Comprehensive Head Motion Correction for Functional Magnetic Resonance Imaging

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

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University of Toronto

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Doctor of Philosophy

Medical Biophysics Department

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2017

Abstract

Head motion artifacts are major confounds that limit use of functional magnetic resonance imaging (fMRI) in neuroscience research and clinical settings. Prospective motion correction is a promising candidate solution for head motion in fMRI that ideally allows the image plane to remain fixed with respect to the moving head (i.e., in the moving reference frame). Prospective motion correction has been shown to correct successfully for rigid body movement artifacts, but residual geometric distortion due to dynamic magnetic field nonuniformities and dynamic changes in receiver coil sensitivity profiles in the moving reference frame still remain a problem.

This thesis focuses on three objectives. First, I investigated and corrected for the influence of respiratory effects on the performance of dynamic geometric correction using Phase Labeling for Additional Coordinate Encoding (PLACE). It was demonstrated that PLACE combined with the dynamic off-resonance in k-space (DORK) method, and temporal averaging substantially improved fMRI data quality in comparison to the results obtained by standard processing and static geometric distortion correction.
Second, I verified that appreciable signal artifacts occur due to coil sensitivity changes in fMRI maps in presence of overt head motion with prospective motion correction using Prospective Acquisition CorrEction (PACE) technique [1]. Sensitivity map compensations were shown to suppress these artifacts and provide improved fMRI results.

Third, I studied signal artifacts resulted from the head motion between the coil sensitivity map measurement (i.e., the calibration step) and data acquisition for fMRI with parallel-imaging reconstruction methods using two parallel imaging schemes: sensitivity encoding (SENSE) and generalized autocalibrating partially parallel acquisitions (GRAPPA) with acceleration factors 2 and 4. Coil sensitivity map compensations were shown to improve fMRI results obtained with PACE in the presence of overt head motion compared to those obtained with no overt head motion.

Overall, prospective motion correction, integrated dynamic geometric distortion correction, and coil sensitivity map correction present an appealing compound approach for suppressing rigid and non-rigid motion artifacts during fMRI. This thesis has developed robust and comprehensive head motion correction strategies that ultimately will expand the patient populations for which fMRI can be performed robustly.
Acknowledgments

I would like to express my sincere gratitude to all the people who helped me to undertake this work. First I would like to thank all of the members of the Graham lab, for their help and support. I also thank the members of my supervisory committee, Dr. Philip Beatty and Dr. Christopher Macgowan, for their constructive criticisms and guidance. I want to give special thanks to my supervisor Dr Simon Graham for his valuable guidance and advice on so many aspects of this thesis, for encouragement, and for providing me with such a wonderful opportunity. Also, I must thank Dr. Jean Chen and her lab for the guidance and opportunities that they have provided me along the way. Last but not least, I transmit a warm thanks to my family and friends for their constant encouragement and support.
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<td>Arterial Spin Labelling</td>
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<tr>
<td>ASRO</td>
<td>Adjusted Sensitivity Roemer Optimal</td>
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<tr>
<td>DOF</td>
<td>Degrees of Freedom</td>
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<td>BOLD</td>
<td>Blood Oxygen Level Dependent</td>
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<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
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<td>DCE</td>
<td>Dynamic Contrast Enhanced</td>
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<td>DMA</td>
<td>Displacement Map Averaging</td>
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<td>Dynamic Off-Resonance in K-space</td>
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<td>False Discovery Rate</td>
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<td>FMRI</td>
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<td>FOV</td>
<td>Field of View</td>
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<td>Acronym</td>
<td>Definition</td>
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<td>GRAPPA</td>
<td>Generalized Autocalibrating Partially Parallel Acquisitions</td>
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<td>PSF</td>
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<td>RF</td>
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<td>SOS</td>
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<td>tSNR</td>
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<td>USM</td>
<td>Updated Sensitivity Maps</td>
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<td>2DFT</td>
<td>2 Dimension Fourier Transform</td>
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<td>Gd DTPA</td>
<td>Gadolinium-DiethyleneTriamine Pentaacetic Acid</td>
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Chapter 1
Introduction

Over the past twenty five years, functional magnetic resonance imaging (fMRI) has become a ubiquitous imaging technique in neuroscience research and clinical settings due to its ability to noninvasively localize brain activity with spatial and temporal resolutions of approximately millimeters and seconds respectively [2]–[4]. Functional MRI assumes that the measured time-dependent signal changes arise from brain activity (studied either in relation to task-related behavioral performance, or in the resting state without task administration). However, head motion is a major potential problem. Because fMRI signals are weak, a few millimeters of motion are sufficient to cause “artifacts”-unwanted signal intensity changes in images- that pose a serious confound. Random head motions increase background artifact, deteriorate the efficiency of brain activity detection and primarily result in false negative activations. Motions correlated with the performance of the task, on the other hand, usually appear as spurious or false positive activations.

Beyond simple strategies such as foam padding and vacuum pillows, which are only partially successful, the traditional processing method to “fix” head motion artifacts is retrospective co-registration of images in the fMRI time series. This procedure aligns all images in the time series to a reference image by optimizing a cost function (a metric that quantifies the similarity between images, such as the least-squares difference in signal intensity) based on image rotation and translation with respect to the reference. Although retrospective co-registration techniques can effectively correct for small, sub-millimeter head motions, they are less accurate for larger movements. In addition, these correction techniques usually assume rigid-body motion. However, head motion can result in non-linear spatial distortions in fMRI data that cannot be corrected by the rigid-body assumption. In addition, these non-rigid body motion artifacts cannot be fully suppressed using simple non-linear registration approaches [5].

Prospective motion correction is an alternative technique that adjusts the imaging scan plane before image acquisition, and has the potential to mitigate the effect of large head motions [6]–[9]. Such head motions are commonly observed in patient populations (e.g., stroke survivors) that are the main interest of clinical neuroscience research. Prospective motion correction maintains the relationship between the imaging frame of reference and the moving head (i.e.,
fMR images remain fixed with respect to the moving reference frame of the head), thus correcting for rigid-body motion artifacts. Even with use of prospective motion correction, however, unavoidable nonlinear spatial distortion must be considered and addressed using additional correction strategies. These nonlinear spatial distortions can arise from magnetic field inhomogeneities as well as the interaction between the head motion and the receiver coil. This PhD thesis presents an augmented prospective motion correction methodology that corrects for dynamic geometric distortion due to dynamic magnetic field inhomogeneities, as well as dynamic changes in receiver coil sensitivity profiles in the moving reference frame of the head. This combined approach is shown to compensate for the predominant motion artifacts present in fMRI data acquired in young healthy adults (simulating head movements of clinical populations).

The first chapter of this thesis reviews the relevant background information motivating the main hypotheses. Chapters 2-4 present the experimental methods developed to test the hypotheses as well as, the experimental results and their implications. Chapter 5 summarizes the conclusions of the thesis and discusses future directions for investigation.

1.1. Functional Neuro-Imaging

In the past few decades, clinical neuroscience has greatly benefited from non-invasive and minimally invasive neuroimaging techniques to study diseases and disorders of the brain. Additionally, neuroimaging has been used ubiquitously for neurological and cognitive psychology research to improve understanding of normal brain function, as well as to develop futuristic therapeutic approaches such as brain-computer interfaces [10]. These neuroimaging techniques include electroencephalography (EEG) [11], magnetoencephalography (MEG) [12], positron emission tomography (PET) [13], and functional MRI (fMRI), among others. The EEG technique detects weak (~μV) electrical signals generated by neuronal activity in the brain using electrodes placed on the scalp. In a similar fashion but with higher spatial resolution, MEG uses extremely sensitive magnetometers to measure the very small magnetic fields (~fT) generated in the brain as a result of neuronal activity. The PET technique measures the emissions from radioactively labeled metabolically active chemicals (called radio-pharmaceuticals) that have been injected into the bloodstream. Functional MRI, the focus of this thesis, measures the dynamic change in the blood oxygenation that is coupled with neuronal activity [2]–[4]. Both
EEG and MEG share high temporal resolution (< 1 ms) [11] [12], but typically have limited spatial resolution (~ 1 cm) and depth penetration. Conversely, PET and fMRI have significantly higher spatial resolutions (1-5 mm), yet lower temporal resolutions. The temporal resolution of PET is dependent on the uptake and decay of the radio-pharmaceuticals [14]. The temporal resolution of fMRI is constrained by the dynamics of blood oxygenation changes, and is usually ~2-3 s [15]. More importantly, unlike PET, fMRI is non-invasive and does not involve any ionizing radiation. Although both PET and fMRI are expensive modalities, fMRI is cheaper and more widely available as it can be performed using most MR systems already installed in clinical sites for radiological purposes. Thus, fMRI has become widely accessed by the neuroscience community.

1.2. Magnetic Resonance Imaging

A brief summary of the basic MR physics is provided below to provide a foundation for the subsequent discussions on fMRI and head motion artifacts.

1.2.1. MR Physics

In MRI, the signal of interest is primarily generated from hydrogen nuclei (protons) present in biological tissues in the form of water. Because protons are positively charged and possess the quantum mechanical property of spin, they have an associated nuclear magnetic moment. When these protons are exposed to a static magnetic field, $\vec{B}_0$, they can align in the direction of the magnetic field (the low energy spin state) or in the opposite direction (the high energy spin state). The number of protons in the low energy state, $n_-$, is slightly larger than that in the high energy state, $n_+$. Because the total number of protons is large, the resulting net nuclear magnetization is observable macroscopically in the direction of $\vec{B}_0$ (the “longitudinal direction”).

Instead of aligning perfectly with the direction of $\vec{B}_0$, the magnetic moments precess around the $\vec{B}_0$ axis. Precession is similar to the “wobbling” motion of a spinning top on a horizontal surface under the influence of gravity, during which the axis of the spinning top rotates around the vertical axis. The frequency of the precession for water molecules is known as the Larmor frequency, $f_0$, described by:

$$f_0 = \gamma |\vec{B}_0|.$$  \hspace{1cm} (1.1)
where $\gamma$ is the gyromagnetic ratio, a fundamental constant equal to 42.56 MHz/T for one hydrogen isotope. At the magnetic field strength of 3 T, therefore the Larmor frequency of hydrogen is 127.6 MHz.

When averaged over a large number of atoms, the net alignment of protons in the direction of the static magnetic field is known as equilibrium magnetization $\vec{M}_0$. By applying a radiofrequency (RF) magnetic field pulse, $\vec{B}_1$, rotating in the transverse plane (i.e., orthogonal to $\vec{B}_0$) at the Larmor frequency, the protons absorb energy and a torque is applied on the equilibrium magnetization such that orientation of magnetization becomes time dependent (subsequently denoted $\vec{M}$), rotating away from the longitudinal direction towards the transverse plane. This interaction between $\vec{M}_0$ and $\vec{M}$ is referred to as “RF excitation” and is illustrated in Fig. 1.

Fig. 1.1. The application of a RF pulse $\vec{B}_1$ in the transverse (xy) plane causes $\vec{M}_0$ to rotate away from its equilibrium value $\vec{M}_0$ along the longitudinal axis (z), while still precessing around it in the laboratory frame of reference. This causes $\vec{M}$ to acquire a transverse component at the Larmor frequency.

The trajectory that the magnetization takes as a function of time is explained by the Bloch equation,
\[
\frac{\partial \vec{M}}{\partial t} = \gamma i \vec{\alpha} \cdot (\vec{B}_0 + \vec{\alpha} \vec{\omega} + \vec{\alpha} \vec{B}_1) = \gamma i \vec{\alpha} \cdot \vec{B}_0 + \gamma i \vec{\alpha} \cdot \vec{B}_1.
\] (1.2)

Equation 1.2 explains the complex behavior of the magnetization as shown in Fig. 1.1. In MR physics, for the sake of simplicity, however, it is common to explain the behavior of the magnetization in the frame rotating at frequency \(\omega\) (equal to the carrier frequency of the \(\vec{B}_1\) excitation field) about the z-axis, called the “rotating frame”. The Bloch equation in the rotating frame is presented by

\[
\frac{\partial \vec{M}}{\partial t} = \gamma \vec{\alpha} \cdot \vec{B}_1 \vec{\omega} - \gamma \vec{\alpha} \cdot \vec{B}_1 \vec{\omega} f f ,
\] (1.3)

where \(\vec{M}\) is the magnetization in the frame and \(\vec{B}_1 = B_1(t) \vec{\omega} \gamma B_0 - \omega/\gamma\) \(\vec{\omega}\), with \(\vec{i}\) and \(\vec{j}\) representing unit vectors in the x- and z-direction, respectively. If \(\omega = \gamma B_0\), then the excitation is said to be “on resonance” and \(\vec{M} = B_1 \vec{\omega}\). In this case, starting from the equilibrium condition, (i.e., \(\vec{M} = \vec{M}_0\)), before RF excitation the magnetization is constant and aligned with the main magnetic field, and during excitation the magnetization simply rotates (flips) towards the transverse plane as shown in Fig. 1.3. For instance, if the excitation is set for a 90° flip angle, then upon turning the RF excitation off, the magnetization is tipped entirely into the transverse plane. The angle to which the magnetization is tipped depends on properties of the RF pulse, including its amplitude, duration and shape. For example, for a rectangular RF pulse of duration \(T\), and amplitude \(B_1\), the flip angle \(\theta\) is given by

\[
\theta = 2 \pi \gamma \int_{t=0}^{T} B_1(t) \vec{\alpha} \cdot \vec{\omega} = 2 \pi \gamma B_1 T .
\] (1.4)

The main consequence of RF excitation \(\vec{M}\) develops a transverse component, called the transverse magnetization and denoted by \(\vec{M}_t\), that rotates at the Larmor frequency.
Fig. 1.2. The on-resonance application of an RF pulse in the transverse (xy) plane causes to rotate (by flip angle $\theta$) away from its equilibrium value along the longitudinal axis ($z$), in the rotating frame of reference. This causes $\vec{M}$ to acquire a transverse component.

After the RF pulse is turned off, the excited magnetization gradually relaxes back to its equilibrium state. (Relaxation refers to a process whereby magnetization recovers in the longitudinal direction, and another whereby transverse magnetization decays to zero. More details on these effects are provided in Section 1.2.2). In addition, the decay of transverse magnetization generates an electromotive force (EMF) in an appropriately oriented RF receiver coil as a result of Faraday induction. The time signal that results from the detection of the rotating transverse magnetization in this manner is called the free induction decay (FID). According to the principle of reciprocity the transmit field is identical to receive sensitivity for a particular coil, and thus this signal is modulated by the transverse component of the RF coil sensitivity profile $\vec{B}_1(x, y, z)$ that is fixed in time. To understand how the RF receiver coil performs, it is useful to consider the received signal $S(t)$:

$$S(t) = -\frac{\partial}{\partial t} \int \frac{1}{\text{vol}} \vec{B}_1(x, y, z) \mu_0 \sigma(x, y, z, t) dV,$$

(1.5)
Hence, the received signal is amplitude modulated at the Larmor frequency and the standard receiver chain includes a demodulator to remove the $2\pi f_0 t$ component of Eq. 1.5. Equation 1.5 shows the signal equation for one coil. However, multi-channel receiver coils typically consisting of 8-64 elements are commonly used in modern MRI experiments to increase signal-to-noise ratio (SNR) and enable “parallel imaging” reconstruction approaches (see Section 1.2.4). In MR physics, SNR is commonly defined as

$$SNR = \frac{\mu_s}{\sigma_n}.$$  

(1.6)

where $\mu_s$ is the signal mean or expected value and $\sigma_n$ is the standard deviation of the noise, or an estimate thereof. The noise detected by a coil is induced from the entire imaging volume, but is weighted by the non-uniform $\vec{B_1}(x,y,z)$ field. The multi-channel coils improve the SNR by reducing the coil element size thus reducing the effective “sensitive volume” and the noise amplitude of the imaged object detected from each coil element. Multiple receiver coils can be combined into an array such that their sensitive volumes overlap slightly and cover the same volume as a larger coil. The signal of the combined coil is approximately the same amplitude as that of a larger coil that covers the same volume. However, assuming that the dominant source of noise is the imaged object and not the electronics, the noise is reduced, and thus the SNR is improved by this approach. Also, this assumption is often reasonable with good coil design and engineering.

Additionally, Eq. 1.5 demonstrates that the strength of the signal is proportional to $B_0$ and the transverse component of the volume integral of the receive coil sensitivity field. For simplification hereafter, the $i2\pi \gamma B_0$ term will be ignored and the effect of the receive coil sensitivity will be revisited subsequently in the thesis.

1.2.2. Signal Contrast

As explained above, after the RF pulse is turned off, the excited magnetization gradually relaxes back to equilibrium in the longitudinal direction. This process involves two different relaxation
processes: 1) the recovery of the longitudinal magnetization parallel to \( \vec{\mu}_0 \), known as “longitudinal relaxation”, characterized by the T1 relaxation time; and 2) the decay of the transverse magnetization, known as “transverse relaxation” characterized by the T2 relaxation time. The longitudinal relaxation and transverse relaxation of the water protons in biological tissue are approximately exponential with time constants T1 and T2, respectively.

The T1 relaxation process is often referred to as spin-lattice relaxation because it involves the exchange of energy from protons to the surrounding medium (lattice) until the initial equilibrium condition \( \vec{\mu}_0 \) is restored. In water, T1 relaxation is affected by the motion of protons on neighboring water molecules causing a fluctuating nuclear magnetic dipole with a transverse magnetic field near particular proton of interest. The dipole fluctuations occurring at the Larmor frequency stimulate the T1 relaxation process. However the dipolar fluctuations occur over a distribution of frequencies. This distribution, known as the “spectral density function”, \( J(f) \), has a typical appearance of a “low-pass filter”, with values that slowly decrease over a frequency ranging from 0 Hz to a characteristic frequency of molecular motion given by the inverse of the “correlation time”, \( 1/\tau_c \). Above this frequency, \( J(f) \) rapidly decreases. The overall result is that T1 is most efficient at low \( \vec{\mu}_0 \) values, and less efficient as \( \vec{\mu}_0 \) increases. The specific relationship between T1 values and magnetic field is complicated by the numerous factors that affect the dynamics of water molecules in biological tissues, and is beyond the scope of this thesis. However, typical T1 values for brain tissues at 1.5 T and 3.0 T [16] are given in Table 1.1. It is evident from this table that T1 processes occur at approximately the time scale of 1 s for most brain MRI applications [17] [18].

<table>
<thead>
<tr>
<th>Tissue</th>
<th>T1 [ms] at 1.5 T</th>
<th>T1 [ms] at 3.0 T</th>
<th>T2 [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grey Matter</td>
<td>1200</td>
<td>1331</td>
<td>110</td>
</tr>
<tr>
<td>White Matter</td>
<td>756</td>
<td>832</td>
<td>79.6</td>
</tr>
</tbody>
</table>

**Table 1.1.** Typical T1 and T2 values for brain tissues.

The T1 recovery of longitudinal magnetization for biological tissues is well approximated by:

\[
M_z(t) = M_0(1 - e^{-t/T_1}) + M_z(0),
\]

(1.7)
where \( M_x(0) \) is the longitudinal magnetization immediately after RF excitation and \( t \) is the measurement time. Because different tissue types have different T1 values, T1 relaxation can be used to produce MR images with “T1-weighted signal contrast”, by sampling Eq. 1.7 at a single specific point in time.

The T2 relaxation process is often referred to as spin-spin relaxation. Because magnetization must eventually return to its initial equilibrium condition \( M_0(t) \), after RF excitation the transverse magnetization must decay to zero. However, the simple vectorial picture of macroscopic magnetization is insufficient to characterize T2 relaxation simply in terms of T1 relaxation times. At the spatial scale of a proton, two different mechanisms contribute to T2 relaxation. First, similar to T1 relaxation, resonant interactions occur between protons on neighboring water molecules influenced by molecular motion. In this case the interactions enable the magnetic moment characteristics of the two protons to swap, with loss of phase coherence in the transverse plane (misalignment of magnetic moments). Secondly, any component of very low frequency molecular motion (i.e., \( J(0) \)) will slightly adjust the Larmor frequency in the local vicinity of a specific proton, and the effect over all protons is a progressive loss of phase coherence. The \( J(0) \) contribution to T2 relaxation ensures that the dependence on \( M_0 \) is much less evident than for T1 relaxation. Again, the specific mechanisms that determine the T2 value for a specific biological tissue are beyond the scope of the thesis. Typical values are provided in Table 1, however. It is evident that the typical timescale for T2 is \( \sim 50-100 \text{ ms} \).

Analogous to Eq. 1.7, the decay of the transverse magnetization is well approximated by:

\[
M_{xy}(t) = M_{xy}(0) e^{-t/T^2},
\]

(1.8)

where \( M_{xy}(0) \) is the transverse magnetization immediately after RF excitation. Analogous to the case for relaxation, T1, T2 relaxation characteristics of different tissues can be exploited to produce MR images with “T2-weighted signal contrast” by sampling Eq. 1.8) at a single specific point in time.

Combining the equations for longitudinal relaxation (Eq. 1.7) and transverse relaxation (Eq. 1.8) with the Bloch equation in the rotating frame (Eq. 1.2), the behavior of the magnetization as a function of time can be described by
where \( \vec{I}, \vec{J} \) and \( \vec{K} \) are unit vectors in the x-, y-, and z-direction, respectively. Equation 1.9 thus describes the evolution of magnetization at all times during an MR experiment.

Another MR contrast mechanism is based on the dephasing of transverse magnetization due to spatial non-uniformities of the static magnetic field \( \vec{B}_0 \). Such field inhomogeneities enhance decay beyond that caused by intrinsic T2 relaxation and create a spatial distribution of Larmor frequencies within tissue, leading to even faster decay of transverse magnetization, characterized by the time constant T2*. The relationship between the T2* and T2 can be described by:

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

(1.10)

where \( T_2' \) represents the external field inhomogeneity effect. Typical values for T2* in brain MR imaging are approximately 25-35 ms. Considering T2* relaxation, the transverse magnetization is represented by:

\[
M_{xy}(t) = M_{xy}(0) e^{-t/T_2^*},
\]

(1.11)

and images specifically generated to the T2* parameter are referred to as having “T2*-weighted signal contrast”. In addition to the T1, T2 and T2*, the strength of the received MR signal reveals information about the proton density (or protons per unit volume) \( \rho \). This property can also be used as a contrast mechanism in MR images although most tissues have similar water content, such that T1-weighted, T2-weighted, and T2*-weighted images typically have better contrast characteristics. In particular, the contrast parameter of major importance for fMRI is T2*, which will be discussed in Section 1.3.

### 1.2.3. Spatial Encoding in MR Imaging

In the context of MRI, the biological tissue being imaged or “spatially encoded” will be referred to as the “imaging volume”. The imaging volume is divided into smaller volume elements called “voxels” (similar to picture elements, or pixels, in a two dimensional image). Typically, a magnetization vector represents the sum of individual spins in each voxel. In practice, a voxel
may contain signal from various tissue types, each occupying a different “partial volume” and exhibiting different MR signal properties. The partial volume affect the detection of boundaries between different tissue types in MRI, depending on the relative size of the voxel to the underlying anatomical structure.

For spatial encoding of magnetization from the imaging volume, MRI systems contain a set of three gradient coils. The gradient coils generate small magnetic fields in the direction of the main magnetic field that vary linearly in the x, y and z directions, allowing linear manipulation of the Larmor frequency in space. In “multi-slice” MRI, the most common form of spatial encoding, the imaging volume is divided into a number of “slices” through selective RF excitation. Each slice is defined by applying a slice-selective RF excitation with a predefined center frequency and bandwidth together with the z gradient magnetic field, \( G_z \). For example, a slice at a given location \( z_0 \) and thickness \( \Delta z \) will have the following frequency dependencies when \( G_z \) is applied:

\[
f(z_0) = \gamma (B_0 + G_z z_0),
\]

and the bandwidth of Larmor frequencies contained in the slice is given by:

\[
\Delta f = \gamma G_z \Delta z.
\]

To select this slice (i.e., avoid exciting magnetization anywhere else in the imaging volume), an RF pulse is applied with frequency characteristics that closely match those of \( f(z_0) \) (Eq. 1.12) and \( \Delta f \) (Eq. 1.13). In practice this is achieved using “sinc” \( (\sin(x)/x) \) RF pulses truncated and apodized to generate localized and smooth slice profiles in the z-direction with negligible ripples or “ringing”. The other slices at different z positions are selected in an analogous manner by maintaining \( G_z \) and the RF pulse bandwidth, while changing the carrier frequency. This scheme can be used for imaging more than one slice (known as “multi-slice”). Sequential and interleaved acquisition schemes are common in multi-slice MRI. Consider an example of 10 slices. In sequential acquisition, the slices are acquired in order \( 1, 2, 3, \ldots \) whereas interleaved acquisition collects odd-numbered sliced followed by even-numbered slice of vice versa (e.g. 1, 3, 5, \ldots , 2, 4, 6, \ldots ). In most MRI applications, interleaved acquisitions are preferred because slice selection is imperfect. There is a slight effect on magnetization outside the transition zone at the edge of each slice, and the sequential multi-slice acquisitions suffer from a “cross-talk” effect that does not occur in interleaved acquisition.
Once the imaging slice is selected, traditionally the y-gradient magnetic field \( G_y \) is used to apply “phase encoding” by manipulating the phase of the transverse magnetization along the y direction. In addition, the x-gradient magnetic field \( G_x \) applies “frequency encoding” to modulate the transverse magnetization in the x direction as a function of Larmor frequency. The MR signal is measured or “read out” during the frequency-encoding period. The terms phase encoding and frequency encoding were coined during the initial development of spatial encoding for MRI, when it was thought that each was separate encoding mechanism. It is now conventional to think of both encoding processes in a common framework in which the MR signal is digitized and stored in a complex matrix, known as “k-space”. Each line of k-space consists a single phase encoding \((k_y)\) value and a vector containing multiple frequency encoding values \((k_x)\). This is typically achieved by turning on the \( G_y \) gradient at a given amplitude for some fixed duration \( t_y \), during which transverse magnetization at different locations along y will exhibit different phases in proportion to position in the y direction. Subsequently, the \( G_x \) gradient is turned on to frequency encode and read out the transverse magnetization. Once k-space is filled sufficiently by acquiring lines at many different \( k_y \) positions \((G_y)\) amplitudes), the data are mathematically processed using an inverse 2-Dimensional Fourier Transform (2DFT) to produce a final image.

The steps involved in 2DFT MRI are described mathematically in detail below. At position \( z_0 \) and thickness \( \Delta z \), the transverse magnetization at time \( t \) is given by:

\[
M_{xy}(x, y, t) = \int_{z_0 - \Delta z/2}^{z_0 + \Delta z/2} M(x, y, z, t) dz .
\]  

(1.14)

where \( M_{xy}(x, y, t) \) is the transverse magnetization at a given position within the slice, which is a function of the MR physical parameters \( \rho(x, y) \), \( T_1(x, y) \), \( T_2(x, y) \), \( T_2^*(x, y) \) and coil sensitivity. Due to precession in the transverse plane, the transverse magnetization can be described in terms of its spatially dependent magnitude and its phase, \( \Phi \), varying in both time and space, i.e., \( M_{xy}(x, y)e^{-j\Phi(x,y,t)} \). The MR signal, \( S(t) \), that is measured by the receiver coil is the sum of the signal contributions from each voxel, \( s(x, y, t) \), within the slice:

\[
S(t) = \int \int s(x, y, t) dx dy = \int \int M_{xy}(x, y)e^{-j\Phi(x,y,t)} dx dy .
\]  

(1.15)
The phase term can be rewritten as

$$
\Phi(x, y, t) = \frac{3}{2}\pi y \int_0^t B(x, y, \tau) d\tau, \tag{1.16}
$$

where $t$ is the time that $M_{xy}$ is allowed to evolve in the transverse plane prior to measurement. During phase and frequency encoding, the magnetic field $B(x, y, t)$ is the sum of the static magnetic field $B_0$ and the magnetic field introduced by the two gradient fields, $G_x$ and $G_y$:

$$
B(x, y, t) = B_0 + G_x x + G_y y. \tag{1.16}
$$

Therefore, substituting in Eq. 1.15:

$$
S(t) = \int_y \int_x M_{xy}(x, y) e^{-j2\pi y \left( \int_0^t G_x(\tau)d\tau + \int_0^t G_y(\tau)d\tau \right)} e^{-j2\pi B_0 t} dx \, dy, \tag{1.17}
$$

In MRI terminology, the time integrals involving $G_x(t)$ and $G_y(t)$ are referred to as $k_x$ and $k_y$, respectively thus defining the k-space coordinates:

$$
\begin{cases}
  k_x = \gamma \int_0^t G_x(\tau) d\tau \\
  k_y = \gamma \int_0^t G_y(\tau) d\tau
\end{cases} \tag{1.18}
$$

where $t$ and $t_y$ are the durations that $G_x$ and $G_y$ are turned on.

It is evident that Eq. 1.17 is very close to the Fourier transform of the image $M_{xy}(x, y)$. However, the time dependence of $S(t)$ and $k_x(t)$ has a special significance. For 2DFT MRI, it is not possible to reconstruct $M_{xy}(x, y)$ simply by collecting a single $S(t)$. Instead multiple versions of $S(t)$ must be acquired to ensure that k-space is sampled sufficiently so that $M_{xy}(x, y)$ can be reconstructed at the appropriate spatial resolution from a matrix $S(k_x, k_y)$. Thus, MR images can be reconstructed by filling the sampled k-space MR signals in the presence of appropriate encoding gradients and taking the inverse 2DFT of all the recorded data $S(k_x, k_y)$.
Experimentally, matrix $S(k_x, k_y)$ is filled using an MRI “pulse sequence” (see Fig. 1.3) which is represented diagrammatically by plotting the RF pulse and gradient waveforms as a function of time during RF excitation and spatial encoding. Following slice selection, a horizontal line of k-space i.e., a frequency encoding line with constant $k_y$ (corresponding to a y-gradient with magnitude $G_y$ and duration $t_y$), is acquired. Other horizontal lines of k-space are acquired by changing the magnitude of $G_y$ (increments of $G_y$) while maintaining $t_y$ and $G_x$ as constant. Fig. 1.3(b) presents the associated k-space trajectory during readout for a single phase encoding step, where TR is the repetition between consecutive RF pulses and TE is the “echo time” when MR signal is measured at the center of k-space $S(k_x = 0, k_y = 0)$.

Mathematically, filling k-space by measuring $S(k_x, k_y)$ corresponds to sampling the 2D Fourier transform of the magnetization $M_{xy}$ discretely in $k_x$ and $k_y$ directions by $\Delta k_x$ and $\Delta k_y$ sampling steps, respectively. In the image domain, this is equivalent to replicating the magnetization $M_{xy}$ at intervals of $1/\Delta k_x$ in the x direction and $1/\Delta k_y$ in the y direction. The separation of these replicates determines the field of view (FOV) of the image that avoids “fold-over” or “aliasing” artifacts, yielding

$$1/\Delta k_x = \frac{1}{G_x \Delta t},$$

$$1/\Delta k_y = \frac{1}{G_y \Delta t},$$

where $FOV_x$ and $FOV_y$ are the FOV in x- and y-direction respectively. After filling k-space sufficiently, a simple inverse 2DFT results in the complex MR image. In typical clinical MRI applications, the magnitude image is used only and the phase image is discarded. However, the phase image can provide useful information in certain applications. For example, the use of MR phase images to map spatial inhomogeneities in the main magnetic field is discussed in Section 1.2.5.2 below.
1.2.4. Parallel Imaging Reconstruction

Parallel imaging reconstruction methods can be used to reduce scan time in MRI, taking advantage of the fact that scan time is linearly proportional to the number of phase-encoding
Increasing the distance between phase-encoding lines in k-space by a factor of $R$, while keeping the k-space maximal extent unchanged, reduces the scan time by the same factor $R$, the quantity commonly referred to as the parallel-imaging acceleration factor. Increasing the distance between the phase-encoding lines is equivalent to decreasing the FOV, causing the object to extend outside the FOV and causing “aliasing” artifacts to occur. Various parallel-imaging strategies have been developed that exploit the spatial non-uniformity of the sensitivity maps of the multi-channel head coils to remove aliasing by performing parallel imaging reconstruction in image space, or to prevent aliasing artifacts by performing parallel imaging reconstruction in k-space. Two of the most commonly used parallel imaging strategies are SENSE (Sensitivity Encoding) [19] and GRAPPA (GeneRalized Autocalibrating Partially Parallel Acquisitions) [20] that enable parallel imaging reconstruction in image space and k-space, respectively. Both methods typically provide an $R$ value ranging from 2-4 and are used extensively in Chapter 4 where they are summarized in more detail.

1.2.5. Echo-Planar Imaging (EPI)

As mentioned above, measured MR signal is often referred to as an “echo”, which is generated by aligning the phase of the precessing spins. Echoes are necessary because the Larmor frequency can be non-uniform across an object due to several mechanisms: 1) spatial inhomogeneities in the static magnetic field, $B_0$; 2) magnetic susceptibility differences between different materials that yield magnetic field variations (for example, between air and tissue); and 3) the application of gradient fields for spatial encoding. Two different pulse sequences are typically acquired to generate two classes of echoes: the “spin echo” and the “gradient echo”. The spin-echo sequence uses two RF pulses to create T2-weighted signals while correcting for all sources of static magnetic field inhomogeneity. In its simplest form, the gradient echo sequence uses a single RF pulse for excitation, a gradient applied for a specific time and amplitude, followed by application of the gradient with opposite amplitude. Data acquisition during the second gradient waveform will sample a gradient echo that specifically refocuses the linear variation in Larmor frequency generated in the gradient direction. The gradient echo amplitude commonly exhibits T2*-weighted signal contrast.

Multi-slice T2*-weighted gradient-echo sequences provide images of the head in approximately 3-4 minutes. As mentioned later in the thesis, fMRI requires much faster spatial encoding, on the
time scale of approximately \(1 \text{ s}\). This is achievable by using a different spatial encoding method known as echo-planar imaging (EPI), which acquires much more substantial portions of k-space in a short time after a single RF pulse. The variant called “single-shot” 2D EPI is most commonly used for fMRI applications, involving acquisition of the entire \(S(k_x, k_y)\) matrix in a single k-space trajectory after a selective RF excitation [6]. The pulse sequence and k-space trajectory for single-shot EPI are shown in Fig 1.4, characterized by a train of rapid “blips” in \(G_y\) and a rapidly oscillating square-wave in \(G_x\). The resultant k-space is a raster scan that encodes the entire slice with one RF excitation. On modern MRI systems, a single slice can be imaged in approximately 50 ms in this manner.
Fig. 1.4. (a) An EPI pulse sequence. (b) The associated k-space trajectory.

Note that in the EPI reconstruction process, either the odd or the even k-space lines must be time-reversed. The time reversal is potentially confounded by “Nyquist ghosting” artifact due to the opposing readout trajectory of odd and even k-space lines (Fig. 1.4). Nyquist ghosts manifest as an aliased image that is shifted by half of the FOV along the phase encoding direction in image space, superimposed over the real image. Nyquist ghosts arise from difficulties involved in driving the imaging gradients with inaccuracies between the alternating polarity, causing slight differences in MR signal amplitude modulation, phase inconsistency, or k-space data displacement between odd and even k-space lines. For example, one source of Nyquist ghosts involves subtle timing differences of the two readout gradient polarities. The artifacts can be compensated by matching the phases of the “centers” of the even and odd k-space lines (i.e., the even and odd gradient echoes) in image reconstruction [21]. The phase difference between the even and odd echoes is commonly estimated from calibration scans prior to imaging, obtained with frequency encoding in the absence of phase encoding.

1.2.5.1. Geometric Distortion in EPI

Fig. 1.4 shows that single-shot EPI uses a lengthy k-space trajectory to acquire the MR signal. Although each line of k-space is acquired rapidly in the $k_x$ direction, there is potential for substantial T2*-weighting across the phase-encoding steps in the $k_y$ direction. This effect leads to artifacts in the y direction after EPI reconstruction.
As mentioned above, $T2^*$-weighting arises from magnetic field nonuniformities introduced by the magnetic susceptibility differences between different materials, such as at tissue-bone and tissue-air interfaces. For the present discussion, it is also assumed that large scale non-uniformities are not present because the MRI system is “well-shimmed” using specialized linear and high-order shim coils with adjustable current. The field non-uniformities arising from magnetic susceptibility introduce erroneous phase or “off-resonance” effects. Pronounced off-resonance effects can lead to loss of phase coherence within voxels (i.e., “intra-voxel dephasing”) that manifests as signal loss. More moderate off-resonance effects can cause a perturbation of the net phase of the MR signal in an imaging voxel. As explained in Section 1.2.3, the phase of the magnetization encodes the signal position and so off-resonance effects can cause magnetization within a voxel to be assigned to an incorrect location (i.e., causing “geometric distortion”). In the context of brain anatomy, the regions that are most strongly affected by $T2^*$-weighted signal loss and geometric distortion are located near air-tissue interfaces, such as the frontal sinuses and the ear canals.

Various image-processing algorithms have been developed to address the geometric distortion problem, after EPI data have been acquired. As this is pertinent to experiments conducted in the thesis, some background on these methods is provided below.

### 1.2.5.2. Static Geometric Distortion Correction in EPI

To reiterate, EPI is susceptible to geometric distortion in the y direction. Thus, most geometric distortion correction techniques for fMRI intend to return mislocalized signals to the true y-locations.

A widely adopted strategy involves mapping the magnetic field non-uniformity, which enables calculation of one dimensional (1D) displacement maps to correct the mislocated signals [22]. A variety of techniques are available for obtaining the field maps. A common technique is the “double echo” approach that measures the field map by acquiring two images with different echo times (TE1 and TE2, with $TE1 > TE2$) separated by $TE = TE1-TE2$. This technique exploits the fact that the phase evolution of $M_{xy}$ is a function of both time and the off-resonance magnetic field. Dividing the phase difference between the two images by the known TE value yields the magnetic field non-uniformity, $\Delta B_o(x,y)$:
\[
\Delta B_0(x, y) = \frac{\Phi_1(x, y) - \Phi_2(x, y)}{2\pi \gamma \Delta E}
\]  \hspace{1cm} (1.20)

where \(\Phi_1\) and \(\Phi_2\) are phase images collected at TE1 and TE2, respectively. One limitation of this approach is that phase values outside the range \([-\pi, \pi]\) are not uniquely determined in \(\Phi_1\) and \(\Phi_2\), and are mapped into this phase range. Thus, “phase-unwrapping” must be applied to remove spatial discontinuities that occur in regions where \(\Delta B_0\) values exceed the available phase range. However, phase-unwrapping is a challenging problem to solve because of a) noise contamination, and b) the cumulative nature of phase unwrapping processes that can cause unwrapping errors from one voxel to propagate into neighboring voxels, and further throughout the image [23].

Other approaches estimate field maps using forward models that require detailed \textit{a priori} knowledge of the spatial variations in magnetic susceptibility, the orientation of the imaging volume with respect to \(\vec{B}_0\), and require intensive computation [24]. Alternatively, 1D displacement maps can be obtained without first calculating \(\Delta B_0\) using a method called Phase Labeling for Additional Position Encoding (PLACE) [25]. The PLACE method involves comparing the phases of two EPI images that differ from one another by a linear phase ramp introduced along the phase encoding direction. The linear phase ramp is created in one image by increasing (or decreasing) the initial phase encoding gradient amplitude in the EPI sequence. This shifts the k-space trajectory in the \(k_y\)-direction by multiples of the k-space sampling interval \(\Delta k_y\), i.e., \(d\Delta k_y\), where \(d\) is an integer. For example, Fig 1.5 shows EPI k-space trajectories separated by two \(\Delta k_y\) steps.
According to the Fourier Shift Theorem, the shift in k-space results in a linear phase ramp in image space that is proportional to the true position of the signal and the shift $d\Delta k_y$, hence

$$\Phi_1 - \Phi_2 = 2\pi \cdot d\Delta k_y \cdot y,$$

where $\Delta k_y = 1/\text{FOV}_y$ and $y$ is the true position of the signal in the phase encoding direction. The $y$ values can then be used to return the signals mislocated due to $\Delta B_0$ effects back to their original locations. Additionally, PLACE is able to correct for Nyquist ghost artifacts by taking advantage of the fact that the artifacts are also phase labeled. One main benefit of PLACE over other algorithms is that it does not require use of phase-unwrapping algorithms. Moreover, PLACE has been successfully integrated as a “static” magnetic field nonuniformity correction in fMRI time series data [26]. The static correction assumes that the head remains still and that the magnetic field map applies at all points in the fMRI time series. However, geometric distortions can vary dynamically due to head motion. In this thesis the PLACE method is further refined to compensate for dynamic geometric distortion, as described in Chapter 2.

### 1.3. Functional MRI

#### 1.3.1. Contrast Mechanisms in functional MRI

To this point in the introduction, the basics of MRI theory, image contrast, and spatial encoding have been briefly summarized. The remaining sections are devoted to summarizing the present
state of fMRI technology as pertinent to the proposed research, starting with the contrast mechanism in functional MRI. When brain neurons are active beyond basal levels, either due to a sensory stimulus (e.g. visual), during spontaneous fluctuations in the resting state, or a behavioral task that requires an active response to be performed (e.g. a motor task), the nearby vasculature experiences a transient increase in the blood flow, volume, and oxygenation known as the hemodynamic response [2]–[4]. This increased blood oxygenation is linked to cellular metabolism, as neuronal activity is an energy-consuming process. It is known that most human tissues are slightly diamagnetic due to their high water content. This is also true of oxygenated blood, which contains oxyhemoglobin. However, the removal of oxygen from the blood produces deoxyhemoglobin, which is paramagnetic. When neurons are activated, they consume oxygen and this leads to the hemodynamic response that increases the oxyhemoglobin content within capillaries and draining veins. This process improves the homogeneity of the magnetic field in at the microscopic level, and thus yields a slight increase in the T2* relaxation time compared to the basal level. The transient change in T2* values is the foundation of the blood oxygenation level dependent (BOLD) fMRI signal contrast mechanism, where local increases in blood oxygenation translate to increased image intensity on T2*-weighted image [2]–[4].

Functional MRI requires the collection of many T2*-weighted images in a time series with adequate temporal resolution to sample BOLD hemodynamic responses appropriately. This is often done by imaging multiple slices of the brain volume over a period of 5-10 minutes. Each image volume typically takes 1-2 s to acquire and with comparatively low spatial resolution (e.g., \(3 \text{ mm} \times 3 \text{ mm} \times 4 \text{ mm}\) in x, y, and z directions, respectively) in relation to the anatomical MRI. The spatial resolution in z-direction is commonly less than that in x and y directions to provide more brain coverage. Unfortunately, BOLD signal changes are small, typically in the 1-5% range at 1.5-3 T [27]. The hemodynamic response is also sluggish compared to electrophysiological neural activity which occurs on a millisecond time scale. The BOLD signal typically increases with a 1 s delay following the onset of a brief neural stimulus, peaks after a period of 5-7 s, and then returns to the baseline 10-15 s later [28]–[30]. For most fMRI applications, the temporal resolution of the hemodynamic response makes EPI and related fMRI spatial encoding options essential.

1.3.2. Experiment Design and Data Processing for fMRI
Although it is possible to map brain activity by fMRI methods where the subject or patient remains at rest, “resting state” fMRI procedures are not the focus of this thesis. Here the focus is on “task-based fMRI” that attempts to measure brain activity associated with specific behaviors. This is typically achieved using one of two experimental approaches: either a “block-design” or an “event-related” design, each with different strengths and weaknesses.

In block-design fMRI experiments, the stimulus of interest (or behavioral task) is repeated over a time period or “block” typically of 15-30 s duration, followed by a block of similar duration that is used to sample the BOLD signal under baseline (or control) conditions. The former block is referred to as the “task block” and the latter is often known as the “rest block” (or “control block”). During the rest block, brain activity is at basal levels in the resting state. Alternatively, a control block is used to separate certain aspects of regional brain activity that are not of primary interest in subsequent brain maps (e.g., motor regions associated with making responses in experiments designed primarily to study regions involved in cognition). To improve statistical power, the task and rest (or control) blocks are alternated over a single fMRI time series or “run” which usually lasts 3-10 min. In event-related fMRI experiments, the stimulus or task duration is typically briefer (~100 ms -3 s) than the duration of the rest condition (~5-30 s). Compared to event-related design, block-design fMRI makes it difficult to evaluate variations in task performance on the time scale of each block, such as performance errors. Event-related signals are weaker and require longer scan times for suitable statistical power, but enable variations in task performance to be evaluated and enable improved measurement of BOLD signal temporal dynamics.

Given that a given EPI slice location is acquired many times in the fMRI time series, the analysis of fMRI data involves comparison of these data with a mathematical model of the expected BOLD response for the given experiment design. The model is generated by considering a) the “task waveform”, typically a binary square wave correctly representing the block or event timing with the task condition given the amplitude “1” and the rest condition given the amplitude “0”; and b) the BOLD hemodynamic response, typically a canonical function with the appropriate time lag and shape. The expected BOLD response is then generated by mathematical convolution of the task and hemodynamic response waveform. One frequently used technique to compare the acquired fMRI data with the expected BOLD response is the general linear model (GLM), a univariate statistical model that treats the measured time series data as a linear combination of
“model functions” (the expected BOLD response, as well as other spurious fluctuations expected in the data, such as linear trends, known as “nuisance regressors”) and noise. For one voxel the GLM is given by

\[ Y = X \beta + e, \]  

(1.22)

where \( Y \) is a \( N \times 1 \) vector of the measured BOLD time series (with \( N \) equal to the number of acquired images in the time series), \( X \) is a \( N \times q \) matrix of regressors called the “design matrix”, where each of the \( q \) columns is a model function, \( \beta \) is a \( q \times 1 \) vector of unknown model coefficients, and \( e \) is the residual error. The GLM analysis aims to find the coefficients \( \beta \) such that the linear combination of the model functions provides the least-squares fit of the measured time series. The solution of Eq. 1.22 can then be written as

\[ \hat{\beta} = (X^T X)^{-1} X^T Y, \]  

(1.23)

where \( \hat{\beta} \) is the vector of estimated coefficients made by computing the pseudo-inverse of \( X \). As part of estimating these coefficients, it is important to perform tests of statistical significance. One typical approach involves rejecting the null hypothesis \( H_0: \beta_i = 0 \) for \( i \in \{1, 2, \ldots, q\} \) in a simple block design experiment. This is equivalent to performing a student’s t-test with

\[ t = \frac{c^T \hat{\beta}}{\sigma_e \sqrt{c^T (X^T X)^{-1} c}}, \]  

(1.24)

where \( t \) is a \( 1 \times q \) vector with each element representing the \( t \) value for each parameter estimate \( i \), \( \sigma_e \) is the variance of the residual error and \( c \) is a \( 1 \times q \) vector called the “contrast”, consisting of a single 1 at the \( i \)-th index and zeros elsewhere. The \( t \)-value can then be evaluated with respect to the \( t \)-distribution with \( N - 2 \) degrees of freedom (DOF), to obtain a \( p \)-value for assessment of statistical significance. The statistical significance is determined with respect to the threshold \( t \) value with \( p = \alpha \), with \( \alpha = 0.05 \) often taken as an acceptable level of type I error.

To obtain fMRI activation maps, the GLM analysis is applied to every voxel independently. Thus, very many individual \( t \)-tests are performed. This procedure leads to the “multiple comparisons problem”: repeated hypothesis testing will increase the total rate of false positive brain activity. Choosing a \( \alpha = 0.05 \) means that 5% of tests will yield a false-positive result. For
example, for a brain volume imaged with $64 \times 64 \times 32$ voxels, 6553 false positives are expected. Several statistical methods have been developed to mitigate this problem by adjusting the p-value threshold. Common approaches in fMRI include Bonferroni correction, the false discovery rate (FDR) and clustering [31]–[33]. Bonferroni correction is rather conservative and although it reduces the probability of false positives, it substantially increases the probability of failing to reject a false null hypothesis (“false negatives”). The FDR correction approach is less conservative compared to Bonferroni correction, reducing false positives by limiting the expected ratio of false positives to the total number of significant discoveries. Assigning a threshold based on the size of activated clusters of voxels can also be used to reject activity that occurs over very small volumes (e.g., 1 voxel), assuming that larger regions of activity are likely to be true positives. Each of these methods is commonly used in fMRI analysis and there is no gold standard.

Finally, the statistically significant results are commonly presented as a color “activation map” overlaid on top of an anatomical grayscale image. The anatomical image is typically acquired as a part of the examination so that the head position during fMRI and anatomical MRI match as closely as possible.

1.4. Head Motion: A Major Confound in fMRI

In the GLM approach summarized in the previous section, the design matrix was stated to include both the model of the expected BOLD signal as well as vectors representing various nuisance covariates. Given the weakness of BOLD signals these nuisance covariates or “signal artifacts” are of considerable concern, as they have the potential to impair the interpretation of fMRI data. Assuming a well-maintained, state-of-the-art MRI system, many sources of artifact can be eliminated before fMRI data are even acquired. However, head motion is usually unavoidable during fMRI. The effect of head motion on fMRI data is complicated, and ranks as the most serious source of artifact affecting fMRI. The effects of head motion in fMRI are central to this thesis and will be described in detail below.

1.4.1. Characteristics of Head Motion

In characterizing head motion, the spatial, temporal, and amplitude properties are all important. Spatial characteristics refer to the direction of motion, considering head as a rigid body.
Typically, the spatial characteristics of head motion are reported in 6 DOF: translations in the x, y, and z directions, and rotations about the x-axis (pitch), y-axis (yaw), and z-axis (roll). The spatial characteristic of the motion influences the type(s) of head motion artifact that is present within a given fMRI dataset, acquired with a given scan plane orientation.

Because acquisition of a single EPI slice occurs in a short time (~50 ms), head displacement during each slice acquisition is usually negligible, whereas head displacement between successive excitations of the same slice is potentially significant in the times series. This temporal characteristic of head motion causes “partial volume artifacts”. More information about this artifact can be found in Section 1.4.3.1. Additionally, the extent that the head motion is correlated to the task waveform has important implications. For example, random head motion increases the effective noise level, obscuring the BOLD signal and resulting in increased false-negative brain activations. Slow head motions can often be corrected by temporal detrending or nuisance regression in the GLM [34]. Task-correlated motion, however, increases the correlation between the task waveform and the fMRI time series data, causing increased false-positive brain activations. Functional MRI experiments can easily include task-correlated motion, as movements associated with task performance are easily transferred to the head. The effects of task-correlated motion are difficult to distinguish from task-related brain activity in the GLM as components of the design matrix become inter-dependent.

Finally, the amplitude of head motion has a substantial impact on the artifacts that are generated. The small amplitude of the BOLD signal unfortunately results in high sensitivity to head motion, necessitating that subjects and patients undergoing fMRI examinations must keep their head still to approximately 1 millimeter and ideally less than this. It is usually the case that head motion in the submillimeter range leads to fMRI data that are usable with careful scrutiny, but that may nevertheless contain non-trivial levels of false positive or false negative activation, even when motion correction strategies are used. However, even this level of motion can remain problematic if fMRI is attempted at high spatial resolution (for example as is possible on ultra-high field MRI systems that are becoming increasingly available at 7.0 T). For larger motion, fMRI data become increasingly contaminated by motion artifact, to the point that the data are unusable. Thus, the strict requirement to limit head motion places a major constraint on fMRI applications.
1.4.2.  Head Motion in Different Populations

Most young healthy adults can control their head motion and hence provide high quality fMRI results. However, controlling head motion is difficult for many patient populations especially those suffering from motor control deficits or cognitive impairment as well as the elderly and pediatrics. For example a previous study evaluated the head motion parameters of schizophrenic patients and age-matched healthy adults during a verbal fluency task [35]. It was found on average that the patients exhibited more problematic task-correlated motion, whereas the healthy adults exhibited primarily linear motion. Another study, compared the head motion parameters between stroke patients (average age 58 years), age-matched healthy adults, and young healthy adults (average age 28 years) during hand gripping and ankle dorsiflexion motor tasks [36]. It was found that the stroke subjects exhibited twice larger head motions (~2 mm) relative to the age-matched healthy adults (~1 mm), who exhibited twice the head motion of the young healthy adults (~0.5 mm). The study also reported the dominant translational and rotational head motion to be in the z- direction and pitch direction, respectively. Additionally, the head motion of stroke patients attained speeds of a few mm/s in some cases. Both these studies emphasize that enhanced motion artifacts are expected in fMRI data due to the larger motion amplitudes exhibited by patient populations compared to healthy adults [35], [36].

It is also the case that the pediatric population, especially younger children, is also affected more prominently than young healthy adults by head motion during fMRI, with reported translational and rotational head motions of approximately 10-12 mm [37][38]. Given the need to perform fMRI of diverse patient populations, there remains a pressing need to develop additional strategies to deal with the effect of head motion.

1.4.3.  Major Head Motion Artifacts

Head motion corrupts fMRI data through multiple artifact mechanisms. Space precludes an exhaustive summary, thus the discussion is restricted to mechanisms that are particularly relevant to the proposed research.

1.4.3.1.  Partial Volume Artifact

The standard fMRI approach is to acquire an EPI undertaken in the static spatial coordinates of the MRI system (i.e., the “static reference frame”). Head motion during fMRI results in a
rotation and/or displacement of the imaging volume and changes the MR signal content of any individual voxel over time. This causes signal fluctuations known as “partial volume artifact”. For example, the signal intensity difference between adjacent voxels in the brain parenchyma is approximately 10-20%, and the signal intensity difference between the adjacent voxels along the edge of the brain is about 10-80%. Therefore, a displacement of 10% of the dimension of a voxel is enough to cause a change in signal intensity of 1-2% and 7-8% in the parenchyma and along the brain edge, respectively. Considering that the in-plane resolution is typically 3 mm for fMRI, a movement as large as 0.3 mm is enough to cause artifactual signal change on the order of the BOLD response.

1.4.3.2. Dynamic Geometric Distortion

It is also increasingly appreciated that fMRI suffers from time-variant geometric distortion variations caused by head motion. As the head moves, the intensity of the signal and its position along the phase encode direction can change as a result of susceptibility-induced magnetic field changes. Dynamic geometric distortion is manifested as signal shift at different locations at different times [24][39]. This signal shift is non-linear with respect to the motion parameters and, hence invalidates the underlying assumption of rigid-body motion as required by common co-registration algorithms used in fMRI. Finally, the strength and extent of geometric distortion is dependent on the position and orientation of the tissue interfaces with respect to the main magnetic field, $B_0$, the amplitude of the head motion, as well as the strength of $B_0$. Yet, the signal shift for typical movements observed in young healthy adults can be as large as ~3 mm at 3 T.

1.4.3.3. Head Motion and Coil Sensitivity

It is now commonplace in fMRI to use multi-channel receiver head coils to improve signal-to-noise ratio, or achieve fMRI at enhanced temporal resolution using parallel-imaging reconstruction. However, these multi-channel head coils have a spatially non-uniform reception field, $\vec{w}(x,y,z)$. As shown in Eq. 1.5Error! Reference source not found., the received MR signal is spatially weighted by the reception field. This creates the possibility that head motion in relation to a fixed multichannel receiver coil could introduce erroneous signal intensity variations that persist in fMRI data, and that might be comparable to or greater than the size of BOLD signals. Thus, after correcting for other major head motion artifact mechanisms, this is a source
of artifact that could adversely impact fMRI datasets. The magnitude of this artifact depends on
the receiver coil geometry, the amplitude and direction of the head motion, acceleration factor (in
parallel imaging), as well as the strength of $B_0$. For typical movements observed in young
healthy adults, the erroneous signal intensity variations due to coil sensitivity changes can be as
large as $\sim$1 mm at 3 T. This artifact mechanism is investigated in Chapter 3 and Chapter 4.

1.5. Motion Suppression

Given that head motion is a major confound in fMRI time series data, substantial attention has
been paid to developing techniques to suppress artifacts. Generally, the head motion suppression
techniques can be categorized as either preventative or corrective. The most important
suppression techniques are discussed below, to provide a foundation for the proposed research.

1.5.1.1. Head Restraints

The simplest and most obvious strategy to prevent head motion is the use of physical restraints.
Foam padding, vacuum pillows placed around the head, as well as thermoplastic masks fitted to
the face and affixed to the MRI system [40] have been shown to reduce head movement with
cooperative and relaxed subjects. However, tight constraints become uncomfortable over time,
with the possibility of exacerbating head motion or confounding brain activity by influencing
task performance. Another restraint approach involves using bite bars with custom-fit dental
molds. Bite bars are extremely useful in younger, healthy subjects, but are too uncomfortable for
many populations, such as the elderly and stroke patients, especially those with swallowing
difficulties [41]. Moreover, safety regulations in clinics mandate that a restraining tool should be
disconnected rapidly in case of an emergency that requires rapid removal of the patient from the
MRI system. Restraints are an incomplete solution, therefore additional strategies are required.

1.5.1.2. Echo Planar Imaging

As indicated in Section 1.2.5, EPI is essential in fMRI to sample BOLD signals with adequate
temporal resolution. An additional advantage of EPI is that each slice is encoded on a very short
timescale ($\sim$ 50 ms) and there is little time for substantial head motion over this period. This is
the reason EPI is also referred to as “snap-shot imaging”, analogous to how a high-speed camera
can “freeze” motion and produce pictures of moving objects without blurring. As discussed
below, EPI provides the additional opportunity to suppress motion that occurs on the timescale
of seconds by translating and rotating individual images back to a common spatial reference as part of post-processing prior to calculation of activation maps. However, the assumption that EPI provides a rigid-body snapshot of head motion is not strictly true. As indicated above, dynamic geometric distortion, and coil sensitivity effects are two factors that have the potential to cause erroneous signal intensity variations that are comparable to the small desirable fMRI BOLD signal, and thus distort the fMRI data.

1.5.1.3. Post-Processing Methods

Post-processing (retrospective) correction techniques aim to compensate for motion-induced artifacts after fMRI time series data have been acquired. Many approaches have been investigated because implementation on a computer is relatively straight-forward in comparison to motion correction during fMRI data collection. Image realignment, also referred to as “image registration”, is the most frequently used retrospective motion correction technique in fMRI primarily correcting for partial volume effects. Image realignment applies 6 DOF transformations to individual images in the fMRI time series such that they best align to a reference image in the same time series. The realignment transformation parameters are estimated from the data by recursively minimizing a “cost function”, which is a similarity measure between the reference and the other image in the time series (e.g., the least-squares difference)[42][43]. Although image registration techniques are useful to correct fMRI data [42], they have several limitations. For example, the accuracy of the estimated transformation parameters depends on the quality of the images. Data that have low resolution, poor SNR, substantial regions of time-varying brain activity [44], or other artifacts such as dynamic geometric distortion limit the estimation accuracy because the assumption of rigid-body motion is weakened. Additionally, most image registration algorithms for fMRI are designed to detect small head movements (i.e., 3-5 mm translations and 1-2 degree rotations) and are likely less reliable for larger motions that may be present in patient populations [42]. Moreover, because of the interpolation, regridding and resampling involved in image alignment, blurring is introduced that may result in spurious activations. Finally, image alignment is slightly more challenging in the case of through-plane head motion, because the spatial resolution of standard fMRI is usually less for the through-plane direction than for the in-plane direction. Newer fMRI approaches are emerging, however, that enable data acquisition with more isotropic voxels.
1.5.1.4. Real-Time Motion Correction Methods

As MRI systems have developed and matured over time, “real-time” imaging has become possible. In the present context, real-time imaging refers to methods that enable spatial encoding to be adjusted, and pulse sequence parameters to be modified during imaging. This capability is distinct from the conventional MRI approach in which a particular pulse sequence is selected, the pulse sequence parameters are determined for appropriate image contrast and image prescription, and then the pulse sequence is executed. With the advancement of real-time imaging, real-time motion correction has received great interest. Real-time motion correction aims to mitigate motion artifacts at the time of data acquisition, rather than by post-processing methods, by adaptively adjusting the scan-plane position and orientation to update the imaging volume by modifying the RF slice select and gradient parameters in the time interval between successive RF excitations. In the ideal case, real-time scan-plane adjustment eliminates partial volume artifacts by maintaining the relative position of the imaging volume within the moving reference frame of the head. Another major benefit that real-time motion correction offers in task-based fMRI (which is the focus of this thesis) is mitigating the potential correlation between the head motion and the task performed, which can otherwise be challenging to correct [45].

There is considerable flexibility with how real-time motion correction can be achieved. Numerous methods have been proposed that differ from one another mainly by how the position of the head is tracked to provide motion information for real-time update of pulse sequence parameters. Ultimately, successful correction depends on the accuracy of the position racking system, as well as the “lag time”, or duration of time between each position measurement and scan-plane, update. Shorter lag time improves performance because there is less time for additional head motion to occur between the position measurement and the subsequent scan-plane update. The position tracking methods used in real-time motion correction can be classified based on whether they measure head position using an MRI measurement, or external hardware that is made compatible with the MRI system environment.

The MRI methods include “navigator”, “active marker” and “image-based” methods. Navigator methods use specialized dedicated k-space acquisitions called navigator echoes to measure head position with one or more DOFs. These echoes are interleaved into the imaging sequence and offer translational and rotational motion information. Although navigator echoes are effective,
interleaving them into the imaging sequence increases the scan duration and hence reduces the temporal resolution of fMRI. Thus, there is a trade-off between the loss of temporal resolution and the frequency of the motion measurements, i.e., number of navigator echoes interleaved into the imaging sequence [46][47]. Additionally, the accuracy of motion information measurements is highly dependent on the spatial encoding accuracy of MRI. Gradient nonlinearity, $B_0$, inhomogeneities and coil sensitivity nonuniformities can all play a role in degrading the position estimates.

The use of an “active” marker has been proposed for motion tracking by MRI methods [48]. An active marker is a device containing a small MRI-sensitive sample enclosed by a small RF coil. A set of such markers is affixed to the head to enable position tracking during MRI. The position of each active marker is measured relative to the magnet iso-center. As the marker is small, the marker position is easily and rapidly determined using a frequency encoding gradient after RF excitation. Employing three active markers offers enough information to estimate head motion with 6 DOF [49][50]. However, the accuracy of each position measurement is adversely affected by the same MRI system imperfections as for navigator echoes. Active marker-based motion tracking also requires switching control of the multi-channel receiver coil, or dedicated receiver channels for each maker.

Image-based methods [1] employ image-registration algorithms to estimate changes in head position between different volume acquisitions. Thus, image-based methods are adversely affected by the MRI system imperfections mentioned above as well as those discussed above for fMRI data processing (i.e., bias from image artifacts, activations, and limited accuracy for large motions). Despite these limitations, the image-based method called Prospective Acquisition CorrEction (PACE) offers a substantial improvement in handling the effects of motion compared to retrospectively corrected and uncorrected data sets, and successfully decreases the variance between successively acquired volumes compared to retrospective correction algorithms [1]. Because PACE is already implemented and available on clinical MRI systems, the method is used as an example of real-time motion correction in this thesis in Chapter 3 and Chapter 4.

It is also possible to perform real-time motion correction for fMRI using “external devices” (i.e., MRI compatible tracking systems). These systems have the potential to provide more accurate position tracking compared to approaches based on MRI. Optical tracking systems have shown
particular promise in improving MR image quality by accurately tracking the head with high temporal and spatial resolution [51][52]. Several implementations have been developed, comprising of either a single video camera [50][53], or two video cameras arranged as a stereoscopic system [54][55][56]. Position tracking is achieved from video recordings of reflective markers affixed to the head. One disadvantage of external tracking systems is that they require extra time for the calibration between the scanner and the tracking system, called “cross-calibration”, which can make them impractical in clinical settings [56]. This procedure is essential to ensure that the head position measured in the camera coordinate frame is properly transformed into the MRI coordinate frame. However, errors in cross-calibration can propagate in the real-time motion correction and introduce additional artifacts [57]. Optical trackers must always have the markers in direct line-of-sight during fMRI [58], which can cause complications if large head motions occur and the view of the markers becomes blocked by the head coil. Furthermore, as the markers are affixed to the skin surface, there is some concern that position tracking may be affected by relative motion between the skin and the skull (e.g., if the subject frowns). For practicality reasons, an external tracking system is not used for real-time motion correction in this thesis.

1.6. Thesis Objectives and Outline

The main aim of this thesis is to develop a robust and comprehensive real-time motion correction system for fMRI. As mentioned above, an ideal real-time motion correction can suppress partial voluming artifact. However, there still remain residual artifacts in the data. Some of the substantial sources of error result from dynamic geometric distortion and head motion-induced coil sensitivity variations. Chapters 2-4 represent methodologies for dealing with these sources of artifact. It should be noted that these chapters have been previously published as scientific research articles [59][60][61]. In addition, multiple people have contributed to these chapters. In each chapter, the specific contributions of each author are declared.

As explained in Section 1.4.3.2, head motion can cause time-varying geometric distortion and signal loss. Because geometric distortion depends on the head position and orientation, it is desirable to correct for geometric distortion at each unique head position. In Chapter 2, dynamic geometric distortion correction is investigated using PLACE (see Section 1.2.5.2). To calculate the PLACE displacement maps in fMRI time series, appropriate image pairs should be employed.
that are selected based on similar head positions. Because PLACE relies on the phase of the image pairs, the distortion correction may be affected by the off-resonance effects induced by respiration. Before calculating the PLACE displacement maps and pairing the images, therefore an off-resonance correction should be performed on the fMRI time series. A previous study has have shown that respiratory artifacts can be effectively suppressed using a correction method called dynamic off-resonance in k-space (DORK) correction [62]. Therefore, in Chapter 2 it is hypothesized that DORK combined with dynamic geometric distortion using PLACE and temporal averaging of PLACE maps acquired at the same head position improves image stability and statistical inference of brain activity in fMRI of young healthy adults.

Aside from dynamic geometric distortion correction, head motion-induced coil sensitivity variations can introduce artifactual signal intensity variations in fMRI data that may be comparable to or greater than the size of BOLD signals when real-time motion correction is employed. The effect of head motion-induced coil sensitivity variation on standard EPI reconstruction is demonstrated in Chapter 3. Two hypotheses are investigated: 1) head motion in relation to fixed multi-channel receiver coils can introduce erroneous signal variations on the order of BOLD signals and thus artifacts in activation maps generated from fMRI with real-time motion correction using PACE; and 2) such artifacts can be suppressed effectively by a procedure that adjusts the orientation and position of the receiver coil sensitivity maps according to head motion.

Accelerated fMRI using parallel-imaging reconstruction techniques has gained attention over the past decade, especially due to the recent advances in very high magnetic-field (e.g., 7 T) MRI systems. On such systems, the T2* value of blood is substantially decreased, accentuating the need to acquire k-space data rapidly. As explained in Section 1.2.4, parallel imaging reconstruction techniques exploit the spatial non-uniformity of the head coil sensitivity maps. However, these techniques are susceptible to variations in coil sensitivity maps that are introduced by head motion. This effect is investigated in Chapter 4. It is hypothesized that: 1) head motion in relation to fixed multi-channel receiver coils can introduce artifact signal variations on the order of BOLD signals, and that the artifacts are observable in activation maps generated by SENSE-fMRI and GRAPPA-fMRI involving real-time motion correction with PACE; and 2) such artifacts in parallel imaging fMRI can be suppressed effectively by a
procedure that adjusts the orientation and position of the receiver coil sensitivity maps to reflect relative positional change between the head and the coil elements.

Finally, Chapter 5 summarizes the conclusions that can be drawn from this work and future work that could be undertaken in the ongoing challenges of suppressing motion artifacts during fMRI.
Chapter 2
Suppressing Respiration Effects when Geometric Distortion is Corrected Dynamically by Phase Labeling for Additional Coordinate Encoding (PLACE) during Functional MRI

A paper published in PLOS ONE, 2016, vol. 11(6), pp 1-19 by
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Contributions: Fred Tam has contributed to image acquisition; Dr. J Jean Chen has helped with data analysis and writing of the article; and Dr. Simon J Graham has contributed to the experiment design, data analysis and writing of the article.

As outlined in Chapter 1, echo planar imaging suffers from geometric distortions caused by magnetic field inhomogeneities, which can be time-varying as a result of small amounts of head motion that occur over minutes during fMRI experiments, also known as dynamic geometric distortion. PLACE is a promising technique for geometric distortion correction without reduced temporal resolution and in principle can be used to correct for motion-induced dynamic geometric distortion. PLACE requires at least two EPI images of the same anatomy that are ideally acquired with no variation in the magnetic field inhomogeneities. However, head motion and lung ventilation during the respiratory cycle can cause changes in magnetic field inhomogeneities within the EPI pair used for PLACE. In this chapter, we exploited the DORK technique and averaging to correct the within EPI pair magnetic field inhomogeneities; and hence proposed a combined technique (DORK+PLACE+averaging) to mitigate dynamic geometric distortion in EPI-based fMRI while preserving the temporal resolution. The performance of the combined DORK, PLACE and averaging technique was characterized through several imaging experiments involving test phantoms and six healthy adult volunteers. Phantom data illustrate reduced temporal standard deviation of fMRI signal intensities after use of combined dynamic PLACE, DORK and averaging compared to the standard processing and static geometric distortion correction. The combined technique also substantially improved the temporal standard deviation and activation maps obtained from human fMRI data in comparison to the results obtained by standard processing and static geometric distortion correction, highlighting the utility of the approach.

2.1. Introduction
As discussed in Chapter 1, fMRI methods typically record signal intensity changes based on hemodynamic responses that accompany neuronal activity, through the blood oxygenation level dependent (BOLD) effect [2], [28], [63]. As BOLD responses evolve on the timescale of seconds, spatial encoding must be conducted much more rapidly than in conventional anatomical MRI. The majority of fMRI studies employ single-shot EPI [64] which, through the use of a raster scan k-space trajectory, typically enables spatial encoding of a single slice in less than 100 ms, and multislice whole-brain coverage in 1-2s. Although EPI enables fMRI with adequate temporal resolution, the raster scan provides much more rapid data acquisition in the frequency encoding direction \((k_x)\) than in the phase encoding (PE) \((k_y)\) direction. This long acquisition time along the PE direction enhances sensitivity to magnetic field inhomogeneity produced by spatial variations in magnetic susceptibility, particularly at air-tissue interfaces [22][65], which cannot be completely suppressed using the conventional static shimming procedures available on whole-body MRI systems. The resulting characteristic EPI artifacts include geometric distortion (localized "compression" or "stretching" of MRI signals in the PE direction) and signal loss (typically near air-filled sinuses) [66]–[68].

Focusing on geometric distortion, a number of methods have been introduced to correct EPI data by first mapping the estimated magnetic field inhomogeneities, then using the field maps to correct for distortions in image post-processing [22], [24], [25], [65], [69]–[76]. Field maps can be produced by various means, such as by subtracting the unwrapped phase images acquired at different echo times [5][6], using multi-channel modulations [69], performing point spread function mapping [70][71] and reversing gradient polarities [72]. In these approaches, preliminary scans are undertaken to generate the estimated field maps that are consequently applied to all images in the EPI time series.

Although beneficial, these approaches may be insufficient in many situations. It is well known that involuntary head motion is present during fMRI in variable amounts depending on the experiment (e.g., study of task-related or resting state brain activity) and the individual that is imaged (e.g., ranging from compliant young healthy adults, to challenging patient populations with cognitive or motor impairments). For instance, head motion can cause partial volume effects induced by tissue misalignment [77] as well as spin history artifacts induced by new magnetization entering the imaging volume [78]. Among the problems introduced by head motion, slight shifts in the location and orientation of the brain with respect to the main magnetic
field produce time-varying magnetic field inhomogeneities, and thus non-rigid “dynamic geometric distortions” in EPI time series data [73]–[75]. Depending on the amount of motion present and the static magnetic field strength of the MRI system, use of a single field map acquired immediately prior to fMRI data collection (subsequently referred to as a “static” field map) may be insufficient to correct dynamic geometric distortions.

Several approaches have been developed to obtain dynamic field maps, as a consequence. One approach is dual echo time EPI [73], however the associated time penalty is a limitation. Another is to predict dynamic field maps using rigid-body motion parameters, but this approach depends on the accuracy of head motion estimates (themselves potentially corrupted by geometric distortion) [74], and on the accuracy of magnetic susceptibility estimates within the head [24]. The use of relative field maps has also been proposed, whereby dynamic maps are estimated by subtracting the unwrapped phase images in the time series from a reference image [75]. Similar to some of the static field map correction methods mentioned above [22]–[65], this approach requires phase unwrapping. Robust phase unwrapping is difficult to achieve, however, especially in the presence of strong magnetic susceptibility or chemical shift effects [22]. Iterative optimization algorithms provide another alternative, whereby the undistorted image and the field map are reconstructed at each point in time using spiral-in/ spiral-out k-space trajectories [76], but with substantially increased computational complexity.

A promising method that overcomes some of the limitations of these recent studies [22], [24], [65], [69]–[76] is known as phase labeling for additional coordinate encoding (PLACE) [25]. The PLACE method requires at least two EPI acquisitions of the same anatomy, with one acquisition using a k-space raster shifted in the ky direction by one PE increment. The resulting phase ramp between the two images encodes the true position of the signal, which can then be retrieved by simple phase calculations without phase unwrapping. The PLACE method has shown promise in correcting static geometric distortions (termed “sPLACE”) equally well as conventional field mapping approaches [26], [79]. In principle, PLACE can also be used to correct for dynamic geometric distortion (termed “dPLACE”) by successively calculating new PLACE maps from EPI pairs throughout time series data collection.

The utility of dPLACE depends on the assumption that there is a negligible change in magnetic field inhomogeneity between EPI pairs. However, in fMRI experiments, dynamic magnetic field
inhomogeneities can arise from EPI time point to time point not only from between the EPI images can arise from head motion, but also from lung ventilation effects during the respiratory cycle. The latter effects are a known source of spurious phase ramps in the ky direction, which can cause subtle, corresponding spatial shifts in a EPI given slice location [62], [80], [81]. Thus, a robust implementation of dPLACE will require additional correction strategies to be adopted.

Pfeuffer et al. [62] performed resting-state fMRI of two healthy young adults and showed that respiratory artifacts were well corrected using a method known as dynamic off-resonance in k-space (DORK) [82]. This method employs the phase from a navigator echo and the centre of the raster scan in k-space to estimate off-resonance effects, and then applies appropriate phase-ramp corrections. Zeller et al. performed additional related work in seven healthy young adults without mapping brain activity [81], reporting more pronounced off-resonance effects observed inferiorly in the brain (closer to the lungs), and that PLACE can be improved by temporal averaging or by using DORK. The DORK-based approach has the advantage of preserving temporal resolution, whereas temporal averaging over the entire time series data collection results in a static field map that suppresses the dynamic field fluctuations of interest.

These initial studies [62], [81] suggest, but do not establish conclusively, that a combined approach involving DORK and dPLACE might be beneficial for fMRI. This assertion needs to be investigated directly. The respiratory correction provided by DORK has a level of experimental error and it is unclear whether the combination of both techniques reduces dynamic geometric distortion sufficiently to improve fMRI results in a practical application. Furthermore, it should be possible to perform more sophisticated temporal averaging to suppress the experimental uncertainty in DORK corrections, recognizing that field maps acquired at the same head position should be highly similar. The present work is consequently designed to investigate these lines of thought. It is hypothesized that DORK combined with dPLACE and temporal averaging of PLACE maps acquired at the same head position improves image stability and statistical inference of brain activity in fMRI of young healthy adults. The experimental findings are subsequently discussed in the context of whether combining DORK, dPLACE and temporal averaging of PLACE maps provides a robust and comprehensive solution for suppressing the effects of dynamic geometric distortion in fMRI studies.

2.2. Materials and Methods
The study was undertaken through successive stages of technical development, initial testing and validation in phantoms, and subsequent human fMRI experiments. The scientific methodology for each component is described in detail below.

2.2.1. Technical Development

2.2.1.1. Phase Labeling for Additional Coordinate Encoding (PLACE)

Pulse sequence modifications were undertaken to enable dPLACE during standard multi-slice single-shot EPI on a research-dedicated MRI system operating at 3 T (Trio with Total Imaging Matrix (TIM), software revision vb17, Siemens, Erlangen, Germany). The modifications had no impact on most pulse sequence elements including radiofrequency excitation, BOLD contrast, repetition time and volume of coverage. For each odd image in the EPI time series, a positive phase encoding increment (a “blip”) was added to the beginning of the train of PE gradient blips. For each even image, a negative blip was added. This resulted in a two-unit shift ($\Delta_k = 2$) in k-space between odd and even complex images, denoted by $I_l$ and $I_m$, acquired at time points $l$ and $m$, where $l$ and $m$ are odd and even numbers, respectively. The original PLACE implementation [25] used a one-unit shift (i.e., $\Delta_k = 1$) in k-space between the two complex images; in preliminary development stages, however, it was observed that increasing the shift to two units yielded less noisy “displacement maps”, as subsequently defined below.

In the original PLACE implementation [25], phase ramp differences are expected in the PE direction within image pairs according to the Fourier shift theorem. In the absence of magnetic field inhomogeneity, the effect is described by

$$I_{l}^{PE} = M_{l}M_{l}^* \exp \left( \frac{2\Delta_k \pi}{i \cdot FOV \cdot y} \right), \quad -\frac{r \cdot V}{2} < y < \frac{r \cdot V}{2}. \quad (2.1)$$

where $M_l$ and $M_m$ are the magnitude of images $I_l$ and $I_m$, respectively; the spatial coordinate $y$ is measured from the isocenter of the PE gradient and represents the physical coordinate in the undistorted images; and $FOV$ is the field of view in PE direction. From Eq. 2.1, $y$ can be extracted as
\[ y = \frac{F_C}{\Delta k\pi} \text{Arg}(f^*\hat{l}_{\text{im}}). \] (2.2)

When magnetic field inhomogeneity is present, however, the resulting geometric distortion implies that in each image, the signals will be mis-located to position \( y' \) instead of their true location \( y \). The spatial shift can be determined simply by applying a linear phase ramp along the PE direction to \( l_l l_{\text{im}}^* \), creating a new complex image \( C \),

\[ C = l_l l_{\text{im}}^* \exp \left( -\frac{2\Delta k\pi}{\text{FOV}} y' \right) = M l_{\text{im}}^* \exp \left( \frac{2\Delta k\pi}{\text{FOV}} (y - y') \right). \] (2.3)

It can be anticipated that an operation analogous to Eq. 2.2 provides a displacement map of the difference, \( \Delta y = y - y' \). (This removes the need to obtain field maps directly, although field maps can be estimated from \( \Delta y \) if needed [83]). However, “crack” and “pile-up” artifacts must be considered, as well as noise. For example, if an image \( P \) pixels wide is directly stretched into a larger image \( Q \) pixels wide \((P < Q)\), there will be at least \( Q - P \) empty pixels (cracks) in the output image. Conversely, compressing an image \( P \) pixels wide into a smaller region \( Q \) pixels wide \((P > Q)\) will result in some pixels receiving signals from more than one source (pile-ups).

To address these problems, according to [25], the complex image \( C \) is expanded in the PE direction by copying each pixel 100 times and performing spatial smoothing. The displacement map \( \Delta y \) is robustly extracted from the expanded and smoothed complex image, \( C_{ES} \), as

\[ \Delta y = \frac{F_C}{2\Delta k\pi} \text{Arg}(C_{ES}). \] (2.4)

Distorted images \( l_l \) and \( l_{\text{im}} \) are then expanded in the PE direction in an analogous fashion, corrected pixel-by-pixel according to \( \Delta y \), then re-binned back to original size.

In the present work, PLACE was performed after EPI data acquisition using custom software developed in MATLAB (the MathWorks, Natick, MA). Two additional steps were included other than the image processing pipeline summarized above. First, additional noise reduction was implemented by complex averaging of data acquired with a multi-channel head coil receiver. Complex averaging not only reduces the overall noise but also leads to a robust combination of
multi-channel data by allowing a magnitude weighting which emphasizes the contribution of regions with higher signals from each channel [84]. Mathematically, multi-channel data were thus combined over all $N_c$ channels according to

$$C = \frac{1}{N_c} \sum_{n=1}^{N_c} M_l(n)M_r(n) \exp \left( \frac{2\Delta_k \pi}{FOV} (y(n) - y') \right).$$  (2.5)

A second, additional procedure was undertaken to ensure that head motion was negligible within EPI pairs. As the initial processing of human fMRI data involved use of a rigid-body registration algorithm (see below) it was possible to use estimates of head motion as constraints. Registration was run on combined (root-sum-of-squares) magnitude images from the multi-channel head coil. Assuming that geometric distortion was not significantly affected by very small displacements, a difference threshold of 0.05 mm for translations and 0.1° for rotations was set to assign image pairs. The search for suitable image pairings started by comparing the head position for each image to that of its neighbouring image in the time series. If neither of the adjacent time points were below the head motion threshold, the search was expanded in time until the difference-threshold conditions were met. Based on the task-based fMRI design (see below), searches were expanded as necessary from the same block of a given task to adjacent task blocks, mitigating the potential for phase confounds arising from the BOLD effect in task and rest conditions.

To perform static geometric distortion correction (sPLACE), the PLACE displacement map obtained from the first pair of EPI images in the time series was applied to all the EPI images in the fMRI time series.

An additional approach was included for dynamic geometric distortion correction (dPLACE), referred to as Displacement Map Averaging (DMA). This approach enabled noise reduction by averaging displacement maps that were obtained for "identical" head positions as determined using the thresholds indicated immediately above. DMA is based on the fact that although ultimately there is a requirement for dynamic geometric distortion correction, the temporal resolution of this correction does not need to be equivalent to that of the fMRI time series data collection. Moreover, the group mean and standard deviation of the number of independent displacement maps that were averaged in DMA was investigated in the human fMRI experiments.
2.2.1.2. Dynamic Off-Resonance in K-space (DORK)

The DORK method assumes that respiration causes a time-dependent frequency shift at a given slice location, leading to linear phase accumulation as EPI data are acquired in k-space. Two phase measurements at different time points are used to estimate both the initial phase of the MRI signal and the frequency offset [82]. This is achieved using a navigator echo (a simple free induction decay without PE) acquired shortly after radiofrequency excitation, and the EPI data acquired at the center of k-space at the echo time $TE$. From these data, acquired at point $t$ in the time series, it is possible to estimate the frequency shift $\Delta \omega_t = \omega_t - \omega_r$ and phase shift $\Delta \varphi_t = \varphi_t - \varphi_r$ in relation to the reference time point $r$. The EPI k-space data $S(t)$ are subsequently processed to yield corrected signals $S'(t)$ according to

$$S'(t) = S(t) \exp(-i(\Delta \omega t + \Delta \varphi t)).$$ (2.6)

This k-space signal correction manifests as a linear shift in the magnitude of the EP images, however, it changes the phase of the EP images on a voxel-by-voxel basis. Therefore, applying DORK before dPLACE is expected to remove the off-resonance effects from the phases of the EP images and consecutively from the PLACE displacement maps that are derived from the phase difference of two EP images.

The vendor-supplied EPI implementation incorporates three optional navigator echoes at the beginning of each slice acquisition to correct for Nyquist ghosts [21]. Data from the second navigator echo were used to enable DORK correction without further modifications to the pulse sequence. Equation (2.6) was performed separately for each channel after data acquisition, again using custom MATLAB software. Corrections were applied independently to odd and even images in the time series because of the k-space shift between the two data sets.

2.2.2. MRI Experiments

All imaging was performed at Baycrest Hospital in Toronto, using a 12-channel "matrix" head coil receiver on the MRI system, and the body coil for radiofrequency transmission. For all imaging sessions, initial tuning included second-order shimming. Multi-slice single-shot EPI (modified to enable dPLACE and DORK) was employed with TE/TR/flip angle = 30 ms/2000
ms/40°, FOV = 204 mm, 32 oblique axial slices 3.5 mm thick, acquisition matrix = 68 × 68, and 0.47 ms echo spacing.

2.2.2.1. Phantom Experiments

Static phantom experiments were designed to show how respiratory effects can corrupt the correction provided when dPLACE is performed alone, and how the combined approach of DORK+dPLACE+DMA can provide static geometric distortion correction in the presence of respiratory effects. The imaging experiments were performed on a 17 cm-diameter spherical agar phantom constructed based on recommendations by the functional Bioinformatics Research Network (fBIRN) Consortium [85] and providing coil loading and MRI characteristics resembling those of the human brain. During the scans, a lung phantom was positioned next to the fBIRN phantom. The lung phantom, subsequently described as "simulated lungs", consisted of two empty plastic bags, each with a volume of approximately 3 L, similar to the ventilated volume of the average human lung. The two bags were covered by light wet towels, and were connected by plastic tubing (2.5 cm diameter) to a breathing mask located outside the magnet bore, 15 cm away from the phantom. The breathing mask was used to inflate and deflate the plastic bags and move the wet towel to introduce dynamic respiration-induced off-resonance effects. Two “runs” (a and b) were performed without use of the breathing mask ("respiration absent"), and an additional two runs (c and d) were performed with a healthy volunteer free-breathing through the mask to generate off-resonance effects for the duration of each scan ("respiration present"). A pneumatic belt (BioPac, Goleta, USA) was placed around the abdomen of the volunteer and the resultant recordings were used as a surrogate measure of ventilation volume in the simulated lungs. Runs b and d were obtained with TR = 80 ms for a single axial slice using the scan parameters that were otherwise identical to runs a and c (as presented above). Runs b and d were undertaken as an experimental control condition, to evaluate the effect of the simulated lungs on the phase evolution in the EPI time series acquired at lower temporal resolution.

2.2.2.2. Human fMRI Experiments

Six healthy right-handed subjects (2 males and 4 females, average age 27, range 22-32) were imaged. All experiments on human volunteers were performed with the approval of the research
ethics board of Baycrest. All subjects gave written informed consent to participate before their imaging session. Foam padding was placed around each the head of each subject to limit motion. Each subject underwent a resting-state and task-based fMRI run. In the resting-state run (e) the subjects were instructed to close their eyes and relax. During the task-based run (f), the subjects performed task-based fMRI involving self-paced bilateral finger tapping tasks with eight alternating 20 s blocks of “task” and “rest” conditions. This run was initiated with a rest block of 28 s, with data discarded from the initial 8 s duration to ensure that magnetization reached the steady state. A summary of all the imaging runs is provided in Table 2.1.

<table>
<thead>
<tr>
<th>Run</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>phantom, respiration absent, TR=2000 ms</td>
</tr>
<tr>
<td>b</td>
<td>phantom, respiration absent, TR=80 ms</td>
</tr>
<tr>
<td>c</td>
<td>phantom, respiration present, TR=2000 ms</td>
</tr>
<tr>
<td>d</td>
<td>phantom, respiration present TR=80 ms</td>
</tr>
<tr>
<td>e</td>
<td>human, resting state, TR=2000 ms</td>
</tr>
<tr>
<td>f</td>
<td>human, task-based, TR=2000 ms</td>
</tr>
</tbody>
</table>

Table 2.1. Summary of all imaging runs.

During task-based fMRI, subjects were presented with a cue to start and stop self-paced bilateral finger tapping. Visual stimuli for each block were back-displayed on a projection screen at the rear of the magnet bore using a liquid crystal display projector (Revolution III, Boxlight 6000, Boxlight Corp, Belfair, WA) through a waveguide in the radiofrequency shield, and viewed by subjects using angled mirrors attached to the top of the head coil. The task was programmed in E-Prime (Psychology Software Tools Inc, Sharpsburg, PA) and lasted 348 s. Subjects were instructed to breathe normally while remaining as still as possible during imaging. The respiratory cycles were monitored during the fMRI using the pneumatic belt, as described above. In addition, all subjects were initially imaged with a T1-weighted 3D magnetization-prepared rapid gradient-echo sequence (TE/flip angle = 2.63ms/6, 1500 ms between inversion preparation pulses, FOV = 256 mm, 160 slices 1 mm thick, and acquisition matrix = 256 × 256), providing images to serve as anatomical reference.

2.2.3. Post-processing Methods
For both phantom and human fMRI experiments, all complex k-space data from each channel were initially reconstructed using custom MATLAB software, with the minimal "baseline" processing consisting of regridding, apodization, and Nyquist ghost correction [21]. To evaluate the performance of sPLACE and dPLACE (with and without DMA and DORK) six different incremental post-processing strategies were investigated: 1) baseline processing to yield magnitude images; 2) sPLACE, 3) dPLACE, 4) dPLACE with DMA, 5) DORK followed by dPLACE, and 6) DORK followed by dPLACE with DMA. Datasets a, c, e and f were processed according to the strategies 1-3 and 6. The remaining strategies, 4 and 5 were only applied to the phantom datasets (a and c) to add additional insight into the comprehensive post-processing strategy (i.e. strategy 6). For ease of presentation, the various acquisition-post-processing combinations are subsequently referred to by a letter-number pair. For example, a2 represents the phantom experiment with respiration absent, EPI with TR=2000 ms, and post-processing with sPLACE correction.

The phase images of datasets b and d were spatially unwrapped using the PRELUDE algorithm [23] of the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl), followed by temporal unwrapping and detrending using MATLAB. Again, the temporal unwrapping was performed independently for odd and even images in the time series. The correlation between the recorded ventilation volume and the time evolution of the spatially-averaged phase images was calculated in MATLAB for odd and even images in the time series individually to assess the performance of the simulated lungs in producing magnetic field fluctuations. A temporal shift was applied to the phase time series to maximize its correlation with the ventilation volume time-course.

Retrospective motion correction was performed using the rigid-body volume registration function in Analysis of Functional NeuroImages (AFNI) software package [42] by aligning all the images in the times series to the tenth image. Moreover, the peak-to-peak (p-p) values were obtained for all six motion parameter estimates (three translation and three rotations) for each subject and the group statistics (mean, standard deviation and range) of the p-p values for each motion parameter were calculated. The directions with the largest p-p range of rotation and translation were determined.

To quantify image stability across fMRI time-series data, temporal standard deviation (tSD) maps were generated using MATLAB for phantom experiments (a and c) and for human imaging
with subjects at rest (e). The tSD value was calculated for each voxel after detrending and motion correction, and was reported as a percentage by normalizing with respect to the mean signal amplitude over the time series. For human imaging, a binary brain mask containing only grey matter and white matter was extracted from the anatomical scans aligned to the motion-corrected fMRI data using SPM12 (Welcome Trust, London, UK). The mask was subsequently applied to all points in the image time series so that only voxels containing brain tissue were included in the analysis. The spatially averaged temporal standard deviation, $tSD$, was also calculated over the whole brain volume as well as over grey matter (the primary source of BOLD signals). The $tSD$ values for sPLACE (e2), DORK+dPLACE+DMA (e6) and the baseline (e1) were compared for statistical significance using two separate directional one-tailed paired t-tests over all six subjects to test the hypothesis that $tSD$ is larger with either e1 or e2 post-processing compared to use of e6. Datasets e3 and f3 were not processed further.

For task-based fMRI, the dPLACE displacement maps after DORK and DMA were assessed by calculating the maximum displacement during the time interval of the fMRI experiment for each voxel and then averaging over the brain volume, yielding the spatially averaged maximum displacement. This metric provides insight about the magnitude of the motion-induced dynamic geometric distortion present in the datasets. Additionally, activation maps were obtained using AFNI after performing slice timing correction; volume registration; detrending; spatial smoothing (Gaussian kernel with 4 mm full width at half maximum); temporal smoothing (3 point median filter); masking fMRI signals to zero outside the brain; and general linear model (GLM) analysis [86]. The GLM was conducted using a “task waveform” boxcar function (with unity amplitude during task blocks and zero during rest blocks) convolved with the canonical BOLD hemodynamic response waveform available in AFNI. Third order polynomial coefficients and the six head motion parameters were also included as nuisance regressors. The results of the GLM analysis were summarized by color activation maps with the threshold for statistical significance determined by correcting for multiple comparisons according to the false discovery rate (FDR) of $q = 0.01$[87]. Activation maps were then overlaid on the respective anatomical images of each subject (previously aligned to the fMRI data) using affine registration in AFNI.

The quality of activation maps was assessed by qualitative visual inspection as well as by two quantitative approaches. First, the number of active voxels (counted over the whole brain) was compared for DORK and dPLACE with DMA (f6), the baseline (f1), and the sPLACE (f2) post-
processing to test the hypothesis that voxel counts increase with use of f6 compared to f1 and f2. Second, the difference between the fitted curve obtained by GLM analysis and the time series was calculated for f6, f1 and f2, yielding voxel-wise residual error signals for each subject. The voxel-wise temporal standard deviation of each residual error signal was then calculated, averaged over the brain volume for each subject, and submitted to two one-tailed paired t-tests as described above. The analogous calculations were also performed for the temporal standard deviation of the residual error signal averaged over grey matter.

2.3. Results

2.3.1. Phantom Experiments

The time evolution of the spatially-averaged phase images (from all channels of the coil combined by complex averaging) was compared with the associated respiratory signal recorded in both the absence (run b) and presence (run d) of respiration. Cross-correlation coefficient values of $-0.05 \pm 0.02$ ($-0.05 \pm 0.02$) and $-0.74 \pm 0.23$ ($-0.75 \pm 0.25$) were found for odd (even) images in the time series data for runs b and d, respectively. These results indicated that the simulated lungs induced off-resonance field fluctuations that were characteristic of respiration.

Because the phantom was stationary during the experiment, the nearest neighbor (adjacent time point) pairing for dPLACE correction always satisfied the displacement threshold. To investigate dPLACE with DMA, the number of averages was limited to 8 to match the practical value observed in human subjects at rest (see human fMRI experiments below).
Fig. 2.1. Phantom experiment results: Temporal standard deviation (tSD) maps in the absence (first row) and presence (second row) of simulated respiration after: 1) no further processing, 2) sPLACE, 3) dPLACE, 4) dPLACE with DMA, 5) DORK and dPLACE, and 6) DORK and dPLACE with DMA.

Fig. 2.1 illustrates the effect of the six post-processing stages (1-6) on tSD values in the absence (run a) and presence (run c) of respiration. First comparing tSD values for a1 and c1, very little difference is observed, indicating that the off-resonance fluctuation caused by the simulated lungs had little effect on magnitude images. This is expected, as the fluctuations in the phase images are known to be much more pronounced [88]. In both a1 and c1, tSD values are appreciable both in regions of Nyquist ghosting and outside the extent of the phantom. There is a very slight trend towards increased tSD values at the upper and lower edges of the phantom in c1 in comparison to a1, which could be indicative of off-resonance effects from simulated respiration. However, since the phantom experiment was conducted with a static phantom, the geometric distortions did not change significantly in a1 and c1 baseline images (i.e., no observable edge artifacts). The application of sPLACE (a2 and c2) has significantly reduced the tSD compared to a1 and c1 respectively, with marginally lower values in absence of respiration (a2) compared to in presence of respiration (c2). This indicates that sPLACE has effectively reduced the static geometric distortion irrespective of the off-resonance frequency fluctuations induced by respiration.

Ideally, in the absence of motion, dynamic geometric distortion correction is expected to perform equivalently to static geometric distortion. Correction using dPLACE alone, however, increases tSD markedly when off-resonance effects from respiration are present (c3). The tSD enhancement observed at the upper and lower edges of the phantom (in the PE direction) suggests that the dPLACE displacement maps contain noise at these locations. The additional noise is likely due to off-resonance respiratory-induced fluctuations as well as partial volume effects that are emphasized as a result of spatial expansion and heavy smoothing involved in dPLACE correction. For a3 in relation to a1, tSD has slightly reduced inside the phantom, and substantial reductions are observed outside the phantom in regions of residual Nyquist ghosts. The true extent of the phantom is better visualized, indicating effective geometric distortion correction, with some elevation in tSD at the edges of the phantom in the y direction due to the partial volume effects discussed above. This difference between a3 and c3 is expected as
dPLACE suppresses geometric distortion but is sensitive to off-resonance frequency fluctuations between image pairs, as previously shown [81][62].

An improvement is achieved by performing dPLACE with DMA, and is clearly evident both in the absence and presence of respiration (a4 and c4, respectively). Use of DMA not only suppresses the cyclic off-resonance fluctuations through averaging, but also reduces the random noise present in the PLACE displacement maps. However, small but noticeable tSD elevations are still observed at the edges of the phantom in a4 and c4. Other than these rim effects, tSD values in a4 and c4 are remarkably similar. The DORK+dPLACE post-processing (a5 and c5) produces tSD values that are substantially improved over the application of dPLACE alone (a3 and c3), and with values within the phantom that are very similar irrespective of whether respiration was present or absent, very similar to dPLACE+DMA results (a4 and c4). However, DORK+dPLACE post-processing shows slightly elevated tSD at the rim of the phantom in comparison to dPLACE+DMA, likely due to experimental error in estimating off-resonance frequency using DORK. Lastly, the final column of Fig. 2.1 shows the results of DORK+dPLACE+DMA (a6 and c6), which demonstrate the best tSD suppression over all of pipelines 3-6: low tSD values within the phantom as well as at the edges due to the use of temporal averaging. No substantial differences in the tSD values for c6 and a6 are observed, indicating that robust static geometric distortion is achieved with correction of off-resonance effects from simulated respiration. Also, comparing DORK+dPLACE+DMA (a6, c6) with sPLACE (a2, c2) no visible difference is observed except for very small increases at the edge of the phantom in a6 and c6. Overall, Fig. 2.1 shows improved temporal standard deviation as a result of using DORK+dPLACE+DMA and good correction for static geometric distortion in presence of respiratory effects. Moreover, the phantom experiments demonstrate how respiratory effects can corrupt the correction provided when dPLACE is performed alone, and how the combined approach of DORK+dPLACE+DMA can provide static geometric distortion correction in the presence of respiratory effects that matches what can be achieved with sPLACE.

2.3.2. Human fMRI Experiments

Although the human fMRI experiments were conducted in young healthy adults and using foam head restraints, small but non-trivial head motion estimates were found through motion
correction in AFNI. The group mean, standard deviation, and the range of the p-p angular rotations (roll, pitch, yaw) and displacements (ΔSI, superior-inferior; ΔRL, right-left; and ΔAP, anterior-posterior) are shown in Figs. 2.2a and 2.2b for subjects at rest and during task-based fMRI, respectively. At rest, the group mean p-p values (black bars) were ≤0.7° over all angular rotations, and ≤0.7 mm over all displacement axes; with group standard deviations (white bars) of ≤0.2° and ≤0.3 mm, respectively; and ranges (error bars) of ≤1.3° and ≤1.7 mm, respectively. During task-based fMRI, head motion was slightly elevated with analogous group mean p-p values of ≤0.9° and ≤1 mm, group standard deviations of ≤0.3° and ≤0.4 mm, and ranges of ≤2.5° and ≤1.9 mm, respectively. For both at-rest and task-based runs, the largest extents of motion were observed in ΔAP and pitch rotation parameters (p<0.05 as measured by Tukey range tests comparing ΔAP with ΔRL and ΔAP, and comparing pitch values with roll and yaw values). Overall, however, motion was constrained to a fraction of the voxel dimension, with even smaller changes observed from time point to time point. Nearest neighbor pairing (ie., sequential images in the fMRI time series) was achieved for dPLACE correction for 90% of points with subjects at rest, and 87% of points during task-based fMRI. For the 13% of points remaining in the latter case, 9% achieved pairings within the same task block, and 4% achieved pairings within adjacent blocks in the fMRI time series.

For dPLACE with DMA, the number of averaged displacement maps had means of 6.3 and 8.5, and standard deviations of 3.8 and 4.6, respectively, for the tasked-based fMRI and for imaging with subjects at rest, over all subjects and time points.

Fig. 2.2. Group mean, standard deviation, and range of p-p head motion for time series data
collection for subjects (a) at rest and (b) during task-based fMRI. $\Delta$SI, $\Delta$RL, and $\Delta$AP denote displacements in the superior-inferior, right-left, and anterior-posterior directions, respectively; roll, pitch and yaw denote the angular rotations about the SI, RL and AP axes, respectively.

Fig. 2.3. tSD maps of three different slices for at rest scans (scan e) of a representative subject after: 1) no further processing, 2) sPLACE, 3) dPLACE, and 6) DORK and dPLACE with DMA. Maps of the percent signal change achieved by the combined approach 6) compared to no further processing 1) are shown at the far right.

Fig. 2.3 shows tSD values for three slice locations from a representative subject at rest (run e) corresponding to the six post-processing stages. The investigation of several slices is important, as previous literature indicates that off-resonance effects are more pronounced in slices that are more inferior and closer to the lungs [89]. In relation to baseline processing (e1), tSD values after dPLACE correction were noticeably increased due to respiratory-induced off-resonance effects especially in the inferior slice location (e3). However, after sPLACE correction (e2) tSD values were visibly decreased but with small edge artifacts still present. The use of DORK+dPLACE+DMA (e6) provided effective dynamic geometric distortion correction and
improved tSD values over the baseline (e1) as well as sPLACE (e2), as also indicated by maps of percent signal change shown in Fig. 2.3 (far right column). The abovementioned trends were observed in all subjects, with a significant reduction in whole-brain tSD value for DORK+dPLACE+DMA compared to use of baseline post-processing (p < 0.05). In addition, there was a trend toward reduced whole-brain tSD values for DORK+dPLACE+DMA compared to use of sPLACE (p = 0.26) that approached significance when only the grey matter tSD was considered (p = 0.09).

Figure 2.4 shows four dPLACE+DORK+DMA displacement maps for task-based fMRI (run f) of the same subject at different points during the image time series, and the associated sPLACE displacement map for comparison. The dynamic displacement maps change visibly over the duration of the fMRI experiment, indicating that the motion-induced dynamic variations in geometric distortion are substantial. More quantitatively, the maximum change in voxel displacement shown in Fig. 2.4 is 1.1 voxels (i.e. 3.3 mm), with a whole-brain average of 0.8 voxels (2.4 mm). The analogous group mean values are 0.7 voxels (2.1 mm) and 0.5 voxels (1.5 mm) for task-based fMRI and resting fMRI runs, respectively.

Figure 2.5 shows brain activation maps derived from task-based fMRI (run f) after DORK+dPLACE+DMA (f6), sPLACE (f2), and baseline processing (f1) for two slices from the same representative subject. Use of sPLACE and DORK+dPLACE+DMA led to an enlargement of the activation areas observed with baseline processing (bilateral primary sensorimotor cortex,
cerebellum). In addition, use of DORK+dPLACE+DMA revealed additional activation of the supplementary motor area that was not observed with the other processing strategies. More quantitatively, Fig. 2.6 shows the number of active voxels over the whole brain across subjects, for post-processing according to f6, f2, and f1. Comparing the spatially averaged temporal standard deviation of the residual error signal, whole-brain values for DORK+dPLACE+DMA were significantly reduced compared to those obtained with baseline post-processing (p < 0.05); and showed a trend toward reduction when compared to use of sPLACE (p=0.18). In addition, the temporal standard deviation of the residual error signal showed a statistically significant reduction for DORK+dPLACE+DMA compared to use of sPLACE, when spatial averaging was conducted over grey matter only (p < 0.05).

**Fig. 2.5.** Activation brain maps for a representative subject after no further processing (baseline), sPLACE and DORK+dPLACE+DMA on two brain slices.
Fig. 2.6. The number of active voxels over the whole brain after baseline (f1), sPLACE (f2), and DORK+dPLACE+DMA (f6) post-processing for all subjects.

2.4. Discussion

This study demonstrates how respiratory effects compromise the PLACE approach for dynamic correction of geometric distortion during fMRI. Robust dynamic correction is achievable by combining DORK and displacement map averaging (DMA) methods prior to executing dPLACE for typical whole-brain fMRI datasets with repetition times of ~2-3 s. The ramifications of the work are discussed below.

First, static phantom experiments with and without cyclic off-resonance fluctuations typical of respiration were performed to implement, debug, and provide early validation of dPLACE. During this process, it was observed that shifting the EPI raster by $\Delta_k = 2$ yielded less noisy displacement maps compared to shifting by $\Delta_k = 1$, particularly in the regions of residual Nyquist ghost. This benefit likely arose because the use of $\Delta_k = 2$ resulted in the same direction of k-space line traversal between each set of two images paired together for PLACE correction, helping to reduce errors in the echo alignments of k-space data that occur with use of $\Delta_k = 1$. The optimal choice of $\Delta_k$ is likely to be scanner-dependent, and is beyond the scope of the present work.

The phantom experiments were also designed as a preliminary step to investigate the impact of various post-processing pipelines for dynamic geometric distortion on image instability, before
proceeding to human fMRI experiments. The phantom experiments were designed without bulk motion with the expectation that the selected dynamic geometric distortion approach should first be able to match the ability of sPLACE to correct for static geometric distortion in presence of respiration induced off-resonance effects. To validate the performance of the simulated lungs in inducing magnetic field fluctuations, additional scans with TR=80 ms were acquired and cross-correlation of the recorded respiratory signal with the global phase fluctuations was calculated both in presence and absence of respiration. The cross-correlation observed between the two time series was within experimental error of the 95% correlation reported in [90] for TR=250 ms, indicating that the phantom experiment was effective in producing off-resonance field fluctuations characteristic of respiration.

It was hypothesized that DORK combined with dPLACE and DMA would improve image stability in phantoms, and improve statistical inference of brain activity in fMRI of young healthy adults. The results that were obtained in phantoms (Fig. 3.1) were strongly supportive. Irrespective of whether simulated respiration was present or absent, DORK+dPLACE+DMA processing robustly improved tSD maps beyond what was observed in the original data (baseline processing) and matching what was achieved by sPLACE for the static phantom. Improvements were observed inside the phantom, and also outside the phantom in zones of Nyquist ghosts. Use of dPLACE in the absence of DORK and DMA caused substantially elevated tSD values in the presence of simulated respiration due to the impact of off-resonance effects on phase differences between EPI pairs [62][81]. This occurred despite the fact that PLACE includes a spatial smoothing process to prevent cracks and pile ups.

Although dPLACE+DMA and DORK+dPLACE processing produced good results compared to use of dPLACE alone, elevated tSD values were observed at the rim of the phantom irrespective of whether simulated respiration was present or absent. For dPLACE+DMA, the elevations were likely due to the effects of averaging substantial phase changes over a limited number of images, whereas for DORK+dPLACE the experimental error in estimating off-resonance frequency using DORK was the likely cause. However, the DORK+dPLACE+DMA approach provides the desired stability, effectively suppressing the rim effect on tSD values. DMA effectively reduces the residual noise remaining in the DORK-corrected PLACE displacement maps. Note that this approach is valid as long as the PLACE displacement maps that are averaged together are acquired at highly similar head positions, and thus affected similarly by geometric distortion.
In the present work, performing DMA over 8 images in the phantom experiments was sufficient to ensure excellent performance of DORK and dPLACE. This observation also reinforces that although ultimately there is a requirement for dynamic geometric distortion correction, the temporal resolution of this correction does not need to be equivalent to that of the fMRI time series data collection. In other words, the dynamic geometric distortion can be implemented as multiple static geometric distortions during the time interval of fMRI experiment.

The excellent results obtained in phantoms made a strong case for progressing to additional validation and hypothesis testing in humans. In human experiments, even compliant young healthy subjects (such as those studied) exhibit small amounts of head motion that potentially can cause dynamic geometric distortion during fMRI. The strategy for pairing EPI images to undertake dPLACE was developed carefully, therefore, based on stringent threshold criteria for assessing whether substantial head motion had occurred. Adjacent image pairs were found to be acceptable for dPLACE correction in the large majority (~90%) of cases throughout the fMRI time series. For the limited cases in which nearest-neighbor pairing was not acceptable, adequate pairing was achieved by searching within the same block and in very few cases the similar adjacent blocks during task-based fMRI. Similar observations were made in a previous study involving dPLACE (but without DORK and DMA) based on motion information obtained from optical position tracking for real-time head motion correction [56]. This previous study used a more generous displacement threshold and thus for almost all (~98%) images in the time series, adjacent image pairs were judged to be acceptable. The present study and [56] do indicate that the image pairings required for dPLACE are not a substantial limitation of the method in the context of fMRI, for experiments involving young healthy adults.

It was important in the present work to evaluate the temporal resolution for dynamic geometric distortion that was practically achievable to provide optimal dPLACE+DORK processing. Using the same motion threshold for establishing image pairs, on average $6.3 \pm 3.8$ and $8.5 \pm 4.6$ displacement maps were averaged for task-based and resting fMRI runs over all the subjects and time points. Utilizing the combined DORK+dPLACE+DMA approach for patient populations (that often exhibit larger head motions) is expected to reduce the number of averaged PLACE displacement maps and may reduce the effectiveness of DORK+PLACE+DMA for fMRI applications. It is possible that this issue can be mitigated by increasing the displacement
threshold slightly while maintaining adequate correction for geometric distortions. Optimizing the displacement threshold is beyond the scope of the present work, however.

Although small amounts of head motion were present in the human fMRI data, dynamic geometric distortion correction (DORK+dPLACE+DMA) proved to be beneficial. Statistically significant improvements were observed in whole-brain tSD (in the resting run) and the number of active voxels and temporal standard deviation of residual error (in the task-based run), relative to baseline processing. Similar trends were observed when comparing DORK+dPLACE+DMA results to those obtained with sPLACE, which achieved statistical significance specifically for task-based fMRI runs when the temporal standard deviation of the residual error was spatially averaged over grey matter. Observing the DORK+dPLACE+DMA displacement maps at various points in the image time series was a useful part of interpreting the results given immediately above. The small head motions that were observed resulted in dynamic changes in geometric distortion that were often a substantial fraction of the voxel size. This suggests that the corrections provided by DORK+dPLACE+DMA would be useful in widespread fMRI applications involving young healthy adults.

It has already been mentioned that if the DORK+dPLACE+DMA approach is to be used in the presence of more substantial head motion, further investigations will be required to optimize the DMA procedure. One issue is the number of images that must be averaged together; another is the type of head motion exhibited by the subject. For example, slowly varying head motions are likely more tractable than more rapid or high-frequency motions. It would be interesting to investigate the robustness of DMA in this regard, and more generally, the PLACE+DORK+DMA approach in populations known to exhibit more problematic head motion (such as stroke patients). However, this is substantially beyond the scope of the present paper as such work would need to include some version of real-time motion correction into the fMRI protocol to satisfy the requirement that PLACE is implemented on EPI pairs that are of the same slice plane [51], [91]–[93].

As expected, some subjects showed more substantial benefit from the DORK+dPLACE+DMA pipeline than others, likely because of subject-dependent anatomical and physiological variations in the amplitude and spatial pattern of respiration-induced off-resonance field fluctuations [89]. Depending on the subject, there may be residual off-resonance effects even after DORK
correction, as the DORK method assumes that respiration causes a global frequency shift within a given image slice. More sophisticated approaches incorporate a spatial distribution of frequency shifts [89], which may be pertinent in the inferior slices closer to the lung cavity, and at higher static magnetic fields. However, the present results indicate that the need to account for a spatial distribution is relatively minor for axial images acquired at 3 T.

It should also be noted that the DORK correction may not perform as well for sagittal and coronal images, where off-resonance effects are more spatially variable within a given slice. In such cases, other off-resonance correction techniques may be employed effectively to make dPLANCE practical [94]. For example [95], the authors have recently compared the performance of several physiological noise correction techniques for mitigating the effects of respiration on PLACE displacement maps, including nuisance variable regression (NVRk) [96], retrospective image-based correction (RETROICOR) [94] and DORK. It was found that among the tested techniques, DORK showed the most promise. Moreover, cardiac effects are also an important noise source in fMRI data (especially those acquired in the resting state). Correction of cardiac noise is not provided by DORK+dPLACE+DMA, as this noise occurs at a higher frequency than both respiratory and head motion, with a complex dependence that relates to the spatial organization of the cerebrovasculature. Nevertheless, the fMRI data acquired and processed by the PLACE+DORK+DMA approach remains amenable to concurrent use of other signal processing approaches to remove cardiac noise (such as RETROICOR).

Considering the fMRI activation maps further, it should be noted that the “ground truth” (i.e., precise knowledge of the true spatial pattern of brain activity associated with the self-paced bilateral finger tapping tasks) is unavailable. In addition, an increase in the number of activated voxels by itself is not necessarily an indication of performance improvement. Similar to the temporal standard deviation at rest, residual errors in the GLM analysis of the task-based fMRI data were also investigated. A statistically significant improvement was observed across the group of subjects as a result of the DORK+dPLACE+DMA approach, compared with baseline processing.

Overall, this study provides a proof-of-concept for practical application of PLACE to correct for dynamic geometric distortion in fMRI time series. Respiratory-induced off-resonance field fluctuations were demonstrated to have an adverse effect on use of dPLACE for human fMRI
with typical long repetition times. Correcting for global off-resonance frequency fluctuations using DORK and DMA enabled application of dPLACE with reduced temporal standard deviation and improved activation map quality. With the aim of developing a robust and comprehensive solution for head motion correction, combining dynamic geometric distortion using PLACE with a real-time motion correction technique is a potential area of future interest, including the application of such work to challenging patient populations.
Chapter 3
A Robust Method for Suppressing Motion-induced Coil Sensitivity Variations during Prospective Correction of Head Motion in fMRI


Contributions: Fred Tam has contributed to image acquisition and setting up the optical tracking system; Dr. J Jean Chen has helped with data analysis and writing of the article; and Dr. Simon J Graham has contributed to the experiment design, data analysis and writing of the article.

As outlined in Chapter 1, prospective motion correction is a promising candidate solution to suppress the effects of head motion during fMRI, ideally allowing the imaging plane to remain fixed with respect to the moving head. Residual signal artifacts may remain, however, because head motion in relation to a fixed multi-channel receiver coil (with non-uniform sensitivity maps) can potentially introduce unwanted signal variations comparable to the weak fMRI BOLD signal (~1-4% at 1.5-3.0 T). The present work aimed to investigate the magnitude of these residual artifacts, and characterize the regime over which prospective motion correction benefits from adjusting sensitivity maps to reflect relative positional change between the head and the coil. Numerical simulations were used to inform human fMRI experiments. The simulations indicated that for axial imaging within a commonly used 12-channel head coil, 5° of head rotation in-plane produced artifact signal changes of ~3%. Subsequently, six young adults were imaged with and without overt head motions of approximately this extent, with and without prospective motion correction using the Prospective Acquisition CorrEction (PACE) method, and with and without sensitivity map adjustments. Sensitivity map adjustments combined with PACE strongly protected against the artifacts of interest, as indicated by comparing three metrics of data quality (number of activated voxels, Dice coefficient of activation overlap, temporal standard deviation of baseline fMRI time series data) across the different experimental conditions. It is concluded that head motion in relation to a fixed multi-channel coil can adversely affect fMRI with prospective motion correction, and that sensitivity map adjustment can mitigate this effect at 3.0 T.

3.1. Introduction
As discussed in Chapter 1, functional MRI is now used very widely as a research tool to measure time-dependent, hemodynamic signal changes that arise from brain activity. However, head motion is a major potential confound. Due to the small fMRI signal changes that arise from the blood oxygenation level dependent (BOLD) effect in response to brain activity (1-4% at 1.5-3.0 T), head displacements of only a few millimeters can be sufficient to generate spurious signal changes artifacts that corrupt fMRI data badly [2]–[4], [27]. Furthermore, these artifacts depend not only on the extent, but also the temporal characteristics of head motion such that the interpretation of brain activity is affected in a complex manner. For example, random head motion acts as a source of temporal noise that increases the number of false negative activations, whereas task-correlated motion increases the number of false positive activations. Correcting for these effects is a difficult problem that remains without a comprehensive solution, despite many years of research [8].

Towards addressing this challenge, one promising class of methods involves "prospective" or "real-time" correction [51], [91], [97], [98]. These methods adjust the scan prescription during imaging to correct for head motion as it occurs, and also require dynamic estimates of head motion parameters so that the position and orientation of the imaging volume can be updated reliably to follow the moving anatomy. These methods were originally developed for anatomical MRI of the brain, assuming that prospective rigid-body correction would be adequate. However, it has become increasingly apparent that such procedures can leave substantial residual artifacts, especially in the context of the fast imaging approaches routinely used in fMRI that involve echo planar imaging (EPI) or spiral k-space readouts. For example, due to the variation in magnetic susceptibility between different brain tissues, head motion causes time-dependent changes in magnetic field uniformity and associated spatial distortions in EPI that cannot be eliminated by rigid-body motion correction [22], [56], [75]. Additionally, nonlinear gradients can induce geometric distortion and lead to signal shifts, thereby interfering with precise localization of anatomical structures even in perfectly prospectively motion-corrected data [99].

Another potential source of residual artifact involves interactions between head motion and the radiofrequency (RF) coils that are used to receive MRI signals [8][7], [100]. This effect has not been studied in relation to prospective motion correction for fMRI, and is the focus of the present work. It is now commonplace in fMRI to use multichannel receiver coils that increase signal-to-noise ratio and enable parallel imaging reconstruction approaches, but which inevitably have
non-uniform spatial sensitivity. This creates the possibility that head motion in relation to a fixed multichannel receiver coil could introduce erroneous signal intensity variations that persist in prospectively motion-corrected fMRI data, and that might be comparable to or greater than the size of BOLD signals (as we will demonstrate in this paper). The erroneous signal intensity variation is expected to be particularly significant with the larger head motions observed in patient populations [101], [102].

Even outside the scope of fMRI applications, the existing literature on interactions between head motion, coil sensitivity and the quality of MRI results is rather limited at present. In one example, rotating a phantom after acquiring coil sensitivity map data was found to cause slight ghosting artifacts in images reconstructed using Generalized Auto-calibrating Partially Parallel Acquisitions (GRAPPA) [103]. In another, multi-slice EPI navigators were used to estimate head motion and combined with GRAPPA-based unaliasing, providing prospective motion correction with good reconstruction fidelity over a range of head positions [104]. Luengviriya et al. [7], [100] showed that for anatomical imaging with prospective motion correction, it is important to take the relative position of coil sensitivity maps into account. Although smaller coils gave better acceleration properties, they were also more sensitive to motion artifacts arising from changes in relative position between the head and the receiver coils. Moreover, inter-scan head motion was also shown to perturb maps of coil sensitivity and to have a negative impact on the accuracy of quantitative T1 mapping [105]. Another study that investigated use of the iterative self-consistent parallel imaging reconstruction (SPIRiT) method [106] showed that residual aliasing remained if subjects moved between acquisitions of the coil sensitivity map and the under-sampled images [107]. In addition, the residual effects of geometric distortions due to gradient nonlinearity in prospective motion-corrected anatomical data are known to require not only gradient “warp” corrections in three-dimensions (3D) but also corrections for coil sensitivity effects [99].

The present study focuses on head motion and multichannel coil sensitivity interactions during fMRI using Prospective Acquisition CorrEction (PACE) for prospective head motion correction [91], and the development of a simple method to correct for coil sensitivity-related artifacts. The PACE method estimates rigid-body head motion parameters from registration of the recently acquired multi-slice image dataset (ie. the “image volume”) to a reference image volume (usually the first) in the fMRI time series data, with a high level of accuracy and adjusts the image volume position and orientation in real-time during data acquisition. The initial development of
PACE showed that the method offers a substantial improvement in handling the effects of motion compared to retrospectively corrected and uncorrected data sets, and successfully decreases the variance between successively acquired volumes compared to retrospective correction algorithms [91]. Here, experiments were designed and implemented to test two hypotheses: 1) head motion in relation to fixed multi-channel receiver coils can introduce artifact signal variations on the order of BOLD signals and thus artifacts in activation maps generated from fMRI with prospective motion correction involving PACE; and 2) that such artifacts can be suppressed effectively by a procedure that adjusts the orientation and position of the receiver coil sensitivity maps according to head motion.

3.2. Materials and Methods

Several steps of increasing complexity were undertaken to investigate the two hypotheses of interest. Briefly, the first step involved theoretical consideration of the different methods commonly used for creating combined images from multi-channel receiver coil data; the mechanism of artifact formation under prospective rigid body motion correction; and development of a correction scheme that involved adjusting the orientation and position of the receiver coil sensitivity maps. Next, the magnitude of the signal artifacts was assessed in progressively more realistic scenarios by numerical simulations. Based on the results of the simulations, imaging experiments were subsequently undertaken with young healthy adult volunteers. The effect of head position and orientation on multichannel coil sensitivity maps was assessed to confirm theoretical assumptions. This was followed by data acquisition involving fMRI with and without PACE, during which subjects were asked to perform overt head motions in the range suggested by the simulations. The resulting activation and temporal standard deviation maps were evaluated in comparison to the case where subjects attempted to remain still and to the case where the proposed correction scheme was implemented.

3.2.1. Theory

The simplest procedure for generating a combined image from multi-channel receiver coil data involves a) generating complex images from each individual receiver coil; and b) reconstructing a final magnitude image using a square root of sum of squares (SOS) procedure. If the 2D image from each coil is denoted by $I_j(x, y)$, where $j \in \{1, \ldots, N\}$ refers to the coil element number (N in total), then the final SOS image $I_{sos}$ is created as
where $\sigma^2_j$ is the noise variance from coil element $j$. Although simple to implement, this procedure provides a sub-optimal result with respect to SNR because noise covariance between coils is not considered. However, an anatomical image with optimal SNR can be reconstructed if the sensitivity maps are known for each receiver coil element. This approach accounts for the fact that image $I_j(x, y)$ results from the product of the spatially dependent complex-valued coil sensitivity $C_j(x, y)$ and the uniform image in absence of coil sensitivity variations, $I(x, y)$:

$$I_j(x, y) = C_j(x, y)I(x, y),$$

and provides a reconstructed image known as the Roemer optimal (RO) combination [108]:

$$I_{RO}(x, y) = \frac{\sum_{jk} \psi_{jk}^{-1} I_j(x, y) I_k(x, y)}{\sum_{jk} \psi_{jk}^{-1} C_j(x, y) C_k(x, y)},$$

where $\psi_{jk}$ is the square $N \times N$ coil noise correlation matrix with non-diagonal elements equal to the noise cross-correlation between coils $j$ and $k$ ($j \neq k$), and the diagonal elements ($j = k$) equal to the noise variance $\sigma^2_j$.

In fMRI, the temporal signal-to-noise ratio (tSNR) is critical for determining success or failure of an experiment [109][110], and is usually less than the SNR of individual images. The tSNR can be described according to

$$tSNR = \sqrt{\frac{N_R}{1 + \lambda^2SNR^2}},$$

where $\lambda$ represents the effect of physiological noise sources [109]. Given that Eq. 3.4 is an ascending function, tSNR is maximal when SNR is maximal and hence the RO combination is also optimal for fMRI purposes.
In the presence of motion, the relative position of the object with respect to the coil sensitivity maps will change. Assuming that the head motion does not significantly affect how the subject “loads” the multichannel coil (likely a good assumption at 1.5 – 3.0 T [107]) and that $\psi_{jk}$ remains unchanged, merely accounting for the orientation of coil sensitivity maps $C_j(x,y)$ according to the subject’s motion in Eq. 3.3 should be sufficient to characterize the artifacts that arise from motion and coil sensitivity interactions. For example, if the head moves in one direction relative to a fixed coil element, this is equivalent to assuming that the head has not moved and the coil has been displaced in the opposite direction in the local “head coordinates” (the frame of reference that moves with the head). The latter scenario is of particular relevance to prospective motion correction methods. For example, in the case that the head rotates by $\theta$ around the z-axis, the prospective motion correction system updates the imaging plane such that the image from the receive coil $j$ will be $I_j(x'(\theta),y'(\theta))$ where

$$\begin{align*}
x'(\theta) &= x\cos(\theta) - y\sin(\theta), \\
y'(\theta) &= x\sin(\theta) + y\cos(\theta). \tag{3.5}
\end{align*}$$

The final combined two dimensional (2D) image $I_{RO}(x'(\theta),y'(\theta))$ is then obtained by applying the same rotation to the coil sensitivity maps in the opposite direction, i.e., $C_j(x'(-\theta),y'(-\theta))$ [111] (see Fig. 3.1). Hereafter, the RO combination (Eq. 3.3) with appropriately adjusted coil sensitivity maps will be referred to as the adjusted sensitivity Roemer optimal (ASRO) combination.
Fig. 3.1. Schematic illustrating how artifact arises in the head frame: (a) the case of no head motion, showing the image superimposed by the intensity profile of one coil element (identified by the white rectangle). The head frame of reference is indicated by the white dashed line. (b) Rotation of the head by angle $\theta$ as observed in the laboratory frame of reference. From this perspective, the head frame rotates by the same angle. (c) The same head motion viewed from the head frame, as achieved by ideal prospective motion correction. From this perspective, the head image appears not to have moved, but the coil sensitivities are rotated in the opposite direction by $-\theta$. See text for further details.

3.2.2. Numerical Simulations

Towards characterizing the regime over which prospective motion correction will benefit from adjusting coil sensitivity maps to reflect relative positional change between the head and the receiver coil, two sets of numerical simulations were performed in MATLAB (MathWorks, Natick, MA). Both simulations included complex-valued coil sensitivity maps and noise correlation characteristics of a 12-channel “matrix” head receiver coil used in subsequent human MRI experiments, described in a section below. The coil sensitivity maps and noise correlation matrix were obtained using a spherical agar phantom (19 cm diameter) constructed based on recommendations by the functional Bioinformatics Research Network (fBIRN) Consortium [85] and providing coil loading and MRI characteristics resembling those of the human brain.
The first simulation was undertaken for preliminary insight. Single shot EPI data were generated of the Shepp-Logan phantom [112] with a 128 by 128 matrix and assuming a spatially uniform $T_2^*$ value of 45 ms. The procedures used for obtaining the coil characteristics are described in the section on MRI experiments (given below), with a change to the FOV (=256 mm), and acquisition matrix size (=128×128) to match the size of the phantom. To generate images for each coil element, the EPI data were multiplied in image space by the appropriate coil sensitivity, and complex white random noise was added in k-space (correlated between the 12 coils) with a typical fMRI SNR of 100 [113]. The position and orientation of the phantom with respect to the imaging plane was held fixed, assuming ideal prospective motion correction. However, the coil sensitivity maps were moved within the phantom coordinate system in the opposite direction of the phantom motion, and subsequently used to generate new images for each channel. Displacements consisting of in-plane translation and rotation, as well as through plane translation and rotation (range 0-5 millimeters, degrees) were each investigated separately. Separate coil images were combined using SOS and RO and the percent signal change arising from interaction between head displacement and coil sensitivity was then calculated in relation to the case of no motion.

The second set of simulations involved time series data synthesized from multi-slice EPI of a human brain. In this case, the intent was to isolate the effect of motion-induced coil sensitivity variation from other motion artifacts in the fMRI time series. For this set of simulations, the coil characteristics were obtained using FOV (=204 mm), and acquisition matrix size (=68×68) to match the size of the EPI brain images. Two regions of interest (ROIs) encompassing bilateral primary motor cortex were manually defined and activation was simulated by increasing the intensity of the selected voxels by 3% (block design; 8 alternating blocks of task and rest; 10-image block duration). Using a constrained second-order dynamic model for realistic head movement representation [114], twenty random in-plane translational motion time series (with identical peak-to-peak (p-p) values) were generated and applied to successive volumes of the simulated time series data, as explained above with SNR of 100. The p-p displacement was chosen to approximate effects observed in human imaging, and also the level shown to produce artifacts comparable to BOLD signal changes in the first simulation (see Fig. 3.4). Images for each coil were combined using SOS and RO. Conventional general linear model (GLM) analysis of the fMRI signals was performed with a boxcar waveform representing the block-design
experiment convolved with a standard hemodynamic response as implemented in the Analysis of Functional NeuroImages (AFNI) freeware package [42]. Activation maps were thresholded using a false discovery rate (FDR) \( q = 0.01 \) for: (i) no motion with SOS; (ii) no motion with RO; (iii) random motion with SOS; (iv) random motion with RO; and (v) random motion with ASRO.

3.2.3. MR Experiments

All imaging was performed at Baycrest Health Sciences in Toronto on a research-dedicated MRI system operating at 3 T (Trio with Total Imaging Matrix (TIM), software revision VB17A, Siemens, Erlangen, Germany), the body coil for RF transmission, the standard 12-channel "matrix" head coil receiver, and second-order shimming. The study was approved by the research ethics board of Baycrest for imaging of young healthy adults, who gave their written informed consent before participating. Multi-slice single-shot EPI was undertaken including PACE with typical scan parameters used to measure BOLD signals during fMRI (TE/TR/flip angle = 30 ms/2000 ms/40º, FOV = 204 mm, 32 oblique axial slices 3.5 mm thick with a 1 mm gap, and acquisition matrix = 68 x 68). Complex k-space data from each receiver channel were initially reconstructed using custom software in MATLAB (the MathWorks, Natick, MA), with the minimal processing consisting of regridding, apodization, and Nyquist ghost correction [21]. The PACE method and further processing of the fMRI data are described below.

3.2.3.1. Head Motion Correction using PACE

The PACE method estimates parameters of 3D rigid body head motion by image-based registration [91]. After real-time reconstruction of the current image volume, a motion detection algorithm is applied, based on rigid-body registration to the first image volume in the fMRI time series. The new position and orientation of the head is then used to adjust the pulse sequence parameters that control slice orientation and position for the next volume acquisition. Updating of the pulse sequence was performed within 3 ms of the start of each scanned volume [91], thus enabling real-time adjustment of position and orientation of the slice stack.

Another significant source of residual artifact in fMRI in presence of head motion is “dynamic geometric distortion” produced by time-dependent changes in magnetic field uniformity [22], [56], [75]. Dynamic geometric distortion causes time-varying "warping" of MRI signals in the phase-encode (y) direction and possible signal loss in EPI. As this source of error could
confound the interpretation of head motion and coil sensitivity effects in this work, dynamic geometric distortion was corrected according to the technique presented in [22][75]. Specifically, data from the multi-channel coil were first combined by complex averaging, reducing the overall noise but also leading to a robust combination of multi-channel data by allowing a magnitude weighting which emphasizes the contribution of regions with higher signals from each channel. Mathematically, multi-channel data were thus combined across all $N$ channels according to

$$m = M_n e^{i\Phi_n} = \frac{1}{N} \sum_{j=1}^{N} M_n(j) e^{i\Phi_n(j)}$$

(3.6)

where $I_n$ is the $n$-th frame in the fMRI time series, and $M_n(j)$ and $\Phi_n(j)$ are the magnitude and phase of the images obtained from coil $j \in \{1, \ldots, N\}$. In the absence of additional correction, each image $I_n$ is warped to some extent as a result of dynamic geometric distortion, as subsequently denoted by the superscript $w$. The corrected “unwarped” image is denoted by the superscript $uw$. The first step in this procedure was to unwrap the phase images $\Phi_n$ for all time points to remove $2\pi$ discontinuities using the Phase Region Expanding Labeler for Unwrapping Discrete Estimates (PRELUDE) algorithm [23] of the FMRIB Software Library v5 (FSL5) (Analysis Group, FMRIB, Oxford, UK) [115], followed by temporal unwrapping and detrending using a custom MATLAB script. Phase-difference maps $\Delta \Phi_n$ (in radians), were then calculated to represent the phase accrual between warped images with dynamic geometric distortion at the $n$-th frame in the fMRI time series ($I_n^w$) and the zero phase reference time-frame ($\Phi_{ref} = 0$). The rationale for choosing the zero phase reference time-frame is that any other $I_{ref}$ will leave a consistent residual geometric distortion within the corrected time series data [75]. The $\Delta \Phi_n$ maps have the following dependency:

$$\Delta \Phi_n = \Phi_n - Arg(I_n^w) = 2\pi. \Delta F_n. TE$$

(3.7)

$$\Delta F_n = \frac{\Delta \Phi_n}{2\pi. TE}, \quad \Delta y_n = \frac{N_y}{BW_y} \Delta F_n$$

where $TE$ is the echo time, $\Delta F_n$ the map of frequency difference (Hz) between the $n$-th and reference time frame, and $BW_y, N_y, \Delta y_n$ are the effective spectral bandwidth (Hz), the
number of voxels in the y-direction, and the map of voxel shift in the y-direction (in fractional voxel units), respectively.

To enhance the reliability of the $\Delta y_n$ map, an additional refinement was added to the procedure described above. The voxels that contained primarily gray or white matter tissues of the brain were segmented using Statistical Parametric Mapping v12 (SPM12) (Wellcome Trust, London, UK) [116]. These voxels represent the tissue of interest and where the field is most reliably known [75]. A binary mask was then generated from the gray matter and white matter segmentation; filled; and dilated by 2 voxels to define the volume over which distortion correction was applied. Two-dimensional cubic interpolation was included to assist in correction at the regions outside the binary mask. The $\Delta y_n$ maps were subsequently used to unwarp the $n$-th time-frame $I_n^w(j)$ for all coils back to the reference time frame, yielding $I_n^{uw}(j)$, by shifting the signal intensity in $I_n^w(j)$ at pixel location $y_n^w$ according to $y_n^{uw} = y_n^w + \Delta y_n$ using cubic spline interpolation for sub-pixel shifts [22]. Image intensity was also corrected to first-order using the derivative of the pixel-shift map along the phase-encode direction [22]. Lastly, retrospective rigid-body motion correction was performed using AFNI on combined images from all the channels to eliminate residual volume-to-volume motion by aligning all the images in the times series to the reference volume.

3.2.3.2. Optical Tracking System, Calibration and Performance

An optical tracking system consisting of two MR-compatible cameras (MRC Systems GmbH, Heidelberg, Germany) was employed to acquire the head position at each time point [56]. The cameras operated under infrared light to avoid affecting visual stimulus presentations during fMRI. To achieve the best field of view for the cameras, the mounts were designed to enable rotations about three axes. The mounts were attached to the interior of the magnet bore by Velcro trademark patches. The distance and the angle between the cameras were 13 cm and $28^\circ$, respectively, providing an approximate FOV of 9 cm $\times$ 9 cm on the subject's forehead viewed through the rungs of the standard 12-channel head coil available on the MRI system.

The calibration and tracking software was written in C++ using the OpenCV library [117]. The tracking system was calibrated in two stages. First, each camera was calibrated for the intrinsic parameters (including radial lens distortion and focal length) by capturing images of a rigid high-contrast checkerboard pattern with known dimensions. The lens distortion parameters were
estimated such that the errors between the imaged patterns and the known dimensions are minimized. Secondly, the tracking system was calibrated for the extrinsic parameters required to make measurements in real-world coordinates. In this stage, both cameras were simultaneously capturing the same rigid high-contrast checkerboard pattern. Using the known dimensions of the checkerboard, the spatial relationship between the two cameras was determined, including the baseline distance between their optical axes, as well as a coordinate frame with real-world dimensional scaling. Nine reflective markers fixed to a low-reflectance surface, referred to as the “tracking tool” were tracked using a “blob tracking function” to follow the position of the tracking tool at 30 Hz from video at 640×480 pixel resolution. The 3D position of the tracking tool was calculated in the tracking system coordinate frame, through triangulation of measurements from the two cameras [56]. The motion parameters, the rotation and translation at time \( t_l \), \( R(t_l) \) and \( T(t_l) \) are estimated such that

\[
\begin{align*}
    \mathbf{x}(t_l) &= R(t_l) \mathbf{x}(t_0) + T(t_l),
\end{align*}
\]

where \( \mathbf{x}(t_0) \) and \( \mathbf{x}(t_l) \) represent the nine points of the tracking tool in the camera coordinates at time \( t_l \) and \( t_0 \), respectively. Determining the spatial transformation between the two sets of data points is known as the problem of absolute orientation (AO). The AO algorithm proposed by Umeyama et al [118] were exploited for this work mainly because of its robustness to noise. The translation and rotation due to head motion between fMRI time points can be determined from the correction matrix

\[
    \mathbf{C} = \mathbf{X}(t_l) - \mathbf{X}(t_0)
\]

where \( \bar{\mathbf{x}}(t_l) \) and \( \bar{\mathbf{x}}(t_0) \) denote the mean vector of the nine points. After decomposing \( \mathbf{C} \) with singular value decomposition (SVD) into \( \mathbf{C} = \mathbf{UDV}^T \), the rotation \( R(t_l) \) is given by

\[
    R(t_l) = \mathbf{U} \begin{bmatrix}
    1 & 0 & 0 \\
    0 & 1 & 0 \\
    0 & 0 & \text{det}(\mathbf{VU}^T)
\end{bmatrix} \mathbf{U}^T,
\]

and the translation \( T(t_l) \) equals,

\[
    T(t_l) = \bar{\mathbf{x}}(t_l) - R(t_l) \bar{\mathbf{x}}(t_0).
\]
The accuracy and precision of the motion parameter measurement was defined as the smallest displacement that yields a mean absolute error of 0.02 mm and standard deviation in absolute error of 0.02 mm. To evaluate the accuracy of the tracking system, the tracking tool was attached to an MRI-compatible optical stage that is capable of moving in three orthogonal directions with 20 μm accuracy. The absolute difference between the measured displacements of the tracking tool and the known applied displacements were calculated, with 10 measurements per position, and its mean and standard deviation were used as metrics to characterize the accuracy of the tracking system. The resulting accuracies were 0.2 ± 0.2 mm, 0.2 ± 0.2 mm and 0.4 ± 0.3 mm for x, y and z directions, respectively. The stability of the tracking system was assessed by the standard deviation of the measured radial position of the static tracking tool over the course of 12 hours. The resulting standard deviation was 0.02 mm, indicating excellent stability.

3.2.3.3. Effect of Head Motion on Coil Loading

The proposed correction procedure relies on the assumption that the spatial sensitivity pattern of a multichannel receiver coil is independent of head position and orientation for small head movements. Given the electromagnetic properties of biological tissues, this assumption is expected to become less valid with increasing static magnetic field strength [119]. Therefore, the assumption was tested explicitly at 3 T. One subject was positioned ten times inside the 12-channel matrix head receiver coil, variably in a 10 mm³ range, and the coil sensitivity profiles and noise correlation matrix were calculated in each case. At each position, a 3D localizer sequence that automatically aligns the imaging volume to the anatomy was run to mimic the effects of prospective motion correction for the static, repositioned object. Two images were then acquired with a 3D T1-weighted magnetization-prepared rapid gradient-echo imaging sequence (TE/flip angle = 2.63 ms/6°, 1500 ms between inversion preparation pulses, FOV = 204 mm, 32 oblique axial slices 3.5 mm thick, and acquisition matrix = 68 ×68): without and with RF excitation. The optical stereo camera motion tracking system was employed during the whole experiment to record the head position [56]. The noise correlation matrix was estimated from the noise images obtained with no RF excitation. In the images acquired with RF excitation, the center portion of k-space (matrix = 32 × 32) was used to obtain coil sensitivity maps. The k-space data from each coil were apodized using a Tukey window [120] to suppress truncation artifacts [121] and inverse Fourier transformed to obtain low-resolution images. Each coil
sensitivity image was subsequently determined using an established technique [19] that involves dividing each low-resolution image by the root sum-of-squares image from all the coil elements, to suppress anatomical features effectively.

The coil sensitivity maps and noise correlation matrix in all positions were compared to that of the first position (the reference position). Using the motion parameters obtained from the optical tracking system, the orientation and location of the coil sensitivity profile at the reference position was adjusted as would be required for the ASRO combination method and the residual difference error was assessed between the corrected coil sensitivity profile at the reference position, and the coil sensitivity profile determined at each position. Analogous difference calculations were performed for the noise correlation matrix data.

3.2.3.4. fMRI Experiments

To investigate the strength of signal artifacts arising from head motion and coil sensitivity interaction during fMRI involving prospective motion correction, and the utility of the proposed correction method, six healthy right-handed subjects were imaged (2 males, 4 females; average age 29; range 22-32). All subjects were initially imaged with a T1-weighted 3D magnetization-prepared rapid gradient-echo sequence (TE/flip angle = 2.63ms/6°, 1500 ms between inversion preparation pulses, FOV = 256 mm, 160 slices 1 mm thick, and acquisition matrix = 256 × 256), providing images to serve as anatomical reference. Also, before the start of each run, the coil sensitivity profiles and noise correlation matrix were calculated in the manner explained above. All the subjects wore MRI-compatible headphones (Siemens, Erlangen, Germany) during imaging, were padded within the head coil to limit motion, and performed task-based fMRI involving self-paced bilateral finger tapping tasks with eight alternating 20 s blocks of “task” and “rest” conditions. The fMRI data collection was initiated with a rest block of 28 s, with data discarded from the initial 8 s to ensure that magnetization reached the steady state. During task-based fMRI, subjects were presented with a cue to start and stop self-paced bilateral finger tapping. Visual stimuli for each block were displayed on a projection screen at the rear of the magnet bore using a liquid crystal display projector (MT1065, NEC Corporation, Itasca, IL) through a waveguide in the RF shield, and viewed by subjects using angled mirrors attached to the top of the head coil. The task was programmed in E-Prime (Psychology Software Tools Inc, Sharpsburg, PA) and lasted 348 s.
The data were acquired as a subset of a larger study. For the purpose of the present study, each subject underwent five different runs of task-based fMRI data collection, with differing instructions to: (a) remain as still as possible while performing the task, designated as the “baseline” level of head motion; (b)(c) perform slow overt in-plane rotations (roll) at discrete time points while performing the task with and without PACE; and (d)(e) perform slow overt through-plane rotations (pitch) at discrete time points while performing the task with and without PACE. Subjects were instructed to perform deliberate head motions (randomly distributed in time), and thus create signal artifacts, when given a verbal cue through the headphones (executed manually as a function of time by one of the researchers, Z.F.). Each subject was given approximately 9 verbal cues per run. For each subject, the order of the runs was randomized to control for order effects (head motion data are shown Fig. 3.6).

To ensure consistency in intra- and inter-subject motion, head position was tracked throughout using the optical stereo camera motion tracking system described above, operating under infrared light to avoid affecting visual stimulus presentations during fMRI [56]. Moreover, training was performed before each fMRI session in an MRI simulator, during which head position tracking data were presented to subjects as real-time visual feedback. In the simulator, head position was tracked using an electromagnetic system (miniBird 800, Ascension Technology Corp., Burlington, VT) with a root-mean-squared accuracy of 1 mm and 0.5°, and displayed as scrolling line plot with separate lines for roll, pitch, and yaw rotation (see Fig. 3.6 for a description of the spatial coordinate system). A pair of static bars in the plot specified a target range of motion as determined from the numerical simulations, i.e., 5°. During training, subjects were instructed to rotate their heads such that the scrolling lines remained within the boundaries set by the bars. During the actual fMRI procedure, subjects were instructed to repeat the same motions.

3.2.3.5. Postprocessing Methods

For all five runs, the acquired k-space data were reconstructed for all channels and corrected for dynamic geometric distortion. The images from all the channels were then combined according to SOS and RO schemes. For runs (b) and (d), specifically, the images were additionally combined using the ASRO correction scheme. For RO combination, the coil sensitivity profiles obtained before each run were used. In ASRO, however, the phase and the magnitude of the complex coil sensitivity profiles were adjusted to account for head movement by appropriately
rotating, translating, and bicubic interpolating according to the parameters recorded by the in-bore motion tracking system. Furthermore, bicubic extrapolation was performed near the edges of the brain for regions which exhibited minimal signal intensity at time zero due to the absence of brain tissue, but higher signal at later times due to head motion. Before performing these operations, the phase of the coil sensitivity maps was unwrapped using the PRELUDE algorithm [23]. For all three combination schemes, a retrospective motion correction was then applied to the combined images as explained above.

To quantify the head motion, the peak-to-peak (p-p) values of all six motion parameter estimates (three translation and three rotations) for each subject were calculated from the motion tracking data. The group statistics (mean, standard deviation and range) of the p-p values for each motion parameter were calculated. The directions with the largest p-p range of rotation and translation were determined.

Activation maps were obtained using AFNI after performing slice timing correction, temporal detrending, spatial smoothing (Gaussian with 4 mm FWHM kernel), temporal smoothing (3-point median filter), masking fMRI signals to zero outside the brain; and general linear model (GLM) analysis [122]. The GLM was conducted using a “task waveform” boxcar function (with unity amplitude during task blocks and zero during rest blocks) convolved with a canonical BOLD hemodynamic response waveform available in AFNI. Third order polynomial coefficients were also included as nuisance regressors. The results of the GLM analysis were summarized by color activation maps with the threshold for statistical significance determined according to the FDR of $q = 0.01$ [87]. Activation maps were then overlaid on the respective anatomical images of each subject (previously aligned to the fMRI data using affine registration in AFNI).

Image stability across the fMRI time-series data was also assessed by temporal standard deviation (tSD) maps generated using MATLAB. The tSD value was calculated for each voxel after detrending, for time points lying inside the rest blocks excluding the first two time points (of each rest block) to prevent the possible confound of activation signals causing increased variance.

Subsequently, for all subjects and runs, fMRI data quality was assessed by qualitative visual inspection as well as by three quantitative approaches. First, the number of active voxels (counted over the whole brain) was compared. Second, the Dice coefficient [123] was calculated...
between whole-brain activation maps of baseline motion (independently for SOS and RO reconstructions) and those of the other runs with in-plane and through-plane motion. The Dice coefficient ranges between 0 and 1, with 0 indicating no overlap and 1 indicating perfect overlap. Third, the spatially averaged temporal standard deviation, $\overline{tSD}$, was calculated over the brain volume for comparison purposes.

3.3. Results

3.3.1. Numerical Simulations

Figure 3.2 shows the percent artifact signal change observed in the first set of simulations, which were designed to investigate the effects of shifting phantom position and orientation within the 12-channel head matrix receiver coil. Simulated artifacts are shown for examples of 3 mm in-plane translation, 5 degrees in-plane rotation, 3 mm through-plane translation, and 5 degrees through-plane rotation (shown in the first row of Fig. 3.2) under SOS and RO combinations. Note that the artifactual signal change does not coincide with the “anatomical” features of the phantom, which are mostly deep within the phantom, but rather is prominent in regions where the coil sensitivity maps change most rapidly, near the phantom’s surface. The artifactual signal change is evident particularly for in-plane changes in position compared to through-plane changes, as expected from the cylindrical coil geometry [124], with 5 degrees in-plane rotation producing the highest percent artifact signal change (approximately ±4%).

A representative ROI is also shown in Fig. 3.2 (a), over which the artifacts were studied in more detail. The ROI was selected conservatively at some depth within the phantom, to provide a moderate estimate of the artifact rather than the worst-case scenario. Figure 3.3 shows the spatial average and the maximum of absolute percent artifact signal change within the ROI for a range of in-plane and through-plane translations and rotations, respectively. The spatial average of the percent artifactual signal change increases as the rotation angle or translational displacement increases in the selected ROI, with artifact levels most pronounced again for in-plane changes compared to through-plane rotations or displacements and for in-plane rotations in particular. The maximum of the percent artifact signal change also increases with increasing rotation angle or translational displacement, with slightly more artifact observed for in-plane changes relative to through-plane changes, and the most prominent effects observed for in-plane rotations. In each case the artifact level was quite similar for each method of coil combination, although the RO
method consistently showed a slightly higher artifact signal change compared to the SOS method.

\[\text{Fig. 3.2.} \text{ Percent artifact signal change due to a simulated shift in phantom position and orientation within a 12-channel head matrix receiver coil. (a,b,c,d) show the four different shifts that were investigated. The sum-of-squares (SOS) and Roemer Optimal (RO) methods are considered for generating combined images from the coil elements, respectively: (e,i) 3 mm in-plane translation, (f,j) 5° in-plane rotation, (g,k) 3 mm through-plane translation, and (h,l) 5° through-plane rotation. Also, a representative region of interest (ROI) is highlighted in (a), used subsequently to study the dependence of the artifact signal change in more detail (see Fig. 3.3).}\]
Fig. 3.3. The spatial average and the maximum of absolute percent artifact signal change over the ROI shown in Fig. 3.2(a) due to coil-motion interaction for RO and SOS combinations in case of (a,e) in-plane translation; (b,f) in-plane rotation; (c,g) through-plane translation; and (d,h) through-plane rotation.

The first set of simulations was used to inform the second set, which was conducted for 20 random in-plane rotational motions (5° p-p, corresponding to ~2% change). Figure 3.4 shows the average t-value activation maps produced from random-effects analysis over each set of 20 motions, as well as those for the case of no motion, for the SOS, RO, and ASRO methods. Compared to the case of no motion (Fig. 3.4(a,c)), random motion reduces the statistical significance of activated voxels (Fig. 3.4(b,d)). Effects for SOS (Fig. 3.4(b)) and RO (Fig.
3.4(d)) are very similar. Lastly, Fig. 3.4(e) shows the average activation map for 5° p-p in-plane rotational motion using the ASRO method, which suppresses the artifacts very effectively.

![Activation Maps](image)

**Fig. 3.4.** Average t-value activation maps with FDR q=0.01 for the second set of simulations involving no motion (left column), and 5° p-p in-plane rotation (right column). Results for SOS are shown in (a) and (b); for RO in (c) and (d); and for ASRO in (e).

### 3.3.2. Effect of Coil Loading

Figure 3.5(a,d) show the magnitude and phase of the coil sensitivity for each element of the 12-channel receiver coil, respectively, as imaged with a young healthy adult in the initial “reference” head position. The associated coil noise correlation matrix for all the elements is shown in Fig. 3.5(g). After the head was rotated nominally 5° in-plane or through-plane, changes in the coil sensitivity map and the noise correlation matrix were observed in head coordinates. Using the rigid-body head motion parameters recorded from the optical tracking system, the orientation and location of the coil sensitivity profile at the reference position were adjusted accordingly to account for the movements. The residual error (percent signal change) between the magnitude of the coil sensitivity profile adjusted from the reference position and the magnitude of the coil sensitivity profile obtained for each nominal rotation is shown in Fig. 3.5(b,c), for the example coil element outlined in red in Fig. 3.5(a). The analogous residual errors
in phase for this coil element are shown in Fig. 3.5(e,f). In both of these representative cases, very small residual errors were observed, indicating that rigid-body adjustments of the coil sensitivity profile obtained at the reference position provided a good estimate of the coil sensitivity profile after head motion. Compared to central locations, the residual error is increased slightly at the edges of the brain because of the interpolation and extrapolation involved in estimating the coil sensitivity. However, these increases are still negligible, with maximum 0.15% and 0.20% residual error observed among the magnitudes and phases of the all coils sensitivity maps, respectively.

In addition, the percent differences between the coil noise correlation matrix at the reference position and that obtained at the two nominal rotations are shown in Fig. 3.5(h,i). Again, negligible residual errors were observed. Similar results were observed across all the head positions that were imaged, which were bounded by the two representative nominal rotations shown in Fig. 3.5.
Fig. 3.5. (a,d) The magnitude and phase of the complex sensitivity profiles of the 12-channel head coil as imaged with a subject in the “reference” head position, respectively. The absolute percent signal difference (residual error) between rigid-body adjustment of the magnitude and phase of the reference sensitivity map, and that of the map obtained after nominal (b,e) 5° in-plane rotation, and (c,f) 5° through-plane rotation, respectively. Adjustment was performed
based on optical position tracking of head position. (g) Multi-channel coil noise correlation matrix at the reference head position. The percent residual error matrices are also shown for (h) 5° in-plane rotation, and (i) 5° through-plane rotation.

3.3.3. fMRI Experiments

Although the human fMRI experiments were conducted in young healthy adults and using foam head restraints, small but non-trivial head motion estimates were recorded by the optical motion tracking system during performance of the "baseline" fMRI run (that included instructions to perform the task while keeping the head as still as possible). The coordinate system in which the motion parameters were measured is shown in Fig. 3.6(a). The group mean, standard deviation, and the range of the p-p angular rotations (roll, pitch, yaw) and displacements (ΔSI, superior-inferior; ΔRL, right-left; and ΔAP anterior-posterior) are shown in Fig. 3.6(b). The group mean p-p values (black bars) were ≤1.4° over all angular rotations, and ≤1.5 mm over all displacement axes; with group standard deviations (white bars) of ≤0.2° and <0.3 mm, respectively; and ranges (error bars) of ≤2° and ≤1.9 mm, respectively. The largest extents of motion were observed in ΔAP and pitch rotation parameters (p<0.05 as measured by Tukey range tests comparing ΔAP with ΔRL and ΔSI, and comparing pitch values with roll and yaw values).

To ensure consistency in the overt motion experiments, the simulator training session prior to fMRI included head motion feedback with 5° rotational targets, a range of motion that the numerical simulations suggested would result in obvious confounding artifact. Despite subjects performing consistently across the group, the original intent of isolating motion only to particular in-plane and through-plane rotations was not achieved in practice during the fMRI experiments. Rather, complex motion was observed across all 6 degrees of freedom, but in two different consistent patterns depending on the instructions. The motion parameters for these runs are shown in Figs.3. 6(c-f), respectively. For fMRI runs involving in-plane rotation with and without PACE (Figs.3. 6(c,d), respectively), head motion was consistent and characterized primarily by increased roll and ΔRL values compared to Fig. 3.6(b). For runs involving through-plane rotation with and without PACE (Figs. 3.6(e,f), respectively), the head motion was also consistent, but characterized primarily by increased ΔAP and pitch parameters compared to Fig. 3.6(b).
Fig. 3.6. (a) Coordinate system for tracking of rigid-body head motion during fMRI experiments. Group mean, standard deviation, and range of p-p head motion for time series data collection for all subjects, for each of the different fMRI runs: (b) baseline; (c) in-plane rotation + PACE; (d) in-plane rotation without PACE; (e) through-plane rotation + PACE; and (f) through-plane rotation without PACE.
Figure 3.7 shows activation maps for the fMRI bilateral finger tapping task for one representative subject. Figure 3.7(a,f) show activation maps for the baseline fMRI run that included no overt head motion, for both SOS and RO combinations, respectively. These maps were found to be very similar, depicting bilateral activity in primary sensorimotor cortex. However, Fig. 3.7(f) (RO combination) showed a slightly larger number of active voxels, as expected due to the tSNR benefit provided by this method (see Theory section above). Figures 3.7(b,g,d,i) show the activation maps in the presence of overt head motion without use of PACE for both SOS and RO combination methods. These activation maps were found to have considerable false activations. For this subject, in-plane rotation (Fig. 3.7(b,g)) resulted in a mixture of false positive and false negative activations compared to the baseline fMRI run (Fig. 3.7(a, f)), whereas through-plane rotation (Fig. 3.7(d,i)) led to extensive false positive activation due to accidental correlation of the head motion with the task waveform (correlation coefficients $\leq 0.6$ for all 6 motion parameters).

The activation maps obtained with PACE prospective motion correction and SOS and RO combinations are shown in Fig. 3.7(c,e,h,j), respectively. These maps were considerably improved over those obtained without PACE, but still showed residual false activation in comparison with the maps observed for the baseline fMRI run. For in-plane rotation with PACE, the residual artifacts were quite pronounced and once more the SOS combination (Fig. 3.7(c)) showed more false positive voxels compared to the RO combination (Fig. 3.7(h)). It should be noted that the subject presented in Fig. 3.7 shows the largest difference between SOS and RO combinations among all six subjects. However, the difference between the two reconstruction methods was not statistically significant over the group (see Fig 3.9(a)). For through-plane rotation with PACE, the residual artifact was less, with false positives confined primarily to an enlargement of the areas of activation observed in the baseline fMRI run. In addition, substantial differences in false positives between the SOS combination (Fig. 7(e)) and the RO combination (Fig. 7(j)) were not observed.

The final two activation maps shown in Fig. 3.7 illustrate performance of the ASRO method. Using the ASRO method for in-plane rotation (Fig. 3.7(k)) and through-plane rotation (Fig. 3.7(l)) produced activation maps that closely resembled those obtained using SOS and RO combination in the baseline fMRI run. The ASRO result for through-plane rotation (Fig. 3.7(l)) showed very minor differences from the baseline results, whereas the ASRO result for in-plane
rotation showed some voxels that were additionally active in the sulcus anterior to the sensorimotor cortex.

Fig. 3.7. Activation maps (t statistic, FDR q=0.01) for a representative subject for each of the fMRI runs and analysis procedures: (a,f) baseline run with SOS and RO combination; (b,g) in-plane rotation with SOS and RO combination; (c,h,k) in-plane rotation + PACE with use of SOS, RO and ASRO methods; (d,i) through-plane rotation with SOS and RO combination; and (e,j,l) through-plane rotation + PACE with use of SOS, RO and ASRO methods.

Figure 3.8 shows the analogous tSD maps for the same representative subject. As anticipated from Fig. 3.7, a number of effects were observed. The tSD values were lowest for the baseline fMRI run (Fig. 8(a, f)); overt head motion without using PACE (Fig. 3.8(b,d,g,i)) yielded substantially increased tSD values; and prospective motion correction using PACE for the in-
plane rotations (Fig. 3.8(c,h)) and through-plane (Fig. 3.8(e, j)) rotations yielded tSD values that were much closer to the values obtained for the baseline fMRI run, but with residual artifacts still apparent. In the latter case, the residual artifacts for the in-plane rotations (Fig. 3.8(c,h)) were slightly larger than for the through-plane motion (Fig. 3.8(e, j)). Throughout, tSD values for the SOS combination (Fig. 3.8(a,b,c,d,e)) were slightly elevated compared to the analogous values for RO combination (Fig. 3.8(f,g,h,i,j)). Lastly, the tSD maps of the ASRO method for the in-plane rotations (Fig. 3.8(k)) and through-plane rotations (Fig. 3.8(l)) showed values very similar to those obtained for the baseline run with RO combination (Fig. 3.8(f)).

Fig. 3.8. Maps of temporal standard deviation (tSD) for a representative subject for each of the fMRI runs and analysis procedures: (a,f) baseline run with SOS and RO combination; (b,g) in-plane rotation with SOS and RO combination; (c,h,k) in-plane rotation + PACE with use of SOS, RO and ASRO methods; (d,i) through-plane rotation with SOS and RO combination; and (e,j,l) through-plane rotation + PACE with use of SOS, RO and ASRO methods.

Similar activation map and temporal standard deviation effects were observed over all subjects, despite the inter-subject variability in head motion and brain activity. Figure 3.9 summarizes the
number of active voxels, the Dice coefficient between the activation maps of baseline motion and those of the other runs with in-plane and through-plane motion, and the spatially-averaged temporal standard deviation, \( tSD \), for all subjects for each fMRI run. Considering first the number of activated voxels (Fig. 3.9(a)), the RO method did not differ substantially from SOS across the group, irrespective of the type of fMRI run. Compared to the baseline fMRI run which contained minimal head motion, overt in-plane and through-plane head rotation caused substantial elevation in the mean activated voxel count, and more variable results across the group (i.e., both false positive and false negative brain activity), when PACE prospective motion correction was not used. When PACE was used, these effects were partly reversed and results were especially good in the case of through-plane rotation, where the mean number and standard deviation of active voxels was very similar to that obtained for the baseline fMRI run. In the case of in-plane rotation, however, residual artifacts remained when PACE was used (i.e., statistically significant \( p < 0.05 \) difference observed in a paired one-tailed t-test for SOS). The residual artifacts were only eliminated by use of the ASRO method, reflected by the statistically significant decrease in active voxel count between the maps obtained using SOS combination and the ASRO method (paired one-tailed t-test, \( p < 0.05 \)).

The Dice coefficients results were highly similar irrespective of whether the activation maps for runs with head motion were compared to those for the baseline motion run reconstructed by SOS or RO methods. Figure 3.9(b) shows the results obtained using the baseline motion run with RO reconstruction as the comparator. A significant increase in Dice coefficient was observed for runs involving in-plane motion and PACE when ASRO was added. A similar increasing trend was observed for through-plane motion, but without statistical significance.

Regarding \( tSD \) values (Fig. 3.9(c)), the RO combination method yielded lower \( tSD \) compared to the SOS method, over all fMRI runs. The runs including overt motion without use of PACE exhibited the largest \( tSD \) values and the use of PACE only partially reversed influence of motion on artifact levels. A statistically significant elevation is still present in \( tSD \) of both RO and SOS combinations for both overt in-plane and through-plane motions compared to the RO and SOS baselines, respectively (paired one-tailed t-test \( p < 0.05 \)). The ASRO method successfully provided further reduction in \( tSD \) values towards the levels observed for the baseline fMRI run. For in-plane rotation, use of ASRO provided a statistically significant
decrease in tSD compared to the level observed with PACE using either RO or SOS method (paired one-tailed t-test, p < 0.05).

Fig. 3.9. Summary of results across all subjects and fMRI runs: (a) number of active voxels; (b) Dice coefficients between the activation map of baseline motion with RO reconstruction and those of the other runs; (c) tSD value, the temporal standard deviation of fMRI time series data
spatially averaged over the whole brain. Error bars represent the sample standard deviation of each metric, over the group of six subjects. Datasets that are statistically significantly different (one-tailed paired t-test, p<0.05) are denoted by a pair of similar symbols. For example, ** is used to indicate that for RO reconstruction, the temporal standard deviation of the baseline data is significantly different from that of the dataset obtained in the presence of overt in-plane head motion.

3.4. Discussion

Through numerical simulations and human fMRI experiments, this study demonstrates that head motions in relation to a fixed multi-channel receiver coil can introduce unwanted signal intensity variations comparable to fMRI BOLD signal changes (1-4% at 1.5-3.0 T). These variations constitute a residual signal artifact that is not eliminated by prospective motion correction assuming simple rigid-body motion. However, robust correction of the residual artifact is achievable by adjusting coil sensitivity maps to reflect relative motion between the head and the receiver coil. The ramifications of the study are discussed below.

Because head motion can affect the quality of fMRI maps of brain activity in a complex manner, numerical simulations were an essential initial step to gain insight into the scale of artifact levels, as well as to design meaningful fMRI experiments and appropriate correction methods. The first set of numerical simulations was important to demonstrate that artifacts arising from interactions of coil sensitivity and head motion are likely to be on the order of fMRI signal changes, especially for motions in the direction that coil sensitivity varies most rapidly. For the studied 12-channel cylindrical head coil, the sensitivity profiles changed much more during rotations about its circular cross section, than during translations along its longitudinal axis. For multi-channel coils with higher channel counts and more localized sensitivity patterns for each coil element, however, an increase in the level of these artifacts is anticipated [100]. For different coil designs, the directional sensitivity of the artifact is expected to change as well.

The second set of numerical simulations showed that motions on the order of 5° p-p in-plane rotation could adversely affect the average t-value activation map obtained when using prospective motion correction, causing a reduction in the significance of activation compared to the case of no motion. For context, this level of head motion can occur in fMRI of patient populations, such as those recovering from stroke [101], [102]. Although young healthy adults
are often able to tolerate fMRI well, performing many behavioral tasks while keeping their head much still within fractions of a millimeter, there is also impetus to perform fMRI of tasks that induce substantial head motion. One example involves studying the brain activity associated with leg movements [8]. In such cases, a robust strategy to correct for all influences of head motion on fMRI data would be required, including the artifacts studied in the present work.

In addition to the insight provided by numerical simulations, additional elements were utilized to isolate and characterize the artifacts of interest. An important imaging analysis step was performed to ensure that residual artifacts observed after PACE were not confounded by dynamic geometric distortion: the time-dependent warping of EPI data that arises from head motion and the different magnetic susceptibilities of tissues in the brain. Note that the distortion correction only compensated for the time-varying field inhomogeneity deviation from a zero phase reference time point due to the different head positions. To correctly compensate for the static inhomogeneities still present in all time-frames, one more stage of correction may be performed on the time-series using the phase differences between EPI images acquired at different echo times [22]. The distortion correction method employed here is an example which has previously been shown to be beneficial for fMRI applications, although other options exist [25], [125], [126].

Additionally, after dynamic geometric distortion correction and combining images from each coil element, retrospective motion correction by rigid-body image coregistration was performed prior to calculation of activation maps. This step was undertaken to account for residual errors inherent to the PACE method, associated with image-based motion detection and delays between the motion occurrence and correction. The errors in image-based motion detection arise from multiple sources, such as from the effect of motion on geometric distortion, or from the fact that motion parameters are estimated from SOS combination in PACE and thus are also susceptible to interactions between motion and coil sensitivity. However, analogous to previous reports [104], the PACE motion estimates are expected to be relatively accurate for the range of head motions investigated in this work. Regarding the delay between motion occurrence and correction in PACE, errors can be introduced when volume-by-volume motion correction is adopted in the presence of rapid head motion. However, our experimental procedures ensured that head motion was slow and that this source of error was minimal. Detailed investigation of these matters is beyond the scope of the present work, in which PACE was employed for ease of
implementation and for proof-of-concept. Other alternatives can be used in the future to improve the quality of prospective motion correction.

Furthermore, retrospective motion correction was applied as the final step before calculating activation maps, instead of earlier, because the other processing steps led to images that could be better approximated as time samples of rigid body motion. Other image processing steps could also be included in the future. For example, motion parameters were not included as nuisance regressors in the present work due to concerns of overfitting or under-fitting [45] and uncertainty over the appropriate choice of parsimonious regressors. Such regression may have utility, but must be performed post hoc after the fMRI time series data are collected. The proposed ASRO method has the potential advantage of correcting for coil sensitivity changes in real-time and, with suitable modifications, could be integrated with image-based prospective motion correction in the future.

Theoretical consideration of coil sensitivity interactions with head motion lead to a correction method that involves updating coil sensitivity maps acquired in a calibration gradient echo scan, according to motion parameter estimates. In future implementations, there is also potential to perform coil sensitivity corrections based on maps that are estimated dynamically as part of the fMRI time series data collection. In the development phase of the present work (data not shown), we compared the coil sensitivity maps obtained from individual time points and those obtained from adjusting the sensitivity maps measured at an initial head position. The sensitivity maps obtained from individual fMRI time points were less robust, as might be expected due to the physical differences between EPI and gradient echo imaging. Thus, the ASRO procedure was chosen as the most expedient to verify the importance of artifacts arising from interactions between coil sensitivity and head motion for fMRI involving prospective motion correction.

The key assumption for ASRO to be effective is that the sensitivity of each coil element is constant, fixed in space and independent of head motion within the laboratory frame of reference. This is not necessarily true for increasing magnetic field strengths and required validation at 3 T. An experiment was conducted to investigate the differences in coil sensitivity maps for a single subject placed in many different head positions and orientations within a multichannel head coil. This experiment demonstrated that loading of the coils did not substantially change as a result of head position and orientation. Furthermore, over the range of
head placements that was investigated, updating the original “reference” coil sensitivity profile according to head motion parameters was found to provide excellent agreement with the true coil sensitivity profiles measured at a given head placement. Therefore, instead of measuring coil sensitivity maps at each point in the fMRI time series, adjustment of the coil sensitivity profiles obtained at a reference position suffices for the ASRO method. By extension, this procedure is expected to work well at lower magnetic field strengths including 1.5 T, but should be further verified at higher fields such as 7T [119] where measurement of time-dependent coil sensitivity maps may be essential. The analogous arguments also apply to the noise correlation matrix, with the proviso that head motions greater than those measured in Fig. 3.6 may require additional attention. For example, one possible approach would be to perform parallel imaging reconstruction and analyze the severity of reconstruction artifacts in relation to full k-space reconstruction, to determine whether a new set of coil sensitivity maps should be acquired [107].

Our results strongly support use of PACE and the ASRO method when used with dynamic geometric distortion correction, but several weaknesses of the study and the proposed methods should be considered. Errors in spatial extrapolation near the edges of the brain, residual uncorrected motion, residual motion-induced geometric distortion in the data, inclined acquisition of slices because of motion during acquisition, as well as alteration of T2* due to motion induced magnetic field distortions [8] are all possible motion confounds that, if not dealt with in a robust fashion, have the potential to cause elevated variability of fMRI signals even after prospective motion correction using PACE, dynamic geometric distortion correction, ASRO and retrospective motion correction. Beyond the methods used in the present work, potential alternative techniques can be employed to mitigate the artifacts arising from motion-induced coil sensitivity map changes, while suppressing the extrapolation/ extrapolation errors at the cost of additional measurement complexity. As mentioned above, coil sensitivity maps can be measured dynamically, but a robust implementation is required in the presence of other artifacts that occur during EPI. Alternatively, it is also possible to record a library of coil sensitivity maps at different head positions prior to fMRI, which can then be referenced appropriately during image reconstruction.

On a different topic, comparisons of the ASRO activation maps against the baseline activation maps constitute a useful but incomplete performance assessment. In particular, the “ground truth” is unavailable (i.e., precise knowledge of the true spatial pattern of brain activity
associated with the self-paced bilateral finger tapping task in each subject). It is impossible to determine how many false positive and/or false negative activations are present in the maps obtained by the PACE+ASRO method. What can be observed, however, is that on average the PACE+ASRO maps are highly similar to those obtained with minimal head motion, as measured by activated voxel counts and the Dice coefficient of overlap. The analogous effects are observed for tSD values.

Furthermore, additional research will be needed to demonstrate the robustness of ASRO, for different fMRI tasks and populations. In this work, the fMRI experiment was conducted assuming that brain activation would be identical under conditions of minimal head motion and during overt prescribed motions. Although this assumption is probably sufficient for the present study, given the inter-subject variability that was observed, there are solid grounds to expect that the activation maps truly are slightly different. For example, the activation maps obtained with overt head motion are expected to engage brain regions involved in control of neck muscles, such as the appropriate areas of primary somatosensory and motor cortex, as well as regions involved in coordinated movement, such as the cerebellum. The attentional demands of the tasks involving minimal head motion and overt head motion are also likely to be different, suggesting differences in prefrontal activity. With careful methodology, it should be possible to elucidate these differences in future studies.

Because of its simplicity, SOS is presently the most common method for combining images from different coil elements during fMRI. The present work showed that there is not much benefit to RO in the face of motion when PACE is not applied. This is likely because the SNR benefit provided by RO is negligible in the presence of artifacts arising from head motion. However, when PACE is used together with robust methods for residual artifact correction, RO (and thus ASRO) become a more worthwhile consideration. Conversely, an analogous coil sensitivity adjustment can likely be made to SOS combination, but this is the topic of future research.

Lastly, the present work investigated ASRO in proof-of-concept software by implementing the coil sensitivity adjustments post hoc, substantially after all fMRI data acquisition was completed. The interpolation and extrapolation procedures consumed the most computational time, and careful software optimization will be required in the future if ASRO is to be integrated with prospective motion correction successfully.
Chapter 4
Head Motion-Coil Sensitivity Interaction in Accelerated fMRI


Contributions: Fred Tam has contributed to image acquisition and setting up the optical tracking system; Dr. J Jean Chen has helped with data analysis and writing of the article; and Dr. Simon J Graham has contributed to the experiment design, data analysis and writing of the article.

As outlined in Chapter 1, parallel imaging is widely adopted to accelerate MRI data acquisition, through various strategies that involve multi-channel receiver coils. Functional MRI (fMRI) can benefit from the acceleration achieved with parallel imaging. However, the non-uniform spatial sensitivity of multi-channel receiver coils may introduce unwanted artifacts when head motion occurs during the few minute long fMRI scans. Although prospective correction provides a promising solution for alleviating the head motion artifacts in fMRI by keeping the image plane fixed with respect to the moving reference frame of the head, the relative position of the fixed multi-channel receiver coils moves in the moving reference frame, potentially resulting in unwanted signal intensity variations comparable to the weak blood oxygenation level dependent (BOLD) fMRI signal (1-8% at 1.5-7.0 T). We used numerical simulations to investigate this effect on fMRI using two parallel imaging schemes: Sensitivity encoding (SENSE) and generalized autocalibrating partially parallel acquisitions (GRAPPA), towards characterizing the regime over which parallel-imaging fMRI with prospective motion correction will benefit from updating coil sensitivities to reflect relative positional change between the head and the receiver coil. Moreover, six subjects were scanned with acceleration factors 2 and 4 while performing a simple finger tapping task with and without overt head motion. Updating coil sensitivities showed significant impact on standard deviation and activation maps in presence of overt head motion compared to that obtained with no overt head motion.

4.1. Introduction

As discussed in Chapter 1, head motion is a major potential confound during functional magnetic resonance imaging (fMRI). Due to the small, time-dependent hemodynamic signal changes (approximately 1-8% at 1.5-7.0 T) that arise from the blood oxygenation level-dependent
(BOLD) effect in response to brain activity, head displacements at the mm level can be sufficient to generate spurious signal intensity changes (artifacts) that corrupt fMRI data badly [2]–[4], [27]. One very promising candidate solution to this problem is prospective rigid-body motion correction, an approach that updates the imaging plane based on tracking the position of the head dynamically. Ideally, such prospective correction allows the image plane to remain fixed with respect to the moving reference frame of the head [8], [52], [91], [92], [127]. In practice, however, prospective motion correction is imperfect and residual errors remain in the fMRI data. For example, due to the difference in magnetic susceptibility of various brain tissues, head motion causes time varying changes in magnetic field homogeneity and the associated spatial distortions in EPI that cannot be corrected by rigid-body motion correction [22], [56], [75]. Additionally, nonlinear gradients can induce geometric distortion and lead to signal displacement, thereby interfering with precise localization of anatomical structures even in perfectly prospectively motion-corrected data [99].

Another potentially important factor to consider is that prospective motion correction does not compensate intrinsically for the relative positional change between the fixed multi-channel receiver coils and the head. Depending on the head motion and coil characteristics, there is potential for interaction effects that can lead to substantial residual artifacts in prospectively corrected fMRI data. For example, a recent study showed that in-plane rotations of approximately 5 degrees were sufficient to cause both false positive and false negative activations in fMRI data acquired using single-shot echo planar imaging (EPI) with the prospective acquisition correction (PACE) scheme and a 12-channel receiver coil [128].

As in the previously mentioned study, the majority of fMRI is presently conducted with conventional imaging reconstruction involving use of imaging gradients to encode k-space in plane, and use of multi-channel receiver coils to enhance image signal-to-noise ratio (SNR). There is a recent trend away from this practice, however, toward use of “parallel imaging” reconstruction methods. These methods involve under-sampled k-space data acquired with multi-channel receiver coils, and use the spatially-dependent sensitivities of the coil elements in the image reconstruction to compensate for the k-space data that are absent [129]. The k-space under-sampling typically provides between two- to four-fold reductions in the time needed to acquire a single image slice at a given spatial resolution. In the fMRI context, such faster acquisitions have multiple benefits. Analysis of resting state fMRI signals is improved due to the
larger number of data points in the fMRI time series, and because physiological noise sources are easier to suppress (respiration and cardiac effects are now adequately sampled) [130]. Geometric distortion, caused by variations in magnetic susceptibility between different tissue interfaces, is reduced by virtue of traversing k-space more rapidly [131], [132]. Rapid k-space traversal also important for maintaining BOLD signal contrast at ultra-high magnetic fields (e.g., 7 T), at which the T2* value of blood is substantially decreased [133]. These benefits are achieved at some expense (e.g., noise amplification, which depends on the multi-channel coil design and worsens with the extent of k-space under-sampling) but the trade-off is often acceptable. Given this, it becomes important to consider the issue of head motion once more, and to consider including prospective motion correction as part of such acquisitions.

Various parallel imaging reconstruction algorithms are available; two common approaches either manipulate the aliased images obtained from the under-sampled k-space data (e.g., sensitivity encoding (SENSE) reconstruction [19]), or manipulate the under-sampled k-space data themselves (e.g., generalized autocalibrating partially parallel acquisitions (GRAPPA) [20]). In all cases, successful reconstruction in the static case is achieved by assuming that each coil element weights the signal at each voxel location in a fixed manner. Therefore, combining parallel imaging reconstruction with prospective motion correction will require an accurate knowledge of how head motion causes the coil weightings to vary over time. If the coil weightings are not handled appropriately, then artifacts are likely to be generated -- possibly with amplitudes similar to those of BOLD signals.

In searching for literature that supports these arguments, it is apparent that the issues of prospective motion correction, parallel imaging, head motion and coil sensitivity have yet to be discussed collectively for fMRI in a definitive manner. However, a number of studies are pertinent. During anatomical MRI, parallel imaging reconstruction errors were reported when maps of coil sensitivity obtained in an initial “calibration” stage were inconsistent with subsequent image acquisition because of motion [103], [106], [107]. Significant image quality degradation was also reported for parallel imaging reconstructions in the presence of the chest wall motion [134]. (Self-calibrating parallel imaging that fully sampled the central region of a variable-density k-space acquisition was then employed to improve the image quality, at the cost of additional scan time.) In a quantitative MRI application involving parallel imaging, inter-scan head motion was shown to perturb maps of coil sensitivity and to have a negative impact on the
accuracy of mapping T1 relaxation time values [105]. However, in another study that involved multi-slice GRAPPA-based EPI navigator echoes to estimate head motion, good reconstruction fidelity was observed over a range of head positions, indicating that the spatially dependent coil sensitivity information used to separate the slices did not substantially differ over a range of head positions [104]. Luengviriya et al. [7], [100] showed that for parallel imaging with prospective motion correction, taking the relative position of coil sensitivity maps into account is of great importance. Their results showed that although smaller coils give better acceleration properties, they are more sensitive to motion artifacts due to the relative positional change between the head and the receiver coils. Lastly, a study using SENSE for BOLD fMRI mentioned that estimating coil sensitivity profiles in the presence of subject motion might not be accurate, although the associated effects on fMRI activation maps were not investigated [135].

The present study consequently attempts to expand on this literature to address the topic at hand more directly. There are two specific objectives: a) to explore the interactions between head motion and multichannel coil sensitivity for their potential to cause artifacts during parallel imaging fMRI (reconstructed using SENSE or GRAPPA) combined with prospective motion correction as implemented by the established Prospective Acquisition CorrEction (PACE) method[91]; and b) to validate in proof-of-concept a simple method to correct for such artifacts. There are also two hypotheses related to these objectives. First, it is hypothesized that head motion at the mm level in relation to fixed multi-channel receiver coils can introduce artifact signal variations on the order of BOLD signals, and that the artifacts are observable in activation maps generated by SENSE-fMRI and GRAPPA-fMRI involving PACE. Secondly, a correction approach is developed based on a recent fMRI study involving standard EPI reconstruction and prospective motion correction that showed the benefits of updating coil sensitivity maps to reflect relative positional change between the head and the coil elements [128]. Thus, it is hypothesized that artifacts in parallel imaging fMRI can be suppressed effectively by a procedure that updates receiver coil sensitivity maps according to head motion estimates obtained using PACE.

4.2. Materials and Methods

Several investigations of increasing complexity were undertaken to investigate the two hypotheses of interest. Briefly, the first step involved theoretical consideration of SENSE and
GRAPPA parallel imaging; the mechanism of artifact formation due to motion-induced alteration of coil sensitivity maps in the moving reference frame of the head (as relevant to prospective motion correction); and development of a correction scheme that involved updating the orientation and position of the receiver coil sensitivity maps. Next, the possible magnitude of the signal artifacts was assessed by numerical simulations. Informed by the simulation results, fMRI experiments were subsequently undertaken involving six young healthy adult volunteer subjects, using SENSE and GRAPPA reconstruction with and without PACE, and with and without the proposed correction scheme. Image quality was evaluated in the resting state, and for maps of brain activity associated with performing a motor task, for subjects attempting to keep their head still as well as during overt head movement.

4.2.1. Parallel Imaging

Parallel imaging techniques enable faster imaging at the expense of an SNR penalty. In addition to the factors that affect SNR in conventional imaging reconstruction, such as a voxel volume and the square root of data acquisition time, parallel imaging is also affected by two additional parameters: the acceleration factor, $R$, and the geometry factor, $g$. For an image with a field of view (FOV) equal to $L$, parallel imaging with acceleration factor $R > 1$ increases the distance between the phase-encoding (PE) lines in k-space by factor $R$ while keeping the maximal extent covered in k-space. This results in reduction of the data acquisition time by the factor $R$. Increasing the distance between PE lines decreases the FOV to $L/R$ in the PE direction resulting in aliasing or wrap-around artifacts which can be removed or prevented by SENSE and GRAPPA reconstruction, respectively. The geometry factor $g$ represents noise magnification that occurs when aliased images are unwrapped and is determined by the coil geometry, the noise correlation between the $N_C$ coil elements (characterized by the noise correlation matrix), and the acceleration factor. Both SENSE and GRAPPA reconstruction techniques exploit the spatial dependency of the $N_C$ coil sensitivity maps. A brief summary of the theory behind SENSE and GRAPPA is given below. In each case, to simplify the equations, an initial pre-processing step was performed to de-correlate the correlated noise obtained from the multi-channel coil elements using the noise correlation matrix.

4.2.1.1. SENSE
In SENSE parallel imaging, the final reconstructed image is generated by manipulating the $N_C$ aliased images generated from the under-sampled k-space data acquired from the coil elements [19]. Let the total number of replicates due to aliasing at pixel location $(x, y)$ be $N_p$. The value of $N_p$ is spatially dependent and is determined by $R$ and by the size and shape of the object. For location $(x, y)$, the image signal of the $j$th coil, $I_j(x, y)$, where $j \in \{1, \ldots, N_C\}$, can be written as a superposition of the original object and $N_p - 1$ displaced replicates:

$$I_j(x, y) = \sum_{n=0}^{N_p-1} C_j(x, y + \frac{nL}{R}) M(x, y + \frac{nL}{R}). \tag{4.1}$$

where $I_j(x, y)$ are the reconstructed aliased images and the functions $C_j$ and $M$ are the aliased coil sensitivities and the magnetization, respectively. The un-aliased coil sensitivities can be obtained in an initial calibration process at the beginning of the scan. If $N_C \geq N_p$, then the system of equations can be solved to obtain $M(y + nL/R)$. The appropriate matrices $I$, $C$, and $M$ can then be defined for simplicity, consisting of the images of all the $N_C$ coils, with dimensions $N_C \times 1$, $N_C \times N_p$, and $N_p \times 1$, respectively. Hence, $I = CM$. The most general solution to Eq. 4.1 is the pseudoinverse [19]:

$$\hat{x} = [(C^+ C)^{-1} C^+] I. \tag{4.2}$$

### 4.2.1.2. GRAPPA

In GRAPPA parallel imaging [20], the missing k-space lines are estimated for each coil receiver channel by applying multiple "blockwise" reconstructions. For acceleration factor $R$, assuming that $S_c(k_y)$ is a measured k-space line for coil $c \in \{1, \ldots, N_C\}$ and $\Delta k_y$ is the distance between the k-space lines in the PE direction in the original images (i.e., unaliased), k-space lines $S_j(k_y - m\Delta k_y)$, for $m \in \{1, \ldots, R - 1\}$ and coil $j \in \{1, \ldots, N_C\}$ are missing and can be estimated according to

$$\hat{S}_j(k_y - m\Delta k_y) = \int \hat{C}(\gamma) M(\gamma) e^{i2\pi k_y \gamma} e^{-i2\pi m\Delta k_y \gamma} d\gamma. \tag{4.3}$$
If “weighting factors” can be found that estimate the desired exponentials, then all the missing k-space lines can be approximated. For example, let \( a(j, c) \) define the coil weighting factors that give \( C_j(y) e^{-i2\pi m \Delta k_y y} \), such that:

\[
\alpha : \sum_{c=1}^{n_c} a(j, c) c_c(y) = C_j(y) e^{-i2\pi m \Delta k_y y}, \tag{4.4}
\]

Then, inserting Eq. 4.4 into Eq. 4.3 gives:

\[
\delta_j(k_y - m \Delta k_y) = \sum_{c=1}^{n_c} a(j, c) \int c_c(y) M(y) e^{i2\pi k_y y} dy \tag{4.5}
\]

\[
= \sum_{c=1}^{N_c} a(j, c) S_c(k_y).
\]

Therefore, each missing k-space line can be estimated by a linear combination of the measured k-space lines. In GRAPPA, instead of estimating each missing k-space line at \( k_y - m \Delta k_y \) from a single measured k-space line \( k_y \), multiple measured lines (also known as “blocks”) are used. This procedure improves the estimation accuracy, particularly if approximation of complex exponentials is difficult by a linear combination of coil sensitivities due to the coil geometry. There is a trade-off between the reconstruction speed and image quality in choosing the block size. Larger blocks slow down the reconstruction but provide better image quality. The procedure for blockwise estimating the k-space value \( \delta_j(k_y - m \Delta k_y) \) for receiver channel \( j \) is given by

\[
\delta_j(k_y - m \Delta k_y) = \sum_{b=0}^{B} \sum_{c=1}^{N_c} a(j, c, m, b) S_c(k_y - b \Delta k_y), \tag{4.6}
\]

where \( N_b \) blocks are used in the reconstruction, and \( \alpha \) is a weighting factor. Analogous to Eq. 4.4, the weighting factor \( \alpha \) is obtained by solving
The matrices $F_j(y, m + Rb) = C_j(y)e^{-i2\pi(m+Rb)\Delta k_y y}$, $C(y, c) = C_c(y)$, and $A_j(c, m + Rb) = a(j, c, m, b)$ are then defined for simplicity with dimensions $L \times (R(N_b + 1))$, $L \times N_c$, and $N_c \times (R(N_b + 1))$ respectively. Hence, $F_j = A_jC$ can also be obtained using the pseudoinverse:

$$A_j = (C^+C)^{-1}C^+ F_j$$

(4.8)

After calculating $A_j$, all the missing lines can be easily estimated using Eq. 4.6. Consecutively, un-aliased images for each coil receiver channel are generated by Fourier transformation, and then typically combined using a sum-of-squares reconstruction to estimate the magnetization $M(x, y)$.

### 4.2.2. Head Motion and Coil Sensitivity Maps

In the presence of motion, the relative position and orientation of the object will change with the respect to the coil elements, which are fixed in space. Assuming that the head motion does not significantly affect how the subject loads the multi-channel coil and that $\psi$ remains unchanged (as has recently been confirmed at 3.0 T [128]), position tracking measurements should be sufficient to characterize the artifacts that arise from motion and coil sensitivity interactions. Considering then the implications for prospective motion correction, if the head moves in one direction relative to a fixed coil element, in the moving reference frame of the head it will appear that the coil has been displaced in the opposite direction. In another example involving rotation of the head by angle $\theta$ around the z-axis, the prospective motion correction system updates the imaging plane such that the image from the receiver coil $j$ will be $I_j(x'(\theta), y'(\theta))$ where

$$\begin{align*}
x'(\theta) &= x_{\text{receiver}} + y_{\text{sensor}} \sin(\theta) \\
y'(\theta) &= y_{\text{sensor}} + y_{\text{sensor}} \cos(\theta)
\end{align*}$$

(4.9)

The final combined 2D image $M(x'(\theta), y'(\theta))$ is then obtained by applying the same rotation to the coil sensitivity maps in the opposite direction, i.e., $C_j(x'(-\theta), y'(\theta))$ [111]. Hereafter, the SENSE and GRAPPA parallel imaging reconstructions (Eq. 4.2 and 4.8) with appropriately
updated sensitivity maps (USM) will be referred to as the SENSE+USM and GRAPPA+USM, respectively.

4.2.3. Numerical Simulations

Towards characterizing the regime over which SENSE and GRAPPA with PACE will benefit from USM, two sets of numerical simulations were performed in MATLAB (MathWorks, Natick, MA). Both simulations included complex-valued coil sensitivity maps and noise correlation characteristics of a 12-channel head receiver coil used in subsequent MRI experiments. The coil sensitivity maps and noise correlation matrix were obtained using a spherical agar phantom (19 cm diameter) constructed based on recommendations by the functional Bioinformatics Research Network (fBIRN) Consortium [85] and providing coil loading and MRI characteristics resembling those of the human brain. Both simulations were also undertaken with acceleration factors for SENSE and GRAPPA that reasonably spanned the range of practical application (R values of 2 and 4).

The first simulation was undertaken for preliminary insight. Simulated k-space data were generated of the Shepp-Logan phantom [112] with a 128×128 matrix, assuming a spatially uniform $T_2^*$ value of 45 ms. The procedures used for obtaining the coil characteristics were performed according to the detailed description provided in the section on MRI experiments (given below), changing the field of view (FOV) from 204 mm to 256 mm, and the acquisition matrix size from 68×68 to 128×128 to match the phantom parameters. To generate images for each coil element, the Shepp-Logan image was multiplied by the appropriate coil sensitivity maps. The k-space data were generated by Fourier Transformation and then under-sampled in k-space by acceleration factors R=2 and 4. Complex white random noise was also added in k-space (correlated between the 12 coils) with a typical fMRI SNR of 100 [113]. The position and orientation of the phantom with respect to the imaging plane was held fixed, assuming ideal prospective motion correction. However, the coil sensitivity maps were moved within the phantom coordinates system in the opposite direction of the phantom motion, and subsequently used to generate new images for each channel that reflected the movement. In-plane and through-plane translations and rotations (range: 0-5 mm, 0-5 degrees) were each investigated separately. For each R value and each type and instance of movement, the separate coil images were combined using SENSE and GRAPPA parallel imaging reconstructions [19] and the
percent artifact signal change arising from the interaction between head motion and coil sensitivity was then calculated in relation to the static case, with the same reconstruction scheme and acceleration factor.

The second set of simulations was more realistic and involved time series data synthesized from multi-slice EPI of a human head. In this case, the intent was to isolate the effect of motion-induced coil sensitivity variation from other motion artifacts. For this set of simulations, the coil sensitivity map FOV and acquisition matrix were chosen to match those of the head EPI data (204 mm and 68×68, respectively). Two regions of interest (ROIs) encompassing bilateral primary motor cortex were manually defined and activation was created by increasing the intensity of the selected voxels by 3% in a block design fashion (8 alternating blocks of “task” and “rest”; 10-image block duration) by increasing the intensity of the selected voxels only in the task blocks. To generate images for each coil element, the successive EPI volumes in simulated time series were multiplied by the appropriate coil sensitivity maps in image space, and then under-sampling of the associated k-space data was performed with acceleration factors R=2 and 4. Analogous to the first set of experiments, complex white random noise was added in k-space (correlated between the 12 coils) with a typical fMRI SNR of 100 [113]. For each R value, and each EPI volume in the simulated time, the separate coil images were combined using SENSE and GRAPPA parallel imaging reconstructions.

Using a constrained second-order dynamic model to simulate realistic head movement [114], twenty random in-plane translational motion time series (with identical peak-to-peak (p-p) values) were generated. Different p-p displacement values were employed within the range selected, that were both realistic of effects observed in human imaging; and that were shown to produce artifacts comparable to BOLD signal changes in the first simulation. These values were 5 mm p-p and 1 mm p-p for acceleration factors R=2 and R=4, respectively. Assuming ideal prospective motion correction, the position and orientation of the head was held fixed with respect to the imaging plane (i.e., the moving reference frame), and the coil sensitivity maps were shifted in the opposite direction as prescribed by the head movement model. Subsequently, these images were used to generate new time series data including the effects of head motion for each receiver channel. Similar to above, all the images were then converted to k-space, undersampled, and corrupted by white noise. The separate coil images were combined using
SENSE and GRAPPA parallel imaging reconstructions for each R value, each EPI time sample in a given simulated time series of images, and for each time series involving random motion.

Conventional general linear model (GLM) analysis of the simulated fMRI signals was performed with a boxcar waveform representing the block-design experiment convolved with a standard hemodynamic response as implemented in the Analysis of Functional NeuroImages (AFNI) freeware package [42]. Activation maps were thresholded using a false discovery rate (FDR) q = 0.01 for acceleration factor 2 and 4 under: (i) no motion with SENSE; (ii) random motion with SENSE; (iii) random motion with SENSE+USM; (iv) no motion with GRAPPA; (v) random motion with GRAPPA; and (vi) random motion with GRAPPA+USM.

4.2.4. MRI Experiments

All imaging was performed at Baycrest Hospital in Toronto on a research-dedicated MRI system operating at 3 T (Trio with Total Imaging Matrix (TIM), software revision VB17A, Siemens, Erlangen, Germany). The body coil was used for RF transmission and the standard 12-channel "matrix" head coil was used for signal reception. The study was approved by the Research Ethics Board of Baycrest for imaging of young healthy adults, who gave their written informed consent before participating. Six healthy right-handed subjects were imaged to address the study objectives (2 males, 4 females; average age 29; range 22-32).

The PACE method [91] was used for practicality, as it is available as standard prospective motion correction software on the research MRI system used in the present work. Briefly summarizing the method, a) the current set of multi-slice images of the brain (i.e., the “image volume”) are rapidly reconstructed using modified sensitivity encoding (mSENSE) [136] immediately after they are acquired; b) rigid-body motion parameters are estimated based on image registration to the first volume in the fMRI time series; and c) the motion parameters are then used to adjust the pulse sequence parameters that control slice orientation and position for the next image volume. All of these steps are performed rapidly, well within the TR value of 2000 ms that was used in the fMRI experiments.

At the start of the imaging session for each subject, the coil sensitivity maps and noise correlation matrix were calculated by acquiring two images with a 3D T1-weighted magnetization-prepared rapid gradient-echo imaging sequence (MPRAGE: TE/flip angle = 2.63
ms/6°, where TE is the echo time, 1500 ms between inversion preparation pulses, FOV = 204 mm, 32 oblique axial slices 3.5 mm thick, and acquisition matrix = 68 ×68): without and with RF excitation. The noise correlation matrix was estimated from the noise images obtained with no RF excitation. In the images acquired with RF excitation, the center portion of k-space (matrix = 32 × 32) was used to obtain coil sensitivity maps. The k-space data from each coil were apodized using a Tukey window [120] to suppress truncation artifacts [121] and inverse Fourier transformed to obtain smooth images. Each image was then scaled by the root sum-of-squares of the images from all coil elements to suppress anatomical image content from the coil sensitivity maps.

After these calibration scans, 3D T1-weighted MPRAGE imaging was repeated at high spatial resolution (TE/flip angle = 2.63ms/6°, 1500 ms between inversion preparation pulses, FOV = 256 mm, 160 slices 1 mm thick, and 256 × 256 acquisition matrix) to provide anatomical reference information. This was followed by accelerated multi-slice single-shot EPI with R = 2 and R = 4, performed with and without PACE, including typical scan parameters used to measure BOLD signals during fMRI (TE/TR/flip angle = 30 ms/2000 ms/40°, where TE is the echo time and TR is the repetition time; FOV = 204 mm; 32 oblique axial slices 3.5 mm thick with a 1 mm gap; and a 68 × 68 acquisition matrix). The number of time points and the duration of the scan were kept constant at 174 and 348 s, respectively, across both R values by including dead time after each slice acquisition in the sequence. Complex k-space data from each receiver channel were initially reconstructed off-line using SENSE and GRAPPA reconstruction schemes in MATLAB, with the minimal processing consisting of regridding, apodization, and Nyquist ghost correction [21].

All the subjects wore MRI-compatible headphones (Siemens, Erlangen, Germany) during imaging, were padded within the head coil to limit motion, and performed task-based fMRI involving self-paced bilateral finger tapping tasks with 8 alternating 20 s blocks of “task” and “rest” conditions. The fMRI data collection was initiated with a rest block of 28 s, with data discarded from the initial 8 s to ensure that magnetization reached the steady state. During task-based fMRI, subjects were presented with a visual cue to start and stop self-paced bilateral finger tapping. Visual stimuli for each block were displayed on a projection screen at the rear of the magnet bore using a liquid crystal display projector (MT1065, NEC Corporation, Itasca, IL) through a waveguide in the RF shield, and viewed by subjects using angled mirrors attached to
the top of the head coil. The task was programmed in E-Prime (Psychology Software Tools Inc, Sharpsburg, PA) and lasted 348 s. Each subject underwent 6 different runs of task-based fMRI data collection, over which certain specific fMRI parameters and the task instructions were varied. Three of the runs were performed with R=2 (runs “a”, “c”, and “e”) and the other three with R=4 (runs “b”, “d”, and “f”). The instruction set and fMRI parameter manipulations were as follow: (a)(b) remain as still as possible while performing the task, referred to as the “baseline” level of head motion, during fMRI without PACE; (c)(d) perform slow overt in-plane rotations (roll) at discrete time points while performing the task during fMRI with PACE; and (e)(f) perform slow overt through-plane rotations (pitch) at discrete time points while performing the task during fMRI with PACE. Subjects were instructed to perform deliberate head motion, and thus create signal artifacts, when given a verbal cue through the headphones (executed manually as a function of time by one of the researchers, Z.F.). Each subject was given approximately 9 verbal cues per run. For each subject, the order of the runs was randomized to control for systematic confounds.

To ensure consistency in intra- and inter-subject motion, head position was tracked throughout using an optical stereo camera motion tracking system with a root-mean-squared accuracy of <0.5 mm and 0.5°, consisting of two MR compatible cameras (MRC Systems GmbH, Heidelberg, Germany) affixed to the magnet bore, operating under infrared light to avoid affecting visual stimulus presentations during fMRI [56]. Moreover, training was performed before each fMRI session in an MRI simulator, during which head position tracking data were presented to subjects as real-time visual feedback. In the simulator, head position was tracked using an electromagnetic system (miniBird 800, Ascension Technology Corp., Burlington, VT) with a root-mean-squared accuracy of 1 mm and 0.5°, and displayed as scrolling line plot with separate lines for roll, pitch, and yaw rotation (see Fig. 4.4 for a description of the spatial coordinate system). A pair of horizontal bars in the plot specified a target range of rotational motion as determined from the numerical simulations (5 degrees). During training, subjects were instructed to rotate their heads such that the scrolling lines remained within the boundaries set by the bars. During the actual fMRI procedure, subjects were instructed to repeat the same motions as they had been trained.

4.2.4.1. Postprocessing Methods
For all six runs, the acquired k-space data were reconstructed by SENSE and GRAPPA parallel imaging reconstructions without USM and with USM. For SENSE and GRAPPA without USM, the coil sensitivity maps obtained before each run were used. For SENSE+USM and GRAPPA+USM, the coil sensitivity maps were adjusted to account for head movement by appropriately rotating, translating, and linearly interpolating according to the parameters recorded by the in-bore motion tracking system. Furthermore, linear extrapolation was performed near the edges of the brain for regions with reduced or negligible signal at time zero due to partial volume effects or the absence of brain tissue, but higher signal at later times due to head motion. For all reconstruction schemes, a retrospective motion correction was then applied to the reconstructed images to remove residual errors.

To quantify the head motion, the peak-to-peak (p-p) values of all six motion parameter estimates (three translation and three rotations) for each subject were calculated from the motion tracking data obtained from the optical system. The group statistics (mean, standard deviation and range) of the p-p values for each motion parameter were calculated. The directions with the largest p-p range of rotation and translation were determined.

Activation maps were obtained using AFNI after performing slice timing correction, temporal detrending, spatial smoothing (Gaussian spatial filter with 4 mm full width at half maximum), temporal smoothing (3-point median filter), masking fMRI signals to zero outside the brain; and GLM analysis [122]. The GLM was conducted using a “task waveform” boxcar function (with unity amplitude during task blocks and zero during rest blocks) convolved with a canonical BOLD hemodynamic response waveform available in AFNI. Third order polynomial coefficients and the six head motion parameters (obtained from AFNI) were also included as nuisance regressors. The results of the GLM analysis were summarized by color activation maps with the threshold for statistical significance determined according to the FDR of $q = 0.01$ [87]. Activation maps were then overlaid on the respective anatomical images of each subject (previously aligned to the fMRI data) using affine registration in AFNI.

Additionally, image stability across the fMRI time series data was assessed by temporal standard deviation (tSD) maps generated using MATLAB. The tSD value was calculated for each voxel after detrending, for time points lying inside the rest block. In addition, the first three time points
of each rest block were excluded to prevent the possible confound of activation signals causing increased variance.

Subsequently, for all subjects, the quality of activation maps was assessed by qualitative visual inspection as well as by two quantitative metrics. First, the Dice coefficient [123] was calculated between the activation maps (of the whole brain) of the baseline run and the other runs with SENSE, SENSE+USM, GRAPPA and GRAPPA+USM reconstruction. The Dice coefficient takes values between 0 and 1 and higher Dice coefficients indicate higher overlap between the two compared activation maps. Second, the spatially averaged temporal standard deviation was calculated over the brain volume, yielding the metric \( t\overline{SD} \). Multiple paired one-tailed t-test were then performed to assess the effect of USM on the two metrics (Dice coefficient and \( t\overline{SD} \)) for all runs except the baseline, for both SENSE and GRAPPA reconstructions.

4.3. Results

4.3.1. Numerical Simulations

Figure 4.1 shows the percent artifact signal change observed in the first set of simulations, which were designed to investigate the effects of shifting phantom position and orientation inside a 12-channel head matrix receiver coil. Simulated artifacts are shown for SENSE and GRAPPA reconstructions for examples of 2 mm (1mm) in-plane translation, 2 degrees (1 degrees) in-plane rotation, 2 mm (1mm) through-plane translation, and 2 degrees (1 degrees) through-plane rotation, where the unbracketed values refer to \( R = 2 \) and the bracketed values \( R = 4 \), respectively. Note that the artifact signal changes are mostly similar for SENSE and GRAPPA throughout, albeit with subtle differences, with prominent changes in the aliased regions where accurate knowledge of the coil sensitivity maps is necessary to unfold the data properly. The artifact signal change is particularly evident for in-plane changes in position compared to through-plane changes, as expected for axial acquisitions within such cylindrical coil geometry [124]. Additionally, the artifact signal change is substantially higher for \( R = 4 \) compared to \( R = 2 \), especially given that the example results shown for the higher acceleration factor were obtained with lower translational and rotational shifts.

A representative rectangular ROI is also shown in the top left of Fig. 4.1, over which the artifacts were studied in more detail. The ROI was selected conservatively to consist of unaliased and
some aliased regions, and to provide a moderate estimate of the artifact rather than the worst-case scenario. Figure 4.2 shows the spatial average of absolute percent artifact signal change within the ROI for a range of in-plane and through-plane translations and rotations, respectively. This artifact signal change increases as the rotation angle or translational displacement increases in the selected ROI, with artifact levels most pronounced again for in-plane changes compared to through-plane changes for both SENSE and GRAPPA reconstruction. For $R=2$, the artifact signal change in the representative ROI is consistently slightly larger for GRAPPA than for SENSE, whereas the opposite is true for $R=4$.

Fig. 4.1. Results of the first set of simulations: percent artifact signal change for SENSE and GRAPPA parallel imaging reconstruction respectively: with acceleration factor $R=2$ under (a,e)
2 mm in-plane translation, (b,f) 2° in-plane rotation, (c,g) 2 mm through-plane translation, (d,h) 2° through-plane rotation; and with R=4 under (i,m) 1 mm in-plane translation, (j,n) 1° in-plane rotation, (k,o) 1 mm through-plane translation, (l,p) 1° through-plane rotation.

Fig. 4.2. Results of the first set of simulations: absolute artifact signal change (%) spatially averaged over the ROI shown in Fig. 4.1, due to coil-motion interaction. Changes are shown for SENSE and GRAPPA parallel imaging with acceleration factors R=2 and R=4 under (a) in-plane translation; (b) in-plane rotation; (c) through-plane translation; and (d) through-plane rotation. Insets shown in (c) and (d) indicate the trends when the artifact signal changes are low.

The first set of simulations was used to inform the second set. Based on the results of Fig. 4.2, 20 random in-plane translational motions were generated with 5 mm p-p that corresponded to ~2.5% spatially averaged absolute artifact signal change for R=2; and 20 random in-plane translational motions were generated with 1 mm p-p that corresponded to ~2.5% change for R=4. Figure 4.3 shows the average t-value activation maps produced from random-effects analysis over each set of 20 motions for SENSE, GRAPPA, SENSE+USM and GRAPPA+USM reconstruction methods with R=2 and R=4. The analogous activation maps obtained without motion are also shown for comparison purposes.

Compared to the case of no motion (Fig. 4.3(a,d,g,j)), random motion reduces the statistical significance of activated voxels (Fig. 4.3(b,e,h,k)). Consistent with Fig. 4.2, the SENSE and GRAPPA activation map results for 1 mm p-p random motion with R=4 are similar to those for 5 mm p-p random motion for R=2. Also, Fig. 4.3(c,f) and (i,l) show USM-corrected SENSE and GRAPPA average activation maps obtained with R=2 and 5 mm p-p random in-plane
translational motion and R=4 and 1 mm p-p random in-plane translational motion, respectively. The USM approach suppresses the artifacts very effectively in all cases.

**Fig. 4.3.** Results of the second set of simulations: average t-value activation maps (thresholded at a false discovery rate FDR of q=0.01) for SENSE and GRAPPA parallel imaging reconstruction, respectively, with acceleration factor R=2 under (a,d) no motion, (b,e) 5 mm peak-to-peak (p-p) in-plane translation, (c,f) 5 mm p-p in-plane translation with updated sensitivity maps (USM); and with acceleration factor R=4 under (g,j) no motion, (h,k) 1 mm p-p in-plane translation, (i,l) 1 mm p-p in-plane translation with USM.

4.3.2. fMRI Experiments
Human fMRI experiments were conducted in young healthy adults with use of foam padding for restraint within the head coil. Despite this, small head motions were recorded by the optical tracking system during performance of the "baseline" fMRI run (that included instructions to perform the task while keeping the head as still as possible). The coordinate system in which the motion parameters were measured is shown in Fig. 4.4(a). The group mean (black bars), standard deviation (white bars), and the range (error bars) of the p-p angular rotations (roll, pitch, yaw) and displacements (ΔSI, superior-inferior; ΔRL, right-left; and ΔAP anterior-posterior) for the baseline runs are shown in Fig. 4.4(b). The group mean p-p values were <1.7° over all angular rotations, and <1.3 mm over all displacement axes; with group standard deviations of <0.4° and ≤0.4 mm, respectively; and ranges of ≤2.5° and ≤1.8 mm, respectively. The largest extents of motion were observed in ΔAP and pitch rotation parameters (p<0.05 as measured by Tukey range tests comparing ΔAP with ΔRL and ΔSI, and comparing pitch values with roll and yaw values).

To ensure consistency in the overt head motion experiments, the simulator training session prior to fMRI included head motion feedback with 5° rotational targets, a range of motion that the numerical simulations suggested would result in obvious confounding artifact in relation to BOLD signal changes. Despite subjects performing consistently across the group, the original intent of isolating motion only to particular in-plane and through-plane rotations was not achieved in practice during the fMRI experiments. Instead, complex motion was observed across all 6 degrees of freedom, in two consistent but different patterns depending on the instructions. The motion parameters for these runs are shown in Figs. 4.4(c,d), respectively, both indicating substantially larger motions than were observed for the baseline case (Fig. 4.4(b)). For fMRI runs involving in-plane rotation with PACE (Fig. 4.4(c)), head motion was consistent and characterized primarily by increased roll and ΔRL values compared to Fig. 4.4(b). For runs involving through-plane rotation with PACE (Fig. 4.4(d)), head motion was also consistent but characterized primarily by increased pitch and ΔAP parameters compared to Fig. 4.4(b).
Fig. 4. (a) Coordinate system for tracking of rigid-body head motion during fMRI experiments. Group mean (black bars), standard deviation (white bars), and range (error bars) of peak-to-peak (p-p) head motion for time series data collection for all subjects, for each of the different fMRI runs: (b) baseline; (c) in-plane rotation + PACE; and (d) through-plane rotation + PACE.

Figure 4.5 shows fMRI activation maps (an oblique axial slice encompassing primary sensorimotor cortex and supplementary motor area) for the bilateral finger tapping task for one representative subject for SENSE and GRAPPA reconstructions with R=2 and R=4. Figures 4.5(a-j) show maps for R=2 whereas Figs. 4.5(k-t) show maps for R=4. Considering first the activation maps for R=2, the SENSE and GRAPPA results for the baseline fMRI condition of minimal head motion are shown in Fig. 4.5(a) and (f), respectively. These maps are very similar, both depicting bilateral activity in primary sensorimotor cortex and the supplementary motor area. Figures 4.5(b,d,g,i) show the activation maps obtained with SENSE and GRAPPA when PACE is used to correct overt head motion. These maps include false positive and false negative activations in comparison to the baseline maps (Fig. 4.5(a,f)). For in-plane rotation with PACE (Fig. 4.5(b,g)), these artifacts are pronounced for both SENSE and GRAPPA reconstructions, observable in anterior and posterior brain regions as well as in the vicinity of the supplementary
motor area. For through-plane rotation with PACE (Fig. 4.5(d,i)), however, artifacts are less evident with false positives confined primarily to the posterior brain. Figures 4.5(c,e,h,j) illustrate the performance of the PACE+USM method in suppressing the false activations for runs with in-plane (Fig. 4.5(c,h)) and through-plane rotations (Fig. 4.5(e,j)), producing robust activation maps that closely resemble those of the baseline runs. The PACE+USM results for through-plane rotation (Fig. 4.5(e,j)) are a minor improvement over those obtained with PACE only (Fig. 4.5(d,i)), whereas the PACE+USM results for in-plane rotation (Fig. 4.5(c,h)) show a substantial correction in comparison to the PACE only counterparts (Fig. 4.5(b,g)).

Analogous trends are observed for R=4. Additionally, for overt in-plane head rotation, the number of false activations is considerably higher (Fig. 4.5(l,q)) compared to those obtained with R=2 (Fig. 4.5(b,g)). This finding is consistent with the numerical simulation results. Also compared to the results for R=2, R=4 produces less activated voxels in the baseline condition of minimal head motion (Fig. 4.5(k,p)), potentially due to the SNR loss caused by use of a higher acceleration factor. Although activation of bilateral sensorimotor cortex is still apparent in these images, activation of supplementary motor area is no longer well observed. The PACE+USM results (Fig. 4.5(m,o,r,t)) provide corrections that are very consistent with the reduced quality of the baseline activation maps.
Fig. 4.5. Activation maps (FDR q=0.01) for a representative subject for SENSE and GRAPPA parallel imaging reconstruction schemes with acceleration factors R=2 and R=4: (a,f,k,p) baseline runs; (b,g,l,q) in-plane rotation with PACE; (c,h,m,r) in-plane rotation with PACE+USM; (d,i,n,s) through-plane rotation with PACE; and (e,j,o,t) through-plane rotation with PACE+USM.

Similar trends in activation maps were observed over all subjects, despite the inter-subject variability in head motion and brain activity. Figure 4.6 summarizes this observation using the Dice coefficient to quantify overlap between activation observed in the baseline condition of minimal head motion, and activation observed under overt head motion including PACE, with or without USM, using SENSE or GRAPPA with R=2 or R=4. Figure 4.6(a) shows group results
for the Dice coefficient when R=2. For in-plane head rotations, a statistically significant increase in Dice coefficient is observed after applying PACE+USM, for both SENSE and GRAPPA (paired one-tailed t-test, p < 0.05). For through-plane head rotations, analogous trends toward increase failed to reach statistical significance. For R=4, as shown in Fig. 4.6(b), all Dice coefficient values are reduced in comparison to the respective values for R=2, again likely due to reduced SNR at higher acceleration factor. The effect is especially evident in the cases where SENSE and GRAPPA are implemented using PACE only. As observed for R=2, PACE+USM produces a statistically significant increase in Dice coefficient for in-plane head rotations for both SENSE and GRAPPA (paired one-tailed t-test, p < 0.05). In addition, the increased artifact levels present under R=4 conditions lead to PACE+USM producing a statistically significant increase in Dice coefficient for through-plane head rotations in the case of SENSE (paired one-tailed t-test, p < 0.05), but only a trend in the case of GRAPPA.

Fig. 4.6. The Dice coefficient of activation overlap between baseline fMRI with minimal head motion, and fMRI in the presence of overt in-plane or through-plane rotational head motion.
using PACE or PACE+USM, for SENSE and GRAPPA with acceleration factor (a) R=2 and (b) R=4.

Figure 4.7 shows the tSD maps for the same representative subject as in Fig. 4.5, using the same organizational layout. As anticipated from Fig. 4.5, a number of effects are observed. Starting with the data for R=2, SENSE and GRAPPA results are very similar throughout. The tSD values are lowest for the baseline fMRI run involving minimal head motion (Fig. 4.7(a, f)), whereas using PACE only during in-plane rotation (Fig. 4.7(b,g)) and through-plane rotation (Fig. 4.7(d,i)) yields slightly elevated tSD values. The elevations obtained using PACE only during in-plane rotation are the largest (Fig. 4.7(b,g)) especially at the edges of the brain where partial volume and coil element proximity effects are expected to be the largest. As expected, the tSD maps obtained with PACE+USM correction are very similar to those obtained with baseline fMRI, both for in-plane rotations (Fig. 4.7(c,h)) and through-plane rotations (Fig. 4.7(e,j)). For R=4, tSD values are significantly larger (Fig. 7(k-t)) compared to the respective values obtained with R=2 (Fig. 4.7(a-j)). There are also visible residual aliasing artifacts in the tSD maps obtained with SENSE at depth within the brain (Fig. 4.7(k,l,m,n,o)) likely due to the local similarities in the sensitivity maps of each coil element in this region, reducing the effectiveness of image reconstruction. Despite the different appearance of the SENSE and GRAPPA tSD results, the overall trends are similar to those observed with R=2: elevated tSD values in the presence of in-plane or through-plane rotational motion when PACE is used alone (Fig. 4.7(l,n,q,s), and values very similar to baseline tSD when PACE is used with USM (Fig. 4.7(m,o,r,t)).
Fig. 4.7. Maps of temporal standard deviation (tSD) for a representative subject for SENSE and GRAPPA parallel imaging reconstruction schemes with acceleration factors R=2 and R=4: (a,f,k,p) baseline runs; (b,g,l,q) in-plane rotation with PACE; (c,h,m,r) in-plane rotation with PACE+USM; (d,i,n,s) through-plane rotation with PACE; and (e,j,o,t) through-plane rotation with PACE+USM.

Similar trends in tSD maps were observed over all subjects, despite the inter-subject variability in head motion and brain activity. Figure 4.8 summarizes the spatially averaged temporal standard deviation, $\bar{\text{tSD}}$, of all subjects for all fMRI runs. Fig. 4.8(a,b) show the $\bar{\text{tSD}}$ values for R=2 and R=4, respectively. The respective $\bar{\text{tSD}}$ values for SENSE and GRAPPA are very similar for all fMRI runs. Also, as expected, the respective $\bar{\text{tSD}}$ values for R=4 are higher than those for R=2. Using only PACE to correct for overt head motion, in-plane rotations exhibit the largest $\bar{\text{tSD}}$ values compared to baseline, and through-plane rotations show elevated $\bar{\text{tSD}}$ values that are
not as large. Use of PACE+USM to correct for head motion causes a reduction in \( tSD \) values that is indistinguishable from baseline levels to within experimental error. For in-plane rotation, PACE+USM provided a statistically significant decrease in \( tSD \) for SENSE with R=2 and R=4, and for GRAPPA with R=4, (paired one-tailed t-test, \( p < 0.05 \)).

**Fig. 4.8.** The spatial average of the temporal standard deviation for the baseline fMRI as well as fMRI in the presence of overt in-plane or through-plane rotational head motion using PACE or PACE+USM, for SENSE and GRAPPA with acceleration factor (a) R=2 and (b) R=4.

### 4.4. Discussion

This study demonstrates that head motions in relation to a fixed multi-channel receiver coil can introduce unwanted signal variations in parallel-imaging fMRI that are comparable to the weak fMRI BOLD signal changes. These variations constitute a residual signal artifact that cannot be mitigated by prospective motion correction assuming simple rigid-body motion. However, coil sensitivity map adjustment to account for the relative motion between the head and the receiver coil elements can achieve a robust correction of the residual artifact. In this work, SENSE and GRAPPA, two fundamentally different parallel imaging reconstruction methods, have been studied with acceleration factor R=2 and R=4 to comprehensively understand the effect of interactions between motion and coil sensitivity maps by numerical simulation and by human
fMRI involving prospective motion correction using PACE. Before, discussing the results of this study, it should be noticed that in this work, GRAPPA estimated the weighting factors directly from the coil sensitivity maps rather than from additional calibration lines, or auto-calibrating signal (ACS) that are often collected along with the undersampled data acquisition [20]. Estimating the weighting factors from the ACS lines entails additional scan time and makes the comparison with SENSE non-trivial, thus in this work weighting factors are obtained from the coil sensitivity maps directly. Use of coil sensitivity maps rather than ACS is the only deviation made from the original GRAPPA technique, which makes the parallel-imaging process employed here similar to the Cartesian parallel magnetic resonance imaging with adaptive radius in k-space (PARS) technique [137]. In the following, the outcomes and implications of this study are further discussed.

Because head motion can affect parallel imaging reconstruction in a complex manner, numerical simulations were a necessary preliminary step to estimate the scale of artifact levels in the fMRI context, as well as to devise proper human fMRI experiments for motions in the direction that coil sensitivity varies most rapidly. For the studied 12-channel cylindrical head coil, the sensitivity profiles changed much more during in-plane motions than during through-plane motions. Thus, higher level of artifact signal change was observed for in-plane motions relative to through-plane motion. Similar results have been obtained for conventional fMRI reconstruction schemes, with larger artifact signal change for in-plane motion compared to through-plane motion [128]. Also, this study showed that the artifact level increased with the increase of the parallel imaging acceleration factor if the scan duration is kept identical, meaning that the main benefit of parallel imaging acceleration is not exploited. This finding makes sense because parallel imaging reconstruction with larger acceleration factor depends more heavily on the coil sensitivity maps information compared to the parallel imaging reconstruction with smaller acceleration factor. Additionally, the two studied parallel imaging reconstruction methods (i.e., SENSE and GRAPPA), didn’t exhibit considerably different artifact levels. According to the simulations, GRAPPA parallel imaging with acceleration factor R=2, exhibited slightly higher artifactual signal intensity changes compared to SENSE parallel imaging with R=; whereas, SENSE parallel imaging with acceleration factor R=4 demonstrates slightly higher artifact level relative to the GRAPPA parallel imaging with R=4.
The second set of numerical simulations showed that for acceleration factor $R = 4$, motions on the order of 1 mm p-p in-plane translation could adversely affect the average t-value activation map obtained when using prospective motion correction, causing a reduction in the significance of activation compared to the case of no motion. For acceleration factor 2, however, 5 mm p-p in-plane translational motion has a similar effect. Overall, as $R$ increases the sensitivity to artifact increases and the motion threshold that induce artifactual signal changes comparable to the weak fMRI BOLD gets smaller. For context, 1 mm p-p head motion can commonly be observed during a few minute long fMRI scan of healthy subjects, 5 mm p-p motion can occur in fMRI of patient populations such as those recovering from stroke [40][102], and in fMRI language tasks for pediatrics, motions of 3 mm p-p are commonly observed [37]. The dominant direction of head motion (in- vs. through-plane) greatly depends on the task. However, nodding (pitch) is often times reported to be the predominant direction of head motion for motor tasks [102], the direction that is more robust to the interaction between the head motion and coil sensitivity maps for the 12-channel coil investigated in this work. Even so, although for activation maps in presence of overt through-plane motion, the issue of head motion-coil sensitivity interaction is relatively minor for conventional reconstruction [128], it becomes increasingly more problematic with increasing the acceleration factor $R$. Therefore, a robust strategy to correct for all influences of head motion on parallel imaging fMRI would be required, including the artifacts studied in the present work.

In addition to the insight provided by numerical simulations, additional care was taken to eliminate other potential confounds, and to isolate the artifacts associated with interactions of coil sensitivity and head motion in parallel-imaging. Thus, after parallel imaging reconstruction, retrospective motion correction by rigid-body image coregistration was performed prior to calculation of activation maps. This step was undertaken to account for residual errors inherent to the PACE method, associated with image-based motion detection and delays between the motion occurrence and correction.

Theoretical consideration of coil sensitivity interactions with head motion led to a correction method USM that involves using the adjusted coil sensitivity maps for parallel imaging reconstruction. The key assumption that is essential for parallel imaging with USM to be effective is that the loading of the coils does not change with the head position. Given the electromagnetic properties of biological tissues, this assumption is expected to become less valid
with increasing static magnetic field strength [119] The assumption was validated at 3T in a previous work [128]. To validate the assumption at 3 T, an experiment was conducted to investigate the differences in coil sensitivity maps for a single subject placed in many different head positions and orientations within a multichannel head coil. This experiment demonstrated that loading of the coils does not substantially change as a result of head position and orientation. Over the range of head placements that was investigated, updating the original “reference” coil sensitivity maps according to head motion parameters measured by the optical tracker was found to provide a good estimation of the true coil sensitivity maps measured at that given head placement. Therefore, instead of measuring coil sensitivity maps at each point in the fMRI time series, adjustment of the coil sensitivity profiles obtained at a reference position suffices for USM. By extension, this procedure is expected to work well at lower magnetic field strengths including 1.5 T, but should be further verified at higher fields such as 7T [119] where measurement of time-dependent coil sensitivity maps may be essential. The analogous arguments also apply to the noise correlation matrix, with the proviso that head motions greater than those measured in Fig. 4.4 may require additional attention.

The human fMRI results showed important consistencies with the numerical simulations. First, the in-plane motion demonstrated higher artifact associated with head motion-coil sensitivity interaction compared to through-plane motion for parallel-imaging fMRI. Second, by increasing the parallel imaging acceleration factor R, the artifact level (manifested by false activation and elevations in the temporal standard deviation values) becomes more significant. Third, updating the coil sensitivity maps effectively compensated for the head motion-coil sensitivity interaction artifacts and produced activation maps comparable to the baseline obtained with minimal head motion. However, one discrepancy between the human fMRI results and the numerical simulations were the relationship between performances of the two parallel reconstruction schemes, SENSE and GRAPPA. In numerical simulation, for R=2, the artifactual signal change in the chosen ROI was consistently slightly larger for GRAPPA than for SENSE, whereas the opposite was true for R=4. In human fMRI data, no such clear trend was observed between the two reconstruction schemes and both SENSE and GRAPPA performed comparably. This difference in the performance observed in the numerical simulations was possibly due to the choice of the ROI in the numerical simulations.
Comparing the activation maps against the baseline activation maps generates an insightful but insufficient assessment because the “ground truth” activation is unavailable (i.e., precise knowledge of the true spatial pattern of brain activity associated with the self-paced bilateral finger tapping task in each subject). It is impossible to truly determine how many false positive and/or false negative activation voxels are present in the maps obtained by USM method. What can be observed, however, is that on average the USM activation maps are highly similar to the baseline ones (obtained under minimal head motion), quantified by Dice coefficient in this study. The analogous effects are observed for tSD values, as well.

The result of the coil sensitivity map variation on the activation maps changes by the choice of the direction of the PE in parallel-imaging in k-space, the acceleration factor $R$, and parallel-imaging reconstruction method. According to the results of this study, the increase of acceleration factor $R$, decreases the overlap between the activation maps obtained for the baseline and the overt head motion conditions. Also, the tSD values noticeably incline for fMRI data obtained with acceleration factor 4 compared to 2. This phenomenon was expected due to gradual SNR decrease with increasing the parallel-imaging acceleration factor. Moreover, as predicted from numerical simulations results, fMRI data obtained by parallel imaging with acceleration factor 4 is affected notably more than that obtained by parallel imaging with acceleration factor 2, pronouncely visible in comparison of the 2x with 4x accelerated fMRI activation and tSD maps under in-plane rotations.

While our results strongly support use of USM method for SENSE and GRAPPA parallel-imaging fMRI, several shortcomings of the proposed method should be considered. Errors in spatial extrapolation near the edges of the brain, residual uncorrected motion, inclined acquisition of slices because of motion during acquisition, as well as change of T2*-values due to motion induced magnetic field distortions [8] are all possible motion artifacts that, if not dealt with systematically, can distort the parallel-imaging reconstructed fMRI images even with utilizing USM, prospective motion correction using PACE and retrospective motion correction. Besides that, further research is needed to demonstrate the robustness of the methodology for different fMRI tasks and populations. Moreover, the fMRI experiment was conducted assuming that brain activation would be identical for both minimal head motion and during overt prescribed motions. Although this assumption is probably sufficient for the present study, given the inter-subject variability that was observed, expecting that the activation maps are slightly
different is not unreasonable. For example, the activation maps obtained with overt head motion are expected to engage parts of the primary somatosensory and motor cortex involved in control of neck muscles, as well as parts of the cerebellum involved in movement coordination. With careful methodology, it should be possible to elucidate these differences in future studies.
Chapter 5
Conclusions and Future Directions

From its initial development in the early 1990s, MRI has become an essential tool for localized, non-invasive imaging of brain activity. The work presented in this thesis has focused on one key problem – the degradation of fMRI data by head motion, with the aim to develop a robust and comprehensive correction technique. In the commentary below, a detailed discussion is provided of the outcomes and objectives of this thesis, as well as the implications and future directions stemming from this work.

5.1. Summary

Chapter 2 tested the hypothesis that DORK off-resonance correction combined with dynamic geometric distortion using PLACE and averaging of PLACE displacement maps acquired at similar head positions improves image stability and statistical inference of brain activity in fMRI of young healthy adults. First, it was shown that the phase of the EPI pairs was affected by the off-resonance effects of respiration, and that dynamic geometric distortion correction by PLACE requires an off-resonance magnetic field correction [62]. Second, it was shown that combining DORK off-resonance correction and averaging of PLACE displacement maps acquired at similar head positions allows deployment of PLACE as a robust dynamic geometric distortion correction (dPLACE). Briefly summarizing the methods that were developed to complete these aims, a standard fMRI EPI sequence was first modified to include the PLACE technique as guided by the original PLACE implementation [25]. Also, after reconstructing the data from the individual channels of the multi-channel head coil, DORK was applied independently to the odd and even images in the time series because of the k-space shift between the two data sets. Displacement maps were obtained retrospectively according to the established PLACE processing pipeline [25] with the three additional steps: a) selecting appropriate image pairs based on head position for calculating the PLACE displacement maps; b) complex averaging the multi-channel head coil data; and c) averaging the PLACE displacement maps acquired at similar head positions. Performance was compared against use of fMRI without distortion correction and with static geometric distortion correction (sPLACE) in which the PLACE displacement map obtained from the first EPI pair was applied to all EPI data in the fMRI time series.
The performance of the combined DORK, dPLACE and averaging technique was characterized through several imaging experiments involving an appropriate test phantom and six healthy adult volunteers. The phantom was kept stationary and was imaged in the presence and absence of dynamic off-resonance effects that simulated respiration, as produced by inflating and deflating two plastic bags covered by a wet towel, near the phantom. The phantom experiments were designed without bulk motion to first demonstrate that dynamic off-resonance effects degrade dPLACE displacement maps; and secondly, to show that the performance of the combined dynamic geometric distortion approach matches that of sPLACE to correct for static geometric distortion even in presence of respiration induced off-resonance effects. This was confirmed by quantifying the temporal standard deviation of fMRI signals for both dPLACE and sPLACE and showing that they were equivalent within experimental error.

Rest and block-design finger-tapping task experiments were performed by six healthy young adults, for each of the three imaging and analysis protocols. The combined technique (DORK+dPLACE+DMA) substantially improved the temporal standard deviation (for at-rest experiments) and activation maps (for finger-tapping experiments) in comparison to the results obtained by standard processing (no geometric distortion correction) and sPLACE, supporting the efficacy of the combined approach in suppressing head motion artifacts.

Chapter 3 tested the hypotheses that: 1) head motion in relation to fixed multi-channel receiver coils can introduce erroneous signal variations comparable to or greater than BOLD signals and thus artifacts in activation maps generated from fMRI with prospective motion correction by the established PACE technique; and 2) such artifacts can be suppressed effectively by a procedure that adjusts the orientation and position of the receiver coil sensitivity maps according to head motion. Towards characterizing the regime over which prospective motion correction will benefit from adjusting coil sensitivity maps to reflect relative positional change between the head and the receiver coil, two sets of numerical simulations were performed. The simulations exploited the complex-valued coil sensitivity maps and noise correlation characteristics of a 12-channel “matrix” head receiver coil used in subsequent human MRI experiments. The sum-of-squares and Roemer optimal reconstructions [108] were used for combining the MR signals acquired from different channels of the multi-channel head coil. The effect of the coil sensitivity-related artifact was compared between the two reconstructions.
The first set of simulations were undertaken to quantify the artifact signal change due to coil sensitivity effect as a function of different magnitudes of motion in different directions. The Roemer optimal reconstruction was affected slightly more than the sum-of-squares reconstruction for all motion directions and magnitudes. These simulations showed that the artifact signal change introduced by interaction between motion and coil sensitivity can be on the order of the BOLD signal for the motions smaller than 5 millimeters/degrees, especially for the in-plane direction when conducting axial imaging with the 12-channel coil under study. The second set of simulations was informed by the results of the first set, and illustrated the effect of these artifact signal changes on the t-statistics of the fMRI analysis. It was observed that the significance of activations was reduced as a result of coil sensitivity effects for in-plane head rotations in the 5 degrees range, and that adjusting the coil sensitivity maps according to head motion can correct the problem.

The results of the simulations were subsequently used to guide illustrative human fMRI experiments. Six human volunteers were imaged with and without overt head motion, with and without prospective motion correction, and with and without adjusting for coil sensitivity effect while they performed a block-design finger tapping task during fMRI. After dynamic geometric distortion correction, all the data were reconstructed with sum-of-square and Roemer optimal reconstructions. The human fMRI experiments demonstrated that head motion in relation to a fixed multi-channel receiver coil can introduce unwanted signal variations comparable to the weak fMRI BOLD signal and hence significantly disrupt the fMRI data quality (as measured by the number of the false activations, temporal standard deviations, and Dice coefficient of overlap between the activation maps acquired without overt head motion and those obtained the in presence of overt head motion with PACE) for both sum-of-square and Roemer optimal reconstructions, particularly in the case of in-plane head motions during axial imaging with the 12-channel coil.

The main assumption of the coil sensitivity adjustment method was that at 3.0T, coil loading did not change as a result of head motions considered in this study. This assumption was tested by assessing whether adjustment of the position and orientation of the coil sensitivity map acquired at a reference position (to reflect the position change between the reference position and the current head position) can create sensitivity maps similar to those acquired at the current head
position. The difference error between the adjusted reference coil sensitivity maps and the maps obtained at the new head positions was negligible for the range of motions investigated.

In Chapter 3, an MRI-compatible optical tracking system was also used to measure head motion and to adjust the coil sensitivity maps to reflect relative positional change between the head and the fixed receiver coil elements. This procedure significantly improved the Roemer-reconstructed fMRI activation maps for motion within 5 mm and 5 degrees p-p range by decreasing the number of false activations and the temporal standard deviation, and resulting in fMRI data quality comparable to the case of no head motion as measured by the Dice coefficient of overlapping brain activity.

In Chapter 4, the effect of motion-induced coil sensitivity changes was also studied on accelerated fMRI involving SENSE and GRAPPA reconstructions. In parallel-imaging reconstruction, such changes in coil sensitivity maps are expected to be of great importance because coil sensitivity is an essential part of spatially encoding the fMRI signals. It was hypothesized that: 1) head motion in relation to fixed multi-channel receiver coils can introduce artifact signal variations on the order of BOLD signals, and that the artifacts are observable in activation maps generated by SENSE-fMRI and GRAPPA-fMRI involving the established real-time motion correction technique, PACE; and 2) such artifacts in parallel imaging fMRI can be suppressed effectively by adjusting the orientation and position of the receiver coil sensitivity maps to reflect relative positional change between the head and the coil elements, as described in Chapter 3.

Two sets of numerical simulations were again used to investigate the extent of the head motion artifact on fMRI using SENSE and GRAPPA schemes with acceleration factors of 2 and 4, towards characterizing the regime over which parallel imaging fMRI with PACE prospective motion correction will benefit from updating coil sensitivities to reflect relative positional change between the head and the receiver coil. Both sets of simulation were again conducted for the 12-channel coil and axial imaging. In the first set of simulations, it was found that in-plane motions generated the largest amount of artifact signal change. There was no significant difference in artifact signal levels between SENSE and GRAPPA; and larger acceleration factors yielded much larger signal artifacts (for in-plane translation, the artifact signal change observed for an acceleration factor of 2 and 5 mm translation equaled that observed with an acceleration factor of
4 and 1 mm translation). In the second set of simulations, this artifact signal change was shown to reduce the significance of activated voxels, with acceleration factor 4 affected much more than acceleration factor 2. Additionally, adjusting the coil sensitivity maps analogous to the process presented in Chapter 3 (i.e., to reflect relative positional change between the head and the coil using the motion data obtained from the optical tracking system) restored and qualified the activation maps to that obtained without head motion.

Six subjects were imaged subsequently by PACE fMRI with acceleration factors 2 and 4 while performing a simple block design finger tapping task with and without overt head motion at levels informed by the numerical simulations. These experiments showed that head motion in relation to a fixed multi-channel receiver coil can create erroneous signal variations in parallel-imaging fMRI that are comparable to the weak fMRI BOLD signal, and thus can disrupt the fMRI data quality. The artifacts were most pronounced for in-plane head motions, with larger artifacts observed for acceleration factor 4 compared to acceleration factor 2, and no significant difference between the activation maps obtained from SENSE and GRAPPA reconstructions. It was also observed that adjustment of the coil sensitivity maps using position tracking data significantly increased the Dice coefficient of overlap between the activation maps acquired without overt head motion and those obtained in the presence of overt head motion with PACE; and significantly decreased the temporal standard deviation of baseline fMRI signals in an analogous manner, such that the effects of head motion were no longer observed.

The methods developed in this thesis represent the initial successful implementation of a robust motion correction system with integrated dynamic geometric distortion correction by PLACE and coil sensitivity compensation. Moving beyond this important step, the remainder of the chapter briefly describes several possible future applications for components of this technology.

5.2. Future Directions

The dynamic geometric distortion correction, coil sensitivity map adjustment technique, and the optical tracking system developed in this work can potentially be employed in a variety of MRI applications involving EPI that are sensitive to geometric distortion changing dynamically in presence of motion, with a resulting degradation in image quality. Examples include diffusion- and perfusion-weighted imaging methods. Moreover, changes of coil sensitivity maps as a result of head motion affect all fMRI protocols that employ multi-channel head coils. The adjustment
of coil sensitivity maps can not only benefit “standard” fMRI involving single-shot acquisition of the full matrix of k-space data (Chapter 3) and accelerated fMRI with parallel-imaging (Chapter 4) but also it can enhance the performance of accelerated fMRI with simultaneous multi-slice techniques that provide further increases in temporal resolution [138][139][140][141]. Furthermore, the optical tracking system developed in this work can also be employed for motion monitoring and feedback. The utility of these motion correction methods and the potential advantages offered by an integrated motion correction approach will be discussed with respect to the above applications in turn.

Additionally, the real-time scan-plane update employed in this thesis (PACE) was adopted as proof-of concept but has known limitations, such as slight error in motion estimation and delays in updating the scan plane. Various approaches are proposed to mitigate these errors, including predictive motion correction, use of external hardware for motion estimation, applying an additional retrospective registration algorithm, and slice-by-slice correction. A brief overview of these techniques is also presented below.

5.2.1. EPI-based MRI Applications

Head motion artifacts are not unique to fMRI and occur to varying extent in all MRI protocols. In particular, diffusion tensor imaging (DTI) [142] and perfusion-weighted imaging by arterial spin labelling (ASL) [143] involve acquisition of many EPI datasets over a prolonged period of time, and subsequent processing of the data to create maps of biophysical parameters (e.g., white matter fiber tracts and cerebral blood flow, respectively). For such protocols, real-time motion correction can suppress the motion artifacts during data acquisition and improve the quality of the biophysical parameter maps.

Using specialized pulse sequences, it is possible to weight MRI signals according to the diffusion properties of water molecules in biological tissues. Briefly, diffusion-weighted data are collected by first applying a gradient pulse (known as “diffusion gradient”) in one direction in space, thus causing the MRI signal to dephase in the transverse plane. After a period of time, a gradient applied with the opposite amplitude and in the same direction will unwind the dephasing for water molecules that are static. If the water molecules undergo motion on a microscopic scale (for example, due to diffusion) perfect phase cancellation is not achieved because the molecules sample slightly different Larmor frequencies in space. Thus, the residual dephasing results in
signal loss. The ratio of the signal intensity with the diffusion gradients to that obtained without diffusion gradients can be used to calculate the diffusion coefficient for each voxel and subsequently to make a map of the “apparent diffusion coefficient (ADC)”\textsuperscript{92}. The application of a diffusion-sensitizing gradient in a particular direction is referred to as diffusion-weighted imaging (DWI). For DTI, the diffusion gradients are applied in multiple directions (a minimum of six) to construct a diffusion tensor that characterizes preferred directions of diffusion. As axons have anisotropic diffusion, DTI provides unique noninvasive capability to map white matter fiber tracts of the brain. However, the diffusion gradients provide sensitivity to multiple sources of motion, not just molecular diffusion. Thus, head motion is an important confound that must be eliminated. Prospective motion correction by optical tracking with a single camera setup has been shown to produce maps with less artifact and recovered anatomical structure compare to the data collected without prospective motion correction [92]. This approach also adjusted the direction of diffusion gradients appropriately with head motion, ensuring that the diffusion-sensitivity gradients were kept along their intended directions with respect to the head to estimate DTI parameters accurately.

Perfusion-weighted imaging involving ASL was conceived at approximately the same time period as fMRI but has only recently become sufficiently robust to become a viable option to the more commonly applied approach (i.e., dynamic contrast enhanced imaging (DCE) [144]). The DCE method involves injection of contrast agent, typically gadolinium-diethylenetriamine pentaacetic acid (Gd DTPA). Part of the impetus for adapting ASL is that the technique uses blood as an endogenous contrast agent to generate perfusion-weighted signals, whereas the exogenous agents used in DCE have health risks to certain patient populations [145]–[147]. In ASL, the protons in the arterial blood are labeled by RF pulses in a preparation phase. In the acquisition phase, the labeled spins that have arrived in the area of interest are subsequently imaged after a period of transit time (typically 1500 ms), generating a “tag image”. The imaging is then repeated without labeling the arterial blood to create another image (called the “control image”). The control image and the tag image are subtracted to produce an ASL image that reflects the amount of arterial blood delivered to each voxel within the transit time. Due to subtraction, the size of the perfusion signal in relation to MR signals from static tissues, SNR is inherently poor in ASL and thus ASL datasets typically involve collection of EPI data in time series lasting in minutes. Furthermore, any misalignment between the control and tag images can
cause artifacts in the ASL image. Thus, head motion confounds ASL perfusion imaging and must be corrected. A recent study has proposed a retrospective automated head motion correction procedure that improves the detection of blood flow [148]. However, the potential benefits of prospective motion correction for ASL have yet to be investigated.

Furthermore, DWI, DTI, DCE and ASL data are often acquired using EPI, and are thus sensitive to geometric distortion in the phase encoding direction. Therefore, these applications could benefit from a robust dynamic geometric distortion correction using PLACE. For example, static geometric distortion correction by PLACE was applied to multi-coil DWI using EPI [84], and showed an improvement in the resulting corrected images in comparison to images that were not corrected for geometric distortion. Use of the integrated motion correction technique outlined here may be able to reduce the sensitivity of DTI, DWI, DSC, and ASL to motion artifacts including the effect of dynamic field inhomogeneity when images are collected using EPI. Moreover, for these applications, use of multi-channel coils is now common practice because of the SNR benefits offered, and hence employing the proposed technique for adjusting the coil sensitivity maps can benefit the outcome of these MRI applications.

5.2.2. Simultaneous Multi-Slice (SMS)

Simultaneous multi-slice (SMS) is another technique for accelerated imaging that has recently gained much attention in the MRI research community [138] especially with the emergence of ultra-high field MRI systems (7.0 T and above) and the associated challenges that arise for EPI from increased inhomogeneity of the magnetic field. The SMS pulse sequence applies a “multi-band” RF pulse (consisting of multiple frequency bandwidths) along with a slice-selective gradient to excite multiple slices at the same time. This results in aliased slices if standard image reconstruction is used with the slices superimposed on each other in a “collapsed image” with spatial aliasing. To control the aliasing pattern and separate the data from each slice, the “controlled aliasing in parallel imaging results in higher acceleration” (CAIPIRINHA) technique was proposed that introduces an in-plane “phase encoding shift” between simultaneously acquired slices and hence increases the distance between aliased voxels [140]. Applying such phase encoding shifts results in improved image quality by reducing “cross-talk” between the slices acquired simultaneously. Akin to in-plane parallel imaging, the acceleration capacity of SMS is limited by the ill conditioning of the parallel imaging reconstruction at high slice
acceleration factors. However, unlike in-plane parallel imaging, SMS does not incur the time dependent reduction in SNR as observed in in-plane parallel acceleration techniques because the resulting reduction in imaging time does not rely on reducing the echo train length. Thus, SMS of EPI acquisition is prone to geometric distortion. Furthermore, parallel-imaging reconstruction techniques and the spatial information of the coil multi-channel sensitivity maps are exploited for separating the aliased slices using either SENSE [139] GRAPPA [140][141] parallel-imaging reconstruction to accelerate in-plane spatial encoding. As shown in Chapter 4 for parallel-imaging fMRI, the effect of head motion on coil sensitivity maps is expected to degrade the quality of images. Therefore, adjusting the coil sensitivity maps according to motion can potentially help mitigate this effect in SMS, in combination with use of prospective motion correction and dynamic geometric distortion correction.

5.2.3. Motion Monitoring and Feedback

In addition to using position tracking techniques for motion correction, position tracking can also be used for monitoring and/or providing visual feedback of motion. A tracking system in a simulator environment is useful for screening patients who may be unable to control their head movements to within acceptable limits (even after substantial training), and then excluding these patients from future fMRI sessions. Discarding data from such patients is common in sites that do not have access to a comprehensive and robust motion correction system. The imaging session is time consuming and costly in this context, and thus there are grounds for avoiding it. It needs to be emphasized that even with effective motion correction techniques that have been developed in this thesis, large head motions (e.g., on the order several centimeters) likely compromise the reliability of the head motion estimates as well as the performance of the dynamic geometric distortion correction and coil sensitivity map adjustment. The accuracy of image registration algorithm using in PACE will drop [1]. In the case of position tracking with external hardware, such as stereo optical cameras, such large motions can result in loss of line-of-sight, with the tracking tool obscured from the cameras, and with the associated loss of data for updating the scan plane. Similarly, dynamic geometric distortion correction is expected to be adversely affected by increasing noise due to the reduced number of averaged displacement maps. The developed coil sensitivity adjustment technique depends on the motion information obtained from the optical tracking system and hence is also affected by the shortcomings of that system. Moreover, large head movements are expected to affect coil loading, and thus changing
the position and orientation of the reference coil sensitivity maps according to head position may fail to provide robust corrections for fMRI. Therefore, in fMRI, early exclusion of patients who cannot control their head movements to within acceptable limits even after substantial training is beneficial. The precise conditions of motion where the new techniques developed in this thesis start to fail is presently not well characterized, and is a topic for future research.

Visual feedback of head motion was exploited in Chapter 3 and Chapter 4, where subjects were trained by providing visual feedback of the true head position measured by an electromagnetic tracking system in an MRI simulator environment. This feedback reduced the variance of head motion across different experiments and provided relatively consistent results in which subjects were able to achieve consistent patterns of head motion across a small group of individuals. Patients can also be trained to reduce their head motion prior to fMRI by performing tasks in a simulator or the magnet bore with visual feedback of head position. Visualization of head position prior to the imaging session can help patients learn to minimize their head movement to within acceptable limits during performance of the task of interest during fMRI (e.g., finger tapping). This training has been shown to cause a lasting reduction of head motion in the simulator, leading to acceptable head motion during actual fMRI experiments involving challenging patient populations [149][150]. Visual feedback of motion can also be used to reduce the amount of head motion during fMRI experiments [151]. However, it should be noted that this latter approach can introduce a “multi-tasking” effect that can confound maps of brain activity or that potentially can affect the performance of the primary task of fMRI interest in patients with impaired brain function.

Lastly, tracking systems can also be used to provide kinematic data to subjects while they are performing sensorimotor tasks involving a particular body part. For example, limb motion visual feedback could help investigate aspects of motor learning and motor control under feedback vs. no-feedback conditions. Furthermore, such feedback is expected to reduce variance of movement between task repetitions, and improve the repeatability of movement across subjects, thereby providing a means to compare BOLD variations robustly across different fMRI experimental conditions and groups.

5.2.4. Other Motion Correction Techniques
Although the volume-by-volume prospective motion correction used in this thesis has shown promise in correction of motion artifacts, more sophisticated methods are available that can provide even better correction, if required. Predictive motion correction, external tracking hardware for motion estimation, additional retrospective registration, and/or slice-by-slice correction are all promising alternatives. A short description of these techniques is provided in this section.

5.2.4.1. Predictive Motion Correction

Despite the attempts for “real-time” motion correction in current MRI systems, there is always a finite lag time between motion measurement/estimation and the subsequent scan-plane update, ranging from ~ 20 ms to 100 ms, depending on MRI system hardware and the real-time motion correction method adopted. This leads to a discrepancy that leaves residual errors in the data due to motion. Depending on the characteristics of motion (e.g. velocity) longer lag times will result in larger errors. Another useful option to decrease this error is “predictive motion correction”, whereby the head position at the time of imaging is predicted based on previous head positions and the known lag time. As an example, using predictive Kalman filtering before real-time scan-plane update has reduced the error from lag [9]. Limitations of such techniques include determining the appropriate filtering constraints and accounting for variable CPU calculation time that changes the effective lag time in the predictive position estimate models. The inclusion of geometric distortion correction and coil sensitivity map adjustment follows naturally and is not detrimentally affected by the predictive motion correction.

5.2.4.2. External Tracking Hardware

The PACE prospective motion correction used in this work estimates the motion parameters by an image-based coregistration algorithm, as explained in Section 1.5.1.4. These estimates can be biased by various artifacts including brain activity; can suffer from limited accuracy for large motions (approximately larger than 3-5 mm in translations and 1-2 degree in rotations); and can only sample motion parameters after acquiring and reconstructing images of the brain. Thus the scan-plane update always lags the head motion by at least one TR interval. One solution that considerably mitigates these problems is to use external tracking systems, i.e., to measure motion as a function of time using equipment other than MRI system hardware. This provides the opportunity to measure head motion with substantially higher temporal and spatial resolution.
through development of the appropriate MRI compatible equipment such as optical tracking systems [51][52][152]. For instance, improved structural image quality at both 3.0 T and 7.0 T has been observed with real-time head motion correction using optical tracking even in experienced and cooperative subjects trained to remain motionless during imaging [152]. Also, real-time slice-by-slice motion correction using optical tracking has been shown to be effective in suppressing false positive activations in fMRI with task-correlated motion [8]. However, the limitations of this approach include long setup time and the necessity for a clear line of sight which impacts RF coil design.

It is worth mentioning that these optical trackers can be used for patient monitoring as described in Section 5.2.3. Also, because of the potential benefits of patient monitoring, development of MR compatible optical tracking systems continues to be an active area of research.

5.2.4.3. Additional Retrospective Registration

Any application of prospective real-time scan-plane update will inevitably have some (ideally small) finite error associated with position measurement/estimation and the lag time. One option to suppress these errors involves applying additional retrospective registration algorithms after real-time correction, to provide a second-order correction to images as done in Chapter 3 and Chapter 4. As discussed in Section 1.5.1.3, retrospective image realignment algorithms are able to correct for sub-millimeter translations and rotations, but perform less effectively as motion amplitudes increase. Therefore, real-time scan-plane update and retrospective image realignment are potentially complimentary. The former is appropriate for suppressing the large motion artifacts, whereas the latter can be used for further correction and reducing small errors. Moreover, estimating the residual motion between image volumes by retrospective motion correction after use of real-time motion correction can be used to assess the accuracy of real-time scan-plane update performance [1][153]. A prospective motion correction with optical tracking and an “in-line” retrospective motion correction hybrid approach was proposed to mitigate residual errors induced by imprecise cross-calibration for anatomical imaging [53][98]. However, a limitation of such work is that retrospective motion correction is challenging to implement time efficiently for in-line applications and will only get more challenging as coil channel count increases, and techniques such as SMS become more pervasive.

5.2.4.4. Slice by Slice Correction
The real-time scan-plane update system adopted in this thesis performed on a volume-by-volume basis, meaning that all slices in a prescribed imaging volume were updated using one set of update parameters. However, there are advantages to performing real-time scan-plane update for each slice individually in a slice-by-slice manner. It thus becomes possible to compensate for motions that occur within a single TR interval. Slice-by-slice correction has been employed in several implementations of real-time motion correction [50], [55], [92], [98], [153]–[155], with promising outcomes.

A comprehensive comparison between the performance of real-time volume-by-volume and slice-by-slice correction has yet to be presented. Future work in this area involves determining under what circumstances and characteristics of motion slice-by-slice correction provides benefits over volume-by-volume correction, given that the time required for imaging a single slice (and by extension the brain volume) can be considerably reduced using SMS methods.

One possible application of the slice-by-slice real-time correction technology is for imaging of patients who exhibit excessive head motions and have difficulty controlling their movements, such as patients with essential tremor or Parkinsonian tremor.

5.2.5. Clinical Implications of the Head Motion Correction Technology

In clinical applications of functional MRI, it is not uncommon to discard fMRI data due to extensive head motion. Use of the developed methodologies including the dynamic optical tracking, dynamic geometric distortion correction, and coil sensitivity map adjustments can reduce or even totally prevent discard of expensive fMRI data and facilitate fMRI of challenging patient populations. Hopefully, this approach will expand the patient populations for which fMRI can be performed robustly. However, modifications to the developed methodologies might be required for clinical use. For example, large (larger than ~5 degrees), fast (larger than ~2 mm/s), or task-correlated head motions might necessitate adjustments to the developed technologies.

5.3. Conclusion

The development of robust and comprehensive head motion correction strategies for fMRI studies is an important avenue of research. Although various techniques exist to correct for head movement, they do not yet offer a complete and robust solution that mitigates both rigid-body and non-rigid head motion artifacts. Real-time scan-plane adjustment with integrated geometric
distortion correction and coil sensitivity map adjustment presents an appealing avenue for suppressing rigid and non-rigid motion artifacts concomitantly. I believe that the integrated motion correction approach that has been developed in this thesis will enable more efficient motion correction strategies in the future. Hopefully, the approach will expand the patient populations for which fMRI can be performed robustly.
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