly affecting the homogeneity in other regions of the head. Nevertheless, there are still very complex and rapidly varying $B_0$ inhomogeneities in the brain alone, especially near air/tissue interfaces in the inferior frontal and temporal lobes, and even when restricted to an ROI, the algorithm still tries to improve the overall homogeneity in that ROI, which may not necessarily result in a significant improvement in the most inhomogeneous regions. Furthermore, the overall effectiveness of this method is limited by the maximum ferroshim cross-section allowed.

Even though increasing the number of ferroshims might lead to better results than those obtained in this preliminary study, it seems unlikely that an effective shimming of the whole brain can be achieved, given the complex $B_0$ inhomogeneities occurring near air/tissue interfaces. Instead, a more effective local shimming can more likely be achieved by using yet smaller ROIs. In fact, Roophansingh et al. more recently improved Jesmanowicz’s method by modeling the magnetic dipoles more accurately [106], and combining it with a user-defined mask to achieve a more effective local shimming in the inferior frontal lobes [107].

Several other promising alternatives for both active and passive local shimming have recently been proposed in the literature, and may prove to be more effective at correcting for susceptibility artifacts at ultra-high field strength. Most of these methods focus on a small ROI, typically the inferior frontal lobes where the $B_0$ inhomogeneity is most severe, rather than attempting to shim the whole brain.

Wilson et al. [46, 47, 108] developed intra-oral diamagnetic shims, consisting of strongly diamagnetic material (highly oriented pyrolytic graphite) of various
sizes and shapes placed in the subject’s mouth to reduce the $B_0$ inhomogeneity in the inferior frontal lobes. An ear shim was also proposed to reduce susceptibility artifacts in the inferior temporal lobes, but was found to be less effective than the mouth shims.

Hsu et al. [109, 110] used a thermally and electrically insulated circular coil placed in the subject’s mouth for local shimming of the inferior frontal lobes. The main advantage of such active shim coils as compared to the diamagnetic passive shims is the ability to remotely and dynamically adjust the current in the coil, and thus the resulting magnetic field. Alternatively, Wong et al. [111] placed such a local shim coil externally over the nose, which is less uncomfortable for the subject and was found to be as effective as the intra-oral coil at reducing susceptibility artifacts in the inferior frontal lobes, while preserving signal in the anterior temporal lobes.

Interestingly, Neufeld et al. [112] proposed to use a “homogeneity helmet” placed around the subject’s head and consisting of a proton-less material with a similar susceptibility to that of biological tissues, in order to reduce the $B_0$ inhomogeneities due to susceptibility differences at the external boundary of the head. We suggested to use a similar approach by placing appropriately shaped paddings around the shoulders in order to reduce the susceptibility differences at these air/tissue interfaces, which were found to result in severe $B_0$ inhomogeneities in the occipital lobes and cerebellum (see section 2.1.3).
3.2 Post-Processing Using Non-Fourier Reconstruction

3.2.1 Introduction

Besides shimming, post-processing methods can also be used to correct for susceptibility artifacts. However, most of the methods proposed in the literature only correct for geometric distortions, but not for signal loss due to intravoxel dephasing, which is particularly severe at ultra-high field strength and can extend far away from air/tissue interfaces (see section 2.3).

Kadah et al. [113] developed a method called Simulated PHase Evolution REwinding (SPHERE) that numerically rewinds the accumulated phase in k-space due to $B_0$ inhomogeneity that is at the origin of susceptibility artifacts. This rewinding process uses an initial estimate of the image and a corresponding $B_0$ map to generate a corrected k-space, which is then Fourier transformed to produce the final corrected image. However, this method works only if the $B_0$ inhomogeneities are small and vary smoothly.

Fernández-Seara et al. [99] developed a method based on the assumption that the susceptibility-induced gradients are linear across a voxel and that the signal decay in the absence of such gradients is exponential. In that case, the time-domain signal is weighted by a sinc function that depends on the amplitude of the susceptibility-induced gradient, which is not known a priori. The algorithm searches for the estimate of this amplitude that yields the best exponential fit to the corrected experimental data. This method is however effective only if the susceptibility-induced gradients are below a certain threshold.
To study the feasibility of post-processing methods for susceptibility artifact correction at ultra-high field strength, we tried to implement another method developed by Kadah et al. [98], and used $B_0$ maps obtained from numerical simulations (see section 2.1).

3.2.2 Methods

In this method, the problem of image reconstruction in the presence of $B_0$ inhomogeneity is formulated as an inverse problem of a linear Fredholm equation of the first kind. Such inverse problems are known to be ill-posed in general and therefore require regularization methods. Some mathematical background on the regularization of linear inverse problems with discrete data is presented in appendix B.

Given a 1D spin density distribution $\rho(x)$ and the corresponding magnetic field deviation from the applied field $\Delta B_0(x)$, the signal of a GE in k-space is given by:

$$s(k_x) = \int_{-\infty}^{\infty} A(k_x, x) \rho(x) \, dx,$$  \hspace{1cm} (3.15)

where

$$A(k_x, x) = \exp \left\{ -j 2\pi \left[ k_x \left( x + \frac{\Delta B_0(x)}{G_x} \right) + \frac{\gamma}{2\pi} \Delta B_0(x) \text{TE} \right] \right\}$$  \hspace{1cm} (3.16)

and $G_x$ is the amplitude of the readout gradient. Eq. (3.15) is a Fredholm integral equation of the first kind with kernel $A(\cdot, \cdot)$ (see appendix B.2). Note that in a homogeneous magnetic field (i.e., $\Delta B_0(x) = 0$), Eq. (3.16) becomes the Fourier kernel $F(k_x, x) = \exp(-j 2\pi k_x x)$ and Eq. (3.15) is simply a Fourier transform. The second term in Eq. (3.16) leads to geometric distortions with a positional
shift given by \( x' - x = \Delta B_0(x)/G_x \), whereas the third term, linear in TE, results in signal loss due to intravoxel dephasing. In the case of SE imaging, only the first two terms are present. Relaxation effects have been neglected (or alternatively included in the function \( \rho(x) \)).

The discrete form of Eq. (3.15) is:

\[
s(k_x) = \sum_{x = -\frac{N_x}{2} \Delta x}^{\frac{N_x}{2} \Delta x} A(k_x, x) \rho(x), \quad -\frac{N_x}{2} \Delta k_x \leq k_x \leq \frac{N_x}{2} \Delta k_x,
\]

where \( N_x \) is the matrix size, \( \Delta x \) the spatial resolution, and \( \Delta k_x \) the resolution in k-space. Eq. (3.17) can be written in matrix form as follows:

\[
s = A \rho,
\]

where \( s \) and \( \rho \) are \( N_x \times 1 \) vectors and \( A \) is an \( N_x \times N_x \) matrix.

From the acquired signal \( s(k_x) \) and the corresponding \( \Delta B_0(x) \) (or equivalently \( A(k_x, x) \)), the spin density distribution can in principle be reconstructed as follows:

\[
\rho(x) = \sum_{k_x = -\frac{N_x}{2} \Delta k_x}^{\frac{N_x}{2} \Delta k_x} A^{-1}(x, k_x) s(k_x), \quad -\frac{N_x}{2} \Delta x \leq x \leq \frac{N_x}{2} \Delta x,
\]

or in matrix form:

\[
\rho = A^{-1} s,
\]

where the inverse matrix \( A^{-1} \) can be computed using singular value decomposition (SVD).

However, for an accurate computation of the signal in k-space, it is critical to oversample the spin density distribution to take into account intravoxel dephasing.
With an $f$-fold oversampling, Eq. (3.17) then becomes:

$$
\hat{s}(k_x) = \sum_{\tilde{x} = -\frac{N_x}{2} \Delta \hat{x}}^{\frac{N_x}{2} \Delta \hat{x}} A(k_x, \tilde{x}) \rho(\tilde{x}) , \quad -\frac{N_x}{2} \Delta k_x \leq k_x \leq \frac{N_x}{2} \Delta k_x ,
$$

(3.21)

where $\hat{N}_x = f N_x$ and $\Delta \hat{x} = \Delta x / f$, or in matrix form:

$$
\tilde{s} = \tilde{A} \tilde{\rho} ,
$$

(3.22)

where $\tilde{s}$ is an $N_x \times 1$ vector, $\tilde{A}$ an $N_x \times \hat{N}_x$ matrix, and $\tilde{\rho}$ an $\hat{N}_x \times 1$ vector. We performed simulations with different oversampling factors and found that $f$ should be at least 4, thus confirming previous findings [8].

The inverse problem is now to reconstruct the spin density distribution from $\tilde{s}$ and $\tilde{A}$. A so-called pseudoinverse $\tilde{A}^\dagger$ of the non-square matrix $\tilde{A}$ can be defined, which satisfies the following properties:

$$
\tilde{A} \tilde{A}^\dagger \tilde{A} = \tilde{A}
$$

(3.23)

$$
\tilde{A}^\dagger \tilde{A} \tilde{A}^\dagger = \tilde{A}^\dagger
$$

(3.24)

$$
(\tilde{A} \tilde{A}^\dagger)^T = \tilde{A} \tilde{A}^\dagger
$$

(3.25)

$$
(\tilde{A}^\dagger \tilde{A})^T = \tilde{A}^\dagger \tilde{A}
$$

(3.26)

where $(\cdot)^T$ denotes the transpose operation. It can be shown that $\tilde{A}^\dagger$ gives the shortest length least squares solution to problem (3.22). Premultiplying Eq. (3.22) by $\tilde{A}^T$ yields:

$$
\tilde{A}^T \tilde{s} = \tilde{A}^T \tilde{A} \tilde{\rho} ,
$$

(3.27)

96
so that if the inverse of $\hat{A}^T \hat{A}$ exists,

$$\hat{\rho} = (\hat{A}^T \hat{A})^{-1} \hat{A}^T \hat{s} \equiv \hat{A}^\dagger \hat{s}.$$ (3.28)

In the presence of additive noise, the inverse problem is ill-posed and it is only possible to seek a regularized solution, for example by using truncated SVD or Tikhonov regularization (see appendices B.7 and B.9). Both of these methods, which are equivalent, were implemented.

Extension of this 1D problem to 2D is straightforward. A 1D Fourier transform is applied in the phase encode direction to simulate the signal in k-space from the spin density distribution. This is done independently of the computation in the readout direction, which is performed as in the 1D case described above. Note that for an accurate simulation, the spin density distribution also has to be oversampled in the phase encoding direction to take into account intravoxel dephasing. A low-pass filter can then be applied to downsample the resulting signal. Conversely, a 1D inverse Fourier transform is applied in the phase encode direction to reconstruct the spin density distribution from the acquired signal.

First, to validate the algorithm, an ideal spin density distribution was used to simulate the signal in k-space, which was in turn used to reconstruct the spin density distribution. These simulations were performed for an air-filled tube orthogonal to $B_0$ surrounded by a CuSO$_4$ solution, for which an analytical solution for the $B_0$ field is available [8, 18]. The spin density was arbitrarily set to 0 for air and 1 for the CuSO$_4$ solution. To evaluate the performance of the algorithm under different noise levels, zero-mean Gaussian noise corresponding to various SNR levels was added to the simulated signal. Both 1D and 2D simulations were performed.

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Second, to test the algorithm with more realistic data, simulations were performed on a phantom containing an identical air-filled tube orthogonal to $B_0$ surrounded by a CuSO$_4$ solution, for which numerical simulations of the $B_0$ field are available (see section 2.1). Again, the spin density was arbitrarily set to 0 for air and 1 for the CuSO$_4$ solution, and both 1D and 2D simulations with different noise levels were performed. Note that in this study, the spin density distribution was derived from the same susceptibility distribution that was used for the computation of the $B_0$ field, so that both were registered. However, if this method is to be applied to real data, experimental $B_0$ mapping techniques (see section 2.2) will be required.

### 3.2.3 Discussion

Unfortunately, none of the simulations performed with the current implementation of this algorithm was successful at correcting for susceptibility artifacts. This can be explained by the fact that the oversampling of the spin density distribution required to take into account intravoxel dephasing results in an underdetermined inverse problem (i.e., with a number of unknowns larger than the number of equations). The solution is not unique and only a normal pseudosolution or generalized solution can be determined (see appendices B.4 and B.5). The solution given by the algorithm, although satisfying the inverse problem, is still far from the true solution.

To overcome this problem, a priori information about the spin density distribution can be used as a means of regularization [98]. One example is a priori information about the localization of the imaged object, i.e., the knowledge that the spin density distribution is significantly different from zero only in a certain
region. One way to use such \textit{a priori} information is to impose certain constraints on the solution based on this information. One type of constraints is linear equality constraints, which, for example, can be applied to force the solution at the points outside the object to be equal to zero.

Other types of \textit{a priori} information about the spin density distribution can be used to constrain the solution, for example, knowledge that it is a nonnegative function. Furthermore, assuming that the spin density distribution is a smoothly varying function, at least within certain regions, it is also possible to penalize its variation. However, the practical implementation of such types of constraints is not straightforward.
3.3 Gradient Compensation Using 3D Z-Shim

3.3.1 Introduction

Besides shimming and post-processing, a variety of acquisition methods have also been developed for susceptibility artifact correction. Since signal loss due to intravoxel dephasing increases with TE (see Eq. (2.15)), a straightforward approach to minimize this effect would be to use a short TE, however at the expense of a reduction of the susceptibility or BOLD contrast, which is optimal for TE \( \simeq T_2^* \).

Since the \( B_0 \) inhomogeneity increases with voxel size, another approach that has been proposed is to use thinner slices or higher resolution, however at the expense of lower SNR, spatial coverage, and/or temporal resolution. Alternatively, several authors proposed to use tailored RF pulses [114, 115, 116, 117, 94, 118], which are designed to excite a volume with a phase distribution that cancels the phase distribution due to the \( B_0 \) inhomogeneities. Besides all of these approaches for susceptibility artifact correction, one of the most commonly used is gradient compensation or z-shimming. In this section and the following, we evaluate the effectiveness of two gradient compensation methods for susceptibility artifact correction at ultra-high field strength.

The basic idea of this approach, originally proposed by Frahm et al. [119, 120, 121], is to add a compensation gradient \( G_z \) to a conventional 2D GE sequence in order to compensate for the susceptibility-induced gradient in the slice direction \( G_{z,susc} \), and recover the signal loss due to intravoxel dephasing. \( G_{z,susc} \) is assumed to be linear across a voxel, and is typically the largest in 2D imaging because the slice thickness is typically larger than the in-plane resolution. In practice, the
compensation gradient $G_c$ is added to the slice rephaser gradient such that its time integral is equal to that of $G_{z,susc}$ at the echo time $TE$:

$$\int G_c dt = G_{z,susc} \  TE . \quad (3.29)$$

The whole sequence has to be repeated for a series of $G_c$ values in order to recover the signal loss in different regions of the imaged slice that experience different $G_{z,susc}$ values. Finally, the resulting images are combined to yield a final corrected image using one of several methods, such as simple summation [119, 122, 123, 124], weighted summation [125, 124], maximum intensity projection (MIP) [91, 92, 126, 127, 124], square root of the sum of squares (SSQ) [128, 92, 129, 130, 131, 124, 132], or Fourier transform [90, 126, 127] (see section 3.4). Constable et al. [92] compared the MIP and SSQ methods and found that the SSQ method provides the most uniform compensation and highest SNR.

It is relatively intuitive to see that z-shim methods become more effective with a larger number of compensation gradients and a finer step size between them, since a larger amount of signal loss can be recovered in different regions experiencing different susceptibility-induced gradients. However, the trade-off is a longer acquisition time, which makes the method less efficient. Nevertheless, Ordidge et al. [128] showed analytically that 90–97% of the signal may be recovered by using only four compensation gradients of appropriate amplitude. As such, most of the methods proposed in the literature use only a limited number of compensation gradients, typically 2 to 4. To optimize the selection of these compensation gradients, Cordes et al. [93] developed an automated algorithm that partitions the images into regions of recoverable signal intensities using a histogram analysis, and determines the proper compensation gradient for each region.
However, even with a limited number of compensation gradients, conventional z-shim methods requiring multiple scans still have a low efficiency, particularly for fMRI applications, which require a high temporal resolution. This has led to the development of various single-scan z-shim methods by several authors.

Yang et al. [122] developed a method called Multi-Gradient Echo with Susceptibility Inhomogeneity Compensation (MGESIC) that consists of a multi-echo GE sequence with compensation gradient blips added in the slice direction between each echo acquisition, so that the compensation is sequentially varied for each echo. The different z-shimmed images are then reconstructed and combined as described above. One problem with such a method is that these images are acquired at different TEs and therefore have different $T_2^*$-weighting. Although this effect can be minimized by keeping the interecho time ΔTE as short as possible, it becomes more pronounced at ultra-high field strength because of the shorter $T_2^*$ decay.

Similarly, Li et al. [130] developed a method called MultiEcho Segmented EPI with z-shimmed BAckground gradient Compensation (MESBAC) consisting of a multishot segmented EPI sequence with a series of compensation gradient blips between each readout.

Song [123] developed a method consisting of a dual-echo EPI sequence with a z-shim gradient added between both acquisitions that yields an uncompensated and a compensated image, which are then combined to yield a final image. To reduce the TE discrepancy and resulting variation in $T_2^*$-weighting and BOLD contrast discussed above, partial k-space acquisitions are used, where the full half k-space of the first image is acquired first, whereas the full half k-space of the second image is acquired last.
Guo et al. [124] improved this method by replacing the sequential EPI acquisitions with spiral-in and spiral-out acquisitions designed such that both images have similar TEs and $T_2^*$-weighting.

Alternatively, Gu et al. [129] acquired the two EPI images in an interleaved way with a series of compensation gradient blips between each readout, again resulting in nearly identical TEs and $T_2^*$-weighting for both images. In addition, the z-shim gradients are optimized for each slice individually, resulting in an optimal compensation of the susceptibility-induced signal losses.

Heberlein et al. [132] developed a method called Simultaneous Acquisition of Gradient-echo and Asymmetric spin-echo for single-shot Z-shim (Z-SAGA) that consists of a z-shimmed GE EPI acquisition followed by a regular ASE EPI acquisition within the same scan, with a timing such that both images are acquired with identical $T_2^*$-weighting.

Unlike all z-shim methods described so far, which are 2D methods, Glover [91] developed a 3D z-shim method that was shown to be more efficient than an equivalent 2D implementation. In addition, this 3D method is expected to be more effective for high resolution imaging applications. In this section, we explore the effectiveness of this method for susceptibility artifact correction at ultra-high field strength.

### 3.3.2 Methods

The 3D z-shim method is based on a 3D GE sequence with an oversampling of the slice encoding, so that k-space coverage is extended in the $k_z$ direction with $n$ additional $k_x$–$k_y$ planes. This extended coverage ensures that the echoes that are shifted along $k_z$ in regions affected by $B_0$ inhomogeneity are fully sampled and
that the signal loss in these regions is recovered. This is equivalent to altering the slice rephaser gradient in 2D z-shim methods. After acquisition of this extended k-space, \( n + 1 \) subsets of these data are reconstructed by 3D Fourier transform using a sliding window in the \( k_z \) direction with \( n + 1 \) incrementing offsets along \( k_z \), resulting in \( n + 1 \) series of z-shimmed images. These images are then combined using either MIP or SSQ to yield the final corrected images. Alternatively, if a corresponding map of the \( B_0 \) gradient in the slice direction (i.e., a map of the susceptibility-induced gradient in the slice direction \( G_{z,\text{susc}} \)) is available, the offset in k-space can be directly computed for each pixel and used to derive the final corrected images.

Because part of the data in k-space is shared between the subsets reconstructed with different offsets along \( k_z \), the 3D z-shim method requires fewer z-shim steps than an equivalent 2D method and is therefore more efficient. Furthermore, it can be shown that this improved efficiency results in an increased SNR [91].

In Glover’s original method [91], the susceptibility-induced gradients were assumed to be predominantly in one direction, so that acquisition of k-space was extended only in one direction along \( k_z \). While this assumption may hold true in some regions, it is certainly not valid in general, especially near air/tissue interfaces in the inferior frontal and temporal lobes, as shown by our \( B_0 \) numerical simulations (see section 2.1) and experimental mapping (see section 2.2). We therefore extended k-space symmetrically in both directions along \( k_z \) in order to recover the signal loss due to both positive and negative susceptibility-induced gradients.

The studies were performed on the 8 T human whole-body MRI system, using a TEM RF head coil with 16 struts and 4 excitation ports. We studied one
postmortem unembalmed human subject, as well as one healthy volunteer and one patient who gave informed consent to the experimental protocol approved by our Institutional Review Board.

High resolution 3D GE images of the brain were typically acquired using the following parameters: 4 ms sinc3 RF pulse, TR 40 ms, TE 8.7 ms, BW 69 kHz, FOV 20 cm, MTX 1024×512, 32 slice partitions of 1 mm thickness with a two-fold oversampling of the slice encoding, axial or coronal acquisition plane, and NEX 1, resulting in a scan time of 10:55 min.

After data acquisition, 17 series of 16 slices were reconstructed by taking the 3D Fourier transform of 16 consecutive slices in k-space with an offset along \( k_z \) ranging from \(-8 \) to \(+8 \). The 17 series of z-shimmed images were then combined using either MIP or SSQ to yield the final corrected 16 slices.

3.3.3 Results and Discussion

Fig. 3.1 shows a coronal slice of the brain of a postmortem unembalmed human subject corresponding to 2 of the 17 z-shimmed images reconstructed with different offsets along \( k_z \), as well as the combined images computed using either MIP or SSQ. As expected, individual z-shimmed images reconstructed with different offsets along \( k_z \) show different regions of signal loss due to \( B_0 \) inhomogeneity, such as in the brainstem or the left lateral inferior temporal lobe. The signal loss in these regions, as well as in the superior frontal lobes, can be recovered on both the MIP and SSQ images. However, the vessel contrast is somewhat reduced, particularly on the MIP image. Residual signal loss in the inferior temporal lobes is caused by complete intravoxel dephasing due to the very large \( B_0 \) inhomogeneity in these regions. Additional signal loss, notably in the left parietal and temporal
lobes, as well as the right inferior temporal lobe, is due to $B_1$ inhomogeneity (i.e.,
low flip angle and/or receive sensitivity), as typically observed on images of the
human brain acquired at ultra-high field strength (see section 2.3). Similar results
were obtained on axial slices for in vivo studies.

These results show that the 3D z-shim method is effective at recovering signal
loss due to $B_0$ inhomogeneity at ultra-high field strength, although the improve-
ment is not very significant. However, it should be noted that these preliminary
studies were actually performed on data that had already been acquired for dif-
ferent purposes, and that the parameters might not have been optimal.
Figure 3.1: Coronal slice of the brain of a postmortem human subject corresponding to 2 of the 17 $z$-shimmed images reconstructed with different offsets along $k_z$, namely 0 (a) and 6 (b), as well as the combined images computed using either MIP (c) or SSQ (d). The individual $z$-shimmed images show different regions of signal loss due to $B_0$ inhomogeneity, particularly in the brainstem (a, red arrowheads) and the left lateral inferior temporal lobe (b, yellow arrowheads), which can be recovered on both the MIP and SSQ images. However, the vessel contrast is somewhat reduced, particularly on the MIP image (c, green arrowheads).
3.4 Gradient Compensation Using GESEPI

3.4.1 Introduction

Yang et al. [90] developed a gradient compensation method called Gradient Echo Slice Excitation Profile Imaging (GESEPI) for $T_2^*$-weighted imaging with $B_0$ inhomogeneity compensation. This method has been used to study the human brain at 3 T [90] and 7 T [133], the rat brain at 9.4 T [90], and the mouse brain at 14 T [134], with applications in the monitoring of tumors [135] and the detection of micro hemorrhages [136]. It has also been combined with spiral [137] and EPI-SENSE [138] imaging for reduction of blurring artifacts, geometric distortions, signal loss, as well as scan time. In this section, we evaluate the effectiveness of the GESEPI method for susceptibility artifact correction at ultra-high field strength by comparing images of the human brain acquired with a conventional GE method and the GESEPI method at 8 T.

3.4.2 Methods

As for all other gradient compensation methods, the GESEPI method recovers signal loss due to intravoxel dephasing in the slice direction, where the voxel size is typically the largest, and consequently the $B_0$ inhomogeneity most severe, in 2D imaging (see section 3.3.1). More specifically, it is based on a conventional 2D GE sequence, with an additional compensation gradient $G_c$ superimposed on the slice rephaser gradient. A series of $N$ GE images are successively acquired using $N$ equidistant $G_c$ values with an increment $\Delta G_c$ and a range $\pm G_{c,\text{max}}$ (i.e., $G_{c,\text{max}} = \frac{N-1}{2} \Delta G_c$). A 3D Fourier transform is then applied to the 3D data set.
to reconstruct a series of \( N \) images representing the slice profile at each pixel. Finally, a subset of these images are summed to yield a final corrected image with a slice thickness equal to that of an equivalent conventional 2D GE image. This method is thus essentially a 3D GE sequence with oversampling of the slice encoding.

The studies were performed on the 8 T human whole-body MRI system, using a TEM RF head coil with 16 struts and 4 excitation ports. We studied a total of 8 postmortem unembalmed human subjects (3 male, 5 female, 57 to 85 years old) with various neuropathologies, as well as 3 healthy volunteers (2 male, 1 female, 32 to 34 years old) who gave informed consent to the experimental protocol approved by our Institutional Review Board.

Images of the brain were acquired using a conventional 2D GE method and the GESEPI method with the typical parameters shown in Table 3.2. Different axial, coronal, and sagittal slices were acquired throughout the brain. A relatively short TR was used for the GESEPI method in order to limit the acquisition time. Nevertheless, the SNR was found to be sufficient, due to the inherent oversampling in the slice direction in this method. On the other hand, a longer TR and corresponding Ernst angle was used for the GE method in order to obtain sufficient SNR.

3.4.3 Results and Discussion

Fig. 3.2 shows a postmortem axial 2D GE image and the corresponding GESEPI image. These results show that the GESEPI method can effectively recover signal loss due to susceptibility differences at air/tissue interfaces, such as in the central inferior frontal lobes just superior to the planum sphenoidale. Furthermore, this
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<tr>
<td>$N$</td>
<td>–</td>
<td>64</td>
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**Table 3.2:** Acquisition parameters for the GE and GESEPI methods.

method can also correct for artifacts due to susceptibility differences between the deoxyhemoglobin contained in vessels and the surrounding tissue, resulting in a better delineation of the vasculature and an improvement in image quality. However, it also results in a slight decrease in vessel contrast, and this trade-off sometimes leads to an increase or decrease in vessel conspicuity, particularly for the smallest vessels. Note that overall signal variation, predominantly in the anterior–posterior direction, is due to $B_1$ inhomogeneity, as typically observed on images acquired at ultra-high field strength (see section 2.3).

Similar results were obtained in coronal, sagittal, and more superior axial slices, although with a less pronounced effect, because of the overall smaller $B_0$
**Figure 3.2:** Axial 2D GE (a) and GESEPI (b) images of the brain of a post-mortem human subject (57-year-old female with Huntington’s disease). The GE image shows the typical susceptibility artifact in the central inferior frontal lobes just superior to the planum sphenoidale, whereas this signal loss is fully recovered on the GESEPI image. Susceptibility artifacts surrounding through-plane vessels are also suppressed on the GESEPI image, resulting in a much better delineation of these vessels (e.g., blue arrowheads). Similarly, in-plane vessels appear thinner and are usually better delineated on the GESEPI image (e.g., red arrowheads), although with a somewhat reduced contrast. This trade-off implies that some of the smallest vessels can sometimes be seen on the GESEPI image, but not on the GE image (e.g., yellow arrowheads), or *vice versa* (e.g., green arrowheads).
inhomogeneity, except in regions close to air/tissue interfaces in the inferior frontal and temporal lobes (see chapter 2). Furthermore, the results were highly dependent on the subject’s anatomy.

In section 4.1, we evaluate different multi-echo implementations of the GESEPI method for $T_2^*$ relaxation time measurement with $B_0$ inhomogeneity compensation, and further discuss several issues common to all methods.
CHAPTER 4

RELAXATION TIME MEASUREMENTS

4.1 \( T_2^* \) Measurements Using mGESEPI and bmGESEPI

4.1.1 Introduction

Knowledge of \( T_2^* \) relaxation times at ultra-high field strength is needed for optimizing acquisition parameters for \( T_2^* \)-weighted imaging and understanding relaxation mechanisms. Standard \( T_2^* \) measurements (e.g., using multi-echo GE sequences) are affected by \( B_0 \) inhomogeneity, which is particularly severe at ultra-high field strength (see chapter 2), resulting in erroneous \( T_2^* \) values.

Yang et al. [139] developed a method called multi Gradient Echo Slice Excitation Profile Imaging (mGESEPI) for \( T_2^* \)-weighted imaging and \( T_2^* \) measurement with \( B_0 \) inhomogeneity compensation. This method has been used to measure \( T_2^* \) values in the human brain at 3 T [139] and 7 T [140], and in the mouse brain at 14 T [139]. We implemented it on the 8 T human whole-body MRI system, but found that it requires prohibitive acquisition times for accurate \( T_2^* \) measurements. We therefore developed a more efficient method that allows significantly faster and accurate \( T_2^* \) measurements [141]. To demonstrate these advantages, we compared
$T_2^*$ measurements using a conventional multi-echo GE method, the mGESEPI method, and the newly developed method in a phantom as well as postmortem and in vivo human brains at 8 T. $B_0$ maps were also experimentally acquired to determine optimal parameters for the mGESEPI and bmGESEPI methods, to correlate the $B_0$ inhomogeneity with the artifacts observed on the $T_2^*$ maps, and to assess the degree of compensation achieved with the mGESEPI and bmGESEPI methods.

4.1.2 Theory

The mGESEPI method [139, 140] is simply a multi-echo version of the GESEPI method (see section 3.4), where a train of $M$ GE images are acquired at different TEs for each compensation gradient $G_c$. For each TE, a corrected image is reconstructed as in the GESEPI method, and a $T_2^*$ map is computed by fitting a monoexponential decay pixel-by-pixel to these $M$ corrected images.

The susceptibility-induced gradient in the slice direction $G_{z,\text{susc}}$ that can be compensated for by a given $G_c$ at a time TE is given by Eq. (3.29). Since the left hand side of this equation is constant, the $G_{z,\text{susc}}$ that can be compensated for decreases as TE increases. This implies that the $T_2^*$ measurements are accurate only if the largest $G_c$ (i.e., $G_{c,\text{max}}$) is able to compensate for the largest $G_{z,\text{susc}}$ ($G_{z,\text{susc, max}}$) at the last echo. However, satisfying this condition at ultra-high field strength requires a large $G_{c,\text{max}}$ and a large number of compensation gradients $N$, resulting in excessive acquisition times for in vivo studies.

We developed a new method based on the mGESEPI method in which the compensation gradient $G_c$ is added as a blipped gradient in the slice direction between each echo acquisition (see Fig. 4.1). As such, $\int G_c \, dt$ is proportional
to TE, so that the same $G_{z,\text{susc}}$ is compensated for at each echo. For the $T_2^*$ measurements to be accurate, the $G_{c,\text{max}}$ required to compensate for $G_{z,\text{susc,\text{max}}}$ is a factor $M$ smaller than in the mGESEPI method, thus allowing a reduction of $N$ as well as the acquisition time by the same factor. This so-called blipped mGESEPI (bmGESEPI) method is therefore more efficient and allows significantly faster and accurate $T_2^*$ measurements.

### 4.1.3 Methods

The studies were performed on the 8 T human whole-body MRI system, using TEM RF coils with a single strut or with 16 struts and 4 excitation ports for the phantom and human studies, respectively.

$T_2^*$ maps were acquired using a conventional multi-echo GE method, the mGESEPI method, and the bmGESEPI method. All echoes were acquired using readout gradients of same polarity to avoid misregistration errors due to susceptibility artifacts, gradient imbalance, and/or eddy current effects. An asymmetric sinc RF pulse was used to shorten the TEs. Furthermore, minimum gradient ramp times and durations as well as maximum gradient strength were used whenever possible to obtain the shortest TEs and interecho spacing $\Delta TE$ achievable in order to cover the $T_2^*$ relaxation decay with a sufficient number of echoes, given the short $T_2^*$ values at ultra-high field strength. A relatively short TR was used to limit the acquisition time of the mGESEPI and bmGESEPI methods. Nevertheless, the SNR was found to be sufficient due to the inherent oversampling in the slice direction in both methods. A spoiler gradient was applied in the readout direction at the end of the sequence.
Figure 4.1: The bmGESEPI pulse sequence shown here is based on a conventional 2D multi-echo GE sequence, where a series of $N$ compensation gradients $G_c$ (with an increment $\Delta G_c$ and a range $\pm G_{c,\text{max}}$) is superimposed on the slice rephaser gradient, as in the mGESEPI sequence, but is also added as a blipped gradient in the slice direction between each of the $M$ echo acquisitions. This ensures that the same susceptibility-induced gradient in the slice direction $G_{z,\text{susc}}$ is compensated for at each echo, thus allowing significantly faster and accurate $T_2^*$ measurements than with the mGESEPI method.
$B_0$ maps were acquired using a 3D dual-echo GE sequence (see section 2.2), and maps of the $B_0$ gradient along the slice direction were computed to obtain an estimate of the susceptibility-induced gradient in the slice direction $G_{z,susc}$. These maps were used for two purposes: first, to determine optimal parameters for the mGESEPI and bmGESESPI methods, and second, to correlate the $B_0$ inhomogeneity with the artifacts observed on the $T_2^*$ maps and assess the degree of compensation achieved with the mGESEPI and bmGESEPI methods.

Unlike in previous studies, where the parameters $G_{c,max}$ and $N$ were determined experimentally [90], we used $B_0$ maps obtained by numerical simulations (see section 2.1) and experimental mapping (see section 2.2) to determine optimal parameters for both the mGESEPI and bmGESEPI methods. First, a $G_{z,susc,max}$ value was determined from maps of the $B_0$ gradient in the slice direction for a particular slice. Note that this value, which is the largest $G_{z,susc}$ to be compensated for, does not necessarily have to be the maximum $G_{z,susc}$ over the whole slice. For example, we chose a value of 1.0 ppm/cm for the phantom study, which is the largest $G_{z,susc}$ in most regions of the phantom. For the human studies, we chose a value of 0.8 ppm/cm, which is well above the $G_{z,susc}$ values in most regions of the brain, with the exception of regions close to air/tissue interfaces, such as in the central inferior frontal lobes just superior to the planum sphenoidale, as well as in the lateral inferior temporal lobes near the mastoid and middle ear air spaces (see chapter 2). Then, the $G_{c,max}$ required for each method was computed from this chosen $G_{z,susc,max}$ value using Eq. (3.29). This value turned out to be 160\% (of the slice rephaser gradient amplitude) for the mGESEPI method and 16\% for the bmGESEPI method for both the phantom and human studies. Note that these values are expressed as percentages, so that they are independent of the
slice rephaser gradient duration, which can be arbitrary. However, they are still
dependent on the slice select gradient time integral, which in turn depends on the
slice thickness (3 mm in all of our studies). The number of compensation gradient
steps $N$ was then set to 80 for the mGESEPI method and 8 for the bmGESEPI
method, in order to keep the same $G_{c,\text{max}}/N$ ratio (or equivalently, the same $\Delta G_c$
increment) for both methods. Note that as discussed in section 4.1.2, the param-
eters $G_{c,\text{max}}$ and $N$, and consequently the acquisition time, are a factor $M$ (10 in
our studies) smaller for the bmGESEPI method, due to its improved efficiency
over the mGESEPI method.

We also studied the performance of the mGESEPI method with a range of
smaller $N$ values and either the same $G_{c,\text{max}}/N$ ratio or the same $G_{c,\text{max}}$ value (see
Table 4.1). However, rather than acquiring all of these additional data sets, we
selected the appropriate data in k-space from the data set acquired with $G_{c,\text{max}}/N$
= 160%/80. For example, the central 8 $k_x-k_y$ planes of k-space were used to
simulate the $G_{c,\text{max}}/N = 16%/8$ acquisition, whereas every 10th $k_x-k_y$ plane along
the $k_z$ direction was used to simulate the $G_{c,\text{max}}/N = 160%/8$ acquisition (see
Fig. 4.2). For these simulations, the data in k-space was interpolated along $k_z$ as
needed.

In addition, since the improved efficiency of the bmGESEPI method allows
trading off some acquisition time for an increased $N$ value, and possibly more
accurate $T_2^*$ measurements, we actually acquired the bmGESEPI method with
$G_{c,\text{max}}/N = 16%/16$, and then simulated the $G_{c,\text{max}}/N = 16%/8$ acquisition for
direct comparison with the mGESEPI method by selecting every other $k_x-k_y$ plane
along $k_z$ in k-space.
<table>
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**Table 4.1:** $G_{c,\text{max}}$ and $N$ parameters used for the mGESEPI and bmGESEPI methods.
Figure 4.2: K-space diagrams showing how the mGESEPI data set acquired with $G_{c,\text{max}}/N = 160\%/80$ (left) was used to simulate mGESEPI acquisitions with smaller $N$ values and either the same $G_{c,\text{max}}/N$ ratio (top row) or the same $G_{c,\text{max}}$ value (bottom row) by selecting appropriate $k_x-k_y$ planes in k-space from the original data set. The numbers at the top of each diagram correspond to $G_{c,\text{max}}$ and $N$ respectively.

We studied a phantom consisting of a 5 mm diameter air-filled tube surrounded by a CuSO₄ solution ($T_1/T_2 \simeq 40/25 \text{ ms}$). The imaged slice was an axial slice 6 mm away from the center of the air-filled tube and was therefore entirely in the CuSO₄ solution. This slice was chosen so as to obtain similar $G^{z,\text{susc}}$ values as for a human brain, based on numerical and experimental $B_0$ maps, so that similar parameters could be used for the phantom and the human studies. $T_2^*$ maps were acquired using the GE, mGESEPI, and bmGESEPI methods and a $B_0$ map was acquired using the dual-echo GE method with the parameters shown in Table 4.2. As described above, additional $T_2^*$ maps were reconstructed using only partial data from the original mGESEPI and bmGESEPI data sets, thus
simulating acquisitions with a range of smaller $N$ values and either the same $G_{c,\text{max}}/N$ ratio or the same $G_{c,\text{max}}$ value as the original data sets.

It should be noted that shim and gradient instability problems on the 8 T MRI system and/or motion resulted in severe ghosting on the images and banding artifacts on the $T_2^*$ maps, especially since multiple echoes were acquired with a short $\Delta TE$ and TR, and maximum gradient strength was used in all of these sequences. For that reason, all $T_2^*$ measurements were performed using multiple NEX. However, different NEX values were used for the GE, mGESEPI, and bmGESEPI methods because each method was more or less severely affected by the artifacts and because the total acquisition times had to stay within practical limits.

We studied another phantom consisting of a 5 mm diameter air-filled tube surrounded by a gel made of 4% gelatin, 1.3 mM CuSO$_4$, and 0.125 M NaCl (for an appropriate loading of the RF coil), which, unlike the first phantom, is completely filled with gel, thus reducing any possibility of motion artifacts. Preliminary studies showed that this phantom is significantly less affected by ghosting and banding artifacts, so that a NEX of 1 can be used for all methods. However, it has a substantially longer $T_2^*$ value, which requires longer TEs and consequently excessively large $G_{c,\text{max}}$ and $N$ values for a comparison between the mGESEPI and bmGESEPI methods with equivalent parameters. Further studies using a new phantom with the same geometry but a shorter $T_2^*$ value are needed to obtain better results.

We also studied a total of 4 postmortem unembalmed human subjects (2 male, 2 female, 72 to 81 years old) with various neuropathologies, and 2 healthy volunteers (1 male, 1 female, both 34 years old) who gave informed consent to the
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**Table 4.2:** Acquisition parameters for the GE, mGESEPI, and bmGESEPI $T_2^*$ measurements and $B_0$ mapping for the phantom study.
experimental protocol approved by our Institutional Review Board. \( T_2^* \) measurements and \( B_0 \) mapping were performed as in the phantom study, but using the parameters shown in Table 4.3. \( T_2^* \) maps were acquired on different axial, coronal, and sagittal slices throughout the brain. Note that since the ghosting and artifacts due to shim and gradient instability were significantly less pronounced in these human studies as compared to the phantom study, a single NEX was used for all \( T_2^* \) measurements. Also note that because of the excessive acquisition time required, the comparison between the mGESEPI and bmGESEPI methods with equivalent parameters was performed only in postmortem studies.

### 4.1.4 Results

Fig. 4.3 shows \( T_2^* \) maps of the phantom obtained with the GE, mGESEPI, and bmGESEPI methods using different \( G_{c,max} \) and \( N \) parameters, as well as a corresponding magnitude image and a map of the \( B_0 \) gradient in the slice direction. The GE \( T_2^* \) map (Fig. 4.3a) shows artificially low \( T_2^* \) values in the central region, resulting from \( B_0 \) inhomogeneity induced by susceptibility differences between the air-filled tube and the surrounding CuSO\(_4\) solution, even though the tube is not contained in the imaged slice. The \( T_2^* \) values are artificially high in the outer regions, which is not fully understood at this time. The low \( T_2^* \) values in the central region can be largely corrected for by using the mGESEPI method with \( G_{c,max}/N = 160\%/80 \), as shown by the more homogeneous \( T_2^* \) map (Fig. 4.3d), however at the cost of an excessive acquisition time. As expected, decreasing both \( G_{c,max} \) and \( N \) progressively reduces the degree of \( B_0 \) inhomogeneity compensation, as shown by the region with lower \( T_2^* \) values appearing in the center of the \( T_2^* \) maps (Figs. 4.3d–i). Reducing only \( N \) while keeping the same \( G_{c,max} \) also results
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**Table 4.3:** Acquisition parameters for the GE, mGESEPI, and bmGESEPI $T_2^*$ measurements and $B_0$ mapping for the human studies.
in artifacts (Figs. 4.3d,j–n), because the $\Delta G_e$ increment becomes too large, i.e., the oversampling becomes insufficient, for an accurate reconstruction of the images. On the other hand, the bmGESEPI method with $G_{c,\text{max}}/N = 16\%/8$ can provide a $B_0$ inhomogeneity compensation that is similar to that achieved by the mGESEPI method with equivalent parameters (namely $G_{c,\text{max}}/N = 160\%/80$), as shown by the very homogeneous $T_2^*$ map (Fig. 4.3o), while requiring only 10% of its acquisition time. Increasing $N$ to 16 resulted in a nearly identical $T_2^*$ map (Fig. 4.3p), thus showing that an $N$ value of 8 was sufficient to provide accurate $T_2^*$ measurements. These results clearly demonstrate the significant advantages of the bmGESEPI method over the mGESEPI method.

Fig. 4.4 shows axial $T_2^*$ maps of the brain of a postmortem human subject obtained with the GE, mGESEPI, and bmGESEPI methods using different $G_{c,\text{max}}$ and $N$ parameters, as well as a corresponding SE image and a map of the $B_0$ gradient in the slice direction. Fig. 4.5 shows some of these images enlarged. The GE $T_2^*$ map (Fig. 4.4a) shows artificially low $T_2^*$ values resulting from $B_0$ inhomogeneity, and anatomical structures are not correctly depicted. Note that signal loss in the right anterior and lateral regions of the brain is due to $B_1$ inhomogeneity, as seen on the SE image (Fig. 4.4b) and typically observed on axial images of the human brain acquired at ultra-high field strength (see section 2.3). The mGESEPI $T_2^*$ map with $G_{c,\text{max}}/N = 160\%/80$ (Fig. 4.4d) shows higher $T_2^*$ values with a clear delineation of the cerebral hemispheres, ventricles, and CSF spaces. In addition, some of the brain nuclei such as the putamen and globus pallidus are depicted with lower $T_2^*$ values than the surrounding brain tissue, due to their high iron content. There are residual artifacts in the central inferior frontal lobes just superior to the planum sphenoidale, where the $B_0$ inhomogeneity is most severe
Figure 4.3: $T_2^*$ maps (in ms) of the phantom obtained using a conventional multi-echo GE method (a) as well as the mGESEPI (d–n) and bmGESEPI (o–p) methods with different $G_{c,\text{max}}$ and $N$ parameters, as shown at the top of each map. Also shown are a corresponding magnitude image (mGESEPI method with $G_{c,\text{max}}/N = 160\% / 80$ at $\text{TE} = 7$ ms) (b) and a $B_0$ gradient map in the slice direction (in ppm/cm) (c). Note that the air-filled tube, which is in the inferior–superior direction at the center of the phantom, is not contained in the imaged slice.
(Fig. 4.4c). However, this is expected because in this region, the $B_0$ gradient in the slice direction, i.e., $G_z$,susc, is larger than the chosen threshold of $G_z$,susc,max = 0.8 ppm/cm. As in the phantom study, decreasing both $G_{c,max}$ and $N$ progressively reduces the amount of $B_0$ inhomogeneity compensation, resulting in low $T_2^*$ values throughout the brain (Figs. 4.4d–i). On the other hand, reducing only $N$, i.e., increasing $\Delta G_c$, results in high $T_2^*$ values with a loss of depiction of the nuclei (Figs. 4.4d,j–n). The bmGESEPI $T_2^*$ map with $G_{c,max}/N = 16\%/8$ (Fig. 4.4o) shows slightly higher $T_2^*$ values than the mGESEPI map with equivalent parameters (namely $G_{c,max}/N = 160\%/80$). However, increasing $N$ to 16 results in a similar $T_2^*$ map as the latter (Fig. 4.4p), while requiring only 20% of its acquisition time. Thus the high efficiency of the bmGESEPI method allows trading off some acquisition time for a larger $N$ value, and therefore more accurate $T_2^*$ measurements.

Results for the three other postmortem human subjects and two healthy volunteers are shown in Figs. 4.6 to 4.11. As in the first postmortem study, the GE $T_2^*$ maps all show artificially low $T_2^*$ values, with anatomical structures not correctly depicted. On the other hand, the bmGESEPI $T_2^*$ maps show higher $T_2^*$ values with a better delineation of anatomical structures, particularly the ventricles and CSF spaces, as well as some of the brain nuclei such as the putamen, globus pallidus, red nuclei, and substantia nigra, which are depicted with lower $T_2^*$ values than the surrounding brain tissue, due to their high iron content. Note that $B_1$ inhomogeneity results in signal loss and artifacts on the $T_2^*$ maps in different regions of the brain, depending on the subject anatomy and RF coil tuning (see section 2.3). Furthermore, there are residual artifacts on all axial bmGESEPI $T_2^*$ maps in the central inferior frontal lobes just superior to the planum sphenoidale,
Figure 4.4: Axial $T_2^*$ maps (in ms) of the brain of a 72-year-old female post-mortem human subject with Alzheimer’s disease obtained using a conventional multi-echo GE method (a) as well as the mGESEPI (d–n) and bmGESEPI (o–p) methods with different $G_{c,max}$ and $N$ parameters, as shown at the top of each map. Also shown are a corresponding SE image (TR 1500 ms, TE 70 ms) (b) and a $B_0$ gradient map in the slice direction (in ppm/cm) (c). Images d, o, b, and c are shown enlarged in Fig. 4.5.
Figure 4.5: Axial $T_2^*$ maps (in ms) of the brain of the same subject shown in Fig. 4.4 obtained using the mGESEPI method with $G_{c,max}/N = 160%/80$ (a) and the bmGESEPI method with $G_{c,max}/N = 16%/16$ (b), as well as a corresponding SE image (TR 1500 ms, TE 70 ms) (c) and a $B_0$ gradient map in the slice direction (in ppm/cm) (d). These images are enlarged versions of images d, o, b, and c in Fig. 4.4, respectively.
where the $B_0$ inhomogeneity is most severe. However, this is expected because the $G_{z,\text{susc}}$ values in this region are larger than the chosen threshold of $G_{z,\text{susc, max}} = 0.8$ ppm/cm. The difference between the GE and bmGESEPI $T_2^*$ maps is not as pronounced in the coronal slice (Fig. 4.9) as compared to the axial slices, because of the overall smaller $B_0$ inhomogeneity, except in regions close to air/tissue interfaces in the inferior temporal lobes (Fig. 4.9d).

Table 4.4 shows the bmGESEPI $T_2^*$ values in different GM and WM ROIs of the brain of the subjects shown in Figs. 4.4 to 4.10 for whom a SE image with good GM/WM contrast was available. Note that because of differences in subject anatomy, slice positioning, and artifacts due to $B_0$ or $B_1$ inhomogeneity across the studies, ROIs could not always be drawn in the same regions for all subjects. Although the GM/WM contrast is not readily apparent on the bmGESEPI $T_2^*$ maps, this table tends to indicate that $T_2^*$ values are generally slightly shorter in GM ROIs as compared to adjacent WM ROIs for both postmortem and in vivo studies, as is the case at lower field strength. Nevertheless, additional studies are needed to confirm this trend and further investigate this behavior.

Table 4.5 shows the bmGESEPI $T_2^*$ values in different brain nuclei of the subjects shown in Figs. 4.4 to 4.11. Again, because of differences in anatomy, slice positioning, and $B_0$ or $B_1$ inhomogeneity across the studies, not all nuclei could be seen in all subjects. As expected, this table shows that for both postmortem and in vivo studies, the nuclei have lower $T_2^*$ values than the surrounding brain tissue, due to their high iron content.

Finally, note that the vessel contrast present on the magnitude images is significantly reduced on the $T_2^*$ maps for both postmortem and in vivo studies. However, this is not unexpected because the $T_2^*$ of venous blood at ultra-high field strength
Figure 4.6: Axial $T_2^*$ maps (in ms) of the brain of an 81-year-old female post-mortem human subject with Alzheimer’s disease obtained using a conventional multi-echo GE method (a) and the bmGESEPI method with $G_{c,\text{max}}/N = 16%/16$ (b), as well as a corresponding SE image (TR 1500 ms, TE 70 ms) (c) and a $B_0$ gradient map in the slice direction (in ppm/cm) (d). Signal loss in the central region of the SE image is due to $B_1$ inhomogeneity.
Figure 4.7: Axial $T_2^*$ maps (in ms) of the brain of a 73-year-old male postmortem human subject with Alzheimer’s disease obtained using a conventional multi-echo GE method (a) and the bmGESEPI method with $G_{c,\text{max}}/N = 16%/16$ (b), as well as a corresponding SE image (TR 1500 ms, TE 70 ms) (c) and a $B_0$ gradient map in the slice direction (in ppm/cm) (d). Signal loss in the left posterior region of the SE image and resulting artifacts on the $T_2^*$ maps are due to $B_1$ inhomogeneity. Note that the putamen and globus pallidus are clearly depicted on the bmGESEPI $T_2^*$ map.
Figure 4.8: Axial $T_2^*$ maps (in ms) of the brain of a 79-year-old male postmortem human subject with alcohol dementia obtained using a conventional multi-echo GE method (a) and the bmGESEPI method with $G_{c,max}/N = 16%/16$ (b), as well as a corresponding bmGESEPI image (TE 26.4 ms) (c) and a $B_0$ gradient map in the slice direction (in ppm/cm) (d). Signal loss in the right posterior region of the magnitude image and resulting artifacts on the $T_2^*$ maps are due to $B_1$ inhomogeneity.
Figure 4.9: Coronal $T_2^*$ maps (in ms) of the brain of the same subject shown in Figs. 4.4 and 4.5 obtained using a conventional multi-echo GE method (a) and the bmGESEPI method with $G_{c,\text{max}}/N = 16%/16$ (b), as well as a corresponding SE image (TR 1500 ms, TE 70 ms) (c) and a $B_0$ gradient map in the slice direction (in ppm/cm) (d). Signal loss in the right temporal and inferior frontal lobes is due to $B_1$ inhomogeneity.
Figure 4.10: Axial $T_2$ maps (in ms) of the brain of a 34-year-old female healthy volunteer obtained using a conventional multi-echo GE method (a) and the bmGE-SEPI method with $G_{c,\text{max}}/N = 16%/16$ (b), as well as a corresponding SE image (TR 1500 ms, TE 50 ms) (c) and a $B_0$ gradient map in the slice direction (in ppm/cm) (d). Signal loss in the left anterior region is due to $B_1$ inhomogeneity.
Figure 4.11: Axial $T_2^*$ maps (in ms) of the brain of a 34-year-old male healthy volunteer obtained using a conventional multi-echo GE method (a) and the bmGESEPI method with $G_{c,\text{max}}/N = 20%/16$ (b), as well as a corresponding bmGESEPI image (TE 26.4 ms) (c). Signal loss in the right posterior region of the magnitude image and resulting artifacts on the $T_2^*$ maps are due to $B_1$ inhomogeneity. Note that the putamen and globus pallidus are clearly depicted on the bmGESEPI $T_2^*$ map.
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**Table 4.4**: bmGESEPI $T_2^*$ values (mean ± standard deviation) in different GM and WM ROIs of the brain of the subjects shown in Figs. 4.4 to 4.10 (STG = superior temporal gyrus, MTG = middle temporal gyrus, SOG = superior occipital gyrus, ITG = inferior temporal gyrus, MOG = middle occipital gyrus).
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<td>left globus pallidus</td>
<td>15.1 1.6</td>
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<td>right globus pallidus</td>
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<td><strong>Fig. 4.7 (postmortem)</strong></td>
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<tr>
<td>right putamen</td>
<td>12.4 0.5</td>
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<td>11.9 0.4</td>
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<td><strong>Fig. 4.8 (postmortem)</strong></td>
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<td>left putamen</td>
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<td><strong>Fig. 4.9 (postmortem)</strong></td>
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<td>right red nucleus</td>
<td>13.2 1.5</td>
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<td>left substantia nigra</td>
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<td><strong>Fig. 4.10 (in vivo)</strong></td>
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<td>right substantia nigra</td>
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<td>left red nucleus</td>
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<td><strong>Fig. 4.11 (in vivo)</strong></td>
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<td>left globus pallidus</td>
<td>17.4 1.8</td>
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**Table 4.5:** bmGESEPI $T_2^*$ values (mean ± standard deviation) in different brain nuclei of the subjects shown in Figs. 4.4 to 4.11.
(\simeq 3\textendash 5 \text{ ms}) is shorter than the shortest TE used for the \(T_2^*\) measurements in our studies (namely 4.4 ms).

### 4.1.5 Discussion

Our studies clearly show that \(T_2^*\) measurements using a conventional multi-echo GE method are severely affected by \(B_0\) inhomogeneity at ultra-high field strength, resulting in erroneous \(T_2^*\) values. The mGESEPI method developed by Yang et al. for \(T_2^*\) measurement with \(B_0\) inhomogeneity compensation can correct for these artifacts and provide accurate \(T_2^*\) measurements, however at the expense of prohibitive acquisition times, particularly for in vivo studies. Previous in vivo human studies used only a limited number of compensation gradient steps \(N\), namely 8 [140] or 16 [139], which is not sufficient to provide accurate \(T_2^*\) measurements at ultra-high field strength, as shown by our studies. In the new bmGESEPI method that we developed and unlike in the mGESEPI method, the same susceptibility-induced gradient in the slice direction \(G_{z,\text{susc}}\) is compensated for at each echo, making this method much more efficient and allowing significantly faster and accurate \(T_2^*\) measurements.

Note that although the studies performed in this work used single slice acquisitions, the bmGESEPI method can be applied to multislice acquisitions as well, with the maximum number of slices ultimately limited by TR. However, parallel imaging techniques such as SENSE [138] or SMASH could be used to further increase the efficiency of the bmGESEPI method and allow extended spatial coverage with reasonable scan times.

Our studies also demonstrate the usefulness of \(B_0\) numerical simulations and experimental mapping for both the development and assessment of susceptibility
artifact correction methods. Unlike in previous studies, where the parameters $G_{c,\text{max}}$ and $N$ were determined experimentally [90], we used $B_0$ maps to determine optimal parameters for the mGESEPI and bmGESEPI methods. Furthermore, these maps were also used to correlate the $B_0$ inhomogeneity with the artifacts observed on the $T_2^*$ maps and assess the degree of compensation achieved with the mGESEPI and bmGESEPI methods.

Some clinical applications of bmGESEPI $T_2^*$ measurements at ultra-high field strength, notably for the assessment of brain iron content in neurodegenerative diseases, are discussed in section 5.2.
4.2 $T_2$, $T'_2$, and $T^*_2$ Measurements Using GESFIDE

4.2.1 Introduction

As with $T^*_2$, knowledge of $T_2$ relaxation times at ultra-high field strength is needed for optimizing acquisition parameters for $T_2$-weighted imaging and understanding relaxation mechanisms. Whereas $T^*_2$ measurements are based on a series of GE images acquired at different TEs, standard $T_2$ measurements (e.g., using Hahn or CPMG SE) are based on a series of SE images acquired at different TEs, and such measurements at ultra-high field strength are affected by substantial variations of the flip angle and receive sensitivity throughout the image volume, resulting from severe $B_1$ inhomogeneity [142, 143, 144, 145] (see section 2.3). Standard Hahn and CPMG SE $T_2$ measurements at 8 T were found to be accurate only in regions where the flip angle (of the excitation pulse) remains within $\pm 20^\circ$ from $90^\circ$ [101].

Ma et al. [146] developed a method called Gradient Echo Sampling of the FID and Echo (GESFIDE) that can provide $T_2$, $T'_2$, and $T^*_2$ measurements in a single scan, and, more importantly, is insensitive to RF pulse imperfections. This method has primarily been used for the assessment of brain iron and trabecular bone marrow at 1.5 T and 4 T [146, 147, 148, 149]. In this section, we evaluate the performance of the GESFIDE method for relaxation time measurements at ultra-high field strength.

4.2.2 Theory

The GESFIDE method is based on a Hahn SE sequence (with an excitation RF pulse $\alpha_x$ and a refocusing RF pulse $\beta_y$) where the FID and ascending portion
of the SE, i.e., the dephasing and rephasing portions of the signal, are sampled with a train of GE images. Assuming that both the reversible and irreversible transverse relaxation can be characterized by single exponentials with relaxation rates \( R_2 \equiv 1/T_2 \) and \( R_2' \equiv 1/T_2' \) respectively, and that \( \beta = 180^\circ \), the transverse magnetization during the FID and ascending portion of the SE can be described by the following expressions:

\[
S(t) = S_0 \exp[-(R_2 + R_2')t], \quad \text{for } t < \text{TE}/2 \quad (4.1)
\]

\[
S(t) = S_0 \exp[-(R_2 - R_2')t] \exp[-R_2' \text{TE}], \quad \text{for } \text{TE}/2 < t < \text{TE} \quad (4.2)
\]

where \( S_0 \) is the initial transverse magnetization. By introducing the apparent transverse relaxation rate:

\[
R_2^* \equiv R_2 + R_2' \equiv 1/T_2^*
\]

and defining the following rate constant:

\[
R_2^- \equiv R_2 - R_2',
\]

Eqs. (4.1) and (4.2) become:

\[
S(t) = S_0 \exp(-R_2^* t), \quad \text{for } t < \text{TE}/2 \quad (4.5)
\]

\[
S(t) = S_0 \exp(-R_2^- t) \exp(-R_2' \text{TE}), \quad \text{for } \text{TE}/2 < t < \text{TE} \quad (4.6)
\]

This shows that \( R_2^* \) and \( R_2^- \) maps can be obtained by sampling the FID and ascending portion of the SE with a train of GE images and fitting Eqs. (4.5) and (4.6) to each series of images pixel-by-pixel, respectively. It is then straightforward to show from Eqs. (4.3) and (4.4) that \( R_2 \) and \( R_2' \) maps can be computed from
the $R^*_2$ and $R_2^-$ maps as follows:

\begin{align}
R_2 &= \frac{R^*_2 + R^-_2}{2} \\
R'_2 &= \frac{R^*_2 - R^-_2}{2}.
\end{align}

Finally, the $T_2$, $T'_2$, and $T^*_2$ maps are computed by taking the inverse of the $R_2$, $R'_2$, and $R^*_2$ maps pixel-by-pixel, respectively.

In principle, an $R^*_2$ map can also be obtained by sampling the descending portion of the SE with a train of GE images, however at the expense of a lower SNR. Nevertheless, this second measurement could then be averaged with the one obtained by sampling the FID to increase the SNR in the final $R^*_2$ map [147].

In the presence of $B_1$ inhomogeneity, the flip angle $\beta$ is spatially varying and is not necessarily equal to 180°. In that case, Eq. (4.6) can be generalized to [146]:

\begin{equation}
S(t) = S_0 \frac{1}{2} \left\{ (1 + \cos \beta) \exp(-R^*_2 t) \\
+ (1 - \cos \beta) \exp(-R^-_2 t) \exp(-R'_2 \text{ TE}) \right\}.
\end{equation}

In other words, the transverse magnetization during the ascending portion of the SE has two components, a dephasing component with rate constant $R^*_2$ and a rephasing component with rate constant $R^-_2$, with relative weights that are functions of $\beta$. In principle, the undesired dephasing component can be spoiled by applying a pair of crusher gradients of sufficient amplitude around the refocusing RF pulse. In that case, deviations of $\beta$ from 180° affect only the signal intensity of the images, but not the relaxation time measurements, making the GESFIDE method insensitive to $B_1$ inhomogeneity. However, it should be noted that this is true only within a range of $\beta$ values for which the crusher gradients can effectively
spoil the dephasing component of the signal, and for which the remaining rephasing component is not significantly attenuated, \textit{i.e.}, the coefficient \((1 - \cos \beta)\) is not too small.

4.2.3 Methods

Our studies were performed on the 8 T human whole-body MRI system, using a TEM RF head coil with 16 struts and 4 excitation ports. We studied a total of three postmortem unembalmed human subjects (1 male, 2 female, 70 to 84 years old) with various pathologies, as well as one healthy volunteer (male, 32 years old) who gave informed consent to the experimental protocol approved by our Institutional Review Board.

First, a “nominal” flip angle was defined as the average flip angle in a 1 cm\(^3\) region of interest (typically located in the hippocampus), and the transmit power level resulting in a nominal flip angle of 90° was determined using a voxel-selective stimulated echo sequence (see section 2.3.2). To quantify the \(B_1\) inhomogeneity, maps of the local flip angle and receive sensitivity were experimentally measured from two series of GE images acquired with TR \(\gg T_1\) and nominal flip angles \(\alpha_0\) and \(2\alpha_0\) (see section 2.3.2).

\(T_2, T_2',\) and \(T_2^*\) maps of the brain were then acquired using the GESFIDE method with the following typical parameters: 8 ms sinc3 RF pulse, TR 1500 ms, TE 58 ms, \(\Delta TE\) 4.3 ms, BW 100 kHz, FOV 16 cm, MTX 256×256, ST 3 mm, coronal or axial acquisition plane, NEX 1, and nominal flip angle 90°/180°. All echoes were acquired using readout gradients of same polarity to avoid misregistration errors due to susceptibility artifacts, gradient imbalance, and/or eddy current effects. Minimum gradient ramp times and durations as well as maxi-
mum gradient strength were used whenever possible to obtain the shortest $\Delta$TE achievable in order to maximize the number of echoes and improve the accuracy of the relaxation time measurements. With the parameters described above, four GE images could be acquired during the FID, five during the ascending portion of the SE, one at the SE, and another five during the descending portion of the SE. Because of the short relaxation times at ultra-high field strength, these last images acquired during the descending portion of the SE had a significantly lower SNR than those acquired during the FID, and were therefore not used to obtain a second $R_2^*$ measurement.

4.2.4 Results and Discussion

Fig. 4.12 shows a coronal SE image of the brain of a postmortem human subject and the corresponding $T_2$, $T_2'$, and $T_2^*$ maps obtained with the GESFIDE method. Also shown are a corresponding $T_2$ map obtained with the GESSE method (discussed in section 4.3) using the same data\textsuperscript{1}, as well as a flip angle and receive sensitivity map.

These results show that the $T_2$, $T_2'$, and $T_2^*$ maps obtained with the GESFIDE method are all fairly noisy, and a comparison between the GESFIDE and GESSE $T_2$ maps shows that the GESFIDE $T_2$ values are generally lower than the GESSE $T_2$ values. This is not unexpected because the $T_2^*$ map is essentially obtained from a conventional 2D multi-echo GE sequence, and, as clearly shown in section 4.1, such measurements are severely affected by $B_0$ inhomogeneity at ultra-high field strength, so that the transverse magnetization during the FID cannot be charac-

\textsuperscript{1}The GESSE $T_2$ map was computed from the three pairs of GE images acquired the furthest away from the SE. Note that unlike in section 4.3, the images were not filtered before computation of the $T_2$ map.
**Figure 4.12:** (See figure on next page.) Coronal SE image (TE 58 ms) (a) of the brain of an 84-year-old male postmortem human subject with Alzheimer’s disease, and corresponding $T_2$ (b), $T_2'$ (c), and $T_2^*$ (d) maps (in ms) obtained with the GESFIDE method. Note that the scale for the $T_2^*$ map is different than the one for the $T_2$ and $T_2'$ maps. Also shown are a corresponding $T_2$ map (in ms) obtained with the GESSE method using the same data (e), as well as a flip angle (in degrees) (f) and receive sensitivity (in %) (g) map.
Figure 4.12: See caption on previous page.
terized by a single exponential with rate constant $R_2^*$ (see Eq. (4.5)), resulting in inaccurate $T_2^*$ measurements. Furthermore, it can be assumed that the transverse magnetization during the ascending portion of the SE is also affected by $B_0$ inhomogeneity at ultra-high field strength, so that it cannot be characterized by a single exponential with rate constant $R_2^-$ (see Eq. (4.6)), resulting in inaccurate $R_2^-$ measurements as well (see further discussion in section 4.3.2). Consequently, the GESFIDE $T_2$ and $T_2'$ maps, which are computed from the $R_2^*$ and $R_2^-$ maps (see Eqs. (4.7) and (4.8)), are also inaccurate.

In addition, the shorter $T_2$ values at ultra-high field strength require a relatively short TE to be used to obtain adequate SNR. This in turn limits the number of echoes that can be acquired for a given bandwidth and matrix size, thereby reducing the accuracy of the relaxation time measurements. Interleaved acquisitions, such as in the Interleaved Multiple-Acquisition GESFIDE (IMA-GESFIDE) method [150], could be used to increase the number of echoes while keeping the same TE, bandwidth, and matrix size, however at the expense of additional scan time. Nevertheless, parallel imaging techniques such as SENSE or SMASH could be used to offset that increase in scan time. However, acquiring a larger number of echoes will not correct for the artifacts due to the severe $B_0$ inhomogeneity at ultra-high field strength.

Our preliminary studies clearly show that the GESFIDE method is not suitable for relaxation time measurements at ultra-high field strength. In the next section, we evaluate the performance of another method for $T_2$ measurements that is related to the GESFIDE method.
4.3 $T_2$ Measurements Using GESSE

4.3.1 Introduction

As discussed in section 4.2.1, knowledge of $T_2$ relaxation times at ultra-high field strength is needed for optimizing acquisition parameters for $T_2$-weighted imaging and understanding relaxation mechanisms. Since standard $T_2$ measurements at ultra-high field strength are affected by severe $B_1$ inhomogeneity, we initially implemented the GESFIDE method for $T_2$, $T_2'$, and $T_2^*$ measurements that is insensitive to RF pulse imperfections (see section 4.2). However, our studies showed that the measurements are affected by severe $B_0$ inhomogeneity at ultra-high field strength.

Yablonskiy et al. [151] developed a method for $T_2$ measurements called Gradient Echo Sampling of the Spin Echo (GESSE) that was shown to be insensitive to $B_1$ inhomogeneity, slice profile imperfections, and $B_0$ inhomogeneity at 1.5 T. In this section, we evaluate the performance of this method for $T_2$ measurements at ultra-high field strength, and compare GESSE and conventional Hahn SE $T_2$ measurements in phantoms as well as postmortem and in vivo human brains [85]. The $B_1$ inhomogeneity was experimentally mapped to quantify the $B_1$ sensitivity of both methods.

4.3.2 Theory

Description of the GESSE Method

The GESSE method uses a sequence very similar to the one used by the GESFIDE method (see section 4.2), except that instead of sampling the FID and ascending
portion of a Hahn SE with a train of GE images, both ascending and descending portions of the SE are sampled symmetrically around the SE. Unlike in the GESFIDE method, the images are not separated by any RF pulses, which makes the GESSE method theoretically insensitive to slice profile imperfections.

The computation of the $T_2$ map is, however, fundamentally different in both methods. In the GESFIDE method, it is assumed that the reversible transverse relaxation can be characterized by a single exponential with relaxation rate $R'_2$ (see section 4.2.2). However, this assumption is not always valid. For example, in a constant magnetic field gradient, the signal decay is weighted by a sinc function, whereas in the presence of multiple sources of magnetic field inhomogeneities, the signal behaves as a Gaussian function in the vicinity of the SE and then decays exponentially further away. In the GESSE method, no assumptions are made about the signal behavior in the presence of static magnetic field inhomogeneities, which makes the method theoretically insensitive to $B_0$ inhomogeneity.

The reversible transverse relaxation due to macroscopic magnetic field inhomogeneities is characterized by a function $f(t)$, which is assumed to be symmetric around the SE, i.e.,

$$f(\text{TE} - t) = f(\text{TE} + t),$$

(4.10)

because of the nature of the refocusing RF pulse. However, no further assumptions are made about its exact shape, which depends on the magnetic field distribution in a voxel. The transverse magnetization during the ascending and descending portions of the SE can then be expressed as:

$$S_-(t) = S_0 \exp(-R_2 t) f(\text{TE} - t),$$

for $\text{TE}/2 < t < \text{TE}$

(4.11)

$$S_+(t) = S_0 \exp(-R_2 t) f(\text{TE} + t),$$

for $t > \text{TE}$.  

(4.12)
Note that in the special case where \( f(t) = \exp(-R_2' t) \), Eq. (4.11) becomes Eq. (4.2), as assumed in the GESFIDE method. Using Eqs. (4.10) to (4.12), it is straightforward to show that a \( T_2 \) map can be computed from each pair of GE images acquired symmetrically around the SE at TE \( \pm n\Delta TE \) as follows:

\[
T_2(n) = 2n\Delta TE \left\{ \ln \left[ \frac{S_-(TE - n\Delta TE)}{S_+(TE + n\Delta TE)} \right] \right\}^{-1}, \quad n = 1, \ldots, N. \tag{4.13}
\]

The resulting \( T_2(n) \) maps can then be averaged to yield a final \( T_2 \) map.

**Theoretical Analysis of the Accuracy of the \( T_2 \) Measurements**

By introducing the shorthand notations \( S_-(n) \equiv S_-(TE - n\Delta TE) \) and \( S_+(n) \equiv S_+(TE + n\Delta TE) \), and denoting the standard deviation of \( S_-(n) \) and \( S_+(n) \) by \( \sigma_-(n) \) and \( \sigma_+(n) \) respectively, the error on \( T_2(n) \) can be computed pixel-by-pixel using the well-known formula for error propagation:

\[
\sigma_{T_2}^2(n) = \left[ \frac{\partial T_2(n)}{\partial S_-(n)} \right]^2 \sigma_-(n)^2 + \left[ \frac{\partial T_2(n)}{\partial S_+(n)} \right]^2 \sigma_+(n)^2,
\]

resulting in the following expression:

\[
\sigma_{T_2}(n) = \frac{T_2^2(n)}{2n\Delta TE} \sqrt{\frac{\sigma_-(n)^2}{S_-(n)^2} + \frac{\sigma_+(n)^2}{S_+(n)^2}}. \tag{4.15}
\]

Note that \( \sigma_{T_2}(n) \) is inversely proportional to \( n\Delta TE \). Indeed, as the echoes used for the computation of \( T_2 \) get closer to the SE, the ratio \( S_-(n)/S_+(n) \) becomes closer to 1, and its logarithm closer to 0, thus resulting in less accurate \( T_2 \) measurements (see Eq. (4.13)). Furthermore, \( \sigma_{T_2}(n) \) also depends indirectly on \( n\Delta TE \) through \( \sigma_-(n)/S_-(n) \) and \( \sigma_+(n)/S_+(n) \), both of which increase with increasing \( n\Delta TE \),
although the exact dependence depends on the shape of the function $f(t)$. In other words, as the echoes used for the computation of $T_2$ get further apart from the SE, the SNR of both images decreases, again resulting in less accurate $T_2$ measurements. This trade-off between long and short $n\Delta TE$ values implies that the optimal value should be in the intermediate range.

In addition, $\sigma_{T_2}(n)$ also depends indirectly on TE through $\sigma_-(n)/S_-(n)$ and $\sigma_+(n)/S_+(n)$, both of which increase with increasing TE due to the $T_2$ decay. This suggests that a relatively short TE should be used, although it should be long enough to allow acquisition of echoes with intermediate $n\Delta TE$ values. Yablonskiy et al. [151] found that the most accurate $T_2$ measurements are obtained with a TE on the order of the $T_2$ of the tissue of interest, and that only echoes acquired with $n\Delta TE > T_2/4$ should be used for the computation of $T_2$.

When more than one pair of echoes are used for the computation of $T_2$, the error in the final $T_2$ map is computed pixel-by-pixel as follows:

$$\sigma_{T_2} = \frac{1}{N} \sqrt{\sum_{n=1}^{N} \sigma_{T_2}^2(n)}, \quad (4.16)$$

where $N$ is the number of pairs of echoes used. The accuracy of the $T_2$ measurements should thus improve when an increasing number of echoes are used, as long as these echoes are acquired with an intermediate $n\Delta TE$. However, the number of echoes that can be acquired is limited by the choice of TE and $\Delta TE$, and further depends on the bandwidth and matrix size, so that an optimal trade-off between all of these parameters needs to be found to obtain the most accurate $T_2$ measurements.
4.3.3 Methods

All studies were performed on the 8 T human whole-body MRI system, using TEM RF coils with sixteen struts and one or four excitation ports for the phantom and human studies, respectively.

First, a “nominal” flip angle was defined as the average flip angle in a 1 cm³ region of interest (located in the hippocampus for the human studies), and the transmit power level resulting in a nominal flip angle of 90° was determined using a voxel-selective stimulated echo sequence (see section 2.3). This reference was then used to set the transmit power level corresponding to a chosen nominal flip angle in subsequent acquisitions.

Our studies can be divided into three parts. We first evaluated the accuracy of GESSE $T_2$ measurements in postmortem human subjects. We then assessed the sensitivity to $B_1$ inhomogeneity of both Hahn SE and GESSE $T_2$ measurements in homogeneous phantoms. Finally, we compared Hahn SE and GESSE $T_2$ measurements in the brain of postmortem human subjects and healthy volunteers.

**Evaluation of the Accuracy of GESSE $T_2$ Measurements**

In a first study, we evaluated the accuracy of GESSE $T_2$ measurements as a function of $n\Delta TE$, $N$, and TE in a postmortem unembalmed human subject (84-year-old male with Alzheimer’s disease). Three GESSE scans were acquired on the same slice of the brain using various TE and number of echoes, namely, TE 58, 50, and 41 ms with 11, 9, and 7 echoes (i.e., 5, 4, and 3 pairs of echoes around the SE and one at the SE), respectively. Other parameters were as follows: 8 ms sinc3 RF pulse, TR 1500 ms, $\Delta$TE 4.3 ms, BW 100 kHz, FOV 16 cm, MTX 256×256,
one 3 mm thick slice, coronal acquisition plane, NEX 1, and nominal flip angle 90°/180°. In this and all subsequent studies, all echoes were acquired using read-
out gradients of same polarity to avoid misregistration errors due to susceptibility
artifacts, gradient imbalance, and/or eddy current effects. Minimum gradient
ramp times and durations as well as maximum gradient strength were used whenever
possible to obtain the shortest ΔTE achievable in order to maximize the
number of echoes and thus improve the accuracy of the $T_2$ measurements.

For each of the three scans, a $T_2$ map was computed from each pair of echoes
acquired symmetrically around the SE using Eq. (4.13), resulting in a total of
12 maps with various $n\Delta$TE and TE. Note that in order to reduce the noise in
the $T_2$ maps, the GE images were first filtered with a 5×5 Hamming filter before
computation of $T_2$. In addition, for each of the three scans, $T_2$ maps computed
from different pairs of echoes were averaged to yield additional $T_2$ maps with
various $n\Delta$TE, N, and TE.

For each of the $T_2$ maps, the mean $T_2$ and standard deviation $s_{T_2}$ were measured
in different ROIs. The corresponding error $\sigma_{T_2}$ was first computed pixel-by-pixel
using Eq. (4.15), then Eq. (4.16) if $N > 1$, and finally the error for each ROI was
computed using the following equation:

$$
\sigma_{T_2}^{\text{ROI}} = \frac{1}{\text{number of pixels}} \sqrt{\sum_{\text{ROI}} \sigma_{T_2}^2}.
$$

(4.17)

It is important to note that $s_{T_2}$ and $\sigma_{T_2}$ are not equivalent, since the former is a
measure of the spatial variation of $T_2$ values in an ROI, whereas the latter is a
measure of the error propagation in the computation of $T_2$ from the GE images,
\textit{i.e.}, a measure of the accuracy of the $T_2$ measurements. Since $s_{T_2}$ also takes into
account intrinsic differences in $T_2$ between different pixels as well as errors due to partial volume effects, motion artifacts, or system instability, it is typically larger than $\sigma_{T_2}$.

In Eq. (4.15), the variables $\sigma_-(n)$ and $\sigma_+(n)$ at a given pixel should be computed as the standard deviation of $S_-(n)$ and $S_+(n)$ in a small region around that pixel, respectively. However, for these human studies, doing so would also take into account intrinsic tissue variability and partial volume effects, and thus result in an overestimation of $\sigma_-(n)$ and $\sigma_+(n)$. We therefore used the standard deviation of the signal intensity in air as an estimate for both $\sigma_-(n)$ and $\sigma_+(n)$. This, on the other hand, may result in an underestimation of $\sigma_-(n)$ and $\sigma_+(n)$, and consequently of $\sigma_{T_2}(n)$, because the noise in a sample may be larger than the noise in air, particularly at ultra-high field strength.

In a second study, we evaluated the reproducibility of the GESSE $T_2$ measurements by performing three identical measurements on a postmortem unembalmed human subject (73-year-old male with Alzheimer’s disease) using the parameters described in the second column of Table 4.7a and a coronal acquisition plane. For each of the three $T_2$ maps, the mean $T_2$ and standard deviation $s_{T_2}$ were measured in different ROIs, and the corresponding error $\sigma_{T_2}$ computed using Eqs. (4.15) and (4.17). Again, the standard deviation of the signal intensity in air was used for $\sigma_-(n)$ and $\sigma_+(n)$ in Eq. (4.15), which may result in an underestimation of $\sigma_{T_2}$.

In addition, the standard deviation of $T_2$ over the three measurements ($\hat{\sigma}_{T_2}$) was measured pixel-by-pixel, and then computed for each ROI using the following equation:

$$\hat{\sigma}_{T_2}(ROI) = \frac{1}{\text{number of pixels}} \sqrt{\sum_{ROI} \hat{\sigma}^2_{T_2}}.$$

(4.18)
Note that both of these studies should preferably have been performed in a homogeneous phantom. However, because of the difficulty in preparing a phantom with $T_2$ and $T'_2$ values close to that of tissue, we performed these studies in postmortem human subjects.

**Evaluation of the Sensitivity to $B_1$ Inhomogeneity of Hahn SE and GESSE $T_2$ Measurements in a Phantom**

To quantify the sensitivity to $B_1$ inhomogeneity of both Hahn SE and GESSE $T_2$ measurements, we studied a 1.5 L homogeneous phantom (4% agarose, 1.3 mM CuSO$_4$, and 0.125 M NaCl (for an appropriate loading of the RF coil)) with a $T_1/T_2$ ratio ($\approx 630/35$ ms) close to that of tissue.

For the Hahn SE method, four single-echo Hahn SE images were acquired with different TEs, and a $T_2$ map computed by fitting a monoexponential decay pixel-by-pixel to these images. The acquisition parameters are shown in Table 4.6a. For comparison with the GESSE $T_2$ maps, the SE images were also filtered with a 5×5 Hamming filter before computation of the $T_2$ map.

For the GESSE method, the TE was chosen to be on the order of the $T_2$ of the phantom, based on preliminary measurements. With the chosen TE, bandwidth, and matrix size, as well as the limitations imposed on $n\Delta$TE (see section 4.3.2), only one pair of GE images was acquired symmetrically around the SE at $\text{TE} \pm \Delta\text{TE}$ with $\Delta\text{TE} = \text{TE}/4 \approx T_2/4$.

To quantify the $B_1$ inhomogeneity, maps of the local flip angle and receive sensitivity were experimentally measured from two series of GE images acquired with $\text{TR} \gg T_1$ and nominal flip angles $\alpha_0$ and $2\alpha_0$ (see section 2.3.2).
<table>
<thead>
<tr>
<th>(a)</th>
<th>Hahn SE $T_2$ measurements</th>
<th>GESSE $T_2$ measurements</th>
<th>$B_1$ mapping</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF pulse length [ms]</td>
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<td>8</td>
<td>8</td>
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<td>RF pulse shape</td>
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<td>sinc3</td>
<td>sinc3</td>
</tr>
<tr>
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<td>3000</td>
<td>3000</td>
<td>3000</td>
</tr>
<tr>
<td>TE [ms]</td>
<td>20, 40, 70, 110</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>$\Delta$TE [ms]</td>
<td>–</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>BW [kHz]</td>
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<td>50</td>
</tr>
<tr>
<td>FOV [cm]</td>
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<td>18</td>
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</tr>
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<td>256×128</td>
<td>128×64</td>
</tr>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ST [mm]</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NEX</td>
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<td>100</td>
<td>1</td>
</tr>
<tr>
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<td>90/180</td>
<td>90/180</td>
<td>60 &amp; 120</td>
</tr>
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<table>
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<th>$B_1$ mapping</th>
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<td>sinc3</td>
</tr>
<tr>
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<td>2000</td>
<td>4000</td>
</tr>
<tr>
<td>TE [ms]</td>
<td>21, 42, 84, 169, 338</td>
<td>200</td>
<td>7</td>
</tr>
<tr>
<td>$\Delta$TE [ms]</td>
<td>–</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>BW [kHz]</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>FOV [cm]</td>
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<td>12</td>
<td>12</td>
</tr>
<tr>
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<td>256×192</td>
<td>256×128</td>
</tr>
<tr>
<td>number of slices</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ST [mm]</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NEX</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>nominal flip angle [°]</td>
<td>90/180</td>
<td>90/180</td>
<td>60 &amp; 120</td>
</tr>
<tr>
<td>scan time [min:s]</td>
<td>5×6:24</td>
<td>6:24</td>
<td>2×8:32</td>
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</tbody>
</table>

**Table 4.6:** Acquisition parameters for the Hahn SE and GESSE $T_2$ measurements and $B_1$ mapping for the agarose (a) and gelatin (b) phantom studies.
Note that because of shim and gradient instability problems on the 8 T MRI system and/or motion, resulting in ghosting on the GESSE images and severe banding artifacts on the $T_2$ maps, the GESSE $T_2$ measurements were performed with NEX 100. On the other hand, the Hahn SE $T_2$ measurements, which were based on single-echo sequences and were significantly less affected by such artifacts, were performed using only NEX 1. For a fair comparison between the GESSE and Hahn SE $T_2$ maps, the GESSE images were first corrected by adding zero-mean Gaussian noise to reduce the SNR by a factor $\sqrt{100} = 10$ before computation of the $T_2$ map.

We also studied a 2 L homogeneous phantom (4% gelatin, 1.3 mM CuSO$_4$, and 0.125 M NaCl), which, unlike the agarose phantom, is completely filled with the gel, thus reducing any possibility of motion artifacts. The acquisition parameters are shown in Table 4.6b. For the GESSE method, three pairs of GE images were acquired symmetrically around the SE, and the pair of echoes acquired furthest away from the SE was used for the computation of the $T_2$ map. Since this phantom was significantly less affected by the ghosting and banding artifacts, a NEX of 1 was used for all methods.

**Comparison Between Hahn SE and GESSE $T_2$ Measurements in the Human Brain**

We also compared Hahn SE and GESSE $T_2$ measurements on 5 postmortem un-embalmed human subjects (2 male, 3 female, 57 to 84 years old) with various pathologies, as well as 4 healthy volunteers (1 male, 3 female, 20 to 49 years old) who gave informed consent to the experimental protocol approved by our Institutional Review Board. For one of the volunteers, only two Hahn SE images were
acquired because the subject could not sustain the long scan time, and for two other volunteers, subject motion resulted in artifacts in the Hahn SE $T_2$ map.

Hahn SE and GESSE $T_2$ measurements as well as $B_1$ mapping were performed as in the phantom study, but using the acquisition parameters shown in Table 4.7. The TE was chosen to be on the order of the $T_2$ of brain tissue, based on preliminary measurements. With the chosen TE, bandwidth, and matrix size, as well as the limitations imposed on $n\Delta TE$, only one pair of GE images was acquired symmetrically around the SE at $\text{TE} \pm \Delta \text{TE}$ with $\Delta \text{TE} \simeq \text{TE}/4$. $T_2$ maps were acquired on different coronal and axial slices throughout the brain. Note that since the ghosting and artifacts due to shim and gradient instability were less pronounced in these human studies as compared to the phantom study, the same NEX was used for both Hahn SE and GESSE $T_2$ measurements.

4.3.4 Results

Evaluation of the Accuracy of GESSE $T_2$ Measurements

First, to evaluate the influence of $n\Delta TE$ on the accuracy of the $T_2$ measurements for a fixed $N$ and TE, we compared the $T_2$ maps computed from each of the five pairs of echoes acquired symmetrically around the SE for the scan acquired with TE 58 ms. The results are shown in Table 4.8. Note that the error $\sigma_{T_2}$ in this and all subsequent tables may be artificially low, as mentioned in section 4.3.3. Also note that a SE image and corresponding GESSE $T_2$ map ($N = 3$, $n\Delta TE = 21.5, 17.2$, and 12.9 ms), flip angle map, and receive sensitivity map are shown in Figs. 4.12a,e,f,g respectively. As the echoes used for the computation of $T_2$ get closer to the SE, both $s_{T_2}$ and $\sigma_{T_2}$ increase significantly, whereas as these echoes
<table>
<thead>
<tr>
<th></th>
<th>Hahn SE $T_2$ measurements</th>
<th>GESSE $T_2$ measurements</th>
<th>$B_1$ mapping</th>
</tr>
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<tr>
<td>RF pulse length [ms]</td>
<td>8</td>
<td>8</td>
<td>8</td>
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<tr>
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<td>sinc3</td>
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<td>1500</td>
<td>5000</td>
</tr>
<tr>
<td>TE [ms]</td>
<td>20, 50, 90, 135</td>
<td>50</td>
<td>7</td>
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<tr>
<td>$\Delta$TE [ms]</td>
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<td>13</td>
<td>–</td>
</tr>
<tr>
<td>BW [kHz]</td>
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<td>50</td>
<td>50</td>
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<tr>
<td>FOV [cm]</td>
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</tr>
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<td>NEX</td>
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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>nominal flip angle [$^\circ$]</td>
<td>90/180</td>
<td>90/180</td>
<td>60 &amp; 120</td>
</tr>
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<td>19:12</td>
<td>2×10:40</td>
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<th></th>
<th>Hahn SE $T_2$ measurements</th>
<th>GESSE $T_2$ measurements</th>
<th>$B_1$ mapping</th>
</tr>
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<td>RF pulse shape</td>
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<td>1500</td>
<td>4000</td>
</tr>
<tr>
<td>TE [ms]</td>
<td>20, 50, 90, 135</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>$\Delta$TE [ms]</td>
<td>–</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>BW [kHz]</td>
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<td>50</td>
<td>50</td>
</tr>
<tr>
<td>FOV [cm]</td>
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<td>16</td>
<td>16</td>
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<td>512×256</td>
<td>256×64</td>
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<td>3</td>
<td>3</td>
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<tr>
<td>NEX</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>nominal flip angle [$^\circ$]</td>
<td>90/180</td>
<td>90/180</td>
<td>60 &amp; 120</td>
</tr>
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<td>total scan time [min:s]</td>
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<td>6:24</td>
<td>2×4:16</td>
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</table>

**Table 4.7:** Acquisition parameters for the Hahn SE and GESSE $T_2$ measurements and $B_1$ mapping for the postmortem (a) and *in vivo* (b) human studies.
get further away from the SE, both $s_{T_2}$ and $\sigma_{T_2}$ also tend to increase in some of the ROIs, although this effect is not very significant with the range of $n\Delta TE$ used in this study. Both of these effects are predicted by the theory (see section 4.3.2).

From these results, we can conclude that echoes acquired with $n\Delta TE < T_2/4$ should not be used for the computation of the $T_2$ maps, thus confirming the finding by Yablonskiy et al. [151].

Second, to evaluate the influence of $N$ on the accuracy of the $T_2$ measurements for a fixed TE, we compared the $T_2$ maps computed from one, two, and three pairs of echoes for the scan acquired with TE 58 ms. The results are shown in Table 4.9. As expected, $\sigma_{T_2}$ and $s_{T_2}$ generally decrease, i.e., the $T_2$ measurements become more accurate, when an increasing number of echoes are used for the computation of $T_2$ (see section 4.3.2).

Third, to evaluate the influence of TE on the accuracy of the $T_2$ measurements for a fixed $n\Delta TE$ and $N$, we compared the $T_2$ maps computed from one pair of echoes acquired symmetrically around the SE at the same $n\Delta TE$ for each of the three scans acquired with different TEs. The results are shown in Table 4.10. As expected, $\sigma_{T_2}$ consistently decreases with a decreasing TE (see section 4.3.2). However, $s_{T_2}$ does not systematically decrease with a decreasing TE, so it cannot necessarily be concluded that the $T_2$ measurements become more accurate.

Finally, since there is a trade-off between increasing $N$ and decreasing TE, we compared $T_2$ maps obtained when simultaneously varying both parameters. The results are shown in Table 4.11. While $\sigma_{T_2}$ remains relatively constant, $s_{T_2}$ does not show a systematic trend, making it difficult to reach a conclusion regarding the accuracy of the $T_2$ measurements.
<table>
<thead>
<tr>
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<th>58</th>
<th>58</th>
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<tbody>
<tr>
<td>N</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>nΔTE [ms]</td>
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<td>17.2</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>$T_2$</td>
<td>$s_{T_2}$</td>
<td>$\sigma_{T_2}$</td>
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<tr>
<td>right SFG WM</td>
<td>41.1</td>
<td>5.0</td>
<td>1.3</td>
</tr>
<tr>
<td>right MFG WM</td>
<td>34.7</td>
<td>4.3</td>
<td>0.4</td>
</tr>
<tr>
<td>right IC (WM)</td>
<td>35.3</td>
<td>6.2</td>
<td>0.4</td>
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<td>nΔTE [ms]</td>
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<td>4.3</td>
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</tr>
<tr>
<td>right MFG WM</td>
<td>31.9</td>
<td>5.5</td>
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<tr>
<td>right IC (WM)</td>
<td>49.6</td>
<td>19.4</td>
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**Table 4.8:** $T_2$ (mean), $s_{T_2}$ (standard deviation), and $\sigma_{T_2}$ (error) (in ms) in different ROIs of the brain of an 84-year-old male postmortem human subject with Alzheimer’s disease for a fixed TE and N, and various nΔTE (SFG = superior frontal gyrus, MFG = middle frontal gyrus, IC = internal capsule).
<table>
<thead>
<tr>
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<td>3</td>
</tr>
<tr>
<td>n\Delta TE [ms]</td>
<td>12.9</td>
<td>17.2, 12.9</td>
<td>21.5, 17.2, 12.9</td>
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</tbody>
</table>

<table>
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<th></th>
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<th>$s_{T_2}$</th>
<th>$\sigma_{T_2}$</th>
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<th>$\sigma_{T_2}$</th>
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<td>1.0</td>
<td>33.9</td>
<td>2.9</td>
<td>0.7</td>
<td>36.3</td>
<td>2.4</td>
<td>0.6</td>
</tr>
<tr>
<td>right MFG WM</td>
<td>33.4</td>
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<td>33.9</td>
<td>4.2</td>
<td>0.3</td>
<td>34.2</td>
<td>3.5</td>
<td>0.2</td>
</tr>
<tr>
<td>right IC (WM)</td>
<td>32.9</td>
<td>4.6</td>
<td>0.4</td>
<td>33.7</td>
<td>5.0</td>
<td>0.3</td>
<td>34.2</td>
<td>5.0</td>
<td>0.2</td>
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</table>

**Table 4.9:** $T_2$ (mean), $s_{T_2}$ (standard deviation), and $\sigma_{T_2}$ (error) (in ms) in the same ROIs as in Table 4.8 for a fixed TE and various $N$ and $n\Delta TE$ (SFG = superior frontal gyrus, MFG = middle frontal gyrus, IC = internal capsule).

<table>
<thead>
<tr>
<th>TE [ms]</th>
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<th>41</th>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>n\Delta TE [ms]</td>
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<td>12.9</td>
<td>12.9</td>
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</table>

<table>
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<th>$s_{T_2}$</th>
<th>$\sigma_{T_2}$</th>
<th>$T_2$</th>
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<th>$\sigma_{T_2}$</th>
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<th>$s_{T_2}$</th>
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<tr>
<td>right SFG WM</td>
<td>33.0</td>
<td>3.6</td>
<td>1.0</td>
<td>37.3</td>
<td>5.1</td>
<td>0.9</td>
<td>39.6</td>
<td>4.9</td>
<td>0.8</td>
</tr>
<tr>
<td>right MFG WM</td>
<td>33.4</td>
<td>5.1</td>
<td>0.4</td>
<td>33.1</td>
<td>3.8</td>
<td>0.3</td>
<td>32.4</td>
<td>3.8</td>
<td>0.2</td>
</tr>
<tr>
<td>right IC (WM)</td>
<td>32.9</td>
<td>4.6</td>
<td>0.4</td>
<td>39.2</td>
<td>6.2</td>
<td>0.3</td>
<td>36.9</td>
<td>5.1</td>
<td>0.2</td>
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</table>

**Table 4.10:** $T_2$ (mean), $s_{T_2}$ (standard deviation), and $\sigma_{T_2}$ (error) (in ms) in the same ROIs as in Table 4.8 for various TE$s$ and a fixed $N$ and $n\Delta TE$ (SFG = superior frontal gyrus, MFG = middle frontal gyrus, IC = internal capsule).
<table>
<thead>
<tr>
<th>TE [ms]</th>
<th>58</th>
<th>50</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>$\Delta$TE [ms]</td>
<td>21.5, 17.2, 12.9</td>
<td>17.2, 12.9</td>
<td>12.9</td>
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<tr>
<td>$T_2$</td>
<td>$s_{T_2}$</td>
<td>$\sigma_{T_2}$</td>
<td>$T_2$</td>
</tr>
<tr>
<td>right SFG WM</td>
<td>36.3</td>
<td>2.4</td>
<td>0.6</td>
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<tr>
<td>right MFG WM</td>
<td>34.2</td>
<td>3.5</td>
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<tr>
<td>right IC (WM)</td>
<td>34.2</td>
<td>5.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Table 4.11:** $T_2$ (mean), $s_{T_2}$ (standard deviation), and $\sigma_{T_2}$ (error) (in ms) in the same ROIs as in Table 4.8 for various TEs, N, and $\Delta$TE (SFG = superior frontal gyrus, MFG = middle frontal gyrus, IC = internal capsule).

The results of the repeat study are shown in Table 4.12. Note that a SE image and corresponding GESSE $T_2$, flip angle, and receive sensitivity maps are shown in Figs. 4.15a,c,d,e respectively. The $T_2$ variation between the three measurements is generally smaller than the standard deviation $s_{T_2}$. On the other hand, the error $\sigma_{T_2}$ is generally smaller than the standard deviation over the three measurements $\hat{\sigma}_{T_2}$. However, $\sigma_{T_2}$ may be artificially low, as mentioned in section 4.3.3, again making it difficult to reach a conclusion regarding the reproducibility of the $T_2$ measurements.

It is important to note that the validity of both of these postmortem human studies is somewhat limited because the error $\sigma_{T_2}$ may be artificially low. Similar studies in a homogeneous phantom are needed to better evaluate the accuracy of the GESSE $T_2$ measurements.
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**Table 4.12:** $T_2$ (mean), $s_{T_2}$ (standard deviation), and $\sigma_{T_2}$ (error) (in ms) in different ROIs of the brain of an 73-year-old male postmortem human subject with Alzheimer’s disease for three identical measurements, and corresponding $\hat{\sigma}_{T_2}$ (standard deviation of $T_2$ over the three measurements) (in ms) (SFG = superior frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, STG = superior temporal gyrus, SN = substantia nigra, GP = globus pallidus).
Evaluation of the Sensitivity to $B_1$ Inhomogeneity of Hahn SE and GESSE $T_2$ Measurements in a Phantom

Fig. 4.13 shows the Hahn SE and GESSE $T_2$ maps of the agarose phantom, the corresponding flip angle and receive sensitivity maps, as well as plots of the Hahn SE and GESSE $T_2$ values as a function of the flip angle. The GESSE $T_2$ map (Fig. 4.13b) is more homogeneous than the Hahn SE $T_2$ map (Fig. 4.13a), which is affected by the substantial variations in flip angle (0° to 140°) (Fig. 4.13c) and receive sensitivity (Fig. 4.13d) across the slice. Note that the banding artifacts in the GESSE $T_2$ map can be attributed to shim and gradient instability. The Hahn SE $T_2$ values tend to increase as the flip angle deviates from 90° (Fig. 4.13e), whereas the GESSE $T_2$ values are independent of the flip angle in the range evaluated (Fig. 4.13f). Both Hahn SE and GESSE $T_2$ measurements become noisier as the flip angle decreases. The Hahn SE $T_2$ values are generally higher than the GESSE $T_2$ values, even at a flip angle of 90°, where the Hahn SE $T_2$ is 37.9 ± 1.6 ms (mean ± standard deviation), whereas the GESSE $T_2$ is 34.6 ± 1.2 ms.

Fig. 4.14 shows the Hahn SE and GESSE $T_2$ maps of the gelatin phantom, the corresponding flip angle and receive sensitivity maps, as well as plots of the Hahn SE and GESSE $T_2$ values as a function of the flip angle. Unlike for the agarose phantom, the Hahn SE $T_2$ map (Fig. 4.13a) is more homogeneous than the GESSE $T_2$ map (Fig. 4.13b), which is affected by the substantial variations in flip angle (Fig. 4.13c) and receive sensitivity (Fig. 4.13d) across the slice. The GESSE $T_2$ values tend to increase or decrease as the flip angle deviates from 90° (Fig. 4.13f), whereas the Hahn SE $T_2$ values are independent of the flip angle up to 120° (Fig. 4.13e). The Hahn SE $T_2$ value at a flip angle of 90° is 272 ± 8 ms
**Figure 4.13:** Hahn SE (a) and GESSE (b) $T_2$ maps (in ms) of the agarose phantom, corresponding flip angle (in degrees) (c) and receive sensitivity (in %) (d) maps, as well as plots of the Hahn SE (e) and GESSE (f) $T_2$ values (in ms) as a function of the flip angle (in degrees). On both plots, pixels with a receive sensitivity lower than 25% and therefore excessive noise were excluded. Note that the GESSE $T_2$ map is more homogeneous than the Hahn SE $T_2$ map and that Hahn SE $T_2$ values tend to increase as the flip angle deviates from 90°, whereas the GESSE $T_2$ values are independent of the flip angle.
(mean ± standard deviation), whereas the GESSE $T_2$ value at a flip angle of 90° is 195 ± 34 ms.

This unexpected behavior is the opposite of what is observed in the agarose phantom and is not fully understood at this time. Potential causes include stimulated or higher order echoes, spatial variations of the phase of the $B_1$ field, asymmetry of the function $f$ around the SE (see Eq. (4.10)), or chemical shift effects that could be different between the agarose and gelatin phantoms. Further studies are needed to address this issue.

**Comparison Between Hahn SE and GESSE $T_2$ Measurements in the Human Brain**

Figs. 4.15 to 4.20 show the results for three representative postmortem human subjects and two representative healthy volunteers. The results for the other postmortem studies were affected by severe brain atrophy as well as overflipping of the flip angles in the center of the brain, resulting in severe signal loss in that region (such as in Fig. 2.16), whereas the results for the other *in vivo* study was affected by severe motion artifacts.

Shown in each figure are a SE image and the corresponding Hahn SE and GESSE $T_2$, flip angle, and receive sensitivity maps. In the central region, where the flip angle is significantly higher than 90°, Hahn SE $T_2$ values are artificially high, as observed in the phantom. In regions where the flip angle and/or receive sensitivity are very low, both Hahn SE and GESSE methods become inaccurate and Hahn SE $T_2$ values are again high. Note that due to differences in subject anatomy and RF coil tuning (see section 2.3), the $B_1$ inhomogeneity and resulting artifacts in the Hahn SE $T_2$ map are more severe on the left side for some subjects,
**Figure 4.14:** Hahn SE (a) and GESSE (b) $T_2$ maps (in ms) of the gelatin phantom, corresponding flip angle (in degrees) (c) and receive sensitivity (in %) (d) maps, as well as plots of the Hahn SE (e) and GESSE (f) $T_2$ values (in ms) as a function of the flip angle (in degrees). On both plots, pixels with a receive sensitivity lower than 25% and therefore excessive noise were excluded. Note that the Hahn SE $T_2$ map is more homogeneous than the GESSE $T_2$ map and that GESSE $T_2$ values tend to increase or decrease as the flip angle deviates from 90°, whereas the Hahn SE $T_2$ values are independent of the flip angle up to 120°.
**Figure 4.15:** (See figure on next page.) Coronal Hahn SE image (TE 50 ms) (**a**) of the brain of a 73-year-old male postmortem human subject with Alzheimer’s disease, and corresponding Hahn SE (**b**) and GESSE (**c**) $T_2$ maps (in ms), as well as flip angle (in degrees) (**d**) and receive sensitivity (in %) (**e**) maps. Note that in the central region where the flip angle is significantly higher than 90°, and in the left temporal and inferior frontal lobes where the flip angle and receive sensitivity are very low, Hahn SE $T_2$ values are artificially high. The arrow pointing to the top shows the substantia nigra and the arrow pointing to the left shows the putamen (most lateral) and globus pallidus (most medial), all of which have lower $T_2$ values on the GESSE $T_2$ map, but are not seen on the Hahn SE $T_2$ map. This is the same subject as in Fig. 4.7.
Figure 4.15: See caption on previous page.
**Figure 4.16**: Coronal Hahn SE image (TE 50 ms) (a) of the brain of a 72-year-old female postmortem human subject with Alzheimer’s disease, and corresponding Hahn SE (b) and GESSE (c) $T_2$ maps (in ms), as well as flip angle (in degrees) (d) and receive sensitivity (in %) (e) maps. Note that in the right temporal and inferior frontal lobes as well as the in left temporal lobe where the flip angle and receive sensitivity are very low, Hahn SE $T_2$ values are artificially high. Also note that some of the brain nuclei such as the red nuclei and substantia nigra have lower $T_2$ values on the GESSE $T_2$ map, but are not seen on the Hahn SE $T_2$ map. This is the same slice as in Fig. 4.9.
Figure 4.17: (See figure on next page.) Coronal Hahn SE image (TE 50 ms) (a) of the brain of a 79-year-old male postmortem human subject with alcohol dementia, and corresponding Hahn SE (b) and GESSE (c) $T_2$ maps (in ms), as well as flip angle (in degrees) (d) and receive sensitivity (in %) (e) maps. Note that in the central region where the flip angle is significantly higher than 90°, and in the right temporal and inferior frontal lobes as well as the cerebellum where the receive sensitivity is very low, Hahn SE $T_2$ values are artificially high. This is the same subject as in Fig. 4.8.
Figure 4.17: See caption on previous page.
**Figure 4.18:** (See figure on next page.) Axial Hahn SE image (TE 50 ms) (a) of the brain of the same subject shown in Fig. 4.15, and corresponding Hahn SE (b) and GESSE (c) $T_2$ maps (in ms), as well as flip angle (in degrees) (d) and receive sensitivity (in %) (e) maps. Note that in the central region where the flip angle is significantly higher than 90°, in the left occipital and posterior temporal lobes where the flip angle is very low, and in the right occipital lobe where the receive sensitivity is very low, Hahn SE $T_2$ values are artificially high. Also note that the putamen and globus pallidus have lower $T_2$ values on the GESSE $T_2$ map, but are not seen on the Hahn SE $T_2$ map. This is the same slice as in Fig. 4.7.
Figure 4.18: See caption on previous page.
**Figure 4.19:** (See figure on next page.) Coronal Hahn SE image (TE 50 ms) (a) of the brain of a 29-year-old female healthy volunteer, and corresponding Hahn SE (b) and GESSE (c) $T_2$ maps (in ms), as well as flip angle (in degrees) (d) and receive sensitivity (in %) (e) maps. In this study, the following acquisition parameters were slightly different than those shown in Table 4.7b: TE 40 ms, ΔTE 10.2 ms, and BW 69 kHz. Note that in the central region where the flip angle is significantly higher than 90°, in the left temporal lobe where the flip angle is very low, and in the right temporal and inferior frontal lobes where the receive sensitivity is very low, Hahn SE $T_2$ values are artificially high. The arrow pointing to the right shows the red nucleus, the arrow pointing to the top shows the substantia nigra, and the arrow pointing to the left shows the putamen (most lateral) and globus pallidus (most medial), all of which have lower $T_2$ values on the GESSE $T_2$ map, but are not seen on the Hahn SE $T_2$ map.
Figure 4.19: See caption on previous page.
Figure 4.18: (See figure on next page.) Axial Hahn SE image (TE 50 ms) (a) of the brain of a 33-year-old male healthy volunteer, and corresponding Hahn SE (b) and GESSE (c) $T_2$ maps (in ms), as well as flip angle (in degrees) (d) and receive sensitivity (in %) (e) maps. Note that the Hahn SE $T_2$ map is severely affected by motion artifacts in the phase encoding direction (left–right) on both sides of the lateral ventricles. Also note that in both posterior temporal lobes and in the left occipital lobe where the flip angle is very low, and in the right occipital lobe where the receive sensitivity is very low, Hahn SE $T_2$ values are artificially high.
Figure 4.20: See caption on previous page.
whereas they are more severe on the right side for other subjects. Also note that some of the receive sensitivity maps are contaminated by residual proton density weighting in the ventricles. Conversely, in regions where flip angles are close to 90°, both Hahn SE and GESSE methods provide similar results, with GESSE $T_2$ values somewhat lower than Hahn SE $T_2$ values. As in the phantom study, banding artifacts in the GESSE $T_2$ map on Fig. 4.19c are likely due to system instability.

Table 4.13 shows the Hahn SE and GESSE $T_2$ values as well as the flip angle for different ROIs of the brain of the subjects shown in Figs. 4.15 to 4.19. Note that because of differences in $B_1$ inhomogeneity across the studies, ROIs could not always be drawn in the same regions for all subjects. The following observations can be made from this table and will be further discussed in the next section. First, the Hahn SE $T_2$ values are generally higher than the corresponding GESSE $T_2$ values, as observed on the $T_2$ maps. Second, the standard deviation of the GESSE $T_2$ values is generally higher than the standard deviation of the Hahn SE $T_2$ values. Third, both Hahn SE and GESSE $T_2$ values are typically higher in WM ROIs as compared to adjacent GM ROIs. This is the opposite of what is observed at lower field strength and may be explained by the fact that the iron distribution is different in GM and WM. This behavior was observed in a number of other postmortem and in vivo studies at 8 T and is being further investigated. Finally, there does not seem to be any significant differences between the postmortem and in vivo studies, which tends to confirm that the contrast at ultra-high field strength is dominated by susceptibility effects, since iron content is not expected to change between live and unembalmed postmortem subjects (less than 48 hours after death).
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**Table 4.13:** Hahn SE and GESSE $T_2$ values (mean ± standard deviation) and corresponding flip angles (mean ± standard deviation) in different GM and WM ROIs of the brain of the subjects shown in Figs. 4.15 to 4.19 (SFG = superior frontal gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, STG = superior temporal gyrus),

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<td>45.8   4.3</td>
<td>40.3   7.7</td>
<td>63.8   3.9</td>
</tr>
<tr>
<td>right cingulate gyrus GM</td>
<td>40.7   2.8</td>
<td>32.7   4.0</td>
<td>113.9  2.2</td>
</tr>
<tr>
<td>right cingulate gyrus</td>
<td>53.3   4.0</td>
<td>48.2   5.5</td>
<td>107.1  2.5</td>
</tr>
</tbody>
</table>
Note that the GESSE $T_2$ maps show some of the brain nuclei such as the red nuclei, substantia nigra, putamen, and globus pallidus with lower $T_2$ values (*e.g.*, arrows on Figs. 4.15c and 4.19c) due to their high iron content, whereas these are not seen on the corresponding Hahn SE $T_2$ maps. However, these nuclei are not as clearly depicted as the rest of the brain because their $T_2$ values are much lower than the TE used in these studies, which was chosen for optimal $T_2$ measurements in GM and WM.

Table 4.14 shows the Hahn SE and GESSE $T_2$ values as well as the flip angle for different brain nuclei of the subjects shown in Figs. 4.15 to 4.19. Again, because of differences in $B_1$ inhomogeneity across the studies, not all nuclei could be seen in all subjects. As for the GM and WM ROIs, the following observations can be made from this table. First, the Hahn SE $T_2$ values are significantly higher than the corresponding GESSE $T_2$ values, whereas the latter are lower than the $T_2$ values in brain tissue, as expected. Second, the standard deviation of the GESSE $T_2$ values is generally higher than the standard deviation of the Hahn SE $T_2$ values. Finally, there does not seem to be any significant differences between the postmortem and *in vivo* studies.

Fig. 4.21 shows the logarithm of the Hahn SE and GESSE signal intensity as a function of TE in representative ROIs from Tables 4.13 and 4.14 for the healthy volunteer shown in Fig. 4.19. In both GM and WM ROIs, the linear dependence of the logarithm of the Hahn SE signal intensity as a function of TE shows that the signal decay in these regions is indeed monoexponential, as assumed in the computation of the Hahn SE $T_2$ maps. On the other hand, there is a significant deviation from this exponential behavior in all of the nuclei, resulting in an overestimation of the Hahn SE $T_2$ values in these regions. This is because
<table>
<thead>
<tr>
<th></th>
<th>Hahn SE $T_2$ [ms]</th>
<th>GESSE $T_2$ [ms]</th>
<th>flip angle [$^\circ$]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fig. 4.15 (postmortem)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left substantia nigra</td>
<td>35.9</td>
<td>28.7</td>
<td>116.6</td>
</tr>
<tr>
<td>left putamen</td>
<td>40.7</td>
<td>23.6</td>
<td>64.4</td>
</tr>
<tr>
<td>left globus pallidus</td>
<td>34.2</td>
<td>25.8</td>
<td>75.6</td>
</tr>
<tr>
<td><strong>Fig. 4.16 (postmortem)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right red nucleus</td>
<td>43.9</td>
<td>28.1</td>
<td>122.7</td>
</tr>
<tr>
<td>left substantia nigra</td>
<td>38.2</td>
<td>22.8</td>
<td>102.5</td>
</tr>
<tr>
<td><strong>Fig. 4.17 (postmortem)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left putamen</td>
<td>37.4</td>
<td>26.6</td>
<td>66.4</td>
</tr>
<tr>
<td>left globus pallidus</td>
<td>36.1</td>
<td>29.4</td>
<td>73.2</td>
</tr>
<tr>
<td><strong>Fig. 4.18 (postmortem)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right putamen</td>
<td>38.3</td>
<td>21.7</td>
<td>124.5</td>
</tr>
<tr>
<td>right globus pallidus</td>
<td>47.9</td>
<td>24.8</td>
<td>134.9</td>
</tr>
<tr>
<td>left putamen</td>
<td>31.8</td>
<td>23.3</td>
<td>76.9</td>
</tr>
<tr>
<td>left globus pallidus</td>
<td>33.2</td>
<td>22.5</td>
<td>92.3</td>
</tr>
<tr>
<td><strong>Fig. 4.19 (in vivo)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right red nucleus</td>
<td>73.9</td>
<td>20.0</td>
<td>134.8</td>
</tr>
<tr>
<td>left substantia nigra</td>
<td>50.1</td>
<td>21.2</td>
<td>135.7</td>
</tr>
<tr>
<td>left putamen</td>
<td>35.7</td>
<td>23.0</td>
<td>90.5</td>
</tr>
<tr>
<td>left globus pallidus</td>
<td>40.9</td>
<td>27.0</td>
<td>97.9</td>
</tr>
</tbody>
</table>

**Table 4.14:** Hahn SE and GESSE $T_2$ values (mean ± standard deviation) and corresponding flip angles (mean ± standard deviation) in different brain nuclei of the subjects shown in Figs. 4.15 to 4.19.
Figure 4.21: Logarithm of the Hahn SE (a) and GESSE (b) signal intensity as a function of TE in some the ROIs used in Tables 4.13 and 4.14 for the healthy volunteer shown in Fig. 4.19 (◇: right superior frontal GM, ◦: right superior frontal WM, □: left red nucleus, △: right substantia nigra, ×: right putamen). Note that all points are above the noise level.

The Hahn SE signal decay is not strictly monoexponential, but depends on water diffusion in subvoxel magnetic field gradients, which can be expressed as:

\[ S(t) = S_0 \exp(-R_2 t - \gamma^2 G^2 D t^3 / 12), \]  

(4.19)

where \( G \) represents the mesoscopic magnetic field gradient due to paramagnetic iron and \( D \) is the diffusion coefficient [152, 84, 153]. The influence of the second term is most prominent in brain nuclei with a high iron content, such as the red nuclei, substantia nigra, putamen, and globus pallidus. This explains why Hahn SE \( T_2 \) values are significantly higher than GESSE \( T_2 \) values in these regions.
4.3.5 Discussion

Our comparisons between Hahn SE and GESSE $T_2$ measurements in phantoms as well as postmortem and \textit{in vivo} human brains at 8 T have shown that the GESSE method offers several advantages over the Hahn SE method. First, it is a single scan method and thus requires a substantially shorter acquisition time, making it more suitable for \textit{in vivo} studies, particularly clinical studies.

In the agarose phantom and the human studies, the GESSE method is less sensitive to $B_1$ inhomogeneity than the Hahn SE method, which is particularly severe at ultra-high field strength. When the flip angle is close to 90°, both methods provide similar results, with GESSE $T_2$ values somewhat lower than Hahn SE $T_2$ values. On the other hand, when the flip angle deviates significantly from 90° and/or when receive sensitivity is too low, the Hahn SE $T_2$ values become artificially high. However, in the gelatin phantom, the GESSE method is more sensitive to $B_1$ inhomogeneity than the Hahn SE method. This unexpected behavior is not fully understood at this time and further studies are needed to address this issue.

While the Hahn SE method is affected by artifacts due to crosstalk in multislice acquisitions, preliminary studies with the GESSE method have shown that it does not appear to be affected by such artifacts, thus allowing multislice acquisitions for whole brain coverage, which is another significant advantage over the Hahn SE method.

Finally, the GESSE method may be less sensitive to $B_0$ inhomogeneity than the Hahn SE method, which is particularly severe at ultra-high field strength, but further studies are needed to address this issue.
One potential disadvantage of the GESSE method as compared to the Hahn SE method is that the GESSE $T_2$ maps are noisier than the Hahn SE $T_2$ maps when the former are computed from a smaller number of echoes as the latter, as was the case in our studies (see Tables 4.13 and 4.14). However, this is not a fundamental limitation of the technique, but rather the result of the choice of acquisition parameters. The shorter $T_2$ values at ultra-high field strength require a relatively short TE to be used to obtain adequate SNR. This in turn limits the number of echoes that can be acquired for a given bandwidth and matrix size. A relatively small bandwidth was used in our studies. Nevertheless, note that simply doubling the bandwidth, which would decrease the readout window by a factor 2 and reduce the SNR by a factor $\sqrt{2}$, would not be sufficient to allow acquisition of an additional pair of echoes around the SE while keeping the same TE, which would at best increase the SNR by a factor $\sqrt{2}$ (see Eq. (4.16)), because additional time is required to include the negative gradient lobe between the readout gradients. Interleaved acquisitions could be used to increase the number of echoes while keeping the same TE, bandwidth, and matrix size, however at the expense of additional scan time. Nevertheless, parallel imaging techniques such as SENSE or SMASH [154] could be used to offset that increase in scan time.

Some clinical applications of GESSE $T_2$ measurements, notably for the assessment of brain iron content in neurodegenerative diseases, are discussed in section 5.2.
CHAPTER 5

CONCLUSION

5.1 Summary

The objective of this research was to develop methods to reduce susceptibility artifacts while optimizing susceptibility contrast for ultra-high field MRI of the human brain. This required knowledge of both macroscopic and mesoscopic susceptibility effects, which in turn required development of $B_0$ mapping and relaxation time measurement methods.

In chapter 2, we developed different methods for $B_0$ numerical simulations and experimental mapping. Simulations have the advantage of not being affected by artifacts and are more flexible, whereas experimental techniques are faster and, more importantly, are eventually required to provide subject-specific $B_0$ maps.

We first developed a finite difference method for $B_0$ numerical simulations using susceptibility distributions obtained from CT images. Our simulations showed regions of high $B_0$ inhomogeneities near air/tissue interfaces in the inferior frontal and temporal lobes. Simulations for different models showed that air/tissue interfaces at the shoulders induce substantial $B_0$ inhomogeneities in the brain, and that tilting the head backwards can significantly reduce some of these inhomogeneities.
We also developed two experimental $B_0$ mapping methods based on a 2D ASE sequence and a 3D dual-echo GE sequence, as well as a phase unwrapping algorithm for computation of the $B_0$ maps. Both experimental techniques were compared to the simulations in phantom as well as postmortem and in vivo human studies, and found to be in good agreement with each other. The 3D GE method generally performed better than the 2D ASE method.

We then used the $B_0$ numerical simulations and experimental mapping, as well as $B_1$ experimental mapping, to correlate the $B_0$ and $B_1$ inhomogeneity with the artifacts observed on GE and SE images of the human brain acquired at 8 T. Our studies showed that ultra-high field MRI is affected by severe artifacts due to both $B_0$ and $B_1$ inhomogeneity, and that $B_0$ and $B_1$ mapping is important in identifying their origin.

In chapter 3, we evaluated the effectiveness of various methods for susceptibility artifact correction at ultra-high field strength, including passive shimming using ferroshims, post-processing using non-Fourier reconstruction, as well as gradient compensation using 3D $z$-shim and GESEPI. Both the $B_0$ numerical simulations and experimental mapping techniques developed in chapter 2 were used in the development and assessment of these methods. While preliminary studies using the ferroshims, non-Fourier reconstruction, and 3D $z$-shim method led to mixed results, the GESEPI method proved to be the most effective at correcting for susceptibility artifacts at ultra-high field strength.

Finally, in chapter 4, we developed and implemented various methods for $T_2$, $T_2'$, and $T_2^*$ relaxation time measurements at ultra-high field strength that are less sensitive to $B_0$ and/or $B_1$ inhomogeneity than conventional methods.
We first developed a new method called bmGESEPI for $T_2^*$ measurements with $B_0$ inhomogeneity compensation that can provide faster and more accurate measurements than a conventional 2D multi-echo GE method and the existing mGESEPI method. These advantages were demonstrated in phantom as well as postmortem and in vivo human studies at 8 T. Again, $B_0$ numerical simulations and experimental mapping were used in the development and assessment of these methods.

We also implemented the GESFIDE method for simultaneous $T_2$, $T_2'$, and $T_2^*$ measurements at 8 T, however preliminary studies showed that this method is affected by severe $B_0$ inhomogeneity at ultra-high field strength.

We then implemented the GESSE method for $T_2$ measurements at 8 T, which is faster and possibly less sensitive to $B_1$ inhomogeneity than a conventional Hahn SE method, and demonstrated these advantages in phantom as well as postmortem and in vivo human studies.
5.2 Applications and Future Work

The methods developed in this work as well as the findings obtained from them will be used to improve acquisition methods for ultra-high field MRI of the human brain. They will also help gain a better understanding of contrast mechanisms at ultra-high field strength, which appear to be dominated by susceptibility effects, unlike image contrast at lower field strength, which is dominated by proton density as well as $T_1$ and $T_2$ relaxation times.

These new methods and findings will also be used for clinical applications, particularly those that benefit from the enhanced susceptibility contrast obtained at ultra-high field strength. One of the primary applications developed on the 8 T MRI system so far has been imaging of the brain venous microvasculature [4, 3, 155, 156, 83, 157], particularly for the assessment of brain tumor and stroke, since it benefits from an enhanced BOLD contrast due to deoxyhemoglobin in venous blood.

Similarly, the enhanced susceptibility contrast obtained at ultra-high field strength makes ultra-high field MRI more sensitive to iron [84], especially in brain nuclei such as the red nuclei, substantia nigra, putamen, and globus pallidus. Assessment of brain iron content is particularly useful in neurodegenerative diseases involving altered iron levels, such as Alzheimer’s and Parkinson’s diseases. Future work aims at studying patients with Mild Cognitive Impairment (MCI), which is an early stage of Alzheimer’s disease, as well as Parkinson’s disease at 8 T using the relaxation time measurement methods developed in this work, specifically $T_2^*$ measurements using the bmGESEPI method and $T_2$ measurements using the GESSE method. Both of these relaxation times can then be used to compute the
\(T'_2\) relaxation time, which was found to be the most sensitive to iron content by several authors [128, 158, 149]. For postmortem human studies, these relaxation times can also be correlated with an independent measure of the iron content using mass spectroscopy [153].

Applications of the methods developed in this work are however not limited to ultra-high field MRI of the human brain. For example, the algorithm for \(B_0\) numerical simulations (see section 2.1) has been implemented in a parallel code that should allow simulations with larger memory requirements, \textit{i.e.}, simulations using larger anatomical regions, higher resolution, and/or a larger buffer size, therefore resulting in more accurate results. Such an improved algorithm could then be used to simulate the \(B_0\) field for a head/thorax model at inspiration and expiration, possibly with varying oxygen concentration in the lungs and airways, in order to study respiratory artifacts in fMRI, as suggested in section 2.1.4. Other applications include simulations of the \(B_0\) field generated by a realistic model of the brain vasculature, as proposed by Marques \textit{et al.} [16, 159], or the development and assessment of various active and passive shimming methods, such as the diamagnetic passive shims and active shim coils discussed in section 3.1.3.
APPENDIX A

PROGRAMS

The Matlab programs and ParaVision pulse programs developed in this work are available by contacting me at truong.31@osu.edu and Dr. Petra Schmalbrock at schmalbrock.1@osu.edu.
APPENDIX B

REGULARIZATION OF ILL-POSED LINEAR
INVERSE PROBLEMS WITH DISCRETE DATA

B.1 Linear Inverse Problems with Discrete Data

In general, a linear inverse problem with discrete data can be formulated as follows [160]: given a class $X$ of functions, a set of linear functionals $\{A_n\}_{n=1}^{N}$ defined on $X$, and a set of real (or complex) values $\{g_n\}_{n=1}^{N}$, find a function $f \in X$ such that

$$A_n(f) = g_n, \quad n = 1, \ldots, N. \quad (B.1)$$

Assuming in addition that $X$ is a Hilbert space and that the functionals $\{A_n\}_{n=1}^{N}$ are continuous, so that there exists a set of functions $\{\phi_n\}_{n=1}^{N} \subset X$ such that

$$A_n(f) = (f, \phi_n)_X, \quad n = 1, \ldots, N, \quad (B.2)$$

where $(\cdot, \cdot)_X$ denotes the inner product in $X$, the inverse problem (B.1) can now be formulated as follows: given a Hilbert space $X$, a set of functions $\{\phi_n\}_{n=1}^{N} \subset X$, and a set of values $\{g_n\}_{n=1}^{N}$, find a function $f \in X$ such that

$$(f, \phi_n)_X = g_n, \quad n = 1, \ldots, N. \quad (B.3)$$
Introducing an $N$-dimensional euclidian space $Y$ such that the values $g_n = \{g_n\}_{n=1}^N$ represent the components of a vector $g \in Y$, and a linear operator $A : X \rightarrow Y$ such that

$$(Af)_n = (f, \phi_n)_X, \quad n = 1, \ldots, N,$$  \hspace{1cm} (B.4)

an equivalent formulation of the inverse problem (B.3) is as follows: given a Hilbert space $X$, a euclidian space $Y$, a linear operator $A : X \rightarrow Y$, and a vector $g \in Y$, find a function $f \in X$ such that

$$Af = g.$$ \hspace{1cm} (B.5)

### B.2 Fredholm Integral Equations of the First Kind

In the particular case where the functionals $\{A_n\}_{n=1}^N$ can be written as

$$A_n(f) = \int_{x_1}^{x_2} a(x, y_n) f(x) \, dx, \quad n = 1, \ldots, N,$$ \hspace{1cm} (B.6)

Eq. (B.1) becomes:

$$\int_{x_1}^{x_2} a(x, y_n) f(x) \, dx = g_n, \quad n = 1, \ldots, N.$$ \hspace{1cm} (B.7)

An equation of the form (B.7) is called a Fredholm integral equation of the first kind [160, 161, 162, 163, 98, 164], where $a(\cdot, \cdot)$ is the kernel of the equation.

### B.3 Ill-Posed Problems

Consider the following problem: given two Hilbert spaces $X$ and $Z$, a linear operator $A : X \rightarrow Z$, and a function $h \in Z$, find a function $f \in X$ such that

$$Af = h.$$ \hspace{1cm} (B.8)
The problem above is said to be *well-posed* (in the sense of Hadamard) if the following three conditions hold [161, 162, 163]:

1. existence: for each \( f \in X \), the problem has a solution;

2. uniqueness: the solution is unique;

3. stability: the solution is stable under perturbation of the vector \( h \), *i.e.*, it depends continuously on \( h \).

The problem is said to be *ill-posed* (in the sense of Hadamard) if it is not well-posed. In this case, regularization algorithms can be used to obtain an approximate solution (see section B.6).

### B.4 The Normal Solution

If the functions \( \{\phi_n\}_{n=1}^{N} \) are not linearly independent, the inverse problem (B.3) may not have a solution. On the other hand, if they are linearly independent (but not necessarily orthogonal), the set of functionals \( \{A_n\}_{n=1}^{N} \) defines a mapping of \( X \) into \( \mathbb{R}^N \) (or \( \mathbb{C}^N \)), which implies that the inverse problem always has a solution [160].

However, this solution is not unique because only the projection of the unknown function \( f \) on the subspace \( X_N \subset X \) spanned by the functions \( \{\phi_n\}_{n=1}^{N} \) can be determined, but not the component of \( f \) orthogonal to \( X_N \). Nevertheless, there always exists a unique solution of minimal norm, *i.e.*, a solution that has minimal distance from the null element of \( X \). This essentially means that the component of \( f \) orthogonal to \( X_N \) is set equal to zero. This solution is called the *normal solution* and is denoted by \( f^\dagger \).
Furthermore, it can be shown that $f^\dagger$ depends continuously on the vector $g$ in the sense that if $\delta g$ denotes a variation of $g$ and $\delta f^\dagger$ denotes the corresponding variation of $f^\dagger$, then

$$\lim_{\|\delta g\|_Y \to 0} \|\delta f^\dagger\|_X = 0,$$

where $\|\cdot\|_X$ and $\|\cdot\|_Y$ denote the norm in $X$ and $Y$ respectively [160].

Consequently, the computation of the normal solution of an inverse problem with discrete data is always a well-posed problem. In fact, the concept of ill-posedness only applies to infinite-dimensional problems. However, in most cases, problem (B.3) is the projection of an ill-posed infinite-dimensional problem on a finite-dimensional space, so that the discrete problem can be strongly ill-conditioned and exhibit numerical instability. The larger the size of the vector $g$, the closer the finite-dimensional problem to the ill-posed infinite-dimensional problem, and therefore the larger the numerical instability [98].

**B.5 The Generalized Solution or Normal Pseudosolution**

If the functions $\{\phi_n\}_{n=1}^N$ are not linearly independent and if the vector $g$ is affected by noise, then, in general, the normal solution of the inverse problem (B.5) does not exist [160]. However, it is possible to define a solution $\tilde{f} \in X$ such that

$$\|A\tilde{f} - g\|_Y = \inf_{f \in X} \|Af - g\|_Y.$$  \hspace{1cm} (B.10)

Such a solution is called the least-squares solution or pseudosolution.

Again, it can be shown that there always exists a unique least-squares solution of minimal norm, which depends continuously on the vector $g$ [160]. This solution is called the normal pseudosolution or generalized solution and is also denoted by
\( f^\dagger \) because when the functions \( \{\phi_n\}_{n=1}^N \) are linearly independent, the generalized solution coincides with the normal solution.

The operator \( A^\dagger : Y \rightarrow X \) defined by

\[
A^\dagger g = f^\dagger
\]

is called the **generalized inverse** or **Moore-Penrose inverse** of \( A \).

### B.6 Regularization Algorithms

*Regularization algorithms* can be used for the approximate computation of the generalized inverse \( A^\dagger \), and consequently the generalized solution \( f^\dagger \). A regularization algorithm is defined by a family of linear operators \( \{A^\dagger_\beta\}_{\beta>0}, A^\dagger_\beta : Y \rightarrow X \), such that [165]:

1. \( \forall \beta > 0 \), the range of \( A^\dagger_\beta \) is contained in \( X_N \);
2. \( \forall \beta > 0, \|A^\dagger_\beta\| \leq \|A^\dagger\| \);  
3. \( \lim_{\beta \rightarrow 0} A^\dagger_\beta = A^\dagger \).

The parameter \( \beta \) is called **regularization parameter** and one of the main problems in regularization theory is to find an optimal value for \( \beta \).

### B.7 Tikhonov Regularization

*Tikhonov regularization* is a particular kind of regularization algorithm that can be used to obtain an approximate solution of Fredholm integral equations of the first kind [161, 162, 163, 164, 165]. To regularize the inverse problem (B.5), constraints on possible solutions \( f \) are imposed by requiring that

\[
\|Af - g\|_Y^2 \leq \varepsilon^2 ,
\]

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where $\epsilon$ is some suitable measure of the noise, and that

$$
\| f \|^2_X \leq \xi^2,
$$

(B.13)

where $\xi$ is some suitable measure of the permitted “amplitude” of the solution. Tikhonov regularization is obtained by combining these two constraints and minimizing the following functional:

$$
\Phi_{\beta}[f] = \| A f - g \|_Y^2 + \beta \| f \|_X^2
$$

(B.14)

for each value of the regularization parameter $\beta$ defined by

$$
\beta = \frac{\epsilon^2}{\xi^2}.
$$

(B.15)

This can be achieved by setting the first variation of the functional $\Phi_{\beta}[f]$ equal to zero, which results in the following regularizing operator:

$$
A_{\beta}^\dagger = (A^* A + \beta I)^{-1} A^* ,
$$

(B.16)

where $A^*$ is the adjoint operator of $A$ defined by

$$
(A f, g)_Y = (f, A^* g)_X.
$$

(B.17)

The inverse of $(A^* A + \beta I)$ always exists, since $A^* A$ is non-negative definite and $\beta > 0$. The generalized solution of the inverse problem is then given by:

$$
f_{\beta}^\dagger = A_{\beta}^\dagger g.
$$

(B.18)

Numerical stability is controlled by the regularization parameter $\beta$, for which the optimal value depends on the signal-to-noise ratio in the data. A trade-off must be made between smoothness (for large values of $\beta$) and fidelity (for small
values of $\beta$) in the approximate solution. A number of methods are available to determine an optimal value for $\beta$ [162, 165].

B.8 Discretization

For practical implementation, the problem needs to be discretized, i.e., expressed in terms of a finite number of unknowns [161, 98]. This can be achieved by applying a quadrature rule so that the integral in Eq. (B.7) becomes a finite sum:

$$\sum_{m=1}^{M} w_m a(x_m, y_n) f(x_m) = g_n, \quad n = 1, \ldots, N,$$

(B.19)

where the $\{w_m\}_{m=1}^{M}$ are weights. In the simple case of the midpoint rule, the weights are all unity.

The inverse problem (B.5) can now be formulated as follows: given a matrix $A \in \mathbb{R}^{N \times M}$ (or $\mathbb{C}^{N \times M}$) and a vector $g \in \mathbb{R}^{N}$ (or $\mathbb{C}^{N}$), find a vector $f \in \mathbb{R}^{M}$ (or $\mathbb{C}^{M}$) such that

$$Af = g.$$

(B.20)

B.9 Singular Value Decomposition

The singular value decomposition (SVD) of a linear operator $A : \mathbb{R}^{M} \rightarrow \mathbb{R}^{N}$, represented by a matrix $A \in \mathbb{R}^{N \times M}$, is given by [98, 164, 166]:

$$A = U \Sigma V^T,$$

(B.21)

where $(\cdot)^T$ denotes the transpose operation and

$$U = [u_1, \ldots, u_N] \in \mathbb{R}^{N \times N}, \quad U^T = U^{-1},$$

(B.22)

$$V = [v_1, \ldots, v_M] \in \mathbb{R}^{M \times M}, \quad V^T = V^{-1},$$

(B.23)
\[ \Sigma = \text{diag}(\sigma_1, \ldots, \sigma_P) \in \mathbb{R}^{N \times M}, \quad P = \min\{M, N\}, \quad (B.24) \]

where the \( \{u_i\}_{i=1}^N \) and \( \{v_i\}_{i=1}^M \) are the \textit{singular vectors} and the \( \{\sigma_i\}_{i=1}^P \) are the \textit{singular values} in decreasing order of magnitude (\( \sigma_1 \geq \ldots \geq \sigma_P \geq 0 \)). The matrix \( A \) can therefore be expressed as:

\[ A = \sum_{i=1}^P \sigma_i u_i v_i^T, \quad (B.25) \]

If \( M = N \) and if the system is well-conditioned, the inverse of the matrix \( A \) can be computed using the SVD as follows:

\[ A^{-1} = V \Sigma^{-1} U^T = \sum_{i=1}^N \frac{1}{\sigma_i} v_i u_i^T, \quad (B.26) \]

where

\[ \Sigma^{-1} = \text{diag} \left( \frac{1}{\sigma_1}, \ldots, \frac{1}{\sigma_N} \right), \quad (B.27) \]

so that

\[ f = A^{-1} g. \quad (B.28) \]

On the other hand, if the system is ill-conditioned, small singular values may be of the same order as the noise and may result in unstable solutions.

\textit{Truncated SVD} is a regularization method where only the singular values larger than a threshold value \( \beta \) (the regularization parameter) are included in the summation \( (B.26) \), \textit{i.e.}, \cite{161, 98}:

\[ A_\beta^\dagger = \sum_{i=1}^{N_\beta} \frac{1}{\sigma_i} v_i u_i^T, \quad (B.29) \]
where \( N_\beta \) is such that \( \sigma_i \geq \beta, \ \forall i \leq N_\beta \), so that

\[
f_\beta^\dagger = A_\beta^\dagger g.
\]  
(B.30)

As mentioned in section B.7, the selection of the regularization parameter \( \beta \) is critical and depends on the noise level. If \( \beta \) is too large, the truncated SVD approximation will diverge.

Alternatively, Tikhonov regularization can also be applied using the SVD. In that case, Eqs. (B.26) and (B.27) become [164, 165]:

\[
A_\beta^\dagger = V \Sigma_\beta^\dagger U^T = \sum_{i=1}^{N} \frac{\sigma_i}{\sigma_i^2 + \beta} u_i v_i^T,
\]  
(B.31)

where

\[
\Sigma_\beta^\dagger = \text{diag} \left( \frac{\sigma_1}{\sigma_1^2 + \beta}, \ldots, \frac{\sigma_N}{\sigma_N^2 + \beta} \right).
\]  
(B.32)
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