Feasibility of functional MRI on point-of-care MR platforms

Arjama Halder,

Supervisor: Chronik, Blaine A., *The University of Western Ontario*
Co-Supervisor: Soddu, Andrea, *The University of Western Ontario*

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Abstract

Magnetic resonance imaging (MRI) has proven to be a clinically valuable tool that can produce anatomical and functional images with improved soft tissue contrast compared to other imaging modalities. There has recently been a surge in low- and mid-field scanners due to hardware developments and innovative acquisition techniques. These compact scanners are accessible, offer reduced siting requirements and can be made operational at a reduced cost.

This thesis aims to implement blood-oxygen-level-dependent (BOLD) resting-state functional MRI (fMRI) at such a mid-field point-of-care scanner. The availability of this technique can be beneficial to get neurological information in cases of traumatic brain injury, stroke, epilepsy, and dementia. This technique was previously not implemented at low- and mid-field since signal-to-noise ratio and the contrast scale with field strength.

Studies were conducted to gauge the performance of an independent component analysis (ICA) based platform (GraphICA) to analyze artificially added noisy resting state functional data previously collected with a 3T scanner. This platform was used in later chapters to preprocess and perform functional connectivity studies with data from a mid-field scanner.

A single echo gradient echo echoplanar imaging (GE-EPI) sequence is typically used for BOLD-based fMRI. Task-based fMRI experiments were performed with this sequence to gauge the feasibility of this technique on a mid-field scanner. Once the feasibility was established, the sequence was further optimized to suit mid-field scanners by considering all the imaging parameters.

Resting-state experiments were conducted with an optimized single echo GE-EPI sequence with reduced dead time on a mid-field scanner. Temporal and image signal-to-noise ratio were calculated for different cortical regions. Along with that, functional connectivity studies and identification of resting-state networks were performed with GraphICA which demonstrated the feasibility of this resting-state fMRI at mid-field. The reliability and repeatability of the identified networks were assessed by comparing the networks identified with 3T data.

Resting-state experiments were conducted with a multi-echo GE-EPI sequence to use the dead time due to long T2* at mid-field effectively. Temporal signal-to-noise was calculated for different cortical regions. Along with that, functional connectivity studies and identification
of resting-state networks were performed with GraphICA which demonstrated the feasibility of this resting-state fMRI at mid-field.

Keywords

Mid-field, 3D multi-echo GE, Single-echo GE EPI, Multi-echo GE EPI, Functional MRI, Resting-state, Task-based BOLD, Independent component analysis, Dual regression, Temporal signal-to-noise ratio, Pseudo signal-to-noise ratio, Physiological to Thermal Noise Ratio
Summary for Lay Audience

Magnetic resonance imaging could provide clinical value in point-of-care imaging such as in the emergency department or in the intensive care unit. These scanners mostly operate at low- to mid-field range which was previously associated with poor performance. Recently there has been a surge of such scanners with high-performance components, and improved acquisition and reconstruction methods enabling techniques that were previously not implemented. One such technique is functional MRI which investigates brain function using the changing concentration of blood oxygen in the brain. This thesis focuses on implementing this technique on a specialized mid-field scanner built for head imaging.

The second chapter of this thesis evaluates the performance of the resting state data analysis platform used throughout this thesis. To do so, higher field data with additional noise was provided to the platform. This was done specifically because the data expected from the mid-field scanner was potentially noisy compared to higher-field functional data. The results from this chapter suggest the detection of resting-state networks from higher field functional data with additional noise.

The third chapter of this thesis focuses on optimizing the gradient echo planar imaging sequence used to perform functional MRI at this mid-field scanner. The T2* contrasts at this mid-field scanner for gray and white matter were measured. Quantities such as signal-to-noise ratio and temporal signal-to-noise ratio were used to calculate the physiological-to-thermal noise ratio and contrast efficiency with such scanners.

The fourth chapter focuses on implementing the optimized sequence for resting-state functional studies on a mid-field scanner. Functional connectivities within resting state networks were detected using the independent component based analysis platform described before.

The fifth chapter focuses on using multi-echo EPI for resting-state studies on this scanner. To ensure the effective use of long T2* and short T1 available at mid-field strength along with the high slew rate gradient multi-echo sequence was chosen. The results from this study suggest increased SNR and the potential for increased functional connectivity detection with further optimization.

Overall, this thesis aims to prove the feasibility of functional MRI both task-based and resting-state at these modern mid-field scanners.
Co-Authorship Statement

The following thesis contains work comprising:


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Dedication

To my Ma,

for giving up on her dreams to make mine come true.
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# Table of Contents

Abstract ............................................................................................................................ ii

Summary for Lay Audience ............................................................................................ iv

Co-Authorship Statement ............................................................................................... v

Dedication ........................................................................................................................ vi

Acknowledgments ........................................................................................................... vii

Table of Contents ............................................................................................................ viii

List of Tables .................................................................................................................... xiii

List of Figures ................................................................................................................... xiv

Chapter 1 ......................................................................................................................... 1

1 Magnetic Resonance Imaging ....................................................................................... 1

1.1 Introduction to MRI .................................................................................................. 2

1.1.1 Nuclear Magnetic Resonance ............................................................................. 2

1.1.2 MRI Hardware ................................................................................................... 7

1.1.3 Pulse Sequences ............................................................................................... 12

1.1.4 Low- and Mid-Field MRI: Introduction ......................................................... 15

1.2 Introduction to Functional MRI ............................................................................. 17

1.2.1 BOLD Contrast ............................................................................................... 17

1.2.2 Task-based BOLD Responses ......................................................................... 18

1.2.3 Resting-state BOLD response ........................................................................ 19

1.2.4 Functional Connectivity ................................................................................ 20

1.2.5 Mid-field Functional MRI: Introduction ....................................................... 20

1.3 Thesis Objective ..................................................................................................... 22

1.4 References .............................................................................................................. 23

2 Identifying resting-state networks from functional data with additional noise ....... 29
2.1 Introduction ................................................................. 29
2.2 Methods ................................................................. 31
  2.2.1 Functional Scans ....................................................... 31
  2.2.2 T1 Weighted Imaging ............................................... 31
  2.2.3 Adding Noise to Functional Scans ................................ 31
  2.2.4 Preprocessing of Functional MRI Scans ....................... 32
  2.2.5 Resting-State Functional Connectivity ......................... 33
  2.2.6 Temporal SNR Calculations ...................................... 34
2.3 Results ................................................................. 35
2.4 Discussion .............................................................. 52
2.5 Conclusions ........................................................... 55
2.6 References .............................................................. 56

Chapter 3 .............................................................................. 60

3 Optimization of Single Gradient Echo Echo-planar Imaging for T2* Contrast at 0.5 T ................................................................. 60
  3.1 Introduction ............................................................... 60
  3.2 Theory ........................................................................ 62
  3.3 Methods ..................................................................... 63
    3.3.1 Scan Description ..................................................... 63
    3.3.2 Creating Cortical Masks ......................................... 64
    3.3.3 T2* Maps of Masked Regions ................................. 64
    3.3.4 Temporal and Pseudo Signal-to-Noise Ratio Calculations ................................................................ 65
  3.4 Results ................................................................. 66
  3.5 Discussion .............................................................. 70
  3.6 Conclusions ........................................................... 71
  3.7 References .............................................................. 72
5.5 Discussion .................................................................................................................. 116
5.6 Conclusions .............................................................................................................. 118
5.7 References .............................................................................................................. 119
Chapter 6 ...................................................................................................................... 124
6 Summary and future work ......................................................................................... 124
6.1 Summary ................................................................................................................ 124
6.2 Future Studies ......................................................................................................... 125
Appendices .................................................................................................................. 126
A. Optimizing GRE EPI Parameters ............................................................................ 126
A.1 Introduction ........................................................................................................... 126
A.2 Optimal Echo time ............................................................................................... 126
A.3 Read-out Gradient Bandwidth .............................................................................. 127
A.4 Geometric Distortion ............................................................................................ 128
A.5 Read-out Gradient Without Ramp sampling ....................................................... 131
A.6 Read-out Gradient With Ramp Sampling ............................................................. 133
A. References ............................................................................................................. 137
B. Feasibility of task-based BOLD fMRI at a 0.5 T Scanner ........................................ 138
B.1 Introduction ........................................................................................................... 138
B.2 Methods ................................................................................................................. 138
B.3 Results .................................................................................................................. 138
B.4 Discussion ............................................................................................................ 141
B.6. Conclusions ....................................................................................................... 142
B. References ............................................................................................................. 142
C. T2* contrast in sub-cortical regions at 0.5 T ............................................................. 144
C.1. Introduction ......................................................................................................... 144
C.2 Methods ............................................................................................................... 144
List of Tables

Table 2.1. Shows the mean displacement, both absolute and relative, calculated after motion correction for the functional data when TR = 2000 ms. ................................................................. 35

Table 2.2. Shows the mean displacement, both absolute and relative, calculated after motion correction for the functional data when TR = 1000 ms. ................................................................. 36

Table 2.3. Shows the quantities calculated with different functional datasets (original 3 T data, modified datasets with artificial noise following the Noncentral $\chi^2$ distribution and Rician distribution of type 1) for each subject with a TR of 2000 ms. ................................................................. 38

Table 2.4. Shows the quantities calculated with different functional datasets (original 3 T data, modified datasets with artificial noise following the Noncentral $\chi^2$ distribution and Rician distribution of type 1) for each subject with a TR of 1000 ms. ................................................................. 39

Table 2.5. Shows the quantities calculated with different functional datasets (original 3 T data, modified datasets with artificial noise following the Rician distributions Type 1 and 2) for each subject with a TR of 2000 ms. ....................................................................................... 40

Table 4.1. Shows the mean displacements both absolute and relative calculated with MCFLIRT for (a) Volunteer 1 for all 6 scans. (b) Volunteer 2 for all 4 scans. .................................................. 83

Table 4.2. Similarity for individual volunteers was calculated across scans with a student’s t-test for each resting-state network to assess the reliability and repeatability of the scans. .... 89

Table 4.3. Relationship between temporal SNR, T2* and similarity score related to functional connectivity for Volunteer 1. ........................................................................................................... 89

Table 5.1. Shows the mean displacements both absolute and relative calculated with MCFLIRT for Volunteers 1 and 2 for a single scan. ................................................................. 105

Table 5.2. Shows the tSNR comparison for Volunteer 1 between the single- and multi-echo scans for different regions................................................................. 112
List of Figures

Figure 1.1. The behaviour of the magnetization before and after the application of radiofrequency pulse. ................................................................. 3

Figure 1.2. Shows the different hardware layers in the MRI system. ......................... 7

Figure 1.3. Shows the 0.5 T cryogen-free main magnet with a gradient insert at Physics & Astronomy department at Western University. ................................................. 8

Figure 1.4. Two head coils are shown here from [26]. (a) 12 channel head matrix coil. (b) 32 channel phased array head coil. ................................................................. 9

Figure 1.5. (a) Hardware layers in MRI system and (b) Gradient coil assembly, (red arrow) Winding of Gx/y fingerprint coils and (blue arrow) Gz maxwell pair. ....................... 11

Figure 1.6. Shows the pulse sequence diagram for (a) gradient and (b) spin echo sequences. ........................................................................................................................ 13

Figure 1.7. Example k-space trajectories focusing on gradient and spin echo sequences. ..... 13

Figure 1.8. Shows the pulse sequence diagram for (a) gradient and (b) spin-echo echo planar imaging sequences. ................................................................. 14

Figure 1.9. Example k-space trajectories for different echo planer imaging sequences. ....... 15

Figure 1.10. Shows scanners at different field strengths from ultra-low to mid-field [12] ... 16

Figure 1.11. Shows the hemodynamic response function at the onset of an external stimulus. ........................................................................................................... 18

Figure 1.12. Shows the spatial extent of activated cortical gray matter in the motor cortex due to bilateral finger tapping. ................................................................. 19

Figure 1.13. Five mean diffusion image slices from a 24-slice DWI acquisition from Synaptive Medical’s 0.5 T system (top) and a 1.5 T system with matched acquisition parameters [36]. 22
Figure 2.1. Shows the probability distribution functions of the different noise models used to generate randomly sampled data for this study ................................................................. 32

Figure 2.2. Shows the workflow used in GraphICA .......................................................... 34

Figure 2.3. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the auditory resting-state network. ........................................................................... 42

Figure 2.4. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the default mode resting-state network with TR of 2000 ms ................................................. 43

Figure 2.5. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the executive control resting-state network. ................................................................. 44

Figure 2.6. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the sensorimotor resting-state network. ................................................................. 45

Figure 2.7. Normalized thresholded z statistics map of higher order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 2000 ms ....................................................... 46

Figure 2.8. Normalized thresholded z statistics map of sensory networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 2000 ms ............................................................. 47

Figure 2.9. Normalized thresholded z statistics map of lower order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 2000 ms .......................................................... 48

Figure 2.10. Normalized thresholded z statistics map of higher order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 1000 ms .......................................................... 49

Figure 2.11. Normalized thresholded z statistics map of sensory networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 1000 ms .......................................................... 50

Figure 2.12. Normalized thresholded z statistics map of lower order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 1000 ms .......................................................... 51

Figure 2.13. Shows p statistics calculated by comparing each network’s z statistics map for individual volunteers to respective representative network maps from the database .......... 52
Figure 3.1. Computer-aided design model of a compact head-only 0.5 T MR Scanner........ 63

Figure 3.2. Example of mono-exponential decay fit performed on a random voxel to estimate the T2* for grey matter. .......................................................... 65

Figure 3.3. T2* maps with data collected at a 2 mm resolution overlaid on a T1 weighted MPRAGE of a healthy volunteer are shown in sagittal, coronal, and axial planes for the following regions: grey matter (GM), white matter (WM), grey matter overlapped with the visual cortex (VC)........................................................................................................ 67

Figure 3.4. Sequence optimization plots for 3.4 mm isotropic resolution.................... 68

Figure 3.5. Sequence optimization plots for 4.0 mm isotropic resolution.................... 69

Figure 3.6. Theoretically calculated optimal TE vs. number of slices for single shot, single echo EPI at 3.4 mm (red) and 4 mm (blue) isotropic resolution for different cortical T2* grey matter values. ........................................................................................................ 70

Figure 4.1. Sagittal, coronal and axial views of temporal SNR maps for different cortical regions of interest for Volunteer 1 overlaid on the T1 scan. .............................................. 84

Figure 4.2. Sagittal, coronal and axial views of T2* maps for different cortical regions of interest for Volunteer 1 overlaid on the T1 scan........................................................................... 85

Figure 4.3. Show higher order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans........................................................................... 85

Figure 4.4. Show lower order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans........................................................................... 86

Figure 4.5. Show sensory resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans. .............................................................. 87

Figure 4.6. The markers represent all the resting-state networks. Each network from individual scans was compared to the database to draw conclusions which suggest that for p-value < 0.05, networks are significantly different from representative networks. In this figure (a) refers to Volunteer 1 and (b) refer to Volunteer 2. ........................................................................... 88
Figure 4.7. Shows higher slew rates (400 T/m/s) can be used to reach high read and phase bandwidths compared to the low slew rate of (45 T/m/s) which will reduce geometric distortion primarily in the phase encoding direction for both with and without ramp sampling.  

Figure 5.1. Sagittal, coronal and axial views of temporal SNR maps for different cortical regions of interest for Volunteer 1 with mean values calculated with both volunteers reported at the end of each column.  

Figure 5.2. Map of functionally connected nodes within the default mode network for Volunteer 1.  

Figure 5.3. Map of functionally connected nodes within the executive control left network for Volunteer 1.  

Figure 5.4. Map of functionally connected nodes within the executive control right network for Volunteer 1.  

Figure 5.5. Shows higher order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.  

Figure 5.6. Shows lower order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.  

Figure 5.7. Shows sensory resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.  

Figure 5.8. Shows the comparison between single- and multi-echo for higher order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.  

Figure 5.9. Shows the comparison between single- and multi-echo for lower order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.  

Figure 5.10. Shows the comparison between single- and multi-echo for sensory resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.
Chapter 1

1 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a powerful medical diagnostic imaging tool due to its incredible soft tissue contrast and non-invasive nature. The clinical value of this technique has transformed healthcare and the number of MRI exams performed grows yearly [1]. The value of MRI can be increased if it can be applied to areas outside the diagnostic imaging department in point-of-care settings, such as in the emergency department or in intensive care units where acute stroke patients or critically ill patients cannot tolerate transport time to the imaging department [2]–[7]. In addition, these scanners will be particularly beneficial in 67% of the world where access to MRI is limited primarily due to cost and poor personal training [8], [9].

However, there are several barriers to installing a traditional higher-field scanner (> 1 T) in such settings, including the scanner's size and weight, vibration, fringe fields, venting of cryogens and safety. This leads to the introduction of low- and mid-field scanners (< 1 T) which will meet these needs while still providing clinically valuable images [10]–[13]. Historically these scanners have been associated with sub-par image quality due to lower signal-to-noise behaviour coupled with a lack of investment in state-of-the-art hardware designed specifically for mid-field.

This research uses a head-only, superconducting mid-field system designed with high-performance system components aimed at achieving comparable image quality to a typical 1.5 T scanner in comparable scan times [11], [14], [15]. The availability of advanced techniques such as blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) on such scanners will provide vital neurological information in severe cases of traumatic brain injury, acute ischemic stroke, epilepsy, and dementia.

This thesis investigates the feasibility of BOLD fMRI on such a mid-field system operating at 0.5 T, specifically focusing on resting state studies. This chapter will begin with an introduction to MRI and fMRI physics and discuss the potential application and limitations of low-field MRI and fMRI. Finally, there is a summary of the remainder of the thesis.
1.1 Introduction to MRI

MRI systems depend on three magnetic fields. $B_0$ is the main magnetic field, $B_{1\pm}$ produces the excitatory and receive magnetic fields generated by radiofrequency (RF) coil and $G_{x,y,z}$ is the magnetic fields due to $x,y,z$ gradients used to form an image. This technique is based on the interaction of a nuclear spin with an external magnetic field $B_0$. The dominant nucleus used in MRI is the proton in hydrogen (spin $\frac{1}{2}$), which is abundant in the human body. The interaction of the proton with the external field results in the precession of the proton spin about the field. Imaging of the human body rests on the ability to manipulate magnetization with a combination of magnetic fields, and then detect the bulk precession in water, fat, and other organic molecules which contain hydrogen proton spins.

1.1.1 Nuclear Magnetic Resonance

Spin is a fundamental property of matter and a spin number associated with a nucleus is based on the number of charged particles it contains. Spin gives the angular momentum of a nucleus and as a result, all nuclei with a nonzero spin have a magnetic moment, which follows Eq’n (1.1).

$$\vec{\mu} = \gamma \vec{J} \quad (1.1)$$

where $\vec{\mu}$ is the magnetic moment, $\vec{J}$ is the angular momentum and $\gamma$ is the gyromagnetic ratio which varies depending on the nucleus. In the clinical setting, the nuclear spin of interest is hydrogen. This is due to the relatively high abundance of hydrogen in biological tissue and the high value of its magnetic moment. From this point onward, whenever nuclear spins or magnetic moments are mentioned, they explicitly refer to hydrogen protons, which have a spin of $\frac{1}{2}$.

In the absence of any external magnetic field, the magnetic moments within a tissue sample are randomly oriented and therefore their net magnetization is zero. However, in the presence of an external magnetic field, the individual magnetic moments exhibit a tendency to align with the field, which creates a net magnetization defined by $\langle \vec{M}(\vec{r},t) \rangle$. This quantity is proportional to the applied field $\vec{B}$ and approximately proportional to a
material specific susceptibility \( \chi \) as described in Eq’n (1.2). \( \chi \) is on the order of \( 10^{-5} \) for paramagnetic materials and \( \mu_0 \) is the permeability of free space.

\[
\mathbf{M} = \frac{\chi}{\mu_0} \mathbf{B} \tag{1.2}
\]

If the net magnetization were rotated by 90° through the application of a short burst of radio frequency magnetic field (\( \mathbf{B}_1 \)) perpendicular to the direction of the main magnetic field as shown in Fig 1.1, it experiences a torque which is perpendicular to both the magnetization and the magnetic field (\( \mathbf{B} \)). As a result, the magnetization will rotate around the field as described by Eq’n (1.3-1.5).

Figure 1.1. The behaviour of the magnetization before and after the application of radiofrequency pulse.

(a) Shows the net magnetization aligned with the main magnetic field before the application of \( \mathbf{B}_1 \). (b) Shows the excited magnetization precess about the applied magnetic field after the application of \( \mathbf{B}_1 \).

\[
M_x(t) = M_x(0) \cos(\gamma B_0 t) \tag{1.3}
\]

\[
M_y(t) = -M_x(0) \sin(\gamma B_0 t) \tag{1.4}
\]

\[
M_z(t) = M_z(0) \tag{1.5}
\]
These equations assume that the main field ($B_0$) is applied in the z direction and $\gamma / 2\pi$ is the gyromagnetic ratio, which for hydrogen is 42.58 MHz/T. $M_x(t)$, $M_y(t)$ and $M_z(t)$ are the components of the net magnetization vector ($\vec{M}$) in the x, y and z directions at time t. $M_x(0)$ is the initial magnetization in the x direction, just after excitation. The previous equations assume that all the magnetization is tipped onto the transverse plane lies along the x-axis. Similarly, $M_z(0)$ describes any magnetization that remains along the z-axis after excitation. With the assumption of no energy loss and perfect field homogeneity, the magnetization ($\vec{M}$) does not relax to its initial value according to the previous equations. $M_z$ does not regrow to its equilibrium value while $M_x$ and $M_y$ do not decay but rather precesses about $B_0$ at the Larmor frequency ($\omega_0$). This frequency depends on the local magnetic field and is given by Eq’n (1.6).

$$\omega_0 = \gamma B_0$$ \hspace{1cm} (1.6)

The transverse magnetization $M_{xy}$ is calculated by combining $M_x$ and $M_y$. After excitation, this magnetization precesses about the applied magnetic field $B_0$. This rotating magnetization will induce a voltage in a receiver coil outside the sample. The size of the detected signal is proportional to the transverse magnetization which itself is proportional to $B_0$ according to Eq’n (1.1). In addition, for a given receiver design the signal amplitude is also proportional to the Larmor frequency as given by Eq’n (1.6). Therefore, the nuclear magnetic resonance (NMR) signal depends on $\gamma$ and $B_0$ as depicted in Eq’n (1.7). According to this relationship, the NMR signal scales with $B_0^2$ which is one of the main reasons for the development of higher-field NMR systems.

$$S_{NMR} \propto \omega_0 B_0 \propto \gamma B_0^2$$ \hspace{1cm} (1.7)

To excite the magnetization out of its equilibrium state, $B_1$ magnetic field is applied to the system which resonates at the Larmor frequency. For hydrogen in a main magnetic field of the order of a Tesla, this resonant frequency is of the order of MHz, hence the excitatory magnetic field is also referred to as a radiofrequency (RF) pulse. The $B_1$ field essentially applies a torque which rotates the magnetization by an angle that depends on
the strength of the field and the duration of the pulse. The excitation magnetization must also relax since precession cannot happen indefinitely. A more accurate description of the behaviour of magnetization is given by the Bloch equations as presented in Eq’n (1.8) [16].

\[
\frac{d\vec{M}}{dt} = \vec{M} \times \gamma \vec{B} - \frac{M_x \hat{i} + M_y \hat{j}}{T_2^*} - \frac{(M_z - M_0) \hat{k}}{T_1}
\]  

(1.8)

In Eq’n (1.8), \( \hat{i}, \hat{j} \) and \( \hat{k} \) are unit vectors along 3 orthogonal axes with the main magnetic field applied in the direction of the \( \hat{k} \) vector, \( T_2^* \) is the transverse decay constant, and \( T_1 \) is the longitudinal relaxation time constant. The solution to Eq’n (1.8) results in the following ‘equations of motion’ as described by equations 1.9 to 1.11. Following excitation, transverse magnetization decays exponentially with the time constant \( T_2^* \), while longitudinal magnetization recovers exponentially with the time constant \( T_1 \). In the following equations, \( M_0 \) is the initial magnetization.

\[
M_x(t) = M_0 \cos(\gamma B_0 t) \exp \left( -\frac{t}{T_2^*} \right)
\]  

(1.9)

\[
M_y(t) = -M_0 \sin(\gamma B_0 t) \exp \left( -\frac{t}{T_2^*} \right)
\]  

(1.10)

\[
M_z(t) = M_0 \left( 1 - \exp \left( -\frac{t}{T_1} \right) \right)
\]  

(1.11)

Eq’n 1.9 and 1.10 describes the behaviour of the magnetization in the transverse plane. Mostly all the magnetic moments in the sample precess at approximately the Larmor frequency. However, the local variations in the magnetic field experienced by spins affect the local rate of precession which causes the spins to dephase over time, ultimately causing the net signal to decrease. The rate at which this occurs is proportional to the quantity of transverse magnetization remaining, and the relaxation follows an exponential decay with the time constant \( T_2^* \). This decay is composed of contributing factors which can be divided into 2 components: \( T_2 \) and \( T_2' \) as given by Eq’n (1.12).
The decay in magnetization due to $T_2'$ occurs due to local variation in the magnetic field. The decay in magnetization due to $T_2$ arises from interactions at the atomic or molecular level and it is dependent of the tissue being imaged. Some of this dephasing can be partly recovered by, for instance, applying a successive pulse following the initial RF pulse. After the initial flip, the magnetization starts to dephase in the transverse plane causing some spins to precess faster relative to others. However, with the application of the $180^\circ$ pulse, the region with spins that were lagging behind the average due to a lower local magnetic field would be ahead of the average. This ultimately leads to a rephased magnetization when the regions with faster spins initially catch up with the average, leading to an overall reduction in signal loss due to $T_2'$ decay. However, magnetization lost due to $T_2$ cannot be regained by pulse sequence manipulation. $T_2$ relaxation is known as spin-spin relaxation [16] and this quantity (on the order of 10s of ms) is always shorter than $T_1$ (on the order of 100s of ms). The total duration of $T_2^*$ limits how long a signal can be acquired during a given excitation since once the transverse signal has decayed away no further information can be recovered from the sample until the next excitation pulse. The length of $T_2^*$ decreases as the main strength increases [17]. Therefore, the efficiency of data acquisition must be a concern at higher field strength scanners, however, recent advances in pulse sequences allow that quite effectively.

Eq’n 1.11 follows the spin-lattice relaxation phenomenon which describes the regrowth of magnetization along the direction of the main field. In this case, the relaxation is proportional to the difference between the current magnetization and the equilibrium magnetization [16]. The regrowth asymptotically approaches its equilibrium levels with time ($t$) after the excitation. $T_1$ describes both the rate at which a sample approaches the maximum magnetization (which starts immediately after the initial $B_0$ field is applied) and the time it takes to regain this magnetization after excitation. Therefore, $T_1$ influences how often a measurement can be taken since there must be enough magnetization that has regrown before it can re-excited. Both $T_1$ and $T_2^*$ are tissue-dependent, suggesting that

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$ (1.12)
these decay rates provide information regarding the sample's composition. This property provides the most common contrast in MRI.

1.1.2 MRI Hardware

The four main components of an MRI scanner that influence the image quality are the main magnet, radiofrequency coils, gradient coils, and shim coils.

![Figure 1.2. Shows the different hardware layers in the MRI system.](image)

1.1.2.1 Main Magnet

The main magnet is responsible for two functions which include polarizing the sample and ensuring the spins within the volume of interest are precessing at the same frequency for signal acquisition. To meet these demands the magnetic field must be strong and uniform, which is achieved by using a single magnet or electromagnet as done in most clinical settings or with two separate magnets/electromagnets as is the case in research settings [18], [19]. If the polarizing field is equal to the field during signal acquisition (e.g clinical scanners), then the final MR signal is proportional to the square of the field strength. This signal dependence is the main reason behind the increased popularity of higher field scanners.

The most common scanners available in hospitals that are approved for clinical imaging operate at 1.5 or 3 T. In the research setting, 7 T systems are available for human imaging with U.S. Food and Drug Administration (FDA) approval up to field strengths of 8 T. Many higher field strength scanners such as 9.4 T and 11.7 T exist in research settings.
and are primarily used for animal studies [20]–[22]. Human imaging has also been conducted on a 10.5 T scanner for radiofrequency safety and preliminary investigation but it required an investigational device exemption since FDA considers all MR scanners with \( B_0 > 8 \) T to be significant risk devices.

The two important properties of the main magnetic field that plays an important role during signal acquisition are field homogeneity and temporal stability. If these are not sufficient then there will be little to no signal, irrespective of the amount of the polarization of the object. The homogeneity requirement suggests that the gradient of the main magnetic field is sufficiently small such that it is negligible in comparison to the applied gradient field. Any deviation of the main magnetic field over the region of interest will result in signal reduction due to faster dephasing of the signal after excitation. Temporal instability of the main field will result in problems similar to those due to field inhomogeneities. Commercially available main magnets, operating at 1.5 or 3 T, typically require homogeneity on the order of 10 ppm peak to peak in a spherical volume approximately 50 cm in diameter while the field decay must be less than 0.1 ppm/hour to maintain temporal stability [23].

![0.5 T cryogen-free main magnet with a gradient insert](image)

Figure 1.3. Shows the 0.5 T cryogen-free main magnet with a gradient insert at Physics & Astronomy department at Western University.

The 5 Gauss line is marked in yellow. Photo Courtesy: Diego Martinez, 2020.
1.1.2.2 Radiofrequency Coils

These coils are used to both excite and detect the MR signal. These two functions can be performed using the same coil or by separate transmit and receive coils. In many applications, the transmit function is performed by the “body” RF coil and the receive function is performed by local surface coils or arrays [24], [25].

Figure 1.4. Two head coils are shown here from [26]. (a) 12 channel head matrix coil. (b) 32 channel phased array head coil.

1.1.2.3 Gradient Coils

These are composed of resistive electromagnets that create linearly varying magnetic fields to spatially encode the MR signal. The z component of each gradient field must vary linearly with respect to each cartesian axis:

\[ G_x = \frac{\partial B_z}{\partial x} \]  
\[ G_y = \frac{\partial B_z}{\partial y} \]  
\[ G_z = \frac{\partial B_z}{\partial z} \]
Gx and Gy are known as the x and y gradient fields, also known as the transverse gradient fields and Gz is known as the z or the longitudinal gradient field. The strength of typical whole-body gradient systems is in the range of 20-50 mT/m for most imaging sequences.

The coil efficiency, given by $\eta$, is an important property used in coil design and performance assessment. It is based on the strength that a gradient field can produce at the center of their imaging region when driven with one ampere of current. Typical whole-body gradient coil efficiency values are between 0.1 and 0.2 mT/m/A.

To achieve gradient strengths with the previously mentioned efficiency values, gradient coils must be driven with current amplitudes on order of a few hundred amperes. Current amplitudes of this magnitude flowing through a conductor will create very significant power dissipation leading to heating of the coil, which can damage the coil and lead to a possible breakdown of the system. To prevent significant heating, gradients are designed to have minimum power dissipation and are actively cooled. Gradient heating is monitored during all the experiments performed as a part of this thesis to ensure it’s within the limits specifically for the longer experiments that lasted for ~ 30 mins.

When pulse sequences are implemented on the scanner, gradient coils are repeatedly powered on and off with frequencies typically ranging from 1-10 kHz. The rate at which a gradient coil can be powered on or off is another important performance property known as its slew rate, given in units of T/m/s. The slew rate of a coil depends on both its design and the amplifier chosen to drive it and is calculated using Eq’n (1.16).

$$Slew \text{ Rate} = \eta \frac{V}{L}$$  \hspace{1cm} (1.16)

In Eq’n (1.16), V is the voltage provided by the amplifier and L is the coil inductance. In theory, the goal is to maximize the slew rate, which would in theory allow for faster imaging with less demand on amplifier performance. Typical whole-body gradient coil inductance values are approximately 800 $\mu$H, and with a high-performance amplifier driving voltages over 1500 V, gradient slew rates can be ~ 200 T/m/s. However, due to peripheral nerve stimulation (PNS) limitations most scanners are operated at slew rates significantly smaller than this [26]–[29]. A detailed discussion on the benefits of high slew
rates for human brain imaging due to its effect on echo planar imaging distortions for a head-only mid-field scanner is included in Chapters 4 and 5 of this thesis.

The main factors to consider for gradient coils include: (1) produce a large uniform gradient field and (2) usually be actively shielded to reduce system-to-system interactions with the main magnet [30]. Active shielding is important since such interactions can lead to eddy currents, which can produce negative effects on image quality as well as other complications.

1.1.2.4 Shim Coils

These coils are used to improve the uniformity of the main magnetic field. Deviations of the main field over the region of interest can result in image artifacts such as spatial distortion, through-plane artifacts, or signal dropout. Therefore, increasing the main magnetic field uniformity will lead to higher image quality. Shim coil primarily fall into two categories: (1) passive shims, composed of strategically placed ferromagnetic material within the magnet bore and/or superconducting electrical circuits within the magnet cryostat; and (2) active shims which are composed of additional room temperature electromagnets. Passive shims are typically used to adjust the main field at the time of initial installation whereas active shims are used to compensate for field distortion when different foreign objects are placed within the bore of the magnet.

![Figure 1.5](image-url)

Figure 1.5. (a) Hardware layers in MRI system and (b) Gradient coil assembly, (red arrow) Winding of Gx/y fingerprint coils and (blue arrow) Gz maxwell pair.
1.1.3 Pulse Sequences

In MRI, RF pulses and gradients can be applied in various ways to obtain a collection of spatial frequencies for spin distributions and density maps in frequency space (k-space), which can be transformed using the inverse Fourier transform to get an image in real-world space.

*Common Terms*

1. **Flip Angle (FA or α in Figure 1.6):** Amount of rotation the net magnetization experiences during the radiofrequency application.

2. **Echo time (TE in Figure 1.6):** Refers to the amount of time between the application of the radiofrequency excitation pulse and the peak of the signal induced in the coil.

3. **Repetition time (TR):** Refers to the amount of time between successive pulse sequences applied to the same slice.

4. **Slice-select gradient (Gz or Gs in Figure 1.6):** Produces a magnetic gradient to isolate a single plane in the object being imaged, by only exciting the spins in that plane.

5. **Frequency-encode gradient (Gx or Gf in Figure 1.6):** Produces a magnetic gradient during MR signal acquisition to encode signals into different frequencies, depending on their position towards the gradient.

6. **Phase-encode gradient (Gy or Gp in Figure 1.6):** Process of locating a MR signal by altering the phase of spins in one dimension with a pulsed magnetic field gradient along that dimension prior to the acquisition of the signal.

7. **Field of view (FOV):** Determines the size of the area to be imaged.

8. **Matrix size:** Determines the number of pixels in the image.

1.1.3.1 Echo formation

As discussed previously, the relaxation of spins in a sample can be manipulated through the application of RF excitatory pulses or gradients to form a maximum magnetization which is called an echo. These echos can be produced in 2 ways: gradient-echo and spin-echo.
Gradient-echo: As a part of this sequence a dephasing gradient is applied after the RF excitation pulse and then followed by a rephasing gradient to produce an echo in the middle of the signal acquisition. This echo reforms with a decay constant of T2*.

Spin-echo: As a part of this sequence an initial RF excitation pulse is followed by the dephasing gradients, which follow a refocusing RF pulse and rephasing gradients. This rotates the M around the transverse plane and reverses the T2' effects leaving a signal contribution that is weighted by T2.

A pictorial representation of these sequences, along with their k-space trajectories is shown in Fig 1.6. and 1.7.

Figure 1.6. Shows the pulse sequence diagram for (a) gradient and (b) spin echo sequences.

Figure 1.7. Example k-space trajectories focusing on gradient and spin echo sequences.
(a) Gradient echo trajectory, a dephasing gradient is applied (green) to move to the start of a line and then a rephasing gradient is applied (black) with the echo centered on kx = 0. (b) Spin echo trajectory, a dephasing gradient is applied (green) to move to the start of a line
and then a refocusing pulse (grey) is applied to flip the magnetization to the opposite end of k-space as well refocus T2’ dephasing, finally a rephasing gradient is applied (black) with the echo centered on kx = 0. Images are taken from [17].

1.1.3.2 Echo Planar Imaging

Acquiring a single k-space line at a time is too slow to be used for the whole brain at temporal resolutions required for functional imaging as it takes on the order of minutes to form a single image. The most common imaging method for fMRI is echo planar imaging (EPI), which typically reads out the entire \( \hat{i} - \hat{j} \) plane of k-space from a single excitation as opposed to a single line per excitation. To achieve this a small phase encoding gradient pulse is applied prior to the collection of each frequency encoding line to alter the spatial frequency sampled in the \( \hat{j} \) direction for each line acquired. This method aims to center the echo on \( k_x = 0 \) and \( k_y = 0 \). The drawback is that one direction of k-space is acquired much more slowly than the other direction which results in blurring. However, it lowers the acquisition time to well under a second. The pictorial representation of k-space trajectories associated with gradient-echo and spin-echo EPI are given in Fig 1.8 and 1.9.

Figure 1.8. Shows the pulse sequence diagram for (a) gradient and (b) spin-echo echo planar imaging sequences.
Figure 1.9. Example k-space trajectories for different echo planer imaging sequences.
(a) GRE EPI trajectory, opposed to one line of acquisition per excitation many lines are acquired. After the initial phase encoding gradient (green), small gradient blips are applied in the y direction to allow for successive line collection from a single RF pulse, collecting the whole plane of k space from a single excitation. (b) SE EPI trajectory where a refocusing echo is applied prior to image acquisition. Figures are taken from [17].

1.1.4 Low- and Mid-Field MRI: Introduction

Recently there is a growing interest in mid-field (0.1–1 T) and low-field (0.01 –0.1 T) MR scanners to increase the accessibility of a traditionally expensive imaging modality [12], [31]. This increased accessibility can be related primarily to reduced purchase, maintenance and infrastructural costs, and increased availability for patients with contraindications such as medical implants, compared to conventional 1.5 or 3 T field strength due to specific absorption rate (SAR) limitations [2], [10], [32], [33]. These systems are designed to be portable, increasing access to MRI by enabling it to be used outside of the radiological department: for instance, in intensive care units (ICU) and emergency rooms primarily aiming at patients who are suffering from acute problems that require immediate intervention, such as stroke, hemorrhage, edema and mass effect [3]–[5], [34]. Importantly, transporting critically ill patients who require life-sustaining equipment and continuous monitoring outside the ICU is difficult, time-consuming, and poses risks of adverse events.
1.1.4.1 Background

The distinction between low-/mid-field and high-field MR scanners did exist in the early days of MR. However, since 1.5 T scanners became the clinical standard, low-field scanners have been neglected. Higher field scanners have a dominant market share due to their higher SNR per unit time since that permits faster imaging, higher resolution, greater contrast sensitivity, and more advanced sequences. Lower field scanners have been commercially available; however, these have not been used due to the lack of investment in the hardware (e.g. improved magnet, gradient, and coil designs) and software (e.g. deep learning reconstruction and post-processing) required to make it viable. Renewed commercial interest has led to FDA clearance of several lower field systems since 2018. As shown in Figure 1.10 these include the 0.064 T Hyperfine Swoop head scanner, 0.066 T Promaxo prostate scanner, 0.5 T Synaptive Medicals intraoperative scanner, 0.55 T Siemens Magnetom Free.Max scanner and 1 T Aspect Embrace neonatal scanner. There have also been multiple studies performed on a prototype 0.55 T scanner with high-performance gradients (a ramped-down 1.5 T Aera; Siemens Scanner) [35].

Figure 1.10. Shows scanners at different field strengths from ultra-low to mid-field [12].

The studies performed for this thesis were done with a head-only, superconducting, cryogen-free 0.5 T scanner (Synaptive Medicals) [2], [11] equipped with high-performance gradient coils ($G_{\text{max}} = 100 \text{ mT/m}$ and Slew Rate = 400 $\text{T/m/s}$) and a 16 channel receive array. This scanner can be installed in under 300 square feet without requiring additional structural support or quench pipe. The weight of the scanner is also under 2500 lbs and the proposed 5 Gauss line measures less than 1.03 m from the outer edge of the magnet enclosure, ensuring that no stray field is present outside of the exam room. This system can be rapidly ramped (< 15 mins) for imaging, and otherwise left idle in a non-magnetic state. Lower RF heating effects at this field strength also allow this system to achieve peak B1+
levels above 50 μT without exceeding patient heating limits. This B1+ can be used for shorter echo trains and higher bandwidth RF pulses.

1.2 Introduction to Functional MRI

Functional MRI is a non-invasive neuroimaging technique introduced in the early 1900s that links brain functions to blood flow in the brain. This technique allows for detailed investigations into novel experimental paradigms involving complex tasks or spontaneous brain activity during resting-state. fMRI experiments can be repeated multiple times to establish the reliability of accurately identifying activated regions in the case of task-based studies and functional connectivity between networks for resting-state studies. Many developments in fMRI have taken place since its early days that have led to improved resolution, acquisition times and image quality.

Studies involving both resting state and task-based fMRI have been performed in a mid-field setting and are provided in Chapters 4 and 5, and Appendix B.

1.2.1 BOLD Contrast

The most common type of fMRI technique is based on blood-oxygen-level-dependent (BOLD) contrast [44]. This technique does not measure neuronal activity directly; rather it measures it indirectly through measurements of the ratio of oxygenated and deoxygenated hemoglobin [45].

The basic principle involves increased neuronal activity in a brain region in response to a stimulus, which causes an increase in cerebral blood volume (CBV), cerebral blood flow (CBF) and concentration of oxygenated hemoglobin delivered to the local area while there is a decrease of deoxygenated hemoglobin [45]. These changes in the concentration of oxy-/deoxy-hemoglobin cause two effects detectable with MRI. Firstly, a local shift in magnetic susceptibility can be detected on MR images as an increase in signal intensity to the local area [46]. Secondly, as the concentration of oxygenated hemoglobin increases, T2 of blood increases, causing additional signal brightening in T2 or T2* weighted images [47].

The BOLD response is characterized by three temporal phases: an initial dip, the main BOLD response, and a post stimulus undershoot. The initial dip is a negative response which lasts for 1-2 seconds thought to be due to the initial demand for oxygen that occurs
before the CBF increases and compensates. The initial dip has been observed to have greater spatial specificity than the main BOLD response [48]. The main BOLD response involves the inflow of oxygenated blood due to the changes in CBV and CBF as described previously; this takes on the order of 6 seconds to reach its peak. After this response peaks there is a post-stimulus undershoot where the area slowly returns to baseline due to the slow recovery of CBV to baseline levels.

Figure 1.11. Shows the hemodynamic response function at the onset of an external stimulus.

1.2.2 Task-based BOLD Responses

A series of susceptibility-weighted images acquired as a part of fMRI studies need to go through preprocessing prior to further analysis, which will be discussed in further detail in Chapter 2. Once preprocessing is completed, the data is ready to be fit to the expected hemodynamic response function (HRF) as shown in Figure 1.8. This HRF can be convolved with a stimulus waveform to estimate the expected voxel response to a stimulus design. This is feasible because the HRF response has linear characteristics, given the space between new stimuli is at least two seconds in length for a one-second event [49].

Previous studies have found inconsistency in the HRF across subjects, and it is necessary to correct these variations [50]. To do this correction, the convolved HRF and its derivative can both be used for signal fitting [51]. The convolved HRF, its derivative and physiological regressors are then fit to a general linear model. This fit gives an estimation of the BOLD activity on a per voxel basis which is usually expressed as percent BOLD change or a t-statistic.
These voxel-wise estimates of the fit can be used to draw inferences on brain regions that are relevant to a specific task-based paradigm. These inferences are usually made using group statistics after multiple corrections. There are many software packages available to draw these conclusions, like FSL [51], which utilizes the gaussian random field theory of activated clusters to determine each cluster's significance, or permutation testing to find a data-driven threshold for significance [51].

![Figure 1.12. Shows the spatial extent of activated cortical gray matter in the motor cortex due to bilateral finger tapping.](image)

(a) collected with a 1.5 T scanner and (b) collected with a 3 T scanner overlaid on top of the structural image [48].

1.2.3 Resting-state BOLD response

An alternative to task-based studies is resting-state fMRI [53], which aims to measure BOLD effects in the absence of a stimulus, where the participant is not performing any active task and is simply instructed to remain still with either eye closed or open while fixating on a cross. In this case, the brain is not directly responding to an input stimulus, however, the neurons are still fluctuating in activity and an activity-correlated BOLD fluctuation can still be measured. This measured response shape cannot be well characterized as in the case of task-based BOLD responses.
This technique can be incredibly useful in situations where the subject is unable to perform complicated tasks in the scanner. Brain areas with high temporal correlation to each other define various resting state networks. These networks have been shown to correspond well with known functional task activation patterns. Previous studies have shown changes in these networks in patients vs healthy controls [54]. The eleven resting state networks that will be studied as a part of this thesis are the auditory, default mode, left and right executive control, salience, sensorimotor, language, hippocampal, lateral, medial, and occipital visual networks [55].

1.2.4 Functional Connectivity

Functional connectivity is a quantity of interest for this thesis, and it essentially investigates the neural activity of regions that are functionally connected even when they are anatomically distant [55], [56]. Functional connectivity can be defined as the synchrony of neural activity among regions. Brain areas that experience signal fluctuations correlated in time are assumed to be functionally connected. Functional connectivity can be studied during active tasks such as finger tapping or visual stimulation and during resting state.

Multiple analysis techniques exist that can be used to study fMRI-based connectivity. The most employed ones are the region-of-interest (ROI) based analysis and independent component analysis (ICA). The first is based on the extraction of the time series of the BOLD signal from a predefined ROI and subsequent identification of the regions showing a significant correlation with the ROI. This time series correlation produces functional connectivity maps [57], [58]. The second is ICA, a statistical technique that does not involve any a priori assumption and allows the exploration of multiple whole-brain networks [59]. This is the method used in this thesis for the functional connectivity maps and will be discussed in greater detail in Chapters 2 and 4. One drawback of this technique is that the components are not always easy to interpret.

1.2.5 Mid-field Functional MRI: Introduction

Functional MRI is generally not attempted at low- and mid-field due to reduced SNR as mentioned previously and reduced BOLD contrast. The elevated SNR and sensitivity may be traded for high spatial resolution to enable applications such as laminar
fMRI and imaging of neural circuits. However, at reasonable resolutions (3.5-4 mm isotropic), it can be an effective tool in acute settings since it can provide vital neurological information in cases of traumatic brain injury and acute ischemic stroke. The feasibility of intraoperative fMRI has also been conducted before which suggests a real-time identification of areas of the brain where potential injury can lead to disabilities (eloquent; for instance language) despite brain shift [3], [7], [60].

1.2.5.1 Background

Initial attempts at low- and mid-field fMRI date back to the early 1990s, and recent research has been limited. These previous studies were mostly task-based focusing on the motor and visual cortex [35], [52]. However, these studies suffered from a lack of sophisticated hardware, acquisition and reconstruction techniques, and physiological noise suppression techniques. A recent visual task-based study performed on a modern 0.55 T whole-body scanner has demonstrated consistent activation in the visual cortex with a percent signal change of ~2 % and temporal SNR (tSNR) in the range of ~35-45.

1.2.5.2 Limitations and Advantages

As mentioned previously, fMRI is generally not attempted at a field strength of less than 1.5 T due to reduced magnetic susceptibility contrast and SNR. SNR in fMRI can be divided into two components: one that includes a contribution from thermal noise from the scanner and the other that includes time series fluctuation, hence including the physiological effects. The SNR contribution from thermal noise scales linearly with field strength while the SNR contribution that includes the physiological contribution reaches an asymptotic limit at higher field strengths for voxel resolutions considered in this thesis, which might limit the beneficial effects of the contrast-to-noise ratio (CNR) that can be achieved with these scanners [61], [62]. This suggests that for low- and mid-field scanners, at certain voxel resolutions physiological noise dominates the signal time-series variance.

In terms of advantages, firstly the fMRI signal is less affected by signal dropouts and image distortions caused by macroscopic susceptibility effects that might be more severe at high field, for instance in the frontal lobe, temporal lobe, and inferior brain [36], [63], [64] and in patients with medical implants. This is demonstrated in Figure 1.13 with
diffusion-weighted images, here the volunteer had dental implants which caused severe distortion in the anterior portion of the brain at 1.5 T compared to 0.5 T.

![Diffusion-weighted images comparison](image)

Figure 1.13. Five mean diffusion image slices from a 24-slice DWI acquisition from Synaptive Medical’s 0.5 T system (top) and a 1.5 T system with matched acquisition parameters [36].

Secondly, T1 is reduced at low- and mid-field strength which might enable more time-efficient sequence design by reducing TR. Lastly, the long T2* suggests the possibility of using other efficient sequences such as multi-echo GRE EPI, where specific regions with elongated T2* can be accurately sampled.

1.3 Thesis Objective

This thesis investigates the feasibility of resting-state fMRI for low- to mid-field scanners in silico as a part of Chapter 2. Optimization of a single echo gradient recalled echo (GRE) echo planar imaging (EPI) sequence for maximum T2* contrast efficiency at mid-field for applications to fMRI was performed as a part of Chapter 3. The optimized single echo GRE EPI sequence was then used to conduct resting state experiments to study functional connectivity between resting state networks at mid-field as a part of Chapter 4. To use the relaxation property at mid-field effectively and gain the most benefit from the high-performance gradients, other avenues like multi-echo GRE EPI sequences were considered and resting state studies were conducted, which will be discussed in detail in Chapter 5. This chapter also focuses on future studies and ways of improving the sequence, preprocessing and analysis steps.
1.4 References


[37] I. Connell and A. Panther, “Increasing MRI Safety for Patients with Implanted Medical Devices: Comparisons of a 0.5 T Head-Only MRI to 1.5 T and 3 T,” ASNR, pp. 779–784, 2011.


Chapter 2

2 Identifying resting-state networks from functional data with additional noise

2.1 Introduction

This thesis focuses on developing functional MRI (fMRI) techniques on mid-field scanners. Functional MRI on mid-field scanners has the potential for various applications such as identifying neurological information that can be vital in traumatic brain injury [1] and stroke [2] in acute settings [3], especially for intraoperative monitoring and point-of-care imaging [3]-[7]. However, the blood-oxygen-level-dependent (BOLD) fMRI is generally not attempted at mid-field (< 1 T) due to reduced magnetic susceptibility contrast and signal-to-noise ratio (SNR) [8], [9]. In the initial days, fMRI studies were performed at these field strengths but those were limited by scanner performance. Therefore, typically these studies are performed at 3 T, and in research settings for higher resolutions 7 T scanners are preferred since both the contrast and SNR scales with field strength [10], [11]. Recently there has been a surge of these low- to mid-field scanners with modern hardware, acquisition, and reconstruction techniques [12]. With these in place, it is relevant to revisit this technique [13]. The goal is to apply similar pulse sequences as used in higher field scanners to produce clinically relevant images at typical resolutions used for fMRI, with a basic limitation in place suggesting these techniques will suffer at this field strength.

The noise in MR images constructed from the real and imaginary parts of the complex raw data in k-space is usually assumed to be Gaussian distribution [16]. If the complex image data is acquired with a single-channel RF receiver coil, then the data will be superimposed by the normally distributed noise both before and after reconstruction. The magnitude of this complex image data will provide the signal which generally follows a Rician distribution and background noise which generally follows a Rayleigh distribution. If the complex image data are acquired by multiple receive coils, then depending on the reconstruction technique (the root of the sum of squares (SoS) [17] of the complex images or spatial matched filter (SMF)), the noise properties can be described by
noncentral $\chi$ distribution or Rayleigh distribution [16]. In low SNR scenarios the noise in magnitude MR images follows Rician distribution [2].

An important technique for accelerated MRI is parallel imaging, using either frequency domain methods such as generalized auto calibrating partially parallel acquisition (GRAPPA) algorithm [19] or image domain methods such as sensitivity encoded MRI (SENSE) [20]. These techniques are based on an under-sampled acquisition of raw data and incorporation of the coil-sensitivity profiles into the image reconstruction process. These images can be combined exactly as conventional data using SoS or SMF and therefore follow similar noise distributions. For this study, understanding the noise distribution for reconstructed images is essential since it guides the choice of artificial noise distribution added to the reconstructed image.

This initial investigation evaluates the performance of an FSL based analysis platform used for preprocessing and statistical analysis of functional scans with artificially added noise. The aim here was not to mimic functional data from mid-field scanners, but to evaluate the performance of the platform given that the functional data was noisy. These limitations include the T2* weighted contrast which will be different at mid-field [21].

In fMRI studies, there are two main noise sources: physiological and thermal [9], [22]. For this simplest analysis, these noise sources were not separated before adding artificial noise. Therefore, it can be said that the noise sources were not accurately modelled. Additionally, the physiological noise source not only includes cardiac and respiration contributions but is linked to hemodynamic-induced signal modulations which as discussed before will be altered at mid-field. The thermal noise source mostly depends on scanner specific electronics which are different at mid-field. Previous studies suggest that the noise contribution to the EPI time-series for medium to large voxel sizes changes with the number of channels on the RF receiver coil [22]. Therefore, the simplistic approach used in this chapter might not be the ideal model for functional data from a mid-field scanner, but it allows us to evaluate the performance of the analysis platform with noisy 3 T data at different TRs [23]. Along with that, it allows us to form a relationship between the temporal SNR of the whole brain and specific regions with the functional connectivity detected within the resting state networks.
2.2 Methods

All imaging protocols were performed on a whole-body Siemens 3 T scanner (St. Joseph Hospital, London Ontario). Imaging was performed on three healthy volunteers (1 male, age = 45 and 2 females, female mean age = 29 ± 3), with informed consent in compliance with health and safety protocols.

2.2.1 Functional Scans

Acquisition 1

A 4 mm isotropic spatial resolution gradient recalled echo (GRE) echoplanar imaging (EPI) sequence with 240 temporal positions was used with FOV = 256 mm x 256 mm x 128 mm, matrix size = 64 x 64 x 32, TE = 32 ms, TR = 2000 ms, effective echo spacing = 265 μs, slice thickness = 4, FA = 90°, total acquisition time = 20 mins and no acceleration was implemented.

Acquisition 2

A 4 mm isotropic spatial resolution GRE EPI sequence with 480 temporal positions was used with FOV = 256 mm x 256 mm x 144 mm, matrix size = 64 x 64 x 36, TE = 21.4 ms, TR = 1000 ms, effective echo spacing = 530 μs, slice thickness = 4, FA = 82°, total acquisition time = 20 mins and no acceleration was implemented.

2.2.2 T1 Weighted Imaging

Structural images were acquired using a 1.1 mm isotropic resolution T1-weighted MPRAGE sequence with field of view (FOV) =240 mm x 256 mm x 256 mm, matrix =218 x 232 x 232, FA = 8°, TE = 2.25 ms and TR = 2.4 s, total acquisition time = 6 mins and no acceleration was implemented.

2.2.3 Adding Noise to Functional Scans

The two noise models used in this chapter were the Noncentral $\chi^2$ distribution and the Rician distribution. The reasons behind these choices were: (a) according to [16], most noise distribution after reconstruction follows the Noncentral $\chi$ distribution for sufficiently high SNR and (b) according to [18], Rician noise model is applicable when SNR is extremely low. The $\chi$ distribution is related to the square root of the $\chi^2$ distribution.
Randomly sampled noise was generated from these distributions as shown in Figure 2.1 with varying parameters. This noise source was added to the pixel intensity at each temporal position in each slice within a functional scan. The following parameters were used for each distribution: (a) Noncentral $\chi^2$ distribution: $\lambda = 40$ and DOF = 5, (b) Rician distribution type 1: $\nu = 1$ and $\sigma = 10$, and (c) Rician distribution type 2: $\nu = 1$ and $\sigma = 20$.

Supplementary section I includes the comparison with the noncentral $\chi$ distribution noise model with the following parameters: $\lambda = 20$ and DOF = 10.

Figure 2.1. Shows the probability distribution functions of the different noise models used to generate randomly sampled data for this study.

2.2.4 Preprocessing of Functional MRI Scans

Preprocessing of the fMRI data was performed using GraphICA [27], an in-house FMRIB Software Library (FSL) [14] based platform. The structural scans were preprocessed by implementing the following steps: bias-field correction (RF/B1-
inhomogeneity correction), brain extraction, tissue type segmentation (CSF, GM, WM) and sub-cortical structure segmentation. The functional scans were preprocessed by implementing the following steps: skull stripping, motion correction, slice timing correction, spatial smoothing, co-registration, ICA-based automatic removal of motion artifacts (ICA-Aroma) [28], high-pass filtering and nuisance regression (WM and CSF).

2.2.5 Resting-State Functional Connectivity

GraphICA calculates functional connectivity (fc) based on independent component analysis (ICA) with dual regression between well-established resting state networks [29], [30]. As a part of this process, a set of independent component maps (IC) were identified for each network. Dual regression was then implemented, which utilized these IC maps as network templates to identify the corresponding spatial fc maps for individual subjects. The dual regression process can be explained in two stages. The inputs to the first stage include preprocessed fMRI data for an individual subject and the IC template maps which are then used to perform spatial regression to extract subject-specific time-series for each IC map. In the second stage, the subject-specific timecourses from the first stage are passed onto a temporal regression along with the subject’s fMRI data to extract spatial maps for each IC map associated with that subject. This technique ultimately allowed the extraction of z statistic maps for each subject at a voxel level. Following this, the T1-weighted image was automatically segmented with a pipeline implemented in Freesurfer 7 (v7.1.0, http://surfer.nmr.mgh.harvard.edu/) [31].

Further parcellation was performed with GraphICA using a gradient-weighted Markov Random Field model procedure described in [32]. This parcellation model contains three competing terms: a global similarity term to group brain locations with similar image intensities, a local gradient term to detect abrupt fc changes between neighbouring brain locations, and a spatial connectedness term to ensure spatial connectedness within parcels. The procedure yielded 832 brain parcels. The average z-value for each parcel was calculated from all voxels within a parcel, producing 832 nodes.

Thresholding was performed using a data-driven approach for network matrices based on the Gaussian mixture model approach [30], where the z statistics corresponding to each node for individual networks were modelled as a mixture of Gaussian distributions.
The calculated maps from individual volunteers were compared against datasets collected with different 3 T scanners. The functional data were collected with 1243 subjects (433 females, mean age = 28 ± 17 and 810 males, mean age = 26 ± 15) while structural data were collected with 1665 subjects (female, mean age = 38 ± 20 and 972 males, mean age = 30 ± 18).

Figure 2.2. Shows the workflow used in GraphICA.

2.2.6 Temporal SNR Calculations

Temporal SNR was computed by performing 240 and 480 repeat acquisitions corresponding to TRs of 2000 and 1000 ms respectively, correcting for motion using MCFLIRT [24], and computing their variance voxel-wise through the time series. For region specific tSNR calculations, standard masks of eight resting state networks (RSNs) as described in [25] were used to mask regions within auditory, default mode, left and right executive control networks and the sensorimotor network. These masks were then binarized and non-linearly registered onto the anatomical image using FMRIB’s nonlinear image registration tool (FNIRT) [24], [26]. These masks were then applied to the
functional data after motion correction and registration to the anatomical images to extract tSNR maps

2.3 Results

According to Table 2.1, after motion correction, the highest absolute and relative mean displacements seen across volunteers for different functional datasets with a TR of 2000 ms were approximately 0.41 mm and 0.22 mm respectively. This table suggests that volunteer 3 suffered the most due to motion.

Table 2.2 provided the same parameters for TR of 1000 ms. According to this table, the worst scenario was seen for volunteer 1 with an absolute and relative mean displacement of approximately 0.51 mm and 0.22 mm when functional data included noise that followed Rician distribution Type 2.

<table>
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(a)

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<td>3</td>
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(b)

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(c)

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<tr>
<td>3</td>
<td>0.41</td>
<td>0.22</td>
</tr>
</tbody>
</table>

(d)

Table 2.1. Shows the mean displacement, both absolute and relative, calculated after motion correction for the functional data when TR = 2000 ms.

(a) 3 T data, (b) modified data with the Noncentral $\chi^2$ distribution noise model (c) and (d) refer to modified data with Rician distribution noise model of varying parameters (Type 1 and 2).
Table 2.2. Shows the mean displacement, both absolute and relative, calculated after motion correction for the functional data when TR = 1000 ms.

(a) 3 T data, (b) modified data with the Noncentral $\chi^2$ distribution noise model and (c) modified data with Rician distribution noise model (Type 1).

After motion correction, tSNR and Image SNR (SNR$_0$) were calculated for individual scans. The image SNR was calculated using ROIs with an area of interest and background, which will cause a bias in these measurements since the data was collected with a multi-channel coil. Temporal SNR and Image SNR (SNR$_0$) are given with Eq’n (2.1) and (2.2) respectively, these quantities can be used to calculate the following ratio of physiological to thermal noise given by Eq’n (2.3) [9].

\[ t\text{SNR} = \frac{\bar{S}}{\sqrt{\sigma_0^2 + \sigma_p^2}} \]  

\[ (2.1) \]
\[
\text{SNR}_0 = \frac{\bar{S}}{\sigma_0}
\]  
(2.2)

\[
\frac{\sigma_p}{\sigma_0} = \sqrt{\frac{(\text{SNR}_0^2}{t\text{SNR}} - 1}
\]  
(2.3)

In Eq’n (2.1), (2.2), and (2.3), \( \bar{S} \) is the mean image signal intensity, \( \sigma_0 \) and \( \sigma_p \) are the standard deviation corresponding to the thermal and physiological noise distributions respectively. The following tables provide the whole brain tSNR, image SNR and the \( \sigma_p/\sigma_0 \) ratios for the 3 T data and multiple modified datasets for different TRs.
Table 2.3. Shows the quantities calculated with different functional datasets (original 3 T data, modified datasets with artificial noise following the Noncentral $\chi^2$ distribution and Rician distribution of type 1) for each subject with a TR of 2000 ms.

(a) Whole brain tSNR, (b) $\text{SNR}_0$ and (c) physiological to thermal noise ratio.
Table 2.4. Shows the quantities calculated with different functional datasets (original 3 T data, modified datasets with artificial noise following the Noncentral $\chi^2$ distribution and Rician distribution of type 1) for each subject with a TR of 1000 ms.

(a) Whole brain tSNR, (b) SNR$_0$ and (c) physiological to thermal noise ratio.
Table 2.5. Shows the quantities calculated with different functional datasets (original 3 T data, modified datasets with artificial noise following the Rician distributions Type 1 and 2) for each subject with a TR of 2000 ms.

(a) Whole brain tSNR, (b) SNR₀ and (c) physiological to thermal noise ratio.

Following the motion correction: tSNR, SNR₀ and the physiological to thermal noise ratios were calculated before implementing high-pass filtering. Table 2.3 (a) suggests that the whole brain tSNR was the highest in volunteer 1 for the collected data with a mean value of approximately 60. While for the modified datasets with additional noise that follows non-central $\chi^2$ distribution and Rician distribution Type 1 respectively, the highest tSNR was seen in volunteer 2 with values of 31 and 51 respectively. The calculated SNR₀ was substantially lower across volunteers when the modified data included noise that follows a non-central $\chi^2$ distribution as can be seen in Table 2.3 (b).
Table 2.4 shows the same quantities calculated for different functional datasets with a TR of 1000 ms. According to Table 2.4 (a), the whole brain was relatively high for volunteers 2 and 3 with mean values of 70 and 68 respectively, however, the standard deviations for these calculations were high, suggesting a greater variation of tSNR across all the regions in the brain. In terms of SNR₀, a similar pattern was observed in Table 2.4 (b) as mentioned previously for Table 2.3.

Table 2.5 shows the same quantities calculated for different functional datasets where the additional noise follows different types of Rician distributions with a TR of 2000 ms. This table shows that for data with additional noise that follows Rician distribution Type 2, both the temporal SNR and SNR₀ are reduced compared to the other scenarios as shown in Table 2.5 (a) and (b) respectively. The temporal and SNR₀ analyses provided in these tables were also performed with the filtered data. These results are provided in the supplementary section.

Temporal SNR and SNR₀ were used to calculate the physiological to thermal noise ratios as shown in Table 2.3, 2.4 and 2.5 (c). According to these tables, if the ratio is less than 1, the fMRI time series is thermal image noise dominated, and if the ratio is greater than 1, then physiological fluctuations are dominant. These results suggest that in all cases the physiological noise was the dominant noise source.

Following this the temporal SNR maps were calculated for cortical regions within specific resting state networks for different noisy data at varying TRs as in shown in Figures 2.3 to 2.7.
Figure 2.3. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the auditory resting-state network.

(a) Collected 3 T data, (b) Modified data with artificial noise, where the noise distribution follows the noncentral $\chi^2$ distribution, (c) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 2 and (d) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 1. All the functional datasets used here were collected with TR of 2000 ms.
Figure 2.4. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the default mode resting-state network with TR of 2000 ms.

(a) Collected 3 T data, (b) Modified data with artificial noise, where the noise distribution follows the noncentral $\chi^2$ distribution, (c) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 2 and (d) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 1. All the functional datasets used here were collected with TR of 2000 ms.
Figure 2.5. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the executive control resting-state network.

(a) Collected 3 T data, (b) Modified data with artificial noise, where the noise distribution follows the noncentral $\chi^2$ distribution, (c) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 2 and (d) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 1. All the functional datasets used here were collected with TR of 2000 ms.
Figure 2.6. Shows the tSNR maps calculated for a single volunteer (number = 1) for regions within the sensorimotor resting-state network.

(a) Collected 3 T data, (b) Modified data with artificial noise, where the noise distribution follows the noncentral $\chi^2$ distribution, (c) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 2 and (d) Modified data with artificial noise, where the noise distribution follows Rician distribution Type 1. All the functional datasets used here were collected with TR of 2000 ms.

Following that, functional connectivity was calculated within each of the eleven well-established resting-state networks. The normalized thresholded z statistics map showing the connectivities are given below. The activity in the blue regions are negatively correlated with the activity in the red regions.
Figure 2.7. Normalized thresholded z statistics map of higher order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 2000 ms.

(a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi^2$ distribution (d) shows the functional connectivity calculated with the modified data which includes artificial noise following the Rician Type 1 distribution. In this figure (1) refers to the default mode network, (2) refers to the executive control network left and (3) refers to the executive control network right.
Figure 2.8. Normalized thresholded z statistics map of sensory networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 2000 ms.

(a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional
connectivity calculated with the modified data which includes artificial noise following the noncentral \( \chi^2 \) distribution (d) shows the functional connectivity calculated with the modified data which includes artificial noise following the Rician Type 1 distribution. In this figure (1) refers to auditory network, (2) refers to sensorimotor network, (3) refers to visual lateral network, (4) refers to visual medial network and (5) refers to visual occipital network.

Figure 2.9. Normalized thresholded z statistics map of lower order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 2000 ms.

(a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral \( \chi^2 \) distribution (d) shows the functional connectivity calculated with the
modified data which includes artificial noise following the Rician Type 1 distribution. In this figure (1) refers to hippocampal network, (2) refers to language network and (3) refers to salience network.

Figure 2.10. Normalized thresholded z statistics map of higher order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 1000 ms.

(a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi^2$ distribution (d) shows the functional connectivity calculated with the modified data which includes artificial noise following the Rician Type 1 distribution. In this figure (1) refers to the default mode network, (2) refers to the executive control network left and (3) refers to the executive control network right.
Figure 2.11. Normalized thresholded z statistics map of sensory networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 1000 ms.

(a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi^2$ distribution (d) shows the functional connectivity calculated with the modified data which includes artificial noise following the Rician Type 1 distribution. In
this figure (1) refers to auditory network, (2) refers to sensorimotor network, (3) refers to visual lateral network, (4) refers to visual medial network and (5) refers to visual occipital network.

![Figure 2.12](image_url)

Figure 2.12. Normalized thresholded z statistics map of lower order networks overlaid on top of T1 scan corresponding to volunteer 2 for TR of 1000 ms.

(a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi^2$ distribution (d) shows the functional connectivity calculated with the modified data which includes artificial noise following the Rician Type 1 distribution. In this figure (1) refers to hippocampal network, (2) refers to language network and (3) refers to salience network.
Figure 2.13. Shows p statistics calculated by comparing each network’s z statistics map for individual volunteers to respective representative network maps from the database.

The markers represent all the eleven resting-state. Row (1) corresponds to TR of 2000 ms, and Row (2) corresponds to TR of 1000 ms. Column (a) refers to the collected 3 T data, (b) refers to the modified data with additional noise that follows the non-central $\chi^2$ distribution and (c) refers to the modified data with additional noise that follows the Rician distribution of Type 1. A solid line is also plotted at p = 0.05. Any network with p values < 0.05 is significantly different from the representative network.

2.4 Discussion

Temporal SNR and SNR$_0$ were used to calculate the physiological to thermal noise ratios as shown in Table 2.3, 2.4 and 2.5 (c). These results suggest that in all cases the physiological noise was the dominant noise source. According to [9], a similar behaviour was observed in this study. For experiments with high flip angles such as 90°, there is an increase in the ratio since such FAs correspond to the highest MR signal which also suggests high physiological noise. Experiments conducted in [9] with the following parameters: $B_0 = 3$ T, TR = 5400 ms, TE = 30 ms, timepoints = 60, FA = 90° and resolution = 4 x 4 x 3 mm$^3$ resulted in a physiological to thermal noise ratio of approximately 1.59 which suggest physiological noise dominance. The experiments conducted in this chapter suggest that volunteer 3 suffers from high physiologically noisy data compared to other
volunteers. This results in a higher ratio for most scenarios. As discussed previously, this volunteer also suffered the most due to motion. Tables 3 and 4 allow a comparison of this ratio for different TRs which suggests a slight decrease in this ratio as TR is reduced. According to [9], [22], [33] for fMRI studies at a 3 T scanner, tSNR is observed to be near its asymptotic limit for conventional spatial resolutions (3 to 4 mm isotropic), limiting further improvements. However, for voxel volumes < 27 mm$^3$ the ratio of physiological to thermal noise is expected to be < 1, thus, the time-course SNR would be dominated by image noise and not physiological noise. For higher field scanners, at smaller voxel volumes, the fMRI experiment is not near the asymptotic limit of tSNR and improvements in image SNR are expected to translate into significant improvements in tSNR. This is the main reason why studies conducted at higher field scanner mostly use higher resolution than 3 to 4 mm isotropic. However, these are the resolutions of interest for later studies conducted with the mid-field scanners.

Figures 2.3 to 2.6 show the temporal SNR maps for regions within specific resting-state networks calculated with the different datasets for a single volunteer when the TR was 2000 ms. As expected, the mean tSNR in all the regions within these networks drops significantly for the datasets with additional artificial noise distributions.

Figures 2.7 to 2.9 show the normalized thresholded z statistics maps calculated to show functional connectivity between regions within well-established resting state networks. Figure 2.7 shows the functional connectivity calculated within the higher-order networks, namely default mode, executive control left and right for different datasets from a single volunteer when the TR was 2000 ms. This figure shows the limitation of this study, for instance, let’s consider (1) the spurious noise sources added to the datasets in columns (c) and (d) do reduce the connectivity in the dorsomedial prefrontal cortex, however, the posterior cingulate cortex and lateral parietal cortex where the connectivity from the collected data was strong, the effect of additional noise remain negligible, since the connection itself is not destroyed. Similar effects are seen in (2) and (3) suggesting that this analysis platform performs reasonably well with noisy functional datasets. Figure 2.8 shows the functional connectivity calculated within the higher-order networks namely auditory, sensorimotor and 3 different visual networks (lateral, medial, occipital). This figure suggests that increased functional connectivity is identified in some cases with
modified datasets which include additional noise. For instance, let’s consider auditory and visual medial. As mentioned, due to the limitations of this study, the strong functional connectivity that pre-existed in the collected 3 T data is preserved. The additional noise which follows Rician distribution Type 1 as shown in column (d) increased the connectivity to regions that were previously not identified to be part of the network as can be seen from column (b). Figure 2.9 shows the functional connectivity calculated within the lower-order networks namely hippocampal, language and salience. A similar behaviour as described in Figure 2.8 was seen in 2.9. According to this figure, the initial connectivity identified within the language network was poor as shown in column (b). This connectivity is further reduced for the dataset with an additional noise following the non-central $\chi^2$ distribution.

Figures 2.10 to 2.12 show the functional connectivity between regions within resting-state networks for different datasets used in this study with a TR of 1000 ms from volunteer 2. These figures allow a comparison between TRs. Reducing TR while keeping the temporal resolution constant will have an impact on scan time. An understanding of the potential to detect functionally connected networks reliably with the reduced TR is essential. However, simply reducing the TR with constant temporal resolution might impact the whole-brain coverage. To address this issue, in recent studies, short TRs are increasingly being used for fast sequences such as simultaneous multi-slice (SMS) imaging which has enabled whole-brain resting-state fMRI scanning at sub-second temporal resolutions [34], [35]. A recent study [36] has shown that SMS acquired scans have enabled the reliable detection of functionally connected networks. This will be further discussed in Chapter 5 and in Chapter 6. For this chapter, we will simply consider the effect on functional connectivity of scans performed with reduced TR using standard techniques.

For the experiments conducted in this chapter, scan duration is kept constant, as TR is reduced greater number of images are acquired. According to Figure 2.10, the functional connectivity within higher-order networks was similar compared to Figure 6, suggesting no negative impact of the reduced TR. However, reduced functional connectivity was detected for most of the sensory networks, specifically in auditory and visual lateral networks as shown in Figure 2.11. The lower-order networks in Figure 2.12 had similar connectivity as Figure 2.9. Both these figures suggest that reduced functional connectivity is detected within the language network for volunteer 2. Reducing TR has an impact on TE
as well which is further reduced to 21.4 ms. For most EPI-based fMRI studies TE is generally equal to T2*, where it is most commonly it is set to ~30 ms at 3 T. However, reducing TE implies that acquiring a signal with optimal BOLD contrast might not be feasible. To add to that, some regions of the brain have even longer T2* than the standard TE used at 3 T [37], adding significant limitations to the study.

Figure 2.13 summarizes the results from this chapter. Column (a) in row (1) provides the p statistics from the data collected with a TR of 2000 ms which suggests that all the networks are not significantly different from the representative network with one from each volunteer being close to being significantly different. Row (1) suggests volunteer 3 remains mostly unaffected by the additional noise in columns (b) and (c). To add to that, some networks even improved in terms of p statistics in columns (b) and (c) compared to (a). The same conclusions are not applicable to volunteer 2, in which case there was an overall decrease in the p statistics corresponding to most networks. Additionally, a specific network was statistically not significant as can be seen in (c). The conclusions for volunteer 1 vary with improvements seen in (b) and overall decrement seen in (c). Column (a) in row (2) provides the p statistics from the data collected with a TR of 1000 ms which suggests that some networks are significantly different from the representative network, specifically for volunteers 1 and 3. Row (2) suggests volunteer 3 shows increased p statistics in column (b) and reduced p statistics in column (c) compared to (a). The p statistics for volunteer 2 were reduced for columns (b) and (c). For some networks, the p statistics for volunteer 1 improved in columns (b) and (c), however, some networks remained statistically not significant in (a), (b) and (c).

2.5 Conclusions

This chapter evaluates the performance of the preprocessing and analysis platform in identifying the functional connectivity within resting-state networks for functional datasets with various additional noise distributions. The results from this evaluation suggest functional connectivities were preserved and correctly identified in most scenarios. This implies the potential of this tool for use with mid-field functional data. As mentioned before, there are several limitations to this simplistic approach and it does not aim to correctly model mid-field data.
2.6 References


Chapter 3

3 Optimization of Single Gradient Echo Echo-planar Imaging for T2* Contrast at 0.5 T1

3.1 Introduction

Blood-oxygen-level-dependent (BOLD) fMRI is a tantalizing tool in acute settings, providing vital neurological information in cases of traumatic brain injury [1], ischemic stroke [2], [3], epilepsy [4] dementia [5] and intraoperatively for surgical guidance [6], [7]. fMRI is typically only used in higher field strength (> 1.5T) systems due to the increase in magnetic susceptibility contrast [3] and SNR [8]. Despite this, many applications of fMRI are possible with modern, high-performance mid-field systems. To do so, optimization of gradient recalled echo (GRE) echo planar imaging (EPI) sequence is essential [9] to achieve maximum T2* contrast and scan efficiency.

A recent study investigating visual task-based fMRI was performed on a 0.55 T whole-body MR scanner (a ramped down Siemens 1.5 T) equipped with high-performance gradient coils and a 16-channel head coil [10]. This study used GRE EPI and transition band steady-state free precession (SSFP) based sequences. The improved field uniformity (spatial and temporal) available at mid-field scanners suggest the possibility of SSFP based sequences, which are sensitive to off-resonance frequency in a narrow band of few Hz (occupies 10-15% of the frequency axis) around resonance (known as transition-band) [11], [12]. Results from this study suggest the feasibility of BOLD fMRI, with both acquisition techniques producing a tSNR of 35 to 45 and a signal change on the scale of

1 This chapter has been adapted from the following Article and ISMRM abstract:


2% producing robust activation in the 4 to 10 minute measurement time typical of standard fMRI. According to this study, the transition-band SSFP signal was significantly impacted by frequency shifts such as concomitant fields, $B_0$ field drift, and subject respiration. Specifically, the effect from concomitant fields was quite large and may compromise the BOLD sensitivity if it is not corrected accurately. However, GRE EPI, which is a standard protocol used at (3 and 7 T for functional imaging), was more robust against frequency changes and less affected by physiological noise.

Previous study focusing on fMRI with pass-band SSFP sequences include [11]. This technique occupies 75% of the frequency axis and is therefore much more compatible with whole-brain coverage than transition-band SSFP. The main downside here is the reduced functional contrast due to smaller signal change than can be achieved with conventional GRE at long TE, and much smaller changes than transition band SSFP [11], [13]. In both transition- and pass-band SSFP, the presence of bands due to frequency inhomogeneity makes whole-brain coverage difficult to achieve. This is particularly problematic in transition-band SSFP since functional contrast is achieved over a very narrow range of frequencies.

GRE EPI sequence will be used for this study, as it is an especially enticing sequence to use at mid-field strength due to the advantageous relaxation properties including the short T1, long T2* [14], compatibility with whole-brain coverage and reduced susceptibility induced field inhomogeneities [15]. Other than fMRI, this sequence is useful for several other applications including susceptibility-weighted imaging (SWI) [16], perfusion [17] and proton resonance frequency (PRF) thermometry [18]–[20]. For example, these advantageous relaxation properties were recently leveraged in diffusion-weighted EPI to help overcome the reduced signal-to-noise ratio inherent to lower field strength systems caused by reduced polarization [21]. The low bandwidth in the phase encode direction implicit to EPI makes it prone to susceptibility-induced distortions; however, this effect is significantly reduced at mid-field [22]–[26]. The reduction in susceptibility-induced field inhomogeneities improves image geometric fidelity, particularly in regions near air-tissues interface such as air cavities and the skull base.

To guide the optimization of GRE EPI, T2* measurements of grey matter (GM), white matter (WM), motor cortex (MC), and visual cortex (VC) were quantified. Protocol
optimizations were then performed by maximizing the T2* contrast efficiency for scan resolution and coverages of typical fMRI acquisitions.

3.2 Theory

The SNR of GRE-EPI including the BOLD contribution has been defined previously [27] as:

$$ SNR_{BOLD} \propto \Delta x \Delta y \Delta z \frac{TE}{T_{AD}} \sqrt{\frac{1 - e^{-TR/T_1}}{1 - \cos(\alpha) e^{-TR/T_1}}} e^{-TE/T_2^*} $$

(3.1)

where $\Delta x$, $\Delta y$, and $\Delta z$ are the dimensions of the imaging voxel, $T_{AD}$ is the duration of the acquisition readout, $\alpha$ is the flip angle, TR is the repetition time, TE is the echo time, and $T_1$ and $T_2^*$ are the longitudinal and transverse relaxation times, respectively.

During an fMRI experiment, multiple images are acquired in a time series within a total scan time $TS = N*TR$, where $N$ is the total number of images. Including the averaging effect of the time series and assuming uncorrelated noise across images, the BOLD SNR becomes:

$$ \overline{SNR}_{BOLD} \propto \Delta x \Delta y \Delta z \frac{TE}{N T_{AD}} \sqrt{\frac{1 - e^{-TR/T_1}}{1 - \cos(\alpha) e^{-TR/T_1}}} e^{-TE/T_2^*} \cdot \sqrt{N} \frac{SNR_{BOLD}}{\sqrt{TR}} $$

(3.2)

$$ \overline{SNR}_{BOLD} = \sqrt{N} \cdot SNR_{BOLD} \cdot \eta_{T_2^*} $$

(3.2)

For a fixed scan duration, equation 3.2 can be re-written as:

$$ \overline{SNR}_{BOLD} = \sqrt{\frac{TS}{TR}} \cdot SNR_{BOLD} = \sqrt{\frac{TS}{TR}} \cdot \eta_{T_2^*} $$

(3.3)

where $\eta_{T_2^*}$ is the efficiency of T2* contrast, given by:

$$ \eta_{T_2^*} = \frac{SNR_{BOLD}}{\sqrt{TR}} $$

(3.4)

$\eta_{T_2^*}$ can be used to compare pulse sequence timing parameters for a given T2* value, where optimal parameters are found when $\eta_{T_2^*}$ is maximized. A detailed description of the derivation is provided in the supplementary section for this chapter.
3.3 Methods

All imaging protocols were performed on a head-only 0.5 T MR scanner equipped with a high-performance gradient system and 16 channel head coil (Synaptive Medical, Toronto) [9].

Images of the scanner are shown in figure 1. Scanner specifications include: weight < 2.5 to 3 tons, fringe field< 1.7 m x 1.7 m, peak gradient amplitude, slew rate respectively = 100 mT/m and 400 T/m/s, adjustable multi-channel receive-only head coil and peak B1+ can exceed 50 μT without exceeding SAR limitations [28].

Imaging was performed on two healthy volunteers (male, ages 36 and 37) with informed consent in compliance with health and safety protocols. For all measurements, subjects were asked to relax while in the scanner with their eyes closed.

Figure 3.1. Computer-aided design model of a compact head-only 0.5 T MR Scanner.

Specifications include: weight < 2.5 to 3 tons, fringe field< 1.7 m x 1.7 m, peak gradient amplitude, slew rate respectively = 100 mT/m and 400 T/m/s, adjustable multi-channel receive-only head coil and peak B1+ can exceed 50 μT without exceeding SAR limitations.

3.3.1 Scan Description

Structural images were acquired using a 1.1 mm isotropic resolution T1-weighted MPRAGE sequence with field of view (FOV) = 236 mm x 236 mm x 180 mm, FA = 26°, TE = 5 ms, TR = 11.2 ms, scan time ~ 6 mins and no acceleration was implemented.

T2* maps were constructed using a 2 mm isotropic resolution 3D multi-echo GRE (meGRE) sequence with FOV = 240 mm x 240 mm x 120 mm, matrix size = 120 x 120 x
60, FA = 32°, TE1 = 5 ms, echo spacing = 3.4 ms, echo train length (ETL) = 26, TR = 97.25 ms and acquisition bandwidth = 43 kHz.

Functional scans were collected at two isotropic spatial resolutions (3.4 mm and 4 mm) for 9 different protocols with varying echo times (range = 25-105 ms, at 10 ms intervals) using single echo GRE EPI sequence. The following parameters were constant for all EPI scans: in-plane FOV = 240 mm x 240 mm, and acquisition bandwidth = 160 kHz. Parameters specific to the 3.4 mm protocols were: ETL = 70; number of slices = 38; slice FOV = 129.2 mm; Flip angle (FA) = [85, 87, 88, 89, 90, 90, 90] degrees; TR = [1738, 2119, 2499, 2879, 3259, 3639, 4019, 4399, 4779] ms. Similarly, parameters specific to the 4.0 mm protocol were: ETL = 60; number of slices = 32; slice FOV = 128 mm; FA = [82, 85, 87, 88, 89, 89, 90, 90, 90] degrees; TR = [1386, 1706, 2026, 2346, 2666, 2986, 3306, 3626, 3946] ms. Flip angles were chosen to be the Ernst angle for the given acquisition TR for GM at 0.5 T (T1 = 715 ms) [29].

3.3.2 Creating Cortical Masks

Region of interest (ROI) masks were created using anatomical T1-weighted images. First, the Brain Extraction Tool (BET) [30] from the FMRIB Software Library (FSL) [31] was applied to obtain the skull stripped brain. Manual adjustments were performed to maximize cortical coverage on the skull stripped brain which was then passed onto FMRIB’s Automated Segmentation Tool (FAST) [32] in FSL to create cortical GM and WM masks.

A visual cortex (VC) mask was created using the Juelich Histological atlas [33]–[37] in Montreal Neurological Institute (MNI) 152 standard space (resolution = 2 mm). These masks were then thresholded at an intensity of 30 and non-linearly registered onto the anatomical image using FMRIB’s nonlinear image registration tool (FNIRT) [38], [39].

3.3.3 T2* Maps of Masked Regions

The 3D meGRE images were registered to the structural image using FMRIB’s Linear Image Registration Tool (FLIRT) [46], [47]. Voxel-wise estimates of T2* were computed over the ROIs by fitting the data to a mono-exponential decay model [48].
3.3.4 Temporal and Pseudo Signal-to-Noise Ratio Calculations

For each functional acquisition with single echo GRE EPI sequence, temporal SNR (tSNR) and pseudo multiple replica SNR (pSNR) [41][25] were computed after linear registration to the anatomical image. Temporal SNR was computed by performing 64 repeat acquisitions, correcting for motion using MCFLIRT [39], and computing their variance voxel-wise through the time series. Conversely, pSNR computed a pseudo time series from a single acquisition and the noise correlation matrix. In total, 128 repetitions of properly scaled and correlated noise were added to k-space data prior to reconstruction to create a pseudo time series. Images in this time series only differ due to thermal noise and do not contain any physiological noise or system instability effects.

The mean and standard deviation of the tSNR and pSNR values for each ROI were calculated. These values were converted to $\eta_{T2^*}$ and compared to theoretical values computed using equation 4. Also, these values were used to compute the ratio of physiological noise to thermal noise as defined in equation 3 of [42], [43] to understand the noise regime of the acquisitions.

Figure 3.2. Example of mono-exponential decay fit performed on a random voxel to estimate the T2* for grey matter.
To identify how sequence optimization changes with slice coverage and field strength, equation 4 was used to compute T2* efficiency values for varying TE and number of slices for GM with the imaging bandwidth and two resolutions investigated in this work at 0.5T, 1.5 T, and 3.0 T. The optimal TE was found for each slice coverage by taking the TE corresponding to the peak T2* efficiency value.

3.4 Results

Figure 3.3 shows an example segmented T2* map overlaid on top of a T1 weighted anatomical image of one of the volunteers with data collected at 2 mm. For each segmented region, sagittal, coronal, and axial formats are shown. The average T2* measured estimates over both volunteers for each segmented region were: GM = 86 ± 10 ms, WM = 77 ± 11 ms and VC = 79 ± 14 ms.

For all EPI scans, the highest absolute and relative mean displacements due to motion were found to be less than 0.2 mm. Figure 3.4 shows the pseudo-replica (blue) and temporal SNR (red), T2* efficiency and physiological to thermal noise variation as a function of TE averaged over two volunteers for a 3.4 mm isotropic protocol. Pseudo-replica SNR, which contains only thermal noise, demonstrates a reduction in SNR as TEs increase in all ROIs. Furthermore, the temporal SNR, which contains contributions from both thermal and physiological noise, was consistently lower than the pseudo-replica SNR. These curves do not follow a simple exponential curve as increasing the TE necessitates an increase in TR and FA as well. Measured T2* efficiencies, derived from the pSNR, and theoretical T2* efficiencies (equation 4) demonstrate good agreement. Physiological to thermal noise ratios are relatively small and increase as TE approaches T2*; however, thermal noise dominates for all echo times measured. Figure 3.5 shows the pseudo-replica (blue) and temporal SNR (red), T2* efficiency and physiological to thermal noise variation as a function of TE averaged over two volunteers for a 4.0 mm isotropic protocol. For this protocol, a substantial drop is observed when comparing pseudo-replica and temporal SNR. This suggests that physiological noise in this protocol is now a substantial contributor. This observation can also be seen by the significant deviation of the tSNR efficiency curve from the theoretical curve and the high physiological to thermal noise ratio.
As expected, tSNR and derived efficiency curves deviate significantly more from their pSNR counterparts at 4 mm resolution than at 3.4 mm resolution. This is due to the increase in physiological noise relative to thermal noise as the voxel size and baseline SNR increase. As can be seen in column (c) of figure 3, this effect is particularly evident for echo times close to $T2^*$, in agreement with prior work [11], [35]. Thermal noise dominates over physiological noise for all measurements except when $TE \approx T2^*$ in the VC regions.

Figure 3.3. $T2^*$ maps with data collected at a 2 mm resolution overlaid on a T1 weighted MPRAGE of a healthy volunteer are shown in sagittal, coronal, and axial planes for the following regions: grey matter (GM), white matter (WM), grey matter overlapped with the visual cortex (VC).

The cumulative mean and standard deviation $T2^*$ measurement acquired with two healthy volunteers are shown in the bottom of each column.
Figure 3.4. Sequence optimization plots for 3.4 mm isotropic resolution.

(a) Mean temporal SNR and pseudo replica SNR; (b) T2* efficiency; and (c) physiological to thermal noise ratio plotted against echo time for rows: (1) grey matter; (2) white matter and (3) grey matter overlapped with the visual cortex, respectively.
Figure 3.5. Sequence optimization plots for 4.0 mm isotropic resolution.

(a) Mean temporal SNR and pseudo replica SNR; (b) T2* efficiency; and (c) physiological to thermal noise ratio plotted against echo time for rows: (1) grey matter; (2) white matter and (3) grey matter overlapped with the visual cortex, respectively.

Optimal TE vs number of slices for the imaging bandwidth and two resolutions investigated in this work for different field strengths (a) 0.5 T; (b) 1.5 T; and (c) 3 T are shown in figure 3.6 for GM. As one can see in the figure, as the number of slices is reduced, shortening the TR, the optimal TE approaches T2*. Additionally, the fall off in optimal TE gets shallower as the field strength increases due to T1 lengthening. Furthermore, as the number of slices increases, increasing TR, the optimal TE bottoms out at 0.5T since the deadtime in the sequence has been removed and there is no signal recovery benefit of a longer TR. Therefore, according to this figure, the optimal TE for 32 slices at 4 mm isotropic voxel size are approximately 60 ms, 68 ms, and 60 ms at 0.5 T, 1.5 T and 3 T respectively.
Figure 3.6. Theoretically calculated optimal TE vs. number of slices for single shot, single echo EPI at 3.4 mm (red) and 4 mm (blue) isotropic resolution for different cortical T2* grey matter values.

(a) T2* = 86 ms, T1 = 715 ms [10] corresponding to 0.5 T, (b) T2* = 84 ms, T1 = 1304 ms [10] corresponding to 1.5 T and (c) T2* = 66 ms, T1 = 1820 ms [11] corresponding to 3 T. The number of slices used in this work for each resolution are denoted by the dashed vertical lines.

3.5 Discussion

The T2* relaxation parameter was measured at a 2 mm isotropic resolution in the following regions: grey matter, white matter, and visual cortex. Measurements of grey (86 ± 10 ms) and white matter (77 ± 11 ms) are in good agreement with recent measurements of grey (86 ± 9 ms) and white matter (72 ± 12 ms) acquired at 0.55 T [11]. To our knowledge, the estimate of the T2* relaxation in the visual cortex (79 ± 14 ms) specifically at 0.5T is not recorded elsewhere in the literature.

The T2* relaxation parameter was measured at 3 mm isotropic resolution in the following regions: grey matter, white matter, and visual cortex. Measurements of grey (86 ± 10 ms) and white matter (77 ± 11 ms) are in good agreement with recent measurements of grey (86 ± 9 ms) and white matter (72 ± 12 ms) acquired at 0.55 T [26].

According to theory, optimal T2* contrast occurs at TE = T2*, which has resulted in long TEs for previously reported fMRI validation studies in the mid-field [42], [43]. However, the results from this work indicate that for single echo GRE EPI at 0.5 T, an optimal echo time for T2* contrast efficiency occurs at TE < T2* for practical readout bandwidths and slice coverage. This is because the T2* is so long in the mid-field that dead time can occur between excitation and acquisition when echo train lengths are short (as is
the case with modest resolution for fMRI). Therefore, there is a trade-off between reducing this deadtime and T2* contrast.

Image distortions [45] along the phase encode dimension prevent simply reducing the readout bandwidth to achieve long TEs and eliminate sequence dead time. This can be illustrated by way of example: Consider the case where T2* = 90 ms and ETL = 60 (4 mm resolution), to achieve TE = T2* without sequence deadtime, the echo spacing between phase encode lines would need to be approximately 3 ms corresponding to a phase encode bandwidth of 5 Hz/pixel. In comparison, the 4 mm protocol used in this work had a phase encode bandwidth of ~43 Hz/pixel, a factor of 8.6 improvement in geometric distortion.

Alternatively, instead of acquiring at a lower bandwidth, one could use a multi-echo readout to eliminate sequence dead time. Multi-echo GRE EPI (meGRE EPI) [47]–[50] increases the acquisition duty cycle, while maintaining long TE and reduced geometric distortion. Furthermore, since meGRE EPI benefits from high slew rate [45], [51], [52], it is an ideal sequence modification for a head-only system equipped with high-performance gradients as was the system used in this study [53]. A detailed comparison of T2* contrast efficiency between single echo and multi-echo EPI at 0.5 T will be done in a future publication.

The average pSNR and tSNR from two volunteers were used to compute the physiological to thermal noise ratio (σ_p/σ_T) for two resolutions across multiple echo times. At 3.4 mm resolution, thermal noise dominance was observed for all echo times measured over all regions of interest. At 4 mm resolution, very slight physiological noise dominance was observed in the visual cortex at echo times close to the region’s measured T2* value. These results suggest that any improvement in SNR from high performance RF coil design or multi-echo EPI protocols will translate to significant improvement in tSNR at voxel sizes ≤ 64 mm³. Furthermore, only modest tSNR improvement can be gained by increasing the voxel size further; however, this would result in greater partial volume corruption, potentially negating any benefits from increased tSNR.

3.6 Conclusions

For peak T2* contrast efficiency, the optimal echo time for GRE EPI sequences implemented at 0.5 T will be less than T2* when echo train lengths are short and deadtime
would otherwise be present in the sequence. For further improvement of GRE EPI at 0.5 T, multi-echo EPI is an enticing option as it would reduce sequence dead time, while maintaining the long echo times necessary for T2* contrast.

3.7 References


Chapter 4

4 Gradient Echo Echoplanar Imaging based Resting-State Functional MRI at a 0.5 T high-performance scanner

4.1 Introduction

Mid-field ( < 1 T) scanners make widespread diagnostic use possible for various applications, including identifying neurological diseases, especially in acute settings [1], [2]. The smaller size, lighter weight and compact fringe field enable easier siting and installation in locations close to the vulnerable patient population, which offers unique application scenarios for point-of-care, intraoperative monitoring [2], [3] and in countries with limited access to MRI. These scanners also offer higher peak B1+ without exceeding the specific absorption rate (SAR) limitation. In general, these scanners provide an increased safety profile due to reduced SAR [3], since this quantity scales with the scanner's main magnet’s field strength. This increased safety expands the eligible population able to undergo MRI exams specifically to those with implantable medical devices considered to be contraindications at higher field strengths.

The availability of imaging techniques such as functional MRI (fMRI) in a point-of-care setting would provide neurological information that can be vital in traumatic brain injury [4], acute ischemic stroke [5], epilepsy [6] and dementia [7]. However, blood-oxygen-level-dependent (BOLD) fMRI is generally not attempted at field strength < 3 T due to reduced magnetic susceptibility contrast [8] and signal-to-noise ratio (SNR) [9]. The SNR and sensitivity gained by imaging at higher field strength can be used to perform studies at high spatial resolutions which is particularly useful in certain applications [10], [11].

The objective is not to perform high-resolution fMRI studies at high field strength, but to evaluate the feasibility of fMRI using gradient recalled echo (GRE) echo planar

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2 A journal manuscript is in preparation.
imaging (EPI) at resolutions (on the order of 3.5-4 mm) clinically relevant for mid-field scanners [12].

There are two main sources of noise in fMRI, thermal and physiological noise. Physiological noise is dependent on the strength of the MR signal [13]. Thus, for the previously defined resolution of interest, an increase in MR signal strength at higher magnetic fields also suggests an increase in physiological noise. This increase in physiological noise counteracts any gains expected from the use of higher field magnets [8], which creates an asymptotic limit on the attainable BOLD contrast-to-noise ratio in the presence of physiological noise [9]. Therefore, the performance gap between high and mid-field scanners for this resolution range should be reduced. Furthermore, the relaxation properties at mid-field as discussed in Chapter 3 including the short T1, and long T2* [14] can potentially be used to reduce TR and increase the read-out window respectively. If the read-out window is reduced it will have two impacts: (1) reduced T2* blurring [15] and (2) reduced geometric distortion.

The pulse sequence used for this study is single-echo gradient recalled echo (GRE) echo planar imaging (EPI) since it is most widely used for fast imaging. Acquisitions of a 2D plane with this sequence take less than 100 ms, which reduces motion artifacts. Along with that, this sequence provides rapid, 2D multi-slice acquisition that enables whole-brain acquisition essential for these applications at clinically feasible scan times. The main driver behind EPI in clinical MRI is the availability of high-voltage gradient drivers and the design of gradient coils that can sustain the higher applied voltage, which allows for high gradient slew rates on the order of 200 T/m/s to be routinely used for the modern, whole-body scanners [16], [17].

The primary disadvantage is the image distortion due to spatial variation of magnetic susceptibility and the main magnetic field B₀ [17]–[19], particularly in regions near air-tissues interface such as air cavities and the skull base [20], [21]. While traversing through 2D k space, phase is accumulated during the finite echo spacing (ESP) between consecutive readouts which makes EPI highly sensitive to B₀ inhomogeneity. This results in nonlinear spatial distortions and nonuniform signal intensity variations such as signal bunching and dropout primarily in the phase-encoded direction however this effect is reduced at mid-field. To further reduce geometric distortion, phase encode bandwidth must
be increased by reducing the echo spacing (ESP) of the EPI train [17], [18]. This can be done in many ways, for example, by increasing the readout bandwidth of the sequence, parallel imaging techniques, etc [22]–[27]. One side-effect of reducing the echo spacing is that the overall acquisition time, $T_{AD}$, is reduced, leading to a loss in SNR. Furthermore, in situations where the $T_2^*$ is long (i.e. at 0.5 T), the desire to place $TE = T_2^*$ and have a short overall echo train length are at odds with one another. However, $TE < T_2^*$, suggests the possibility of reduced echo spacing.

Reducing ESP is difficult with whole-body MRI systems due to peripheral nerve stimulation (PNS) [28], since this limits the maximum permissible slew rate, and this value is further reduced at increased gradient amplitudes [29]. To add to that, the available power supply also limits the gradient performance [17]. An effective way to address both the power and PNS concerns is to utilize a smaller gradient coil for head-only imaging [30]–[32], which is the intention with Synaptive’s 0.5 T [3]. This scanner offers a maximum gradient amplitude of 100 mT/m and slew rate of 400 T/m/s.

Previous studies suggests that attempts of BOLD-based fMRI at modern low to mid-field scanners have been limited. During the development of functional imaging, task-based studies were performed at these field strengths [33]–[39]; however, they suffered from the lack of development in hardware, acquisition/reconstruction techniques, and physiological noise suppression techniques. Despite the drawbacks, these studies successfully demonstrated the possibility of task-based BOLD fMRI in the motor and visual cortex.

A recent visual task-based study performed on a modern 0.55 T whole-body scanner has demonstrated consistent activation in the visual cortex with a percent signal change of ~2 % and temporal SNR (tSNR) in the range of ~ 35-45 [40]. Similarly, a motor task-based study performed on a modern 0.5 T head-only scanner has shown consistent activation in the right motor cortex with a percent signal change of ~1.8 % and tSNR in the range of ~50-54.5 after temporal filtering [41]. These studies have successfully shown the feasibility of task-based fMRI at modern mid-field scanners. However, to our knowledge, until now there has not been any study that probes the feasibility of resting-state fMRI with these scanners. Resting state is particularly important for patients who cannot cooperate with extensive tasks due to severe medical conditions.
This investigates the feasibility of resting state BOLD fMRI at a modern 0.5 T scanner equipped with a high-performance gradient coil. For this evaluation, we optimized the GRE EPI protocol for this scanner to achieve full brain coverage at a resolution of 4 mm isotropic with an echo time that was lower than the T2* to maximize the T2* contrast efficiency for good temporal SNR and minimize the dead time to effectively increase the scan efficiency. To characterize the well-established eleven resting-state networks, a functional connectivity study was performed. The signal and noise associated with the scans were also further investigated.

4.2 Methods

All imaging protocols were performed on a head-only 0.5 T MR scanner equipped with a high-performance gradient system and 16 channel head coil (Synaptive Medical, Toronto) [3]. Imaging was performed on two healthy volunteers (male, ages 36 and 40), with informed consent in compliance with health and safety protocols.

4.2.1 Scan Description

Structural images were acquired using a 1.1 mm isotropic resolution T1-weighted MPRAGE sequence with field of view (FOV) = 236 mm x 236 mm x 180 mm, FA = 26°, TE = 5 ms, TR = 11.2 ms, scan time ~ 6 mins and no acceleration was implemented.

Functional scans were acquired using a 4 mm isotropic resolution single-echo GRE EPI sequence. The scan parameters are as follows: Temporal position = 800, FOV = 240 mm x 240 mm x 128 mm, matrix size = 60 x 60 x 32, acquisition bandwidth = 160 kHz, echo train length = 60, number of slices = 32, FA = 90 degrees, TR ~ 2.4 s, TE ~ 55 ms, Scan duration ~ 30 mins. Scans were repeated on different days with 6 scans on the first volunteer and 4 scans on the second volunteer to assess the similarities between resting-state networks.

T2* maps were constructed using a 2 mm isotropic resolution 3D multi-echo GRE (meGRE) sequence with FOV = 240 mm x 240 mm x 120 mm, matrix size = 120 x 120 x 60, FA = 32°, TE1 = 5 ms, echo spacing = 3.4 ms, echo train length (ETL) = 26, TR = 97.25 ms and acquisition bandwidth = 43 kHz.
4.2.2 Creating Cortical Mask

Region of interest (ROI) masks were created using structural T1-weighted images. First, the Brain Extraction Tool (BET) [42] from FMRIB Software Library (FSL) was applied to obtain the skull-stripped brain. Manual adjustments were performed to maximize cortical coverage on the skull-stripped brain which was then passed onto FMRIB’s Automated Segmentation Tool (FAST) [43] in FSL to create cortical GM masks.

The standard masks of eight resting state networks (RSNs) as described in [44] were used to mask regions within auditory, default mode, left and right executive control networks and the sensorimotor network. These masks were then binarized and non-linearly registered onto the structural image using FMRIB's nonlinear image registration tool (FNIRT) [45].

4.2.3 T2* Mapping of Masked Regions

The 3D meGRE images were registered to the structural image using FMRIB’s Linear Image Registration Tool (FLIRT) [46], [47]. Voxel-wise estimates of T2* were computed over the ROIs by fitting the data to a mono-exponential decay model [48].

4.2.4 Temporal SNR of Masked Regions

For each acquisition, temporal SNR (tSNR) was computed after linear registration to the anatomical image. tSNR was computed by performing 800 repeat acquisitions, correcting for motion using MCFLIRT [47], and computing their variance voxel-wise through the time series.

4.2.5 Functional Connectivity: Preprocess

Preprocessing of the fMRI data was performed using GraphICA [49], an in-house FSL based platform. The structural scans were preprocessed by implementing the following steps: bias-field correction (RF/B1-inhomogeneity correction), brain extraction, tissue type segmentation (CSF, GM, WM) and sub-cortical structure segmentation.

The functional scans were preprocessed by implementing the following steps: skull stripping, motion correction, slice timing correction, spatial smoothing, co-registration, ICA-based automatic removal of motion artifacts (ICA-Aroma) [Ref], high-pass filtering and nuisance regression (WM and CSF).
4.2.6 Functional Connectivity and Identifying Resting State Networks

GraphICA calculates functional connectivity (fc) based on independent component analysis (ICA) with dual regression between well-established resting state networks [50], [51].

ICA combined with dual regression was performed by identifying a set of independent component (IC) maps for each network. These maps were used as templates for each network to identify the corresponding spatial fc maps (z statistics) for individual subjects at a voxel level. Further parcellations were implemented to the segmented anatomical images using a gradient-weighted Markov Random Field model procedure [52]. This parcellation model contains three competing terms that determine the optimal trade-off properties for the final segmentation: global similarity term to group brain locations with similar image intensities, local gradient term to detect abrupt fc changes between neighbouring brain locations, and spatial connectedness term to ensure spatial connectivity within parcels. After applying this model 832 brain parcels were produced. The average z statistics for each parcel were calculated from all voxels within a parcel producing the same number of nodes.

Thresholding of the functional connectivity maps was performed using the Gaussian mixture model approach [51], where the z statistics corresponding to each node for individual networks were modelled as a mixture of Gaussian distributions. The optimal number of Gaussian distributions used to model the z statistics for each network was chosen based on minimizing Bayesian Information Criterion (BIC) [53]. Parameters such as weight, mean and covariance corresponding to each underlying distribution were calculated. These parameters were used to compute the weighted mean and standard deviation for the combined distribution with the assumption that each underlying Gaussian distribution was independent. Individual thresholds were calculated for each network with the weighted mean within one standard deviation of the combined distribution.

The calculated maps from individual volunteers were compared against datasets collected with different 3 T scanners. The functional data were collected with 1243 subjects (433 females, mean age = 28 ± 17 and 810 males, mean age = 26 ± 15) while structural data were collected with 1665 subjects (female, mean age = 38 ± 20 and 972 males, mean age = 30 ± 18).
4.3 Results

Temporal SNR, T2* and functional connectivity for the masked cortical regions. These regions are part of the auditory, default mode, executive control, and sensorimotor networks. Functional connectivities were calculated and eleven resting state networks were identified. Each of these networks was compared to the representative networks from 3 T scanners.

To perform the temporal SNR analysis motion correction was performed on the functional data. The tSNR for each volunteer was calculated before applying the high pass filter. The results from each scan for each of the volunteers are presented in Table 4.1 which suggests Volunteer 2 scan number 3 suffered the most from motion related corruption.

<table>
<thead>
<tr>
<th>Scan Number</th>
<th>Absolute Displacement (mm)</th>
<th>Relative Displacement (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.29</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>0.32</td>
<td>0.04</td>
</tr>
<tr>
<td>4</td>
<td>0.37</td>
<td>0.03</td>
</tr>
<tr>
<td>5</td>
<td>0.26</td>
<td>0.03</td>
</tr>
<tr>
<td>6</td>
<td>0.18</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 4.1. Shows the mean displacements both absolute and relative calculated with MCFLIRT for (a) Volunteer 1 for all 6 scans. (b) Volunteer 2 for all 4 scans.
Figure 4.1. Sagittal, coronal and axial views of temporal SNR maps for different cortical regions of interest for Volunteer 1 overlaid on the T1 scan.

The cumulative mean and standard deviation calculated with 6 scans for this volunteer is reported at the end of each column.

Following the tSNR calculations T2* maps for the same masked regions were calculated for both the volunteers. Figure 4.2 shows an example T2* map corresponding to the masked regions overlaid on top of a T1 scan of Volunteer 1. The T2* measured estimates for each masked region overlapped with the gray matter were: 85 ± 7 ms in auditory, 86 ± 7 ms in default mode, 89 ± 6 in left and right executive control, and 86 ± 6 ms in sensorimotor network.

Following this functional connectivities were calculated for each volunteer separately. These functionally connected regions join to form a specific resting state network. Figures 4.3 to 4.5 show different brain networks where there exists functional connectivity. The blue regions in these maps were negatively correlated with the activity in the red regions. These figures show these networks with normalized thresholded z statistics map averaged over the multiple repeats performed overlaid on top of the T1 scan corresponding to individual volunteers.
Figure 4.2. Sagittal, coronal and axial views of T2* maps for different cortical regions of interest for Volunteer 1 overlaid on the T1 scan. The cumulative mean and standard deviation T2* measurement acquired with two healthy volunteers are shown in the bottom of each column.

Figure 4.3. Show higher order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.
The first column shows the expected functional connectivity from the database, the second column shows the average functional connectivity calculated with 6 scans from Volunteer 1 and the third column shows the average functional connectivity calculated with 4 scans from Volunteer 2. Here DMN refers to default mode network and ECN refers to executive control network.

![Image](image_url)  

**Figure 4.4.** Show lower order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the average functional connectivity calculated with 6 scans from Volunteer 1 and the third column shows the average functional connectivity calculated with 4 scans from Volunteer 2.
Figure 4.5. Shows sensory resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the average functional connectivity calculated with 6 scans from Volunteer 1 and the third column shows the average functional connectivity calculated with 4 scans from Volunteer 2.

Following the identification of the eleven resting state networks, repeatability and reliability studies were conducted to ensure that these networks were identified consistently across scans and volunteers. To do so, the z statistics calculated for the defined 832 nodes for each network across scans were compared with the expected z statistics for that node from the 3 T scans as shown in Figure 4.6.
Figure 4.6. The markers represent all the resting-state networks. Each network from individual scans was compared to the database to draw conclusions which suggest that for p-value < 0.05, networks are significantly different from representative networks. In this figure (a) refers to Volunteer 1 and (b) refer to Volunteer 2.

Figure 4.6 provides a general understanding of how all the networks performed across scans and volunteers. However, this does not focus on each network individually. To do so, a similarity score was calculated for individual volunteers across scans as shown in Table 4.2. These scores were calculated based on a t-test, with the null hypothesis that a z statistic of 0 was identified for each node across scans. Based on this, a ratio was calculated with the number of times the null hypothesis was rejected and the total number of nodes for specific network where the z statistic was not equal to 0.

Following the similarity assessment, a relationship was established between the quantities calculated: T2*, temporal SNR and similarity score associated with functional connectivity as shown in Table 4.3.
Table 4.2. Similarity for individual volunteers was calculated across scans with a student’s t-test for each resting-state network to assess the reliability and repeatability of the scans.

<table>
<thead>
<tr>
<th>Networks</th>
<th>Volunteer 1 Similarity Score (no of scans = 6)</th>
<th>Volunteer 2 Similarity Score (no of scans = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td>0.45</td>
<td>0.42</td>
</tr>
<tr>
<td>Default Mode</td>
<td>0.46</td>
<td>0.51</td>
</tr>
<tr>
<td>Executive Control Left</td>
<td>0.47</td>
<td>0.41</td>
</tr>
<tr>
<td>Executive Control Right</td>
<td>0.56</td>
<td>0.55</td>
</tr>
<tr>
<td>Hippocampal</td>
<td>0.57</td>
<td>0.75</td>
</tr>
<tr>
<td>Language</td>
<td>0.64</td>
<td>0.70</td>
</tr>
<tr>
<td>Salience</td>
<td>0.65</td>
<td>0.46</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>0.61</td>
<td>0.72</td>
</tr>
<tr>
<td>Visual Lateral</td>
<td>0.58</td>
<td>0.34</td>
</tr>
<tr>
<td>Visual Medial</td>
<td>0.34</td>
<td>0.37</td>
</tr>
<tr>
<td>Visual Occipital</td>
<td>0.44</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Table 4.3. Relationship between temporal SNR, T2* and similarity score related to functional connectivity for Volunteer 1.

<table>
<thead>
<tr>
<th>Regions</th>
<th>tSNR [A.U.] (Before Filtering)</th>
<th>tSNR [A.U.] (After Filtering)</th>
<th>T2* [ms]</th>
<th>Similarity Score across Scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td>54.47 ± 5.65</td>
<td>61.27 ± 6.56</td>
<td>85.29 ± 6.61</td>
<td>0.45</td>
</tr>
<tr>
<td>DMN</td>
<td>42.61 ± 4.54</td>
<td>47.12 ± 5.52</td>
<td>86.27 ± 6.93</td>
<td>0.46</td>
</tr>
<tr>
<td>ECN (Combined)</td>
<td>44.73 ± 4.49</td>
<td>50.08 ± 5.19</td>
<td>89.79 ± 5.92</td>
<td>0.51</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>47.68 ± 6.52</td>
<td>57.62 ± 7.01</td>
<td>85.97 ± 6.27</td>
<td>0.61</td>
</tr>
</tbody>
</table>

4.4 Discussion

The benefits of head-only scanners as used in this study equipped with gradients with high slew rates can be seen in Figure 4.7 since it leads to increased read and phase gradient bandwidth. The increased phase gradient bandwidth produces reduced distortions. The bounds in this figure are determined with (i.e. entire echo train) or without ramp sampling (only flat-top). More about this was discussed in Chapter 3 Appendix A.
Figure 4.7. Shows higher slew rates (400 T/m/s) can be used to reach high read and phase bandwidths compared to the low slew rate of (45 T/m/s) which will reduce geometric distortion primarily in the phase encoding direction for both with and without ramp sampling.

For this experiment, a scanner equipped with high slew rate gradients was used. The direct relationship between slew rate, and echo spacing is given by Eq’n (3.A.5) in Chapter 3 Appendix A. As the slew rate increases, echo space decreases which suggests reduced pixel shift. The read bandwidth for this study was set to 160 kHz, which suggests a phase bandwidth of roughly 40 Hz/pixel given the gradients are operating at a high slew rate. However, for instance, we consider this scanner operating a reduced slew rate, for a read bandwidth of 160 kHz the corresponding phase bandwidth would be roughly 20 Hz/pixel which is even lower than the typical phase bandwidth of 30 Hz/pixel used in EPI. At such bandwidths, the amount of displacement due to field inhomogeneity is increased substantially. Therefore, a high slew rate head-only scanner as used in this study might offer benefits that haven’t been explored before with similar mid-field fMRI studies performed with whole-body scanners.

To quantify the T2* contrast underlying the fMRI study, T2* contrast maps were calculated using the meGRE sequence for established resting state networks. According to figure 4.2, the T2* values vary approximately between 80 to 95 ms across established
resting state networks. The T2* calculated as a part of this paper is within range with the relaxation parameter calculated in [2]. Another quantity of interest in fMRI studies as mentioned previously is the temporal SNR. The temporal SNR before filtering across these regions is approximately between 35 to 55. After performing high pass filtering with a cutoff frequency of 0.01 Hz, the tSNR increased to vary between 45 and 65.

Figures 4.3, 4.4 and 4.5 present the resting state networks identified across scans for both volunteers with average thresholded z-statistic maps. As described before, the blue regions within the network are anticorrelated with the red regions within the networks. The spatial pattern for the default mode network in Fig 4.3 row (1) suggests a positive correlation of activity between the posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC) which matches with the expected functional connectivity pattern seen with the 3 T data for volunteer 1. However, the reduced correlation was detected between these two regions for volunteer 2. The left and right inferior lateral parietal lobes (IPL) also demonstrated a negative correlation with the PCC and MPFC as expected for both the volunteers. Fig 4.3 rows (2) and (3) show the spatial pattern of the averaged thresholded z statistics for the left and right executive control network. A positive correlation of activity was identified between both the left inferior frontal gyrus and left IPL for both volunteers which is consistent with the 3 T data. Similar behaviour was seen between these two regions in the right hemisphere as well for Volunteer 1. However, the functional connectivity between all the regions in the right hemisphere for volunteer 2 was different from the expected since no anticorrelation was detected. Figure 4.5 presents all the sensory networks. Most networks demonstrated spatial patterns with functional connectivities similar to what is expected. This is especially true for sensorimotor in row (2) and visual medial in row (4). Figure 4.4 presents the lower-order networks including the hippocampal network in row (1) exhibiting a positive correlation of activity for most regions within this network for both volunteers. The language network in row (2) for both volunteers shows reduced spatial similarity and functional connections in the left and right lateral parietal lobes show positive correlation with the other regions in the network. However, the salience network in row (3) for volunteer 2 is different from the expected functional connectivity at 3 T. Figure 8 accesses the similarity between the z statistic for the 832 predefined nodes across scans by comparing it with the database. This figure suggests that for all scans for both
volunteers, there lies a larger cluster of markers on the left of the dashed line compared to the right implying fewer networks are significantly different from the representative networks.

The repeatability of the detected resting-state network was calculated based on comparing the z statistics calculated for the defined 832 nodes for each network across scans to the expected z statistics for that node from the 3 T scans. According to this, there were a greater number of networks observed on the left side of the dotted line compared to the right for all the scans for both volunteers suggesting the detection of a higher number of networks. To assess the reliability of each network individually similarity index was calculated as shown in Table 4.2. To do so, a sample t-test was performed, which provides the number of times within a confidence interval the null hypothesis of no functional connectivity for nodes within a specific network was rejected. With the quantity a ratio was calculated with the total number of nodes within that network. If similar z statistics were seen for specific nodes across scans it led to a higher similarity score for each volunteer. According to Table 4.2, executive control left, hippocampal, language and sensorimotor were very reliable across scans for both volunteers with scores > 0.5. These scores are particularly important as they don’t include any averaging effect that might have affected the spatial pattern seen in Figures 4.3, 4.4 and 4.5, and lead to a true conclusion regarding the ability to detect specific resting-state networks consistently across scans for respective volunteers. According to Table 4.2, the sensorimotor network was consistently present in most scans for both volunteers, which suggests a potential application since this is a large-scale network that includes the somatosensory and motor regions. Recent literature has shown motor networks found in resting-state fMRI studies could be used as target locations for repetitive transcranial magnetic stimulation (rTMS) in stroke patients with severe hemiplegia since the motor task-based fMRI studies performed with affected limbs will not provide accurate target locations [54]. There have also been rTMS studies for Major Depressive Disorder (MDD) that focus on target regions like the dorsolateral prefrontal cortex (DLPFC) which has been resting-state functional connectivity maps [55].

It was hypothesized that the quantities calculated in this paper, including the temporal SNR and T2\* contrast, will have an impact on the functional connectivity of resting state networks for individual volunteers. If the functional connectivity was detected
with a higher consistency, that leads to an increased similarity score. The relationship between these quantities was discussed in Table 3 for specific masked networks. The T2* contrast was within the range described previously. The temporal SNR for certain networks was higher compared to others both before and after filtering. It was expected that networks with higher tSNR will exhibit higher similarity scores for both volunteers, which was seen in the executive control and sensorimotor networks. However, this was not the case for the auditory network, which suggests that functional connectivity is not only affected by these quantities as expected but that there are other parameters at play. Further investigation to fully characterize this relationship is essential.

Another important factor to consider here is the 30-minute scan time that was used for this study. Further investigation needs to be performed to effectively reduce the scan time to typical fMRI measurement times without sacrificing any resting state network essential for diagnostic applications.

In this chapter we implemented the optimized sequence from Chapter 3 for resting state fMRI which suggested that the optimal echo time is not equal to T2* to decrease dead time in the sequence. However, another effective way to fill the dead time is to use multi-echo GRE EPI. The other reason behind using this sequence is that T2* varies considerably over the brain, such that the optimal TE for best BOLD contrast is region dependent. For instance, at 3 T motor and visual cortices have T2* around 40-60 ms whereas orbitofrontal and inferior temporal cortices have T2* of about 20 ms due to closeness to the tissue-air boundaries of sinuses. At 0.5 T motor and visual cortices have T2* around 79 ms and 88 ms respectively. Thus, selecting a single TE for fMRI gives less than optimal BOLD contrast for most of the brain. Therefore, acquiring images at multiple TEs and combing them effectively is one way to mitigate signal losses in areas with short T2* while enhancing the contrast throughout the brain.

4.5 Conclusions

Resting-state BOLD fMRI is feasible at mid-field strength scanners operating at 0.5 T with the EPI acquisition technique. At 4 mm isotropic resolution, the temporal SNR produced was in the range of 35 to 55, and T2* contrast was elongated in gray matter in the range of 80 to 95 ms. The functional connectivity detected resembles the 3 T scanner
for all eleven resting-state networks considered in this paper. This suggests promising applications of these functional maps in the case of stroke patients for rTMS, especially in a point-of-care setting.

4.6 References


[29] J. P. Reilly, “Maximum pulsed electromagnetic field limits based on peripheral nerve stimulation: Application to IEEE/ANSI C95.1 electromagnetic field


Chapter 5

5 Multi-echo Gradient Echo Echoplanar Imaging based Resting-State Functional MRI at a 0.5 T high-performance scanner.³

5.1 Introduction

Mid-field (< 1 T) scanners make widespread diagnostic use possible for various applications. These compact scanners can be used in locations close to vulnerable patient populations and offer potential use in emergency room applications, intraoperative monitoring [1]–[5] and in countries with limited access to MR [6]. The availability of imaging techniques such as functional MRI (fMRI) on such a scanner would provide neurological information that can be vital in traumatic brain injury [7], acute ischemic stroke [8], epilepsy [9], and dementia [10]. However, blood-oxygen-level-dependent (BOLD) fMRI is generally not attempted at field strength < 1.5 T due to reduced magnetic susceptibility contrast and signal-to-noise ratio (SNR) [11]–[13]. The SNR and sensitivity gained by imaging at higher field strength can be used to perform studies at high spatial resolutions which is particularly useful in certain applications such as laminar fMRI and imaging of neural circuits [14], [15].

This chapter aims to evaluate the performance of resting state fMRI using multi-echo gradient recalled echo (GRE) echoplanar imaging (EPI) at clinically relevant resolutions. Multi-echo EPI (ME) imaging allows for increased fMRI sensitivity and reduced signal loss in areas of the brain with susceptibility-related signal dropout and/or short T2* [16].

According to Chapter 3, the T2* for grey matter at 0.5 T is approximately 86 ± 10 ms. But the prolonged T2* causes dead time in the sequence leading to decreased scan efficiency, this dead time can be effectively filled with multi-echo sequences. The other reason behind using this sequence is that T2* varies considerably over the brain, such that the optimal TE for best BOLD contrast is region-dependent. For instance, at 3 T motor and

³ A journal manuscript is in preparation.
visual cortices have T2* around 40-60 ms [17] whereas orbitofrontal and inferior temporal cortices have T2* of about 20 ms due to closeness to the tissue-air boundaries of sinuses. At 0.5 T motor and visual cortices have T2* around 79 ms and 88 ms respectively. Thus, selecting a single TE for fMRI as is the case with single echo EPI gives less than optimal BOLD contrast for most of the brain. Therefore, acquiring images at multiple TEs and combing them effectively is one way to mitigate signal losses in areas with short T2* while enhancing the contrast throughout the brain [18].

5.2 Background on Multi-echo EPI

Standard fMRI uses 2D EPI to acquire slice images at a single TE after excitation, one slice at a time. ME-fMRI uses a different approach, acquiring a single slice image at the earliest TE possible after a normal excitation pulse. Following that another image of the same slice is then acquired immediately afterwards, at a longer TE, and so forth up to the desired number of images and TEs without another excitation again. This happens for each slice of the brain volume. With this approach, there is no cost for acquiring the early TE since standard EPI sequences are idle during the early period after excitation, which in our case is long. This will help with signals from regions of the brain with shorter T2* than TE which in our case is 86 ± 10 ms.

Another important benefit is that the T2* signal decay can be modelled for each voxel [19]. This information can be used to relate signals to their physical processes and mitigate artifacts of many kinds. Depending on tissue properties and variation of the local magnetic field different voxels have different T2* decay [17].

Multi-echo images from early TEs have high signal intensity but a low level of contrast between grey, white matter and CSF. Intermediate TEs have lower average signal intensity but more contrast. Late TEs have even lower signal intensity, in general, but relatively higher signal intensity in voxels with the slowest decays i.e. longest T2*s.

5.2.1 Estimates of T2* and S0

From ME-fMRI, each voxel’s T2* can be estimated from the data based on how signals scale across echoes. The first approach involves fitting each voxel’s signal values across TEs to a monoexponential decay [17], [19] as shown in Eq’n (5.1).
\[ S(TE) = S_0 e^{-\frac{TE}{T2^*}} \]  

This fit approach provides 2 parameters: T2* and S0. The T2* map rendered from this fit provides information regarding the tissue oxygenation state. The S0 map shows coil sensitivity, which is based on where the head is in the coil and the geometry of the coil elements. S0 and T2* can be estimated from a single volume of fMRI data, but that tends to be noisy. Therefore, to reduce the noise and produce accurate estimates, T2* and S0 values can be computed from an average of signals over time. The second approach involves a log-linear fit, which can be potentially beneficial since it is computationally efficient but might require some regularization to handle small signal amplitude at long TEs.

### 5.2.2 Combination Techniques

Previous literature shows several ways of combining the echos which is an important factor in ME imaging [20]. Echos can be combined using simple summation where the signal from each echo (i.e., equal weights) is summed together [21]. In the TE-weighted combination, the signal from each echo is weighted based on the echo time, suggesting that echos collected closer to the optimum TE value will have a higher weighting factor compared to other echos [22]. In the T2*-weighted method, the voxel-wise signal from each echo is weighted by their T2* value, which is estimated using a log-linear fit [21],[23], [24]. The echos can also be weighted by the calculated voxel-wise contrast to noise ratio (CNR) [23] and similarly temporal signal-to-noise ratios (tSNR) [22].

### 5.3 Methods

All imaging protocols were performed on a head-only 0.5 T MR scanner equipped with a high-performance gradient system and 16 channel head coil (Synaptive Medical, Toronto) [25]. Imaging was performed on two healthy volunteers (male, ages 36 and 40), with informed consent in compliance with health and safety protocols.

#### 5.3.1 Structural Scans

Structural images were acquired using a 1.1 mm isotropic resolution T1-weighted MPRAGE sequence with field of view (FOV) = 236 mm x 236 mm x 180 mm, FA = 26°,
TE = 5 ms, TR = 11.2 ms, scan duration ~ 6 mins and no acceleration was implemented. Preprocessing was performed using GraphICA [26], an FSL [27] based platform which involved the following steps: bias-field correction (RF/B1-inhomogeneity correction), brain extraction, tissue type segmentation (CSF, GM, WM) and sub-cortical structure segmentation.

5.3.2 Functional Scans

Functional scans were acquired using a 4 mm isotropic resolution multi-echo EPI sequence. The scan parameters are as follows: Temporal positions = 138, FOV = 240 mm x 240 mm x 128 mm, matrix size = 60 x 60 x 32, acquisition bandwidth = 160 kHz, echo train length = 30, FA = 90 degrees, TR ~ 4.38 s, TEs = [11.7, 28.1, 44.5, 60.9, 77.3, 93.7, 110.1, 126.5] ms, scan duration ~ 10 mins and no acceleration were implemented. For these scans for each TE, the corresponding image had a matrix size of 60 x 60 x 32 x 138. To achieve an optimally combined image with the same matrix size, a T2*-weighted combination [22] was used for this study which follows Eq’ns (5.2) and (5.3).

\[ w_n^{T2*} = \frac{TE_ne^{-TE_n/T2^*}}{\sum_{i=1}^{N} T_E_i \times e^{-TE_i/T2^*}} \]  

(5.2)

\[ S(x, t) = \sum_{n=1}^{N} S(x, t, TE_n) \times w_n^{T2*} \]  

(5.3)

Following this, the optimal combined functional images were passed onto the standard preprocessing steps in GraphICA which involved skull stripping, motion correction, slice timing correction, spatial smoothing, co-registration, ICA-based automatic removal of motion artifacts (ICA-Aroma) [28], high-pass filtering and nuisance regression (WM and CSF).

5.3.3 Functional Connectivity and Identifying Resting State Networks

GraphICA calculates functional connectivity (fc) based on independent component analysis (ICA) with dual regression between well-established resting state networks [29], [30].
ICA combined with dual regression was performed by identifying a set of independent components (IC) maps for each network [29]. These maps were used as templates for each network to identify the corresponding spatial fc maps (z statistics) for individual subjects at a voxel level. Further parcellations were implemented to the segmented anatomical images using a gradient-weighted Markov Random Field model procedure [31]. This parcellation model contains three competing terms that determine the optimal trade-off properties for the final segmentation: global similarity term to group brain locations with similar image intensities, local gradient term to detect abrupt fc changes between neighbouring brain locations, and spatial connectedness term to ensure spatial connectivity within parcels. After applying this model 832 brain parcels were produced. The average z statistics for each parcel were calculated from all voxels within a parcel producing the same number of nodes.

Thresholding of the functional connectivity maps was performed using the Gaussian mixture model approach [30], where the z statistics corresponding to each node for individual networks were modelled as a mixture of Gaussian distributions. The optimal number of Gaussian distributions used to model the z statistics for each network was chosen based on minimizing Bayesian Information Criterion (BIC) [32]. Parameters such as weight, mean and covariance corresponding to each underlying distribution were calculated. These parameters were used to compute the weighted mean and standard deviation for the combined distribution with the assumption that each underlying Gaussian distribution was independent. Individual thresholds were calculated for each network with the weighted mean within one standard deviation of the combined distribution.

The calculated maps from individual volunteers were compared against datasets collected with 3 T scanners from different vendors at several sites (GraphICA database, [26]). The functional data were collected with 1243 subjects (433 females, mean age = 28 ± 17 and 810 males, mean age = 26 ± 15) while structural data were collected with 1665 subjects (female, mean age = 38 ± 20 and 972 males, mean age = 30 ± 18).

5.4 Results

This chapter focused on temporal SNR and functional connectivity for the same cortical regions as used for the single echo EPI scans in Chapter 4. These regions are part
of the auditory, default mode, executive control, and sensorimotor networks. Functional
connectivities were calculated and eleven resting state networks were identified. Each of
these networks were compared to the representative networks from 3 T scanners. Despite
the different scan times preliminary comparisons of identified networks were performed
between the single-echo and multi-echo EPI protocol.

To perform the temporal SNR analysis motion correction was performed on the
optimally combined echos. The tSNR for each volunteer was calculated both before and
after applying the high pass filter. The result shows Volunteer 2 suffered the most from
motion and the absolute mean displacement was approximately 0.5 mm.

<table>
<thead>
<tr>
<th>Volunteer Number</th>
<th>Absolute Mean Displacement (mm)</th>
<th>Relative Mean Displacement (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>0.45</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 5.1. Shows the mean displacements both absolute and relative calculated with
MCFLIRT for Volunteers 1 and 2 for a single scan.

The temporal SNR maps are calculated without filtering from Volunteer 1 with the
mean values calculated with both the volunteers reported in Figure 5.1. In this figure, each
column was calculated with the regions in the auditory, default mode, executive control,
and sensorimotor networks.
Figure 5.1. Sagittal, coronal and axial views of temporal SNR maps for different cortical regions of interest for Volunteer 1 with mean values calculated with both volunteers reported at the end of each column.

Following this functional connectivities were calculated for each volunteer separately. These functionally connected regions join to form a specific resting state network. Figures 5.2, 5.3 and 5.4 show functionally connected nodes within default mode, executive control left and right networks for Volunteer 1. The green colored regions are the regions that were found in the network (functionally preserved) and were not significantly different when compared with the 3 T data. The orange colored regions were regions that were missing in this network (functionally not preserved) and were not significantly different when compared with the 3 T data. The blue colored regions were the regions that were found in this network (functionally preserved) and were significantly different when compared with the 3 T data. The red colored regions are the regions that were not found in the network (functionally not preserved) and were significantly different when compared with the 3 T data. All the comparisons were corrected for multiple tests using the Bonferroni procedure and within 95% confidence level.
Figure 5.2. Map of functionally connected nodes within the default mode network for Volunteer 1.

Figure 5.3. Map of functionally connected nodes within the executive control left network for Volunteer 1.
Figure 5.4. Map of functionally connected nodes within the executive control right network for Volunteer 1.

Figures 5.5 to 5.7 show different brain networks where there exists functional connectivity. The blue regions in these maps were negatively correlated with the activity in the red regions. These figures show these networks with normalized average thresholded z statistics map overlaid on top of the T1 scan corresponding to individual volunteers. The average z statistics demonstrating the group behaviour with both volunteers for different networks were also shown in these figures overlaid on top of the T1 scan of Volunteer 1. Along with that, the results here are compared with the networks identified with the 3 T data.
Figure 5.5. Shows higher order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the average functional connectivity from volunteers 1 and 2, the third column shows the functional connectivity from Volunteer 1 and the last column shows the functional connectivity from Volunteer 2. Here DMN refers to default mode network and ECN refers to executive control network.
Figure 5.6. Shows lower order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the average functional connectivity from volunteers 1 and 2, the third column shows the functional connectivity from Volunteer 1 and the last column shows the functional connectivity from Volunteer 2.
Figure 5.7. Shows sensory resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the average functional connectivity from volunteers 1 and 2, the third column shows the functional connectivity from Volunteer 1 and the last column shows the functional connectivity from Volunteer 2.

In the next section, a preliminary comparison of temporal SNR, functional connectivity and identification of resting state networks was performed between the single-echo and multi-echo EPI techniques despite of the overall scan time difference. This comparison was performed with results associated with Volunteer 1. The temporal SNR of both the single and multi-echo scans for different regions along with the whole brain is
given below in Table 5.2. Figures 5.8 to 5.10 show different brain networks with normalized thresholded $z$ statistics map overlaid on top of the T1 scans for both single and multi-echo scans.

<table>
<thead>
<tr>
<th>Regions</th>
<th>Volunteer 1 Single Echo</th>
<th>Volunteer 1 Multi Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain</td>
<td>46.4 ± 14.3</td>
<td>64.3 ± 19.9</td>
</tr>
<tr>
<td>Auditory</td>
<td>55.0 ± 13.5</td>
<td>76.7 ± 20.2</td>
</tr>
<tr>
<td>DMN</td>
<td>45.8 ± 11.3</td>
<td>62.7 ± 16.1</td>
</tr>
<tr>
<td>ECN</td>
<td>48.4 ± 11.3</td>
<td>58.7 ± 16.7</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>51.5 ± 16.4</td>
<td>60.9 ± 21.8</td>
</tr>
</tbody>
</table>

Table 5.2. Shows the tSNR comparison for Volunteer 1 between the single- and multi-echo scans for different regions.
Figure 5.8. Shows the comparison between single- and multi-echo for higher order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the functional connectivity from Volunteer 1 associated with the single-echo scans performed in Chapter 4, the third column shows the functional connectivity from Volunteer 1 associated with the multi-echo scans performed in this chapter.
Figure 5.9. Shows the comparison between single- and multi-echo for lower order resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the functional connectivity from Volunteer 1 associated with the single-echo scans performed in Chapter 4, the third column shows the functional connectivity from Volunteer 1 associated with the multi-echo scans performed in this chapter.
Figure 5.10. Shows the comparison between single- and multi-echo for sensory resting state networks with normalized thresholded z statistics maps overlaid onto T1 scans.

The first column shows the expected functional connectivity from the database, the second column shows the functional connectivity from Volunteer 1 associated with the single-echo scans performed in Chapter 4, the third column shows the functional connectivity from Volunteer 1 associated with the multi-echo scans performed in this chapter.

The scan time associated with the single echo protocol as described in Chapter 4 was approximately 30 mins. However, the scan time here was approximately 10 mins. Therefore, the comparisons performed here do not truly encapsulate the underlying gains achieved with the multi-echo technique. To roughly estimate this gain, consider the following relationship given in Eq’n (5.4) [33].
Assuming the scan time was kept constant for these experiments, single-echo would have roughly 267 time points in the 10 min duration, which is 51% more time frames compared to the multi-echo scans. With 1.8 times tSNR improvement, the quantity defined in Eq’n (5.4) suggests gains with multi-echo compared to single-echo would be approximately 1.3 in gray matter.

5.5 Discussion

Multi-echo acquisition requires repetitive echo train measurements, often some measurements are performed with undesirable echo times which go past the T2* decay window. This most likely won’t be the situation at 0.5 T since the T2* is long as shown in previous chapters. The use of gradients with a high slew rate, however, can further reduce the duration of the EPI echo spacing. Advancements in MRI scanner hardware have enabled high-performance gradients, which can directly impact the implementation and performance of the multi-echo acquisition. The head-only scanner used for this study is equipped with gradients that offer a peak gradient strength of ~100 mT/m and slew rate of ~400 T/m/s on all gradient axes simultaneously without peripheral nerve stimulation limitations [1]. In comparison, conventional 3 T whole-body MR scanners typically offer up to 200 T/m/s gradient slew rate and 40-80 mT/m gradient amplitude. These gradient systems on the 0.5 T scanner are particularly beneficial for EPI-based acquisition. The higher gradient slew rate effectively minimizes the echo spacing [34], which offers the possibility of acquiring a greater number of echoes before the signal disappears due to the longer T2* of ~85 ms. Specifically, with the intended spatial-temporal resolution, the echo spacing on this scanner is 16.42 ms, which has been reduced by 47% from the echo spacing of 31.2 ms on a whole-body scanner with a slew rate of 200 T/m/s slew rate. The last echo time is roughly 127 ms, which can yield a late echo with substantial signal and T2* information. In the future, this can be further optimized. On a whole-body, 3 T scanner, where the T2* is roughly 30 ms, the last echo is generally acquired at 81.5 ms. At this stage, the echo signal is too weak to be useful. As mentioned in Chapter 4, the reduced echo spacing also offers additional benefits of substantially improved magnetic
susceptibility-induced geometric distortions in phase encoding direction, which is a problem for EPI sequences.

As seen from Table 5.1, the motion parameters for volunteer 2 were high compared to volunteer 1, suggesting increased corruption of the functional data due to motion. Future studies must be conducted with a greater number of volunteers. Experiments with high motion corruption should be eliminated. Following motion correction, temporal SNR calculations are performed before implementing filtering techniques.

According to Figure 5.1, the weighted temporal SNR was the highest for regions of interest within the auditory resting-state network. Individually calculated tSNRs suggest the same result. Temporal SNRs calculated for all the regions of interest were comparatively lower for volunteer 2. Overall, for all the regions of interest within different resting-state networks, the temporal SNRs were greater than 50.

Figures 5.2 to 5.4 are examples of functionally preserved and not preserved regions compared to the database within resting-state networks displayed as nodes and on top of the corresponding T1 scan for a single volunteer. According to these figures, green- and orange-colored regions are of interest. The green regions are found within the network and are not significantly different when compared to the database, whereas the orange regions are those missing from the identified network, but statistically, it is not significantly different from what is expected from the database.

Figure 5.5 suggests spatial overlap between regions identified within higher-order networks and the data collected from multiple scans at 3 T. Comparison with suggested regions, ideally part of the network especially in the default mode network, are missing in individual volunteers group analysis suggests greater similarities, highlighting the importance of future studies with more volunteers to remove any biases in connectivity analysis. Similar observations were made for most of the sensory networks as shown in Figure 5.7. Regions within the visual occipital network were not identified significantly in Volunteer 1. For the lower-order networks, hippocampal performed well in terms of functional connectivity as can be seen in Figure 5.6.

Table 5.2 compares the tSNR for the different regions within respective resting-state networks from a single echo scan to a multi-echo scan performed for volunteer 1.
According to this, tSNRs corresponding to the multi-echo scan were higher compared to the single-echo scan by a factor of ~1.5 for most regions.

Figures 5.8 to 5.10 allow comparison between single- and multi-echo scans in a single volunteer. In terms of the higher-order networks in figure 5.8, functional connectivity in the dorsomedial prefrontal cortex within the default mode network is missing in multi-echo scans compared to single-echo scans. However, executive control left and right networks performed well in the multi-echo scans compared to single-echo. For the sensory networks in figure 5.9, the regions within visual occipital network were not identified well in the multi-echo scans. Figure 5.10 shows the lower order network and according to this figure, regions within hippocampal were well identified compared to language and salience networks in multi-echo.

According to Appendix F, most resting state networks could be reliably detected for single-echo scans when the scan time was approximately 15 mins. Future studies must be conducted with increased scan time for multi-echo protocol as a starting point and test-retest reliability studies must be performed with this data to assure reliable detection of networks.

TRs associated with the multi-echo scans were quite long. Therefore, as accelerating acquisitions with simultaneous multi slice (SMS) or multiband (MB) techniques must be considered, in which several slices are excited with multiple radiofrequency bands [35]. Both acceleration techniques can be combined. The main contributions of SMS/MB technique are reduced acquisition time and increased temporal and/or spatial resolution [36], [37]. According to [38] BOLD contrast-to-noise ratio increases with the square root of the number of slices. SMS/MB methods can provide better time resolutions and possibly higher CNR values, depending on the MB factor. For instance, [39] proved that using a MB factor higher than 2 produces significant improvement in BOLD sensitivity using a 3 T scanner as compared to unaccelerated sequences for motor and visual task related experiments.

5.6 Conclusions

This chapter establishes the feasibility of resting-state fMRI with multi-echo EPI acquisitions. Comparisons between single-echo and multi-echo techniques suggest
improvements in terms tSNR, sensitivity and accuracy of certain resting state networks, despite the temporal resolution loss with multi-echo. Current work focusing on SNR calculation using the pseudo-replica method for the ME acquisition suggests similar improvements as well. The EPI-based sequence as mentioned before utilizes the high-performance gradients effectively to provide improved image quality by reducing echo spacing, yielding reduced geometric distortion and signal loss in regions of the brain with rapid spatial variation of susceptibility. This has the potential to improve image registration between EPI time series with anatomical images and enhance the resting-state functional network detected for seed-based mapping (popular alternative to ICA-based studies) when the seed region suffers from geometric distortions. From a technical point of view, the sample size of the study must be increased, choice of echo number needs to be evaluated, denoising techniques specific to multi-echo sequences can be included in the preprocessing pipeline. Along with that the combination method used can be altered, GraphICA needs to be further optimized to support the analysis for multi-echo acquisitions. Clinically the enhanced sensitivity of multi-echo fMRI studies can be used for studies related to aging and neurodegenerative diseases, such as dementia as the brain suffers from signal dropout in regions with iron deposition and increased partial volume effect due to brain atrophy [33], [40]. To add to that, multi-echo fMRI provides opportunities for improved functional connectivity detection in regions, such as the hippocampus and anterior cingulate cortex, which would benefit studies related to memory or cognition.

5.7 References


Chapter 6

6 Summary and future work

6.1 Summary

The purpose of this thesis is to implement BOLD based functional MRI techniques available on a 0.5 T point-of-care scanner equipped with a high-performance gradient coil. As mentioned throughout this thesis this is typically not attempted since SNR and contrast scales with field strength.

To start with, simulation studies were performed with higher field data where the goal was to access the performance of the analysis platform that will be used later for potentially noisy functional scans. With the analysis platform in place, the focus was to look at sequences that can be implemented for fMRI at this field strength.

Throughout this research, different techniques were considered such as steady-state free precession sequence and GRE-EPI sequence. Ultimately, an EPI based sequence was chosen and optimized to suit the 0.5 T scanner. To gauge the feasibility, first, a finger-tapping experiment was performed to access the activation in the motor cortex. Following this task experiment, the sequence was optimized. For this optimization, T2* contrast mapping and EPI scans were performed to calculate the temporal-SNR and pseudo-SNR. Optimizing these quantities is essential to maximize the statistical return on scan time investment.

With the sequence in place, resting state experiments were conducted with multiple volunteers for repeated scans. Quantities such as temporal-SNR, pseudo-SNR and functional connectivity within well-established resting-state networks were calculated. A similarity index was calculated over multiple scans to establish if the networks were reliably identified. To improve the application of EPI sequences on this scanner for multiple applications, the T2* weighted contrast available at 0.5 T must be used effectively.

To do so, multi-echo sequences were considered. This will use the increased T2* by using the dead time effectively with a combination of early and late echos. To add to this, with these sequences, the gradients could potentially also be used more efficiently. Gradients with a high slew rate will produce reduced geometric distortion in the phase encoding direction, which is quite common in EPI sequence.
6.2 Future Studies

(1) Chapter 3: For the optimization, the T2*, temporal and pseudo-SNR calculations were performed in the visual cortex. These could be supplemented with a visual task-based experiment to form a clear relationship.

(2) Chapter 4: Inherently short T1 should be further used to our advantage. Implementing simultaneous multi-slice or Hadamard encoding will reduce the TR.

(3) Chapter 5: (a) Combining multi-echo techniques with SMS and/or multi-band approach to get further enhancement. (b) Multi-echo denoising techniques must be investigated in detail. (c) The optimal number of echos required for these scans must be studied in detail.

(4) Appendix C: The sample size of volunteers used for T2* contrast mapping for subcortical regions at 0.5 T must be increased.

(5) Appendix F: The effect of scan length on the reliability of resting-state functional connectivity estimates should be studied in detail.

In general, these measurements must be repeated with multiple volunteers to reliably draw any further conclusions.
Appendices

A. Optimizing GRE EPI Parameters

A.1 Introduction

This appendix aims to optimize other parameters of GRE EPI to achieve the optimal TE as described in Chapter 3 to maximize SNR and minimize distortions. In this analysis phase encoding blips are not considered at all. Instead, we consider the extremes which include: (1) acquisition with the read-out gradient only on the flat tops and (2) acquisition with the read-out gradient during the entire echo-train, i.e. during flat-tops and ramps.

A.2 Optimal Echo time

Theoretically, BOLD signal is maximized when $TE = T2^*$ which applies in situations where the flip angle and TR remain constant over varying TE as described in [27]. However, TR will increase as TE increases for a time-optimized stack of interleaved slices. Taking this into account, the total SNR is calculated for different TE values for a range of $T2^*$. The result from this calculation is shown in Fig A.1a., computed with a resolution = 3.2 mm (isotropic) and the number of slices = 40. This figure shows that the total SNR peaks at a lower TE than the expected $T2^*$. The calculation is repeated for multiple slices since TR changes with the number of slices. Fig A.1b., shows the TE value corresponding to the peak total SNR for a range of $T2^*$ for a varying number of slices. In this figure, the optimal TE increases and gets closer to the $T2^*$ as the number of slices increases. Additionally, when $T2^* \leq 40$ ms, TE seems to converge to a single optimal value for varying slices. A detailed description of this is provided in Chapter 3.
A.3 Read-out Gradient Bandwidth

Standard GRE EPI sequence includes an oscillating readout gradient together with a phase encoding gradient consisting of multiple short blips between two readout gradient polarities. Additionally, this sequence includes slice-selective excitation and adequate pre-dephasing. For the readout gradients, several waveforms are considered such as the sinusoidal and trapezoidal waveforms. For the rest of this analysis, trapezoidal readout gradients will be used.

Eq'n. (2) from Chapter 3 is modified to include the read bandwidth and the corresponding minimum TE value for a trapezoidal read gradient. The modified total SNR is given by Eq'n. (A.1), where $T_{AD}$ is modified to include $n_x, n_y$ which correspond to the matrix sizes in the read and phase encoding directions respectively, $rBW$, which is the chosen read bandwidth and $T_{E_{\text{min}}}$ which is the minimum TE value required for a certain bandwidth. Inverse linear relationships are established between the minimum TE, TR values and read bandwidth respectively.

$$\overline{SNR}_{BOLD} = C \Delta x \Delta y \Delta z \frac{1}{\sqrt{rBW}} \frac{(1 - E) \sin \alpha}{(1 - \cos(\alpha) E)} e^{-T_{E_{\text{min}}}/T^*}}$$  \hspace{1cm} (A.1)
During an fMRI experiment, multiple images are acquired in a time series within a total scan time $TS = N \times TR$, where $N$ is the total number of images. For this analysis scan duration was assumed to be 1, so Eq’n (A.1) can be rewritten as Eq’n (A.2). Figure A.2 is computed with a constant $T2^*$ of 70 ms, constant slew rate (SR) for the read gradient of 150 T/m/s, resolution of 4 mm (isotropic), number of slices = 32 and $FOV = 240 \times 240 \ mm^2$.

\[
SNR_{BOLD} = C \Delta x \Delta y \Delta z TE \frac{\sqrt{\Delta x \Delta y \Delta z}}{rBW} \frac{1}{T_R} \left( 1 - E \right) \frac{\sin \alpha}{1 - \cos(\alpha) E} e^{-\frac{TE_{min}}{T2^*}} \tag{A.2}
\]

Figure A.2 (a) Shows total SNR as a function of read bandwidth which peaks at ~ 27 kHz, for $T2^* = 70$ ms, SR = 150 T/m/s, resolution = 4 mm (isotropic), number of slices = 32 and $FOV = 240 \times 240 \ mm^2$. (b) Shows total SNR as a function of minimum TE values which has an inverse linear relationship with the read bandwidth. According to this the total SNR peaks when $TE = T2^*$.

A.4 Geometric Distortion

The human head consists of multiple adjacent compartments of different tissues with varying electric and magnetic properties. Local differences between tissue-specific magnetic susceptibilities introduce tiny magnetic gradients within the object if placed in an external magnetic field. The static magnetic field inhomogeneities due to these local gradients cause typical image artifacts in GRE-EPI images. The focus here is on geometric
distortion. The distortions are notably worse near air cavities and the skull base [39]. In fMRI this can result in misregistration of the EPI scans relative to high-resolution anatomical images which can lead to misinterpretation of functional activation and connectivity maps for both task-based and resting-state studies [77]. Additionally, due to this misregistration, these maps cannot be trusted when fMRI is used for presurgical planning.

Generally, for EPI the susceptibility-induced geometric distortions are negligible in the readout direction and very prominent in the phase encode direction. A simple way for reducing image distortions is to use multi-shot EPI instead of single-shot EPI, however, this involves increased acquisition time and increased sensitivity to patient motion between echos. Another method would be to acquire $B_0$ field maps for distortion correction using either a separate acquisition or reversed-polarity EPI readout. However, even with additional postprocessing using these maps, EPI correction is often not effective in areas of high susceptibility variation. Previous literature has focused on improving $B_0$ shimming procedures and shimming hardware to compensate for nonlinear $B_0$ variation.

The most straightforward means to reduce geometric distortion in GRE EPI is to increase the phase encode bandwidth by reducing the echo spacing (ESP) of the EPI train. This can be done in many ways, for example, by increasing the readout bandwidth of the sequence, parallel imaging techniques, etc. One side-effect of reducing the echo spacing is that the overall acquisition time, $T_{AD}$, is reduced, leading to a loss in SNR. Furthermore, in situations where the $T2^*$ is long (i.e. at 0.5 T), the desire to place $TE = T2^*$ and have a short overall echo train length are at odds with one another. However, as discussed in Chapter 3 the effective $TE < T2^*$, suggesting the possibility of reduced echo spacing.

To estimate the distortion for varying bandwidth and ppm, the amount of field offset, and corresponding frequency shifts are calculated using Eq’n. (A.3). The resulting pixel shifts which affect the total displacements are estimated using this Eq’n (A.3) and are shown in Fig A.3. These figures correspond to two different resolutions of 3.2 mm isotropic for a constant FOV = 240 x 240 mm$^2$.

$$ppm = \frac{\Delta B}{B_0}, \quad \Delta f = \frac{\gamma}{2\pi} \Delta B$$  \hspace{1cm} (A.3)
Assuming a range on the order of 0.5 to 2 ppm off-resonance in several inhomogeneous regions of the brain for a 0.5 T scanner, estimates of displacements for varying read bandwidths are calculated. Figure A.3 shows that at low read bandwidth (~25 kHz) for inhomogeneities $\leq 1$ ppm, displacement is approximately less than 13 mm. This displacement is further increased by higher inhomogeneities at reduced bandwidths. As previously discussed, the peak total SNR occurs when the read bandwidth is $\sim 27$ kHz, which, as can be seen in Fig 3., can lead to considerable distortion. Given the amount of geometric distortion, it is imperative to consider the read bandwidth selection.

![Figure A.3 Displacement as a function of field inhomogeneity for (a) varying low range of read-out bandwidths, (b) varying high range of read-out bandwidths with the resolution = 3.2 mm isotropic.](image)

Therefore, to achieve optimal BOLD efficiency while maintaining minimal distortion, other factors influencing the read gradients must be considered. To do so, trapezoidal read gradients with different slew rates and varying bandwidths were implemented. Simplifications were made for the rest of the analysis; phase encoding blips were not considered. For the first case, acquisitions are performed during the flat top period only (i.e. without including ramp sampling). For the second case, acquisitions occur during the entire echo train (i.e including ramp sampling). Optimal BOLD signals were collected after applying the gradients with and without ramp sampling at varying echo times.
A.5 Read-out Gradient Without Ramp sampling

Signal acquisition is performed when the phase encoding gradient is not active, and the readout gradient can be used to sample parallel k-space lines. If the k-space data is sampled at the constant rate only during the plateau of the readout gradient, then k-space samples are linearly related to the time domain signal. Thus, signals digitized with a constant dwell time (i.e. fixed bandwidth) can be directly used for fast Fourier transform without re-gridding. For this case, the acquisition time for a single echo is given by Eq’n. (A.4). Without ramp sampling (RS), the minimal echo spacing (ESP) corresponding to this case is given by Eq’n. (A.5).

\[ T_{AD} = \frac{2\pi n_x}{\gamma FOV_x G_x} \]  

(A.4)

\[ t_{ESP,\text{min}} = \frac{2\pi n_x}{\gamma FOV_x G_x} + \frac{2G_x}{S_R} \]  

(A.5)

In Eq’n. (A.4), \( T_{AD} \) is the acquisition time, \( n_x \) is the matrix size and \( FOV_x \) is the field of view in the read encoding direction and \( G_x \) is the read gradient amplitude. In Eq’n. (A.5) \( t_{ESP,\text{min}} \) is the minimum echo spacing which includes contribution \( T_{AD} \) and slew rate given by \( S_R \).
Figure A.4 shows the optimal BOLD signal acquired for varying read-out gradient bandwidths. For this figure, total ramp sampling was not employed. Here, (a) refers to high read-out bandwidth operating at an increased slew rate and (b) refers to low read-out bandwidth operating at a reduced slew rate. The optimal signal is calculated with echoes collected at different echo times for a single echo image. The peak signal occurs at low read bandwidth for both slew rates. However, since geometric distortion increases at low read bandwidth, it seems reasonable to consider higher bandwidth.

Figure A.5 shows the optimal BOLD signal acquired for varying phase gradient bandwidths operating at different slew rates. According to this figure, the effective bandwidth in the phase encode direction is further reduced at a lower slew rate with a maximum value of \(~16\) Hz/pixel for the corresponding high read gradient bandwidth which leads to prominent geometric distortions in the phase encode direction. This is because for high read gradient bandwidths the corresponding amplitude for the echo train increases.
However, for reduced slew rates, the time it takes to reach the high amplitude causes the echo spacing to increase which ultimately leads to increased distortions. Therefore, these figures clearly show that high read bandwidths are essential to reduce distortion in the read direction while high slew rates are essential to reduce distortion in the phase direction.

Figure A.5 Optimal BOLD signal as a function of varying phase gradient bandwidths. The signal encoded with these gradients is done during the flat top period (without ramp sampling). (a) The applied gradient had a $G_{\text{max}}$ of 40 mT and SR of 400 T/m/s. For the simulations, the initial magnetization had a value of 100. (b) The applied gradient had a $G_{\text{max}}$ of 26 mT and SR of 45 T/m/s. For the simulations, the initial magnetization was scaled by 10% to account for the extra 0.05 T.

A.6 Read-out Gradient With Ramp Sampling

If $T_{\text{AD}}$ is kept constant for both cases (i.e., with and without ramp sampling) then the readout gradient amplitude must be increased to compensate for the constant $T_{\text{AD}}$ and is given by Eq’n. (A.6).

$$G_{\text{x, (with RS)}} = \frac{T_{\text{AD}}}{T_{\text{AD}} - T_{\text{ramp}}} G_{\text{x, (without RS)}}$$  \hspace{1cm} (A.6)

where $T_{\text{ramp}}$ is the ramp time and is given by $G_{\text{x, (with RS)}} / S_R$. This relationship can be further modified if $T_{\text{acq}}$ with ramp sampling is divided into two components from $T_{\text{plateau}}$.
and $T_{ramp}$. Due to the gradient limitation, $G_{x,(with/without RS)} \leq G_{x,max}$ follows an upper limit for realizable ramp sampling times given by $T_{ramp} \leq \sqrt{G_{x,max} - G_{x,(without RS)}T_{plateau}/S_R}$. The relationship provided in Eq’n. (A.6) can be simplified to isolate the gradient amplitude associated with ramp sampling as shown in Eq’n. (A.7).

$$G_{x,(with RS)}^2 - T_{acq}S_RG_{x,(with RS)} + T_{acq}S_RG_{x,(without RS)} = 0$$ (A.7)

Re-gridding is now a part of the standard image reconstruction pipeline given the current computational capabilities, thus trapezoidal readout gradient with ramp sampling is preferred. Ramp sampling speeds up the EPI acquisition by minimizing ESP. Long ESP not only compromises the EPI data acquisition efficiency but also leads to increased image artifacts such as distortion, chemical shift displacement, signal loss, and blurring [14]. One way to shorten ESP is to increase the slew rate [14] through gradient hardware design. Slew rates above certain thresholds, however, can cause several patient safety concerns, including pain, peripheral neurostimulation, induced respiration, and even cardiac magnetostimulation [14], [78], [79]. The other approach is to use ramp sampling to eliminate idle time on the ramps by acquiring k-space data during the entire trapezoidal lobe.

Figure A.6 Optimal BOLD signal as a function of varying read-out gradient bandwidths. The signal encoded with these gradients is done with total ramp sampling. (a) The applied
gradient had a $G_{\text{max}}$ of 40 mT and SR of 400 T/m/s. For the simulations, the initial magnetization had a value of 100. (b) The applied gradient had a $G_{\text{max}}$ of 26 mT and SR of 45 T/m/s. For the simulations, the initial magnetization was scaled by 10% to account for the extra 0.05 T.

Figure A.6 shows the optimal BOLD signals acquired for varying read gradient bandwidths operating at different slew rates. For this figure total ramp sampling was employed. Here, (a) refers to high read-out bandwidth operating at an increased slew rate and (b) refers to low read-out bandwidth operating at a reduced slew rate. The optimal signal is calculated with echoes collected at different echo times for a single echo image. In this figure, the peak signal occurs at low read bandwidth for both slew rates. Since geometric distortion increases at low read bandwidth, it seems reasonable to consider higher bandwidth. However, with ramp sampling at a reduced slew rate, the optimal signal disappears at higher read bandwidths.

Figure A.7 shows the optimal BOLD signal acquired for varying phase gradient bandwidths operating at different slew rates. As discussed before, the effective bandwidth in the phase encode direction is reduced at a lower slew rate with a maximum value of ~23 Hz/pixel for the corresponding high read bandwidth. This leads to prominent geometric distortions in the phase encode direction. Therefore, these figures clearly show that high read bandwidths are essential to reduce distortion in the read direction while high slew rates are essential to reduce distortion in the phase direction even with ramp sampling. Figure A.8 summarizes the results of the different slew rates discussed here both with and without ramp sampling.
Figure A.7. Optimal BOLD signal as a function of varying phase gradient bandwidths. The signal encoded with these gradients is done with total ramp sampling. (a) The applied gradient had a $G_{\text{max}}$ of 40 mT and SR of 400 T/m/s. For the simulations, the initial magnetization had a value of 100. (b) The applied gradient had a $G_{\text{max}}$ of 26 mT and SR of 45 T/m/s. For the simulations, the initial magnetization was scaled by 10% to account for the extra 0.05 T.

Figure A.8. Shows higher slew rates can be used to reach high read and phase encoding bandwidths which will reduce geometric distortions in both read and phase encoding directions for both with and without ramp sampling. The bounds for both slew rates = 400 T/m/s and 45 T/m/s are determined by total ramp sampling and flat top readouts.
A. References


B. Feasibility of task-based BOLD fMRI at a 0.5 T Scanner

B.1 Introduction

A feasibility study involving motor tasks was performed with GRE EPI protocol as a part of the BOLD fMRI optimization at a head-only high-performance 0.5 T scanner. The results in this experiment were compared to another task-based study involving visual stimuli performed with a whole-body 0.55 T scanner (ramped down 1.5 T Siemens scanner) using similar protocol.

B.2 Methods

All scans were acquired on a head-only 0.5 T MR system equipped with a high-performance gradient set and 16-channel head coil (Synaptic Medical, Toronto, Canada) [2]. For this preliminary investigation, data was collected from one volunteer for a duration of 19 mins and 38 s. The following parameters were used for the EPI scans: field of view = 240 × 240 mm², resolution = 4 mm (isotropic), number of slices = 32, TE = 70 ms, TR = 2944 ms, flip angle = 90°. A bilateral finger tapping paradigm was performed using a block design with alternating 20 s of rest and activity (frequency = 0.025 Hz). The structural acquisition was performed using T1 weighted 3D FLASH with the following parameters: field of view = 260×260×180 mm³, resolution = 1.1 mm, FA = 26°, TE = 5.2 ms and TR = 11 ms. Data processing was performed using FEAT [3] in FSL which consists of motion correction (mean absolute displacement = 0.23 mm), slice time correction, non-brain removal, high pass temporal filtering of 40 s cut-off length, spatial smoothing with 5 mm FWHM Gaussian kernel, B0 unwrapping, noise pre-whitening and statistical analysis based on the general linear model.

B.3 Results

Fig B.1 shows a representative slice's anatomical image and the thresholded Z statistic images superimposed on top of the raw EPI data. The Z statistic images were thresholded using clusters determined by Z > 2 and a cluster significance threshold of P = 0.05. The activated regions seen in this figure are visually consistent with the expected spatial pattern behaviour in the bilateral primary motor cortex. The number of voxels
activated in the right side of the brain was 54 with a maximum Z value of 6.3 whereas the number of voxels activated on the left side of the brain was 44 with a maximum Z value of 6.7. Fig B.2 shows the time series behaviour of the normalized raw and filtered EPI data in the activated regions.

Figure B.1 Results from a representative subject. (Left) shows the T1-weighted anatomical image. (Right) show a few slices of the thresholded Z statistics on top of the raw EPI image. Z statistic images were thresholded using clusters determined by $Z > 2$ and a cluster significance threshold of $P = 0.05$.

Figure B.2 Averaged time course of the raw and filtered EPI data within the activated regions on the right side of the brain.

The percent change in signal of an averaged time course for a masked region on the right side of the brain consisting of 30 activated voxels is shown in Fig B.3 The spectra of the averaged time courses are shown in Fig B.4 which identifies the peak frequency to be $\sim 0.025$ Hz which corresponds to the task-related frequency. After filtering, the
corresponding mean temporal SNR calculated over these regions was \( \sim 54.5 \). Fig B.5 shows the tSNR maps with the mean values for the whole brain along with the ROIs created with the masked region before and after filtering.

![Figure B.3](image1)

Figure B.3 Averaged time course behaviour of a masked region consisting of 30 voxels in the activated regions on the right side of the brain.

![Figure B.4](image2)

Figure B.4 Spectra corresponding to the same mask consisting of 30 voxels in the activated regions on the right side of the brain.
Figure B.5 tSNR maps with the mean values for the whole brain along with the ROIs created with the same mask consisting of 30 voxels in the activated regions on the right side of the brain before filtering given in rows (a) and (b) and after filtering given in rows (c) and (d).

**B.4. Discussion**

Mid-field scanners with reduced siting requirements can expand access to MRI [4]. The availability of imaging techniques such as fMRI in a point-of-care setting can provide neurological information which can be vital in cases of traumatic brain injury and acute ischemic stroke [5,6]. This preliminary study demonstrates the feasibility of functional imaging at 0.5 T with the standard technique irrespective of the reduced activity-induced magnetic susceptibility contrast. Detailed experiments will be conducted in the future with optimized parameters and a greater population size. Previous studies (1) performed with visual stimuli show consistent activations with a percent signal change of ~2.5%. The resulting tSNR in the occipital lobe after filtering within an ROI of 106 voxels was ~ 57.9. This initial investigation with a motor task shows a percent signal change of ~1.8 +/- 0.4 % and the tSNR before filtering with an ROI of 30 voxels was ~ 54.5. The current EPI
protocol uses a TE of 70 ms, which results in the elongation of TR and dead time prior to the echo train. In future work, we intend to investigate and characterize the relationship between BOLD sensitivity and scan efficiency at 0.5 T. Even so, any dead time should be intelligently filled to increase SNR, for instance by asymmetric acquisition [7]. At the same time, simultaneous multi-slice (SMS) acquisition [8] can be utilized to reduce the TR further. EPI at low fields offers reduced susceptibility-induced geometric distortions and signal loss. This is especially important for structures near the skull base, where it has been shown that the increased signal dropout from field inhomogeneities at high fields overwhelms any advantage of increased voxel activation [9]. Furthermore, the increased safety profile of 0.5T offers the possibility of expanding the eligible population able to undergo fMRI exams, for instance, post-implantation of therapeutic devices such as deep brain stimulation (DBS) leads [10].

B.6. Conclusions

This preliminary work is intended to show the feasibility of performing task-based BOLD fMRI experiments on a mid-field 0.5 T head-only scanner using a standard EPI sequence with echo times close to the effective T2* contrast of grey matter at 0.5 T.

B. References


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C. T2* contrast in sub-cortical regions at 0.5 T

C.1. Introduction

A study investigating the T2* contrast at 0.5 T in sub-cortical regions within the brain with multi-echo GRE protocol (meGRE). These measurements are particularly important for the optimization of sequences sensitive to magnetic susceptibility such as susceptibility-weighted imaging (SWI). SWI suffers from the same drawbacks as fMRI including low SNR and long echo time at 0.5 T. However, recently there have been studies focusing on optimizing the sequence parameters and implementing denoising techniques that can extend this technique for clinical applications at low fields [80], [81]. To our knowledge, T2* measurements in these sub-cortical regions have not been reported before at 0.5 T. These measurements can help optimize the sequence for studies using the susceptibility-weighted maps as guiding tools for deep brain stimulation [82], [83].

C.2 Methods

All imaging protocols were performed on a head-only 0.5 T MR scanner equipped with a high-performance gradient system and 16-channel head coil (Synaptive Medical, Toronto) [21], [22], [24]. Imaging was performed on one healthy volunteer (male, age 36) with informed consent in compliance with health and safety protocols. For all measurements, subjects were asked to relax while in the scanner with their eyes closed.

C.2.1 Segmentation of 3D T1 Weighted Imaging

Structural images were acquired using a 1.1 mm isotropic resolution T1-weighted MPRAGE sequence with field of view (FOV) = 236 mm x 236 mm x 180 mm, FA = 26°, TE = 5 ms, and TR = 11.2 ms.

Region of interest (ROI) masks were created using anatomical T1-weighted images. First, the Brain Extraction Tool (BET) from FMRIB Software Library (FSL) was applied to obtain the skull-stripped brain [5], [9]. Manual adjustments were performed to maximize cortical coverage on the skull-stripped brain which was then passed onto FMRIB’s Automated Segmentation Tool (FAST) in FSL to create cortical GM and WM masks. [60]
A visual cortex (VC) mask was created using the Juelich Histological atlas in Montreal Neurological Institute (MNI) 152 standard space (resolution = 2 mm). These masks were then thresholded at an intensity of 30 and non-linearly registered onto the anatomical image using FMRIB's nonlinear image registration tool (FNIRT) [61].

C.2.2 T2* Mapping of Segmented Regions

Data were collected at 2 and 3 mm isotropic resolutions using a 3D multi-echo GRE (meGRE) sequence with FOV = 240 mm x 240 mm x 120 mm, matrix size = 120 x 120 x 60, FA = 32°, TE1 = 5 ms, echo spacing = 3.4 ms, echo train length (ETL) = 26, and TR = 97.25 ms.

The 3D meGRE images were registered to the anatomical image using FMRIB’s Linear Image Registration Tool (FLIRT) [3]. Voxel-wise estimates of T2* were computed over the ROIs by fitting the data to a mono-exponential decay model [62].

C.3 Results

Figure C.1 T2* maps with data collected at 2 mm resolution overlaid on a T1 weighted MPRAGE of a healthy volunteer are shown in sagittal, coronal and axial planes for the following regions: (a) Accumbens, (b) Caudate and (c) Pallidum. The cumulative mean and standard deviation of T2* measurements over that region are provided at the bottom of each column.
Figure C.2 T2* maps with data collected at 2 mm resolution overlaid on a T1 weighted MPRAGE of a healthy volunteer are shown in sagittal, coronal and axial planes for the following regions: (a) Putamen, (b) Substantia Nigra and (c) Subthalamic Nucleus. The cumulative mean and standard deviation of T2* measurements over that region are provided at the bottom of each column.

Figure C.3 T2* maps with data collected at 3 mm resolution overlaid on a T1 weighted MPRAGE of a healthy volunteer are shown in sagittal, coronal and axial planes for the following regions: (a) Accumbens, (b) Caudate and (c) Pallidum. The cumulative mean and standard deviation of T2* measurements over that region are provided at the bottom of each column.
Figure C.4 T2* maps with data collected at 3 mm resolution overlaid on a T1 weighted MPRAGE of a healthy volunteer are shown in sagittal, coronal and axial planes for the following regions: (a) Putamen, (b) Substantia Nigra and (c) Subthalamic Nucleus. The cumulative mean and standard deviation of T2* measurements over that region are provided at the bottom of each column.

C.4 Discussion

According to Figures 1 and 3 the T2* for Accumbens and Caudate increased slightly at a lower resolution, however, for Pallidum the T2* decreased slightly at a lower resolution. The T2* measurements for the subthalamic nucleus and substantia nigra in Figures 2 and 4 suggest that these values are close and distinguishing these regions might be difficult and require increased resolution. According to Figures 2 and 4, the T2* for substantia nigra and subthalamic nucleus decreased slightly at a lower resolution, however, for Putamen the T2* increased slightly at a lower resolution. These changes were within the standard deviation calculated for the measurements. Detecting these sub-cortical regions with SW maps is of particular interest since it can guide treatment plans with deep brain stimulations specifically important for Parkinson's disease and other related disorders.
C.5 Conclusions

This appendix includes initial T2* measurements conducted with one volunteer at different resolutions. Future studies will include repeating this measurement with multiple volunteers at a few more resolutions typically used for SWI.

C. References


D. Measurement of gradient-induced heating of cryogen-free main magnet

D.1 Introduction

This appendix focuses on the work done to investigate gradient-induced heating of the cryogen-free magnet used in this thesis. As discussed previously, scanners built with such magnets can relax siting requirements and offer lower operating costs. These systems rely on a cold head to draw heat away from superconducting coils instead of the coils being directly immersed in the cryogen which uses little to no cryogen, thus improving accessibility needs. However, unlike the traditional cryogen systems, these magnets have limited ability to regulate temperature. This can cause problems when the magnet is exposed to gradient-induced eddy current heating because the absence of a large heat sink of liquid helium could result in a greater variation in possible temperatures of the coils.

Gradient-induced eddy current heating can cause problems in the main magnet system. This is especially relevant for high-strength or asymmetric gradient systems where unwanted fields may leak beyond the gradient into the magnet compared to traditional whole-body gradient coils [36], [84]. Even though there are several ways of correcting gradient-induced eddy current fields, important concerns regarding the heating of the magnet during imaging remain since it can cause field stability issues or in the worst case the magnet might heat enough to quench. Previous literature focusing on the thermal characteristics of cryogen-free MR magnets has shown main field stability can be affected by magnet temperature [85]. This appendix explored the effect of gradient coil operation on the main magnet, starting with the effect on the temperature of the coils.

D.2. Method

Temperature dynamics were investigated with a set of 7 temperature probes placed throughout the main and shield coils of the compact cryogen-free superconducting 0.5 T magnet. The voltage output from these probes was exported using a NIDAQ system, using a LabVIEW program that was designed to collect data for 400 s. A prototype asymmetric gradient coil designed for head-only imaging with this magnet was connected to a gradient amplifier which offers a peak current of 900 A. Two gradient sequences were tested using
the different gradient components: (a) a single long trapezoidal pulse (similar to diffusion gradient) and (b) a series of bipolar trapezoidal lobes (similar to EPI). Details on the gradient parameters used in this study are provided in the figures. The investigation was performed over the course of a typical scan duration of 5 mins.

Study Description

1. The heating induced by different gradient axes was measured to determine which had the largest heating effect by comparing heating after 400 s of gradient operation.

2. The gradient axis that produced interaction from (1) was compared to itself at different gradient strengths.

To model the effect of varying gradient strength on the temperature of the main magnet over the duration of the gradient operation, a fit was performed with the function $A(1-e^x)$. The heating model was used to describe the predicted settling time (time until the temperature reached equilibrium).

D.3 Results

![Graph showing x-axis Gradient Induced Heating](image)

Figure D.1 Shows the magnet’s temperature behaviour for repeated diffusion gradient pulse along with the fit (parameters for the fit are in Table 1). The sequence used in these trials was a single lobe of trapezoidal pulse with a rise time of 0.1 ms, total duration of 200 ms and TR of 2000 ms. It allows a comparison of the heating for different gradient strengths.
Table D.1 Shows the fit parameters of the following function: $A(1-e^{-x})$, with the time constant being the quantity of interest since it estimates the settling time it takes for the magnet coils to reach an equilibrium temperature.

<table>
<thead>
<tr>
<th>Gradient Strength (mT/m)</th>
<th>Maximum Temperature Rise (mK)</th>
<th>Heating Time Constant $\tau$ (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 mT/m</td>
<td>8.28</td>
<td>192.3</td>
</tr>
<tr>
<td>130 mT/m</td>
<td>10.6</td>
<td>167.5</td>
</tr>
</tbody>
</table>

Figure D.2 Shows the main magnet heating from the x,y,z axis gradients running EPI style pulse sequences. The sequence consists of 40 cycles of 0.9 ms duration of bipolar lobes and had a maximum field strength of 71.4 mT/m in the x and y axis gradients and a 75.75 mT/m in the z axis gradient.

D.4 Discussion

The induced heating in all cases was less than 0.015 K, which makes it unlikely that the gradient operation could induce a quench by heating the magnet. Although this induced heating is not likely a destabilizing factor in the operation of the main magnet system, the effect of induced heating is still an important factor to consider during gradient design. Gradient-induced heating was monitored during each experiment conducted as a part of this thesis. The results from figure 2 suggest that the x-axis interacted the most with the main magnet. This may be due to the geometry of the gradient, the design of the main
magnet itself causing resonances, or less effective shielding on this component of the gradient. Interaction effects seen in the x-axis coil were minimized and further investigation regarding these fields were measured and characterized on this system.

D.5 Conclusion

As a part of this appendix, the gradient-induced heating of the cryogen-free main magnet coupled with an asymmetric head-only gradient coil was studied with trapezoidal pulses being run on different axes. The study suggests that the resultant temperature change in all cases was less than 0.015 K, with the worst case seen with the x-axis.

D. References


E. Measurement of scanner stability for functional imaging with ACR phantom

E.1 Introduction

Functional MRI is a demanding application since the signal changes are quite small, and any instrumental variations can easily compromise the BOLD contrast. As a part of this appendix, we investigated scanner instabilities using the method detailed in [86]. This was an initial investigation and there are certain limitations to this analysis which are also discussed in this appendix.

E.2 Methods

In this investigation, time series of images are acquired of an ACR phantom. Single image SNR values are calculated and compared with the fluctuations observed on a time series of images as a function of regions-of-interest (ROI) size. True CNR in fMRI depends on the underlying fluctuations in the time series. However, to distinguish true Johnson noise (coming from both the RF coil and patient resistance) from additional scanner variations, these sources must be quantified separately.

The ACR phantom was placed in the scanner, and images were acquired using the following parameters: GRE EPI sequence was implemented with the following parameter: FOV = 240 mm x 240 mm x 120 mm, resolution = 3 mm isotropic, TE = 70 ms, TR = 4126.7 ms, ETL = 80, FA = 26°, number of temporal positions = 145.

Two relatively large ROIs were selected, one in the middle of the phantom and one in the background away from both the phantom and any image artifacts associated to estimate the SNR. To estimate this quantity, the mean of the ROI in the middle of the phantom was measured for each image, $i$, given by $m_i$, and the standard deviation of the background was measured, given by $s_i$. $\text{SNR}_0$ was calculated as the ratio of the average mean to the average standard deviation, corrected for the different statistics of the noise in the phantom compared with the background as given by Eq’n (E.1). In absence of scanner instability, $1/\text{SNR}_0$ would be the relative deviation of the time series of a single pixel.

$$\text{SNR}_0 = \frac{\sum_{\text{images},i} m_i}{1.6 \sum_{\text{images},i} s_i}$$

(E.1)
The standard deviation over time from several ROIs with increasing linear size, \( n \), from a single pixel (\( n = 1 \)) to the largest size (\( n = 20 \)) was measured. Here a linear size of 20 refers to 20 x 20 square ROI. If the noise source were primarily due to the scanner and phantom, then the standard deviation would decrease like \( 1/n \) as given by Eq’n (E.2).

\[
\begin{align*}
F_{n,\text{theory}} &= \frac{1}{n \times SNR_0} \\
\end{align*}
\] (E.2)

If there are amplitude fluctuations that have some correlation distance larger than a single pixel (caused by instabilities in RF amplifier, gradient amplifier, center frequency, shim etc.), then the fluctuations will not fall as quickly as \( 1/n \). The relative fluctuations of the \( n \times n \) pixel ROI of the \( N \) point time series \( F_n \) is given by Eq’n (E.3).

\[
F_n = \sqrt{\frac{1}{N-1} \sum_{\text{images}} (m_i^n - \overline{m^n})^2} \\
\] (E.3)

In Eq’n (E.3), \( m_i^n \) is the mean of the \( n \times n \) ROI on the \( i \)th time series images and \( \overline{m^n} \) is the average of \( n \times n \) ROI across the \( N \) images:

\[
\overline{m^n} = \frac{1}{N} \sum_{i=1}^{N} m_i^n \\
\] (E.4)

To estimate the spatial scale at which the scanner instability affects the EPI measurements \( F_n \) and \( F_{n,\text{theory}} \) was plotted as a function of \( n \). For instance, \( F_1 > F_{1,\text{theory}} \) then the CNR of the fMRI scan might suffer even on a 1 x 1 pixel map. However, if \( F_1 \approx F_{1,\text{theory}} \), but \( F_n > F_{n,\text{theory}} \), for \( n > 4 \), then pixel by pixel map will not get affected but ROI analyses on regions greater than 16 pixels in size will suffer.

**E.3 Results**

\( F_n \) calculated as a part of this study provides an absolute measure of the ROI-dependent stability while the ratio \( F_n/F_{n,\text{theory}} \) provides a measure to quantify how much a particular coil/ROI size combination might be compromised by instability. Figure E.1

\[155\]
suggests that the relative fluctuation deviates slightly from the theoretical behaviour when ROI length is greater than 15.

![Graph showing relative fluctuation as a function of ROI length.](image)

Figure E.1 Shows the relative fluctuation of the experimental dataset along with the theoretical behaviour as a function of ROI length.

**E.4 Discussion**

The experimental results match within reason with the theoretical behaviour. However, with a human subject in the scanner, additional fluctuations are important such as patient motion, the physiological fluctuation due to respiration and cardiac pulsation affecting the limit of detectable activation for task-based fMRI studies. One of the major limitations of this study was that [86] conducted the study with a single-channel RF body and head coil. However, the study conducted here was with a multi-channel RF head coil, which suggests the use of a quantity like pseudo-SNR from Chapter 3 for single image SNR measurement.

**E.6 Conclusions**

As a part of this appendix, we have successfully measured fluctuations as a function of ROI size, which allows us to distinguish scanner instabilities from the white noise in the
system. These measurements can be used to understand hardware limitations and
detectability in fMRI studies.

E. References

imaging of activation in the brain,” *Magn Reson Med*, vol. 36, no. 4, pp. 643–645,
F. Test-retest reliability of resting-state networks

There has been increasing use of functional MRI to examine the difference in resting state functional connectivity between normal control groups and populations of interest. However, this requires an understanding of the reliability of these functional connections and the time required to effectively scan to get a reliable network. This appendix examines the similarity of “connected” functional connections to access the intersession for various scan lengths. To do this analysis, each 30 mins scan conducted in Chapter 4 for individual volunteers was truncated into shorter time frames ranging from 3 to 28 mins. The scans performed for Chapter 4 were not conducted on the same day. Each of these datasets was preprocessed separately and functional connectivity was calculated based on the same method described in Chapter 4. Dice coefficients as mentioned in [Ref] were calculated for individual volunteers for respective resting state networks since it can provide the commonality of connectivity values from different scans of the same individual that survive a given threshold. The results from this study suggest that intersession reliability increases with scan length. However, most networks were reliably identified within the scan time of approximately 15 mins. Future studies must include intraclass correlation coefficient (ICC) calculations which would allow us to gauge the intrasession reliability of each network.

Figure F.1. Dice coefficients are shown for 10 scan lengths for volunteer 1 for the default mode network. Bars represent the mean values for the computed z statistics while the error bars are the standard deviations.
Figure F.2. Dice coefficients are shown for 10 scan lengths for volunteer 1 for the executive control network left. Bars represent the mean values for the computed z statistics while the error bars are the standard deviations.

Figure F.3. Dice coefficients are shown for 10 scan lengths for volunteer 1 for the auditory network. Bars represent the mean values for the computed z statistics while the error bars are the standard deviations.

F. References


Supplementary I

Figure I.1. The coloured regions on the normalized thresholded z statistics map overlaid on top of T1 scan corresponding to volunteer 2. The functional datasets used here are from volunteer 2 and these correspond to TR of 1000 ms. These maps show different brain networks where there exists functional connectivity. The activity in the blue regions are negatively correlated with the activity in the red regions. (a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi^2$ distribution (d) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi$ distribution. In this figure (1) refers to the default mode network, (2) refers to the executive control network left and (3) refers to the executive control network right.
Figure I.2. The coloured regions on the normalized thresholded z statistics map overlaid on top of T1 scan corresponding to volunteer 2. The functional datasets used here are from volunteer 2 and these correspond to TR of 2000 ms. These maps show different brain networks where there exists functional connectivity. The activity in the blue regions are negatively correlated with the activity in the red regions. (a) Shows the expected functional connectivity from the database, (b) shows the functional connectivity calculated with the raw 3 T data collected, (c) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi^2$ distribution (d) shows the functional connectivity calculated with the modified data which includes artificial noise following the noncentral $\chi$ distribution. In this figure (1) refers to the default mode network, (2) refers to the executive control network left and (3) refers to the executive control network right.
Figure I.3. Shows p statistics calculated by comparing each network’s z statistics map for individual volunteers to respective representative network maps from the database. The markers represent all the eleven resting-state. Row (1) corresponds to TR of 2000 ms, and Row (2) corresponds to TR of 1000 ms. Column (a) refers to the collected 3 T data, (b) refers to the modified data with additional noise that follows the non-central $\chi^2$ distribution and (c) refers to the modified data with additional noise that follows the non-central $\chi$ distribution. A solid line is also plotted at $p = 0.05$. Any network with p values $< 0.05$ is significantly different from the representative network.
Curriculum Vitae

EDUCATION

2023  Doctor of Philosophy  
Department of Medical Biophysics  
University of Western Ontario, London, Canada  
Supervisors: Dr. Blaine Chronik and Dr. Andrea Soddu

2018  Master of Science (Physics)  
Department of Physics and Astronomy  
University of Western Ontario, London, Canada  
Supervisor: Dr. Blaine Chronik

2017  Bachelor of Science (Physics)  
Department of Physics and Astronomy  
Queens’ University, Kingston, Canada  
Supervisor: Dr. Alexander Wright

PUBLICATIONS AND PRESENTATIONS

a. Articles published in peer-reviewed journals


b. Articles under review in peer-reviewed journals

1. Arjama Halder, Chad T. Harris, Curtis N. Wiens, Andrea Soddu, Blaine A. Chronik. “Optimization of Single Gradient Echo Echo-planar Imaging for T2* Contrast at 0.5 T: Application to fMRI”, Accepted, 2023.

c. Other peer-reviewed contribution
2. Halder A. et al., Investigating the effect of reduced TR in detection of RSNs at a low field MR scanner. ISMRM, London UK, Date: May 7-12, 2022.
3. Halder A. et al., Gradient induced electric field within a shoulder cut-out gradient coil built for head and neck imaging. ISMRM, Virtual, Date: May 15-20, 2021.
6. Halder A. et al., Validating low frequency quasi-static solvers in SEMCAD and Sim4Life for simulating the effects of gradient field on devices. ISMRM, Virtual, Date: July 20-24, 2020.
7. Halder A. et al., Ultra-low frequency electric field probes for gradient coils field measurement during medical device testing. IEEE (CCECE), Talk, Calgary Canada, Date: May 17, 2019