DEVELOPMENT AND APPLICATION OF METHODS FOR REAL-TIME FMRI NEUROFEEDBACK

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Medical Biophysics
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Abstract

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Doctor of Philosophy
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2013

Improving stroke recovery is a topic of considerable interest in the developed world. Motor deficits following stroke can significantly impact quality of life, and motor rehabilitation strategies are urgently needed to promote brain recovery. One technique that has had therapeutic success in other domains is neurofeedback (NF), a strategy whereby a person is trained to gain volitional control of their neurological activity. The NF technique has proven efficacious in disorders ranging from epilepsy to attention deficit disorders based on feedback of electroencephalography (EEG) signals, and the potential exists for NF applications in the recovery of motor function following stroke. Using functional magnetic resonance imaging (fMRI), NF can be applied to precisely defined regions of interest (ROIs), facilitating the targeted treatment of affected functional areas. The combination of fMRI and NF is still relatively new, and much work remains in the characterization and optimization of fMRI NF strategies.

In a two-pronged approach, this thesis focuses on the application of ROI-based NF to the motor system using traditional fMRI measurements and also the development and analysis of acquisition strategies intended for use in ROI-based NF. First, a study of the mechanisms governing the successful application of NF in primary motor cortex ROIs is presented, using kinaesthetic motor imagery (imagining the sensation and execution of movement) to engage the motor system. Second, an investigation of fMRI signal contrast enhancement properties using multi-echo fMRI acquisition methods in dense sampling
regimes is considered. Third, a novel acquisition method is introduced, designed using parallel MRI principles to provide fast and detailed sampling of fMRI signals in selected ROIs, called Constrained Source Space Imaging (CSSI). To conclude, the potential future directions for fMRI NF research and the CSSI technique are discussed, including thoughts toward the continued development of NF as a potential motor therapy for stroke patients.
Dedication

For my parents, Arthur and Kelly Chiew, upon whose shoulders I now stand.
Acknowledgements

“No man is an island entire of itself...” – John Donne

I don’t know the rest of that poem, but there are a lot of people that I need to thank and acknowledge, without whom this thesis would not have been possible. First my supervisor, Dr. Simon Graham, who has helped not only guide my work, but also my development as a person and as a scientist. My supervisory committee members, Dr. Stephen Strother and Dr. Bojana Stefanovic, who have provided me many opportunities to improve myself over the years.

From my time at the Rotman Research Institute, I have to thank Dr. Michael Marxen for his friendship and mentorship. I am also grateful for the office cutlery he passed to me when he left. I thank Dr. Lily Riggs, for her convenient companionship has provided a Hermione to my Harry, or an Arya to my Jon. I must also credit her for teaching me that the Basal Ganglia are in fact a collection of multiple brain structures. Annette Weekes-Holder has gracefully put up with my destructive presence in the fMRI suite, for which she should be commended.

At the Sunnybrook Research Institute, Robert Staruch, Brandon Helfield, Arvin Arani, and Ryan Jones have all helped shape my Medical Biophysics experience, both on and off the ice. My fellow and former Graham lab members have been a supportive and friendly bunch, including Audrey Kuo who helped me get off my feet, Fred Tam with his nocturnal technical support, and Tara Dawson for her help and smiles. I should also thank Dr. Stephen LaConte for his technical assistance in setting up the real-time fMRI framework, which was instrumental to the completion of this thesis.

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<th>Definition</th>
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<tbody>
<tr>
<td>$\gamma$</td>
<td>Gyromagnetic Ratio of $^1H$</td>
</tr>
<tr>
<td>$\omega_0$</td>
<td>Larmor (Resonant) Frequency</td>
</tr>
<tr>
<td>$\Phi$</td>
<td>Coil Sensitivity Encoding Matrix</td>
</tr>
<tr>
<td>$\sigma_0^2$</td>
<td>Intrinsic Noise Variance</td>
</tr>
<tr>
<td>$\sigma_B^2$</td>
<td>BOLD-like Physiological Noise Variance</td>
</tr>
<tr>
<td>$\sigma_{CORR}^2$</td>
<td>Noise Correlation Gaussian Kernel Width</td>
</tr>
<tr>
<td>$\sigma_{NB}^2$</td>
<td>Non-BOLD Physiological Noise Variance</td>
</tr>
<tr>
<td>$\sigma_P^2$</td>
<td>Physiological Noise Variance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>$B_0$</td>
<td>Main Magnetic Field</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood-Oxygenation Level Dependent</td>
</tr>
<tr>
<td>BSR</td>
<td>Bootstrap Ratio</td>
</tr>
<tr>
<td>CNR</td>
<td>Contrast to Noise Ratio</td>
</tr>
<tr>
<td>CSSI</td>
<td>Constrained Source Space Imaging</td>
</tr>
<tr>
<td>DFT</td>
<td>Discrete Fourier Transform</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo Planar Imaging</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>FOV</td>
<td>Field-Of-View</td>
</tr>
<tr>
<td>GLM</td>
<td>General Linear Model</td>
</tr>
<tr>
<td>InI</td>
<td>Inverse Imaging</td>
</tr>
<tr>
<td>kMI</td>
<td>Kinesthetic Motor Imagery</td>
</tr>
<tr>
<td>LH</td>
<td>Left-Handed</td>
</tr>
<tr>
<td>LI</td>
<td>Laterality Index</td>
</tr>
<tr>
<td>LV</td>
<td>Latent Variable</td>
</tr>
<tr>
<td>M</td>
<td>Magnetization</td>
</tr>
<tr>
<td>M1</td>
<td>Primary Motor Cortex</td>
</tr>
<tr>
<td>MECV</td>
<td>Multi-Echo Coarse Voxel</td>
</tr>
<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
</tr>
<tr>
<td>MREG</td>
<td>Magnetic Resonance Encephalography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NF</td>
<td>Neurofeedback</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
</tr>
<tr>
<td>PLS</td>
<td>Partial Least Squares</td>
</tr>
<tr>
<td>R</td>
<td>Parallel Imaging Acceleration Factor</td>
</tr>
<tr>
<td>R2</td>
<td>Transverse Relaxation Rate</td>
</tr>
<tr>
<td>R2*</td>
<td>Transverse Relaxation Rate Including Static Inhomogeneity</td>
</tr>
<tr>
<td>rCNR</td>
<td>Relative Contrast to Noise Ratio Enhancement</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>RH</td>
<td>Right-Handed</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root Mean Square Error</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SMA</td>
<td>Supplementary Motor Area</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
</tr>
<tr>
<td>STEAM</td>
<td>Stimulated Echo Acquisition Mode</td>
</tr>
<tr>
<td>T</td>
<td>Tesla (Magnetic Field Strength)</td>
</tr>
<tr>
<td>T1</td>
<td>Spin-Lattice Relaxation Time</td>
</tr>
<tr>
<td>T2</td>
<td>Spin-Spin Relaxation Time</td>
</tr>
<tr>
<td>T2*</td>
<td>Transverse Relaxation Time Including Static Inhomogeneity</td>
</tr>
<tr>
<td>TCI</td>
<td>Total Correlation Index</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
</tr>
<tr>
<td>vMI</td>
<td>Visual Motor Imagery</td>
</tr>
<tr>
<td>W</td>
<td>Coil Noise Covariance Matrix</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

This thesis focuses on functional magnetic resonance imaging (fMRI) methods for real-time fMRI neurofeedback (NF). The following introduction provides a discussion of the clinical motivation and context for the thesis, concise overviews of the theory, techniques and technologies involved, statements of the hypotheses and an outline for the research described hereafter. Specifically, the introductory topics of interest are: stroke and stroke rehabilitation; biofeedback and NF; magnetic resonance imaging (MRI) principles; and finally fMRI, from basic application to advanced techniques.

1.1 Stroke and Stroke Recovery

A brief consideration of stroke is important to provide long term motivation for this thesis. Stroke is broadly defined as a disruption of blood flow in the brain arising from clotting or other blockages of flow (ischemia) or from uncontrolled bleeding (hemorrhage). In an ischemic stroke, oxygen deprivation affects neuronal cell metabolism, whereas in a hemorrhagic stroke, damage is caused through physical pressure and blood-tissue reactions. In both cases, lesions are produced in the brain parenchyma that can result in paralysis (partial or complete), motor or sensory impairment, and language, memory, and cognitive problems, depending on the lesion location. According to the Heart and Stroke Foundation, in Canada more than 50,000 strokes occur each year, of which 75% result in some level of disability or impairment ranging from mild cognitive impairment to complete paralysis of one side of the body [1]. About 300,000 Canadians live with the effects of stroke at any given time [1], indicating that research into therapies and rehabilitation methods for chronic stroke is very important toward making a difference in the quality of life following this form of brain injury.
1.1.1 Stroke Treatment

Treatment for stroke begins in the acute stage, and is focused on repairing immediate physiological damage. Re-canalization or restoration of blood flow using tPA (tissue plasminogen activator) is one option, depending on patient factors such as the interval since stroke onset. Hemorrhagic stroke, although more frequently fatal, can also be treated using medications for hypertension and tissue swelling. In both cases surgery may also be possible to re-vascularize or bypass the clot, or to halt bleeding. These treatments can be effective in improving clinical outcomes, although some treatments like application of tPA can be dangerous and need to be applied very soon after stroke (within 3 – 4.5 hours) [2, 3], resulting in availability to only a small proportion of stroke patients (estimated to be about 2% in the United States in 2005 [4]).

In the sub-acute and chronic stages of stroke (days to months), there is usually some level of spontaneous recovery. One factor identified in spontaneous neurological recovery is amount of the surviving tissue in the ischemic penumbra [5], which is the portion of brain tissue characterized by reduced blood flow and functional impairment, but without permanent structural damage and with potential for recovery. In most cases, however, stroke survivors are still left with some motor deficit that can impact the ability to walk, talk, swallow, perform complex hand or arm movements, and that generally affects the balance and coordination required to perform daily tasks [6]. In contrast with the immediate focus on recanalization taken in acute treatments, chronic stroke treatments are more concerned with behavioural problems and other long term impairments that arise from stroke.

1.1.2 Stroke Recovery

Although there are existing rehabilitation methods for numerous stroke deficits (e.g. language, cognition [7]), continual research into therapies for recovery of motor function is important due to the ubiquity of motor deficits, their quality of life implications and the difficulty in achieving adequate motor recovery in many patients. Currently, physical therapy is the most conventional method for rehabilitation of motor function. Treatment techniques can vary from centre to centre, as no consensus for rehabilitation methodology exists, but repetitive, task-based practice techniques are currently viewed as the most promising method for promoting stroke recovery [8].

Constraint-induced movement therapy (CIMT), for example, is a technique in which patients are forced to their affected arms by limiting the movement of their healthy side. In a well cited study of cortical reorganization following CIMT, it was shown that
improved motor performance corresponded to expanded neural representation of the affected muscle regions [9] (i.e., spatially expanded functional recruitment of brain regions). This evidence suggests that a direct focus on improving cortical motor representations could possibly aid the motor recovery process, and supports the search for rehabilitation strategies that incorporate brain-related changes.

In addition to CIMT, a variety of other methods have been investigated as viable alternatives or complements to existing, traditional physical therapies. One example of a strategy that is designed to facilitate motor recovery with a focus on the brain is functional electrical stimulation therapy, which uses externally driven electrical stimulation to drive muscle movement for the purposes of strengthening the afferent-efferent (nerve pathways toward and away from the brain, respectively) feedback circuits [10]. In moving towards the development and optimization of such rehabilitation methods, neuroimaging is starting to play a significant role in visualizing and characterizing stroke recovery in the brain, through the ability to study spatial and temporal patterns of brain activity.

1.1.3 Neuroimaging in Stroke

In stroke management, neuroimaging typically plays the largest role in the acute stage to assess the anatomical extent of damage and to determine the extent of the ischemic penumbra. Although computed tomography (CT) is the diagnostic standard for imaging in acute stroke, current evidence is supporting the use of MRI techniques such as diffusion-weighted imaging, which can be more sensitive than CT for detecting ischemic stroke [11]. With the development of functional neuroimaging modalities such as positron emission tomography (PET) and fMRI, these methods are increasingly applied in a basic science role to observe brain recovery following stroke. For example, fMRI has been used to investigate brain reorganization involved in motor recovery [12] or the neurovascular changes that result from strokes [13]. At present, most fMRI studies of stroke recovery are observational, with imaging used to track and record measures of recovery without having a direct impact on treatment. This thesis however, investigates a new and emerging application of fMRI involving real-time feedback of brain signals, where the neuroimaging can potentially play a direct role in promoting recovery. The real-time interactive fMRI technique proposed here for study is a form of biofeedback, a topic that warrants some introductory discussion.
1.2 Biofeedback and Neurofeedback

1.2.1 Biofeedback

Simply stated, biofeedback experiments involve making a person aware of their biometric signals (signals derived from some biophysical process) in a manner that enables them to gain control over said processes. It is believed that operant (or instrumental) conditioning is a primary mechanism governing biofeedback. Operant conditioning involves modification of behaviour according to the consequences of voluntary actions. For subjects in biofeedback experiments, the “behaviour” is some sensory stimulus mediated by the biometric signal (e.g. visual display of muscle electrical activity), and the “consequence” is related to the modulation of the feedback metric derived from the measured signal (e.g. reward for increased electrical activity, or penalty for decreased electrical activity). In this manner, the subjects can learn to control their behaviour to produce a desired biometric response. The direct analogy with typical electronic feedback is evident, whereby the biometric outputs are fed back to the subject to facilitate conscious modulation of the self, effectively “closing the loop”. When the biometric signals originate from the electrophysiological activity of the brain, this process is commonly referred to as “neurofeedback” (NF).

In the 1970s, an interoceptive theory for learned visceral control [14] proposed an explanation for the biofeedback mechanism of action, where interoception refers to the ability to perceive internal physiological states, and visceral control refers to the control of internal systems or organs. This theory states that the facilitating effect of external feedback on the learned control of the [internal organs] is mediated by enhanced awareness of internal cues. In other words, when external feedback coincides with naturally occurring afferent information, persons can learn to recognize and direct their attention to interoceptive cues and thus become ‘aware’ of their ongoing visceral activity.” However, studies have shown that successful self-regulation of brain activity can occur without accurate perception of brain state [15]. In addition, the brain does not possess an internal sensory system, and hence has no mechanism by which to monitor its own electrochemical activity for self-regulation [16].

More research is required to identify the neurological mechanisms of biofeedback, although a few potential brain regions have been suggested to play some role. One such region is the nucleus basalis (in the basal ganglia), which has a role in successful conditioning [17]. A study using simultaneous electroencephalography (EEG) and fMRI identified a circuit involving the cortex, basal ganglia and thalamus, that is believed to be important for successful self-regulation [16]. An additional fMRI study implicated the
Table 1.1: Applications of Biofeedback

<table>
<thead>
<tr>
<th>Application</th>
<th>Biometric</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches, Migraines[24]</td>
<td>EMG in the frontalis muscle, blood volume pulse measurements in the temporal artery, peripheral skin temperature</td>
<td>0.61 – 0.7 (Hedge’s d)</td>
</tr>
<tr>
<td>Anorectal control[19]</td>
<td>EMG in anal sphincter, anal canal pressure</td>
<td>62.4 – 67.2% (treatment success rate)</td>
</tr>
<tr>
<td>Dysfunctional voiding[25]</td>
<td>EMG in pelvic and abdominal muscles, urinary flow rates</td>
<td>53 – 100% (treatment success rate)</td>
</tr>
<tr>
<td>Jaw clenching[26]</td>
<td>EMG in temporal muscle</td>
<td>48% (decrease in # of clenching events)</td>
</tr>
<tr>
<td>Autism[27]</td>
<td>EEG power in frequency bands (delta, theta, alpha, beta, gamma), sensorimotor rhythm (SMR), mu rhythm</td>
<td>21 – 40% (reduction in symptoms)</td>
</tr>
<tr>
<td>Insomnia[28]</td>
<td>EEG frequency band amplitudes, SMR</td>
<td>15.9% (increase in sleep efficiency)</td>
</tr>
<tr>
<td>ADHD[29]</td>
<td>EEG beta, theta, SMR</td>
<td>0.76 – 5.35 (Glass’s Δ)</td>
</tr>
<tr>
<td>Epilepsy[30]</td>
<td>EEG SMR</td>
<td>82% (seizure reduction success rate)</td>
</tr>
</tbody>
</table>

anterior and posterior cingulate cortex, ventral striatum, putamen and midbrain [18] in this role. However, this small body of research is suggestive, rather than definitive.

1.2.2 Clinical Applications of Bio- and Neurofeedback

Biofeedback has been widely studied in therapeutic intervention, with applications ranging from treatment of anorectal disorders [19] to treatment of attention deficit hyperactivity disorder (ADHD) [20]. Biofeedback provides subjects with explicit, quantitative feedback regarding physiological or biometric signals of interest, for example: heart rate, skin conductivity, brain electrical potentials, blood pressure, respiratory frequency, and cerebral blood flow. The Association for Applied Psychophysiology and the Society for Neuronal Regulation jointly developed a 5 point scale for evaluating the clinical efficacy of biofeedback methods [21], with scores based on the amount and quality of demonstrated clinical evidence. Examples of biofeedback treatments rated at a high level of 4 (efficacious) or 5 (efficacious and specific) include those for hypertension (level 4) [22], migraines (level 4), and tension headaches (level 5) [23]. Table 1.1 shows a brief sampling of the literature regarding bio- and neurofeedback across a wide range of clinical applications, along with their reported effect sizes.

Given the potential benefits, biofeedback has also been investigated for promoting both motor and cognitive recovery from stroke [31]. Although most motor-related biofeedback focuses on using electromyography (EMG, a device for measuring muscle electrical
activity) approaches, the focus of this thesis will be on NF and motor signals originating from the brain. Two of the most popular methods for performing NF in the recent literature are EEG and fMRI. In brief, EEG uses surface electrodes attached to the scalp to measure voltage fluctuations that arise from neuronal electrical activity, and fMRI uses MRI signal changes that arise from changing properties of the neuronal vasculature. Although other methods exist for rapid measurement of brain signals, such as magnetoencephalography (MEG) and functional near infrared spectroscopy (fNIRS), the discussion below focuses on EEG and fMRI NF, because EEG has been most heavily adopted, and fMRI may provide improved technical capabilities in some circumstances.

1.2.3 EEG Neurofeedback

The majority of NF research has been performed using EEG, where feedback is typically represented by metrics related to electrode potential (e.g. continuously updating traces, maximum amplitude values or spectral power). As early as 1934, there were attempts to facilitate a self awareness of the EEG alpha (8 – 12 Hz) rhythm by translating the measured potentials to audio signals [32]. Some of the most well known examples of EEG NF relate to treatment of ADHD and epilepsy [33, 34]. For example, in epilepsy one strategy is to enhance the activity of the SMR (12-15 Hz, over the sensorimotor cortex), which can result in a clinically significant drop in seizure activity in most patients that do not respond to pharmacotherapy [30]. In addition to these clinical applications, EEG NF has also been shown to have beneficial effects on simple task performance. By performing feedback on the amplitude of cortical potentials, increased negativity can lead to reaction time improvements in hand movements, signal detection, and arithmetic tasks [35, 36].

1.2.4 fMRI Neurofeedback

Using fMRI to perform NF is a more recent development, with much of the work appearing in the last decade. Most studies have been exploratory, investigating the feasibility of voluntary modulation of BOLD signal characteristics via real-time fMRI feedback. Because EEG source localization involves solving challenging inverse problems, the results often contain large uncertainties in the spatial configuration of source activity. Furthermore, source localization algorithms are typically complex and difficult to perform in real-time, restricting signals to analysis in the sensor space. In contrast, as subsequent sections will explain, fMRI can provide millimetre spatial resolution throughout the brain, with well characterized point spread functions and data reconstruction methods suitable for real-time processing. This facilitates NF associated with small, localized regions of
interest (ROI) chosen based on their functional relevance to the task under study. Areas that have been studied in ROI-based fMRI NF include: various primary and secondary motor regions \[37, 38, 39, 40, 41\]; emotion regions such as the anterior insula \[42, 43\], the anterior cingulate \[44\], the amygdala \[45\], or a mix \[46, 47\]; auditory regions \[48, 49\]; and language regions \[50\].

Many characterizations of the fMRI signal have been explored for use in fMRI NF, including time series signal plots, spatial extents of activation in brain maps, and activation signal amplitude representations (as bars, arrows or other abstract forms). To date however, almost all NF, whether EEG or fMRI-mediated, has focused on using these characteristics to reflect the amplitude of brain activity, with NF used to modulate activation amplitude as a function of time. The work presented in this thesis continues to focus on fMRI signal amplitude, but examines some relatively unexplored facets of fMRI NF, including the interactions between multiple regions in a functional network. The technology necessary to provide basic ROI and amplitude-based fMRI NF exists, using standard fMRI data acquisition methods and real-time data and signal processing. A study of fMRI NF is presented in Chapter 2 of this thesis.

Although alternative approaches to NF exist, such as characterization of brain activity by whole brain classification techniques such as support vector machines \[51\], this thesis focuses strongly on the ROI-based approach. One particular advantage of MRI over EEG is the ability to provide millimetre spatial localization of the signals of interest, combined with superior signal-to-noise ratio (SNR) properties. As mentioned above, this advantage allows the targeting of specific, precisely localized ROIs in a NF experiment. However, these advantages come with decreased ability for fMRI to resolve brain dynamics temporally, due to constraints in both the measurement process and the intrinsic limitations of measuring hemodynamics. Some other disadvantages of fMRI include increased cost, hardware complexity, and limited availability.

Thus, additional research is necessary to explore the potential benefits of fMRI NF and to determine its application niche. The following sections provide a concise overview of MR imaging principles, laying the groundwork to discuss basic fMRI concepts and a few other pertinent fMRI topics. Collectively, these sections provide background for the work in this thesis, the latter portion in particular, which is focused the analysis and development of methods for enhancing fMRI acquisition and signal reconstruction, with direct application to real-time fMRI NF.
1.3 Magnetic Resonance Imaging

1.3.1 Essential Physics

MRI is an application of nuclear magnetic resonance (NMR), a phenomenon first discovered by Bloch and Purcell in 1946 [52, 53] that won them the Nobel Prize in Physics in 1952. The hydrogen nucleus ($^1$H) is the primary nucleus of interest within water molecules, which are highly abundant in biological tissue (other nuclei such as $^{13}$C, $^{19}$F, $^{23}$Na, and $^{31}$P share the same property of having a net spin angular momentum which is needed for NMR). To create an image, a sample or subject is placed in a homogeneous static magnetic field ($B_0$). The net spin angular momentum in $^1$H due to the sole proton has an associated magnetic moment, and the static magnetic field induces a net magnetization $\vec{M}$ from the ensemble of water molecules in the sample.

The Bloch equation is a first order, linear partial differential equation that describes the dynamic behaviour of $\vec{M}$ in response to externally applied magnetic fields, as well as the intrinsic relaxation parameters that govern its transient return to static equilibrium after a perturbation:

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

(1.1)

where $\hat{i}$, $\hat{j}$ and $\hat{k}$ are unit vectors in the x, y and z directions respectively, $\vec{M}$ is the vector magnetization, $\vec{B}$ is the vector magnetic field, $\gamma$ is a fundamental constant, the gyromagnetic ratio of $^1$H, and $T_1$ and $T_2$ are scalar relaxation time constants. A common convention in MRI is the decomposition of $M$ into two orthogonal components: $M_z$, the longitudinal component, and $M_\perp = M_x \hat{i} + M_y \hat{j} = M_x + iM_y$, the complex component in the transverse plane perpendicular to $B_0$. This convention of representing the two-dimensional (2D) vector magnetization $M_\perp$ as a complex scalar quantity is notationally and mathematically convenient, and one can always substitute the x-component for the real part, and the y-component for the imaginary part to return to a vector notation. More often, the complex $M_\perp$ is represented as a magnitude and phase, which lends itself to easier geometric interpretation.

In this classical vector description of MRI, the direction of the vector $M$ is manipulated through a sequence of modulated radio frequency (RF) magnetic field pulses and time-varying magnetic field gradients, which are small magnetic fields that vary linearly in magnitude along the x, y, and z dimensions but always point in the $\hat{k}$ direction. Both the RF magnetic fields and the gradient magnetic fields are superimposed on the static primary field, $B_0 \hat{k}$, which is always present. The term “pulse sequence” typically refers
to a particular choice and combination of these RF and gradients pulses combined with data acquisition, with specific timing parameters. After application of an appropriate RF pulse, the creation and subsequent precession of \( M_\perp \) in the transverse plane induces voltages (via Faraday’s law of induction) in a tuned receiver apparatus. The rate of precession is called the resonance or Larmor Frequency, defined as \( \omega_0 = \gamma B_0 \).

Analysis of the received signals reveals information about the spin density of the sample \( \rho \), as well as relaxation properties of the sample. Spin-lattice, or \( T_1 \) relaxation, characterizes recovery of \( M_z \) along the longitudinal \( B_0 \) direction. Spin-spin, or \( T_2 \) relaxation, characterizes decay of magnetization in the transverse plane. Lastly, \( T_2^* \) relaxation characterizes the combined effects of \( T_2 \) relaxation and magnetic field inhomogeneity within biological tissue, denoted by \( T_2' \), where \( 1/T_2^* = 1/T_2 + 1/T_2' \). These contrast parameters are tissue dependent, and pulse sequences are designed to provide appropriate signal contrast from specific relaxation parameters or parameter weightings (e.g., \( T_1 \)-weighted contrast) for various clinical and research applications. Contrast is specified in the pulse sequence partially through the particular configuration of RF and gradient pulses, as well as sequence properties such as the RF excitation flip angle, echo time (TE), and repetition time (TR). The flip angle of an RF pulse represents the degree to which \( M \) is rotated, measured relative to the longitudinal axis, whereas TE and TR generally refer to timing parameters representing the time at which \( M_\perp \) forms a local maximum (i.e. magnetization is maximally in-phase), and the amount of time between pulse sequence repetitions.

### 1.3.2 MRI Technology and Equipment

Modern MRI systems are composed of many sub-components. These systems most commonly range from 1.5 Tesla (T) to 3.0 T in \( B_0 \) magnetic field strength, although ultra-high field systems at 7.0 T are gaining popularity. In the vast majority of cases, \( B_0 \) is generated by a persistent current in a superconducting coil immersed in liquid helium. Resistive coils are used to generate spatially varying magnetic fields gradients for imaging, and can be selectively turned on and off by the application of currents. Linear variations are produced by the \( x, y, \) and \( z \) gradient coils for use in imaging applications. Higher order spatial variations (up to 2nd order) are used for suppressing unwanted field variations and improving field uniformity over the imaging volume.

Coils are also used to transmit and receive the RF magnetic signals, for excitation and measurement of the sample magnetization, respectively. Although single RF coils can be designed for both transmit and receive (transceive coils), most MRI systems employ
separate coil pairings. A body coil, often built into the bore of clinical MRI systems, provides reasonably uniform excitation of the entire patient due to the large coil diameter. Receive coils are typically placed close to the body, and typically exhibit non-uniform coil sensitivity that is maximal at the skin surface and attenuates as a function of depth within the patient. Spatial uniformity is often traded for higher SNR provided by these coils due to enhanced induced signals from near the tissue of interest and because the small sensitive volume of the coil reduces the induced electronic noise. These receive coils can consist of a single coil loop (surface coil), or an array of coil loops encompassing a volume. Coil arrays [54] are now more commonly used in brain imaging applications, with various cylindrical [55] or partially spherical geometries [56]. In these arrays, anywhere from 4, 8, 12, 16 or 32 or more separate receiver channels can receive information from the precessing magnetization simultaneously, both linearly or in quadrature configurations. Each receive coil can be sensitive to a different volume of the sample, a property of which can be exploited for parallel imaging (see §1.6).

For fMRI experiments, additional equipment and apparatus are also often used. A projector and screen or head-mounted display are typically used to present visual information to the subject. Equipment is also used to monitor respiratory and cardiac fluctuations. A respiratory bellows can be strapped to a subject’s chest to measure respiration via chest expansion, and a photoplethysmograph placed on a finger or toe measures qualitative blood oxygenation and volume changes through the skin using infrared light absorption. This information can then be used in fMRI signal processing to remove unwanted signal fluctuations (see §1.4.4).

1.3.3 K-Space and Image Formation

The MRI signals detected at receiver coils can be expressed as:

\[ s(t) = -\frac{\partial}{\partial t} (\vec{B}_c(\vec{r}) \cdot \vec{M}_\perp(\vec{r})) \] (1.2)

which is simply a statement of Faraday’s Law of Induction, combined with the principle of reciprocity, which states that the ability of a coil to detect magnetization at a particular location is related to the strength of the field produced at that position by a unit current in the coil. Here, \( s(t) \) is the measured voltage signal, \( \vec{B}_c \) represents the vector field produced by the coil with a unit current, and \( \vec{r} \) is a spatial position vector. The component of \( \vec{B}_c \) perpendicular to \( \hat{k} \) is often represented as a complex scalar value, \( \Phi_c \), analogous to the treatment of \( M_\perp \).

More specifically, for precessing magnetization in the absence of all magnetic fields
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except $B_0$, and ignoring signal relaxation:

$$s_c(t) = \int_{Volume} M_\perp(\vec{r}) \Phi_c(\vec{r}) e^{-i\omega_0 t} d\vec{r}$$  \hspace{1cm} (1.3)$$

where $s_c(t)$ is the signal measured by coil $c$, $M_\perp(\vec{r})$ is the spatial distribution of transverse magnetization, and $\Phi_c(\vec{r})$ is the coil sensitivity for coil $c$. In MRI, the most common method for image formation is Fourier encoding. Formally:

$$s_c(\vec{k}, t) = \int_{Volume} M_\perp(\vec{r}) \Phi_c(\vec{r}) e^{-i\omega_0 t} e^{-2\pi i \vec{k} \cdot \vec{r}} d\vec{r}$$  \hspace{1cm} (1.4)$$

where $\vec{k}$ is a vector representing the reciprocal image space, or k-space, $(k_x, k_y, k_z)$ in units of $1$/length, that dictates the spatial frequency of the Fourier encoding function $exp(-i\vec{k} \cdot \vec{r})$. As data are collected at various discrete $\vec{k}$ locations, the reciprocal space becomes more fully characterized. When the reciprocal space is full (to the desired extent in k-space), data collection is finished, and the three dimensional (3D) image can be recovered using an inverse discrete Fourier Transform (DFT).

One reason that Fourier encoding is so ubiquitous is its simplicity in application. Using a set of orthogonal linear gradient magnetic fields, one can generate all the Fourier encoding steps needed to fill k-space. A 1D Fourier encoding example is presented below, with omission of the other dimensions for clarity.

A linearly varying magnetic field (for instance along the x-axis) can be represented as:

$$\frac{dB_x}{dx} = G_x$$ \hspace{1cm} (1.5)$$

where $G_x$ is the magnetic field gradient strength, commonly represented in units of $\text{mT/m}$. When the gradient is applied, the resultant net field is:

$$B(t) = B_0 + G_x x$$ \hspace{1cm} (1.6)$$

When this is substituted into the Larmor Equation, the new Larmor frequency becomes:

$$\omega = \gamma \cdot (B_0 + G_x x) = \omega_0 + \gamma G_x x$$ \hspace{1cm} (1.7)$$

Replacing $\omega_0$ with this new $\omega$ in equation 1.3, the signal becomes:

$$s_c(t) = \int_{Volume} M_\perp(\vec{r}) \cdot \Phi_c(\vec{r}) \cdot e^{-i\omega_0 t} \cdot e^{-i\gamma G_x x t} d\vec{r}$$ \hspace{1cm} (1.8)$$

Ignoring precession of the signal at the Larmor frequency (by representing the signal...
equation in a reference frame rotating at frequency $\omega_0$), and now allowing the gradient $G_x$ to be time-dependent yields:

$$s_c^o(t) = \int_{Volume} M_\perp(\vec{r}) \cdot \Phi_c(\vec{r}) \cdot e^{2\pi i \gamma \int_0^t G_x(\tau) d\tau} d\vec{r} \quad (1.9)$$

where $s_c^o$ denotes the signal after demodulation of the carrier frequency $\omega_0$). Here the influence of $G_x(t)$ is now integrated over time, and equation 1.9 reduces back to 1.8 when $G_x(t)$ is constant and the Larmor precession term is re-introduced. With the following definition:

$$k_x(t) = \frac{\gamma}{2\pi} \int_0^t G_x(\tau) d\tau \quad (1.10)$$

the baseband signal equation takes the form:

$$s_c^o(t) = \int_{Volume} M(\vec{r}) \cdot \Phi_c(\vec{r}) \cdot e^{-2\pi i k_x(t) x} d\vec{r} \quad (1.11)$$

With $k_y(t)$ and $k_z(t)$ defined similarly, and $\vec{k}$ defined as $k_x \hat{i} + k_y \hat{j} + k_z \hat{k}$, then:

$$s_c^o(t) = \int_{Volume} M(\vec{r}) \cdot \Phi_c(\vec{r}) \cdot e^{-2\pi i \vec{k}(t) \cdot \vec{r}} d\vec{r} \quad (1.12)$$

Thus, $s_c^o$ is the continuous Fourier Transform of $M_\perp(\vec{r}) \cdot \Phi_c(\vec{r})$, given that $M_\perp$ is non-zero only inside the sample volume. For now, the effects of $\Phi_c(\vec{r})$ are neglected, as this term typically varies slowly and smoothly with space. Also, from this formulation, the TE in a gradient-echo sequence can be viewed as the time at which the 0th moment of the readout gradient waveform is nulled, corresponding to the $k = 0$ point in k-space along that gradient axis, and a local signal maximum (the gradient-echo).

Ignoring for now other practical limitations due to noise, acquisition time, or motion in human subjects, one can theoretically design an MRI measurement to cover any range of spatial frequencies $k_x$, $k_y$ and $k_z$ in “k-space”, with an arbitrary sampling density. The pattern and order in which k-space is covered is typically called the k-space “trajectory”. Output images of the spatial distribution of $M_\perp$ are obtained by applying the inverse DFT to the k-space data. The desired spatial resolution dictates the extent that k-space must be sampled. Practically speaking, spatial resolution is limited by a number of factors, including gradient strength and switching limits, SNR, imaging time, and signal decay.
The key relationship between spatial resolution and k-space sampling is:

\[ \Delta x = \frac{1}{k_{x\text{Max}}} \]  

(1.13)

where \( \Delta x \) is the voxel spacing in image space, and \( k_{x\text{Max}} \) is the largest spatial frequency sampled. The same holds for \( \Delta y \) and \( \Delta z \) using \( k_{y\text{Max}} \) and \( k_{z\text{Max}} \), respectively. This is intuitive when one considers that higher spatial frequencies contain more detail for reconstruction of edge detail in images, required for higher spatial resolution. The image field-of-view (FOV) is also a function of a simple k-space property,

\[ FOV_x = \frac{1}{\Delta k_x} \]  

(1.14)

where \( FOV_x \) is the extent of the reconstructed image boundary, and \( \Delta k_x \) is the distance between k-space samples. Higher k-space sampling densities (smaller distance between samples) lead to larger FOVs. This is intuitive, considering that while no more detail is attained without any higher frequencies, more data is being acquired with denser sampling of a resolution-fixed \( k_{x\text{Max}} \) k-space interval. More k-space samples leads directly to more image voxels, which extends the FOV, and follows directly from the definition of the DFT, in which N k-space samples produces N unique image voxels.

It should be noted that the equations for \( \Delta x \) and \( FOV_x \) are symmetrical with \( \Delta k_x \) and \( k_{x\text{Max}} \), due to the symmetry in the forward and inverse Fourier transforms. Because encoding in the x-, y- and z-directions are independent of one another, resolution and FOV extents can be different in different directions. Furthermore, it is common to employ Fourier encoding in only two dimensions, using other techniques such as slice-selective excitation to provide spatial selectivity along the third direction (usually designated as z) direction. Briefly, slice selective excitations typically employ a combination of band-limited RF pulses and linear gradients to excite magnetization in “slices” of user-defined width, so that 2D imaging can be performed without needing to encode in k-space along the entire slice direction.

This elegant and powerful k-space interpretation of spatial localization is based on the principles initially developed by Lauterbur and Mansfield in the mid 1970s (e.g. \[57, 58\]), which led to their shared Nobel Prize in Medicine in 2003. The first descriptions of the k-space representation of MRI data came in the early 1980s, first by Brown et al. in 1982 [59] and with subsequent elaboration by Ljunggren [60] and Twieg [61] in 1983. In §1.6, the theory of spatial encoding is generalized to include the extra information contained in the coil sensitivities. In almost all applications of MRI however, the primary burden of spatial encoding is placed upon the gradients in populating k-space. The following
sections describe the application of standard MRI methods to the measurement of brain function, from the basis of the biophysical signals to the methods for statistical inference of brain activity.

1.4 Functional MRI Basics

Functional MRI employs MRI techniques to measure an index of brain physiology, rather than brain anatomy. Most fMRI acquisitions measure quantities related to blood flow and the vascular system. For example, arterial spin labelling (ASL) techniques measure blood perfusion, and blood oxygen level dependent (BOLD) fMRI is sensitive to changes in blood oxygenation. Of the two techniques, BOLD fMRI is primarily used to infer neuronal activity, and this thesis focuses solely on the application and development of BOLD fMRI methods. All subsequent mention of fMRI relates to BOLD fMRI signals, unless otherwise specified.

There are considerable differences between the data generated by fMRI compared to that generated by anatomical MRI. Anatomical MRI provides static, high resolution images that help visualize the spatial configuration of tissues. Typically, fMRI involves time-series data acquisition as a 4-dimensional (4D) dataset, with three spatial dimensions and one time dimension. A succinct introduction into the complex relationship between BOLD contrast and neurovascular activity, as well as fMRI acquisition and analysis methods, is provided below.

1.4.1 The BOLD Response

The term BOLD was first coined in a 1990 paper by Ogawa et al. describing the use of the BOLD effect as a marker for “physiological events” that change the blood oxygenation state of the brain [62]. This initial work built on research in the late 1980s [63, 64], that investigated how the transverse relaxation rate $T_2$ depends on blood oxygenation [65].

The most common contrast parameter exploited in fMRI is $T_2^*$, and this type of relaxation is typically captured using “Gradient Echo” pulse sequences. At field strengths of 1.5 T and 3.0 T, these sequences provide more BOLD signal contrast than sequences sensitized to $T_2$ relaxation. Hemoglobin (Hb) is present in the blood pool in both oxygenated (oHb) and deoxygenated (dHb) states, where the exact proportion is mediated by various vascular and metabolic factors. The magnetic properties of these two states are different: oHb is diamagnetic (i.e. small, negative magnetic susceptibility); dHb is paramagnetic (i.e. larger, positive susceptibility). The existence of this difference is
critical to the measurability of the BOLD response in MR imaging. Because dHb is paramagnetic, positive contributions to the net magnetic field are produced from each paramagnetic molecule. This creates local magnetic field inhomogeneity within the vascular compartment and surrounding tissue, contributing to changes in the $T_2$ and $T_2'$ decay constants which is detected by $T_2^*$-weighted imaging.

The $T_2$ and $T_2'$ changes are mediated by the same effect, on different spatial scales. In fMRI, $T_2$ changes are mediated by dynamic, small-scale inhomogeneities that impart random, un-refocusable phase changes due to local water diffusion. During signal measurement, spins that experience different magnetic field variations along their diffusion paths will dephase, leading to an apparent drop in $T_2$. Generally, smaller vessels and capillaries are small enough to produce field gradients that change significantly over diffusion length scales ($D = 1 \, \mu m^2/\text{ms}$), which is why $T_2$-weighted fMRI is considered more sensitive to small vessels. In contrast, $T_2'$ effects are caused by field inhomogeneities that are large with respect to diffusion length scales, which are easily refocused by reversing the phase evolution of magnetization in the transverse plane using RF pulses. This is why $T_2$-weighted fMRI is measured using the spin-echo technique, to avoid unwanted $T_2'$ contrast, whereas $T_2^*$-weighted fMRI is measured using gradient-echo techniques, which incorporates both $T_2$ and $T_2'$ effects. The strength of dynamic averaging $T_2$ effect, however, depends on the square of the field strength $[66]$, which is why its application is typically restricted to fields $> 3.0$ T. Because most of the work here contains development at 3.0 T, discussion is subsequently confined to $T_2^*$ (or $T_2'$) BOLD effects. It should be noted that at field strengths of 3.0 T and below, the intravascular compartment can also contribute significantly to the measured BOLD signal $[67]$. This is due to the direct effect of dHb on the blood $T_2$ and $T_2^*$ via water exchange through red blood cells and plasma water diffusion, which does not have a large impact on BOLD signals at 4.0 T or above due to the rapidly diminishing $T_2$ and $T_2^*$ values of blood at higher field strengths.

The relationship between the positive (MR signal increase) BOLD response and increased neuronal activity has been characterized by relating the BOLD signal with local field potentials measured in neuronal assemblies $[68]$. The causal biological relationship, however, between neuronal activity and the BOLD response is still an area of open research. One proposed mechanism is that with neuronal firing, the accompanying calcium signalling in astrocytes mediates a vasodilatory response in the cerebral microvasculature $[69]$. Cerebral blood flow, volume, oxygen extraction to the surrounding brain tissue, and local vascular structure all contribute to the ensuing changes in the oxygenation content of blood, resulting in a signal that is a complex function of many physiological variables.

This complex output produces values that cannot easily be expressed in physical
units and is why most BOLD fMRI is considered non-quantitative, although biophysical BOLD models do exist. Units of percent signal change are commonly used to express BOLD amplitudes; for example, typical motor BOLD responses reach amplitudes of a few percent with a maximum about 4-5 seconds after initial response (measured at 4.0 T), although there is significant intra- and inter-subject variability [70]. Negative BOLD responses can occur as well, in which a sustained decrease in MR signal can result from factors such as neuronal inhibition and reduced blood flow [71].

Examples of some of the biophysical BOLD models include the dHb dilution model, which characterizes the steady-state BOLD response as a function of the cerebral blood flow (CBF) and blood volume (CBV), rate of metabolic consumption of O2 (CMRO2) [72, 73]. Another model of the BOLD response, called the “Balloon Model” [74], captures transient response dynamics by modelling vascular volume changes as an elastic compartment that responds to input pressures and blood flow, coupled with equations for dHb content and the MR signal dependence on volume and dHb to describe a BOLD signal change. In effect, changes in CBF, CBV and oxygen extraction and CMRO2 modify the amount of dHb present in the non-arterial blood during neuronal “activity”, resulting in changes of the apparent voxel averaged $T_2$ and $T_2^*$ relaxation times, which is measured as the BOLD signal. What follows is a more detailed explanation of how this BOLD signal contrast is generated by MR.

1.4.2 BOLD Contrast

In $T_2^*$-weighted fMRI, the contrast of interest arises from the observed changes in $T_2^*$:

$$S = S_0 e^{-TE \cdot R_2^*}$$  \hspace{1cm} (1.15)

where the decay rate $R_2^* = 1/T_2^*$ and $S_0$ is the MR signal at time $t = 0$ (immediately after the RF pulse). Differentiating with respect to $R_2^*$ yields:

$$\frac{dS}{d(R_2^*)} = -TE \cdot S; \Delta S = -TE \cdot \Delta R_2^* \cdot S$$  \hspace{1cm} (1.16)

From equation 1.16, it is evident that the signal contrast is proportional to $TE$, $\Delta R_2^*$, and $S$. Because $S$ decays exponentially, $\Delta S$ goes to zero when the TE is very small or very large. Because $S$ is also dependent on $TE$ (see equation 1.15), the overall dependence of $\Delta S$ on $TE$ can be expressed as:
\[
\frac{d(\Delta S)}{d(TE)} = -\Delta R^* \cdot S + TE \cdot R^* \cdot \Delta R^* \cdot S = (-1 + TE \cdot R^*) \cdot \Delta R^* \cdot S \quad (1.17)
\]

Setting equation 1.17 equal to zero indicates that a maximum of \( \Delta S \) occurs at \( TE = T2^* \), and that the strength of the BOLD signal contrast scales linearly with \( \Delta R^* \).

### 1.4.3 fMRI Acquisition Parameters and Data

As mentioned, most fMRI acquisition methods acquire 4D datasets, building a time series of 3D image data. To do this efficiently, large portions of k-space are acquired after each excitation. Commonly, 3D volumes are composed by concatenating a stack of 2D images (resulting in a non-isotropic voxel point spread function), each defined by a slice selective excitation. The spatial encoding of each slice can be performed by measuring k-space using a number of different readout trajectories, but the most popular is echo planar imaging (EPI). During EPI, 2D k-space is covered in a rectangular raster pattern, acquiring each row in 2D k-space in succession (e.g. from the bottom up). The EPI acquisition scheme provides data at a reasonable spatial resolution (3 mm x 3 mm x 5 mm is a typical voxel size) across the brain with TR of 1 – 2 s, depending on the extent of spatial coverage desired. Such rapid sampling is required to capture transient features of the BOLD hemodynamic response occurring on the scale of seconds.

Because MRI signal contrast is dictated by a combination of TR and TE, contributions of \( T1 \)-weighting and \( T2^* \)-weighting are present in the images. However, because fMRI signals are interpreted as percentage signal changes, any signal components that are constant with respect to brain activity do not contribute to the fMRI signals of interest. One effect, the \( T1 \)-related signal enhancement due to inflow of new, fully relaxed spins (at thermal equilibrium) from outside the imaging regions may increase dynamic signal amplitudes at short TRs. To understand this phenomenon, consider some magnetization that has been exposed to repeated RF excitations at short TRs. If the TR is not significantly longer than the \( T1 \) of that magnetization, the spins will not have enough time to return to thermal equilibrium. Now consider the replacement of that magnetization with new, fully relaxed magnetization, through inflow or some other mechanism. A signal increase will be observed due to the increase in available longitudinal magnetization for the subsequent measurement. Strategies to mitigate \( T1 \)-related inflow effects exist, including reduction of the excitation flip angle or using a specially modified imaging sequence \[75\].

Judicious choice of TE also must be made to balance considerations of BOLD signal contrast, acquisition time, and unwanted signal “artifacts”. As seen in the previous
section, maximum $T2^*$ contrast occurs at $TE = T2^*$. Setting the TE value too low incurs a BOLD contrast penalty. At 3.0 T, although $T2^*$ of grey matter is approximately 50 ms, the TE values are often set at approximately 30 ms for EPI acquisitions, to avoid geometric distortion arising from magnetic field inhomogeneity [76] and signal attenuation. Geometric distortions such as image shearing or stretching are particularly pronounced in EPI acquisitions because of the relatively long duration of the k-space data collection, during which phase errors can accumulate. Signal attenuation due to $T2^*$ relaxation can also cause image blurring, due to the convolution filter incurred by weighting k-space samples with exponentially decreasing signal amplitudes.

In addition to the BOLD signals of interest, fMRI time series data also include contributions from various noise sources, including head motion, respiratory and cardiac physiological effects, intrinsic noise (also referred to as thermal, or electronic noise), and MRI system instability. Head motion can introduce spurious signal change due to position changes within the MRI system [77], as well as image blurring and distortion [78, 79]. Signal fluctuations can also arise from cardiac pulsatility, from magnetic susceptibility effects related to lung cavity volume changes while breathing, and even from changes of $CO_2$ in arterial blood related to respiration rate fluctuations [80]. Intrinsic noise contributions are typically dominated by time-varying magnetic fields generated by ions undergoing random motion in tissues, which subsequently couple with the receive coils [81] and add Gaussian white noise. All these sources of noise reduce the fMRI signal-to-noise ratio (SNR). A simple model of fMRI noise developed by Kruger et al. [82] models physiological (signal-dependent) and intrinsic (signal-independent) noise effects and their TE-dependent variances:

$$\sigma^2 = \sigma_0^2 + \sigma_P^2 = \sigma_0^2 + c_1(TE)(\Delta R2^*)(S^2) + c_2S^2$$ (1.18)

where $\sigma^2$ is the total fMRI noise variance, $\sigma_0^2$ is the intrinsic noise variance, and $\sigma_P^2$ is the physiological noise variance. The constants $c_1$ and $c_2$ govern the strength of the “BOLD-like” and “non-BOLD” noise terms respectively, which in this model are both proportional to the signal S.

### 1.4.4 fMRI Data Analysis

Analysis of a 4D fMRI dataset is normally preceded by a number of pre-processing steps prior to the estimation of brain activity. For example, head motion artifacts in fMRI signals can be reduced through retrospective (post-acquisition) 3D motion registration [83] and physiological noise by monitoring respiratory and cardiac signals and applying
retrospective gating algorithms to correct for artifacts according to the position of the fMRI signals within the respiratory or cardiac cycle [84].

In addition to head motion correction and physiological noise removal, pre-processing of fMRI data can involve a number of operations, including: removal of non-brain voxel data (i.e. “masking”); slice timing correction to adjust the timing of slices that are acquired at different time points (in EPI for example, slices are acquired sequentially in time, distributed across the volume TR, and interpolation is used to bring the data from each slice to a common time point); spatial normalization to warp brains onto a standard template for inter-subject comparison; and spatial smoothing with a 2D Gaussian kernel to increase SNR. Although detailed discussion of the benefits of each pre-processing operation are not presented here, it is important to recognize that there is no standard governing consistent application of these pre-processing operations. In fact, some believe that no “one size fits all” pre-processing pipeline can exist, and that pipelines should be evaluated and optimized for each subject individually [85].

Two major fMRI analysis techniques are now briefly reviewed, as they are widely adopted and used subsequently in this thesis. The General Linear Model (GLM) is the most common approach, and the Partial Least Squares (PLS) method is employed in Chapter 2.

Statistical analysis in fMRI began in the early 1990s by building voxel-wise statistical parametric maps (SPMs) from correlation coefficients calculated between the voxel fMRI signal and a model waveform [86] representing the task design (see below). Soon after, Friston et al. introduced the GLM framework to PET and fMRI analysis [87]. The GLM method builds voxel-wise SPMs from a multiple linear regression. In the GLM, the measured time series is modelled as a linear combination of one or more regressors or explanatory variables (EVs), nuisance covariates that model expected, but undesirable signal contributions, plus a random error term (frequently a zero mean Gaussian distribution, although more sophisticated autoregressive noise models or noise-whitening procedures can be incorporated into the GLM analysis [88]).

In fMRI experiments, there are two major classes of experiments that can be undertaken. In “block-design” experiments, subjects are typically asked to perform tasks or receive sensory stimuli over repeated, sustained intervals, whereas in “event-related” experiments, tasks or stimuli are repeated across numerous short instances or events. Timing information relating to the onset and duration of these tasks and stimuli can be used to populate the regression model. For brevity, only block-designed experiments are discussed here, although fMRI analysis principles are similar for both cases.

The basic formulation of the GLM is (for each voxel):


\[ Y = X\beta + \epsilon \]  

(1.19)

where \( Y \) is a \( N \times 1 \) time series vector of the measured BOLD data; \( X \) is a \( N \times q \) matrix of regressors, where each of the \( q \) columns is a time series EV or nuisance regressor; \( \beta \) is a \( q \times 1 \) vector of regression coefficients; and \( \epsilon \) is the noise term. The variable \( X \) is often referred to as the “design matrix”, and typically contains one column representing a baseline signal, and at least one other model EV representing the expected BOLD signal in response to stimulus or change in cognitive state. To account better for the temporal response to neuronal activity, hemodynamic impulse response functions (HRFs) can be convolved with experimental timing data, such as stimulus presentation waveforms or button press times, to produce expected BOLD responses. Approaches have also been developed to deconvolve neuronal timing data and the HRF using finite impulse response models, so that the HRF waveform can be determined from the data specific to each voxel and task [89]. Nuisance regressors can include terms like low order polynomial waveforms that represent slow baseline signal fluctuations.

Solving the linear system presented in equation 1.19 typically proceeds by ordinary least squares estimation of the vector \( \beta \):

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

(1.20)

where \( \hat{\beta} \) is the vector of estimated model coefficients made by computing the Moore-Penrose pseudo-inverse of \( X \). One example of simple null hypothesis testing \( H_0 : \beta_q = m \) (where \( m \) is often taken to be 0) can proceed by computing the following t-statistic:

\[
T = \frac{c^T \hat{\beta} - m}{\sqrt{\hat{\sigma}^2 c^T (X^T X)^{-1} c}}
\]  

(1.21)

where \( c \) is a vector with a single non-zero component selecting the \( q^{th} \) model coefficient, \( m \) is the value \( \beta_q \) is being compared with, and \( \hat{\sigma}^2 \) is an estimate of the residual variance. With t-statistics for each model component for each voxel, SPMs can be drawn after thresholding the t-values for significance. This type of analysis only evaluates whether the fMRI time series at each voxel was significantly “activated” during experimental conditions, where “activated” here means that the model estimate corresponding to the condition is significantly different than 0. Often a two-tailed t-test is performed, because activation can take the form of positive or negative BOLD responses. Clustering can also be performed on the resultant SPMs to produce multi-voxel regions with significant responses to conditions that meet some minimum volume threshold criterion. Correcting
for multiple comparisons can be performed on a per-voxel or per-cluster basis [90], and
to facilitate comparison between SPMs, the t-score statistics can be converted to z-
scores. The GLM framework also supports other significance testing methods, such as
the analysis of variance (ANOVA), to answer different questions pertaining to the chosen
experimental design.

Although GLM approaches have become pervasive in fMRI analyses, they are univari-
ate. They analyze single voxels independently, although spatial smoothing can reduce the
number of independent degrees of freedom. However, it is reasonable physiologically to
expect network connectivity between different brain regions, and thus related patterns of
activations. Numerous multivariate methods have been developed to generate images of
brain activity according to these expectations. In each, data from all voxels are analyzed
and decomposed as a whole. In addition to PLS [91], examples of multivariate analy-
sis methods include independent component analysis (ICA) [92] and canonical variates
analysis (CVA) [93]. Typically, a priori models of BOLD signal responses (like EVs) are
not necessary to produce spatial maps of brain activity by multivariate methods. In-
stead, assessments of activation are derived from features within the data, often without
requiring specific hypothesis testing.

In PLS, the primary analysis step is the singular value decomposition SVD of a cross-
covariance matrix:

\[ A \Sigma B^T = \text{SVD} [S] = \text{SVD} [\text{cov}(X, Y)] \] (1.22)

where \( A \) and \( B \) contain the left and right singular vectors respectively, and \( \Sigma \) is a diagonal
matrix of singular values. The matrix \( S \) is a cross-covariance matrix between the data
contained in \( X \) and \( Y \). This covariance matrix is built up in a number of different
ways, resulting in different types of PLS analysis (task PLS, behavioural PLS, seed
PLS, spatiotemporal PLS). For example, let \( X \) contain the fMRI image data, containing
\( m \) vectors of \( k \) elements, where \( m \) is the number of voxels, and \( k \) is the number of
experimental conditions, with the BOLD time series data averaged across each condition.
The specific choice of \( Y \) determines the type of PLS analysis: task-PLS results if \( Y \)
contains experimental design contrasts (e.g., dummy variables labelling different task
conditions); behavioural-PLS results if \( Y \) contains behavioural data (e.g. reaction time
measures); and seed-PLS results if \( Y \) is generated from averaged BOLD data from a seed
voxel in the brain. In these cases, the \( n \) elements of \( Y \) must have dimension \( k \), so that \( S \)
has dimension \( n \times m \), and \( S_{ij} \) refers to the covariance between \( Y_i \) and \( X_j \).

The SVD in equation 1.22 produces a decomposition of the data such that the columns
in \( A \) are singular vectors, or saliences, for the external data \( Y \), and and the columns of
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$B$ correspond to the saliences for the image data. When the original data are projected onto the saliences, the results are called latent variables (LVs):

$$LV_x = XB$$
$$LV_y = YA$$

(1.23)

PLS produces pairs of LVs that maximize their shared covariance. The number of LVs output is $k \times g$, where $g$ is the number of subject groups, because $k$ is almost always smaller than $m$.

Tests for statistical significance are performed non-parametrically in PLS through two mechanisms: permutation testing and bootstrap resampling. In the permutation test, task condition labels are randomly swapped within subjects and across groups without replacement, and a full PLS decomposition is performed for each permutation. This is typically repeated for 500 or 1000 permutations, and a null distribution of singular values is built for each LV. If only $p\%$ of the permuted singular values exceeds the originally computed singular value, then the LV corresponding to that singular value is statistically significant if $p < \alpha$ for some threshold $\alpha$ (where $\alpha$ is typically chosen to be 0.05). Following the permutation test, a bootstrap resampled estimate of the reliability of each voxel salience is calculated. Within conditions, subjects are resampled into new groups with replacement. Again, PLS decompositions are performed, and after some number of resamples, typically around 100, estimates of the standard error for the saliences of each can be found. The bootstrap ratio for each voxel is then defined as:

$$BSR = \frac{\text{salience}}{SE(\text{salience})}$$

(1.24)

where $SE(\cdot)$ denotes the standard error of the mean. Bootstrap ratios are similar to $z$-scores, and are also thresholded for significance. BSR values greater than 3 correspond to 99% confidence intervals. The LV maps are not subject to multiple comparison corrections because the salience decomposition is calculated in a single mathematical operation [94]. At this stage, the spatial BSR map for each significant LV is comparable to the SPM output by a GLM analysis, and interpretation can proceed accordingly.

1.5 The Multi-Echo Coarse Voxel Sequence

In section 1.4.3, equation 1.16 described the fMRI signal contrast as a function of TE. In conventional acquisitions, $\Delta S$ is sampled once at a specifically chosen TE value. Multi-
echo fMRI techniques extend this approach by sampling the contrast curve at multiple TE values following the same excitation, where the multiple contrast samples can be combined into a single representative $T2^*$-weighted data point. This enhances the fMRI signal contrast in the measured data, depending on the combination method used and the noise characteristics of the measured data. Following multi-echo signal combination, multi-echo datasets are identical to those from conventional acquisition, and can be analyzed by traditional means. This approach is useful not only because it can produce contrast-to-noise ratio (CNR) increases of 200 – 500% compared to traditional single-echo acquisitions [95], but because it can also provide multi-contrast information. For example, signals acquired at low TE values are primarily spin-density and $T1$-weighted, with little $T2^*$-weighting. This information can be used to distinguish and remove spurious signal changes that do not correspond to the fMRI signals of interest [96]. Furthermore, multiple samples of the $T2^*$ signal decay can enable more quantitative signal processing strategies, such as direct estimation of the $T2^*$ values.

Two different approaches can be used to acquire multi-echo fMRI data: full-FOV and reduced-FOV methods. In full-FOV methods, the spatial resolution and coverage of the data are the same or similar to those of conventional acquisitions. Because time is required to traverse all of k-space in a single EPI shot per slice, only a small number of echoes can be acquired, even with the use of parallel imaging methods to speed up acquisition times (see §1.6) [97]. In reduced-FOV methods, spatial coverage is reduced for expanded sampling of the echo time domain, and hundreds of echoes can be measured in a single excitation [98].

The most common type of whole-brain multi-echo acquisition employs a multi-echo EPI readout. The number of echoes that can be collected depends on the imaging parameters, particularly the number of slices and the TR. In a 36-slice acquisition with a 2.5 s TR for example, only 4 echoes were acquired, even after using parallel imaging acceleration methods [99]. Because imaging time in EPI acquisitions is proportional to the number of acquired slices, reducing the number of slices can increase the number of possible echoes measured. An older study using a 4-slice acquisition, without any parallel imaging, was able to collect 12 echoes with a TR as low as 1 s [100]. Because reducing the number of slices and increasing the parallel imaging acceleration factors can only improve imaging times up to a certain limit, acquisition of a larger number of echoes requires reduction of the FOV. Removing one or more dimensions of spatial encoding allows for more time spent crossing the k-space origin, collecting signal contrast information rather than spatial information. Early fMRI studies using spectroscopic imaging techniques like point resolved spectroscopy (PRESS) collected 1024 points (equivalent to echoes) at 1
ms intervals [101]. This spectroscopic acquisition however, acquired fMRI data from only a single coarse voxel (20 x 20 x 20 mm³).

The multi-echo coarse voxel (MECV) prototype technique developed in the Graham laboratory sought to find a compromise between full-brain coverage with few echoes, and single voxel coverage with many echoes [98]. In the MECV technique, an arbitrarily oriented column of voxels is acquired (i.e., reducing the 2D FOV), while acquiring up to 256 gradient echoes per excitation. This acquisition facilitated simultaneous data collection from certain selected brain regions, such as both primary motor cortices, and the dense sampling of gradient echoes facilitated the exploration of different echo combinations to boost fMRI signal contrast and facilitated real-time fMRI for NF. The reduced FOV provided by the MECV acquisition is suitable for ROI-based NF because the columnar FOV can measure fMRI data from at least two different ROIs across the brain, and most ROI-based NF is performed with one or two ROIs.

The MECV pulse sequence diagram in Fig. 1.1 shows the combination of outer volume suppression for spatial presaturation and unipolar “flyback gradients” for multi-echo readout used in the MECV sequence. To isolate the column of magnetization, selective RF pulses were applied in two orthogonal directions and used to suppress magnetization in those regions, leaving a plane of unsuppressed magnetization in each case. To reinforce spatial localization, a slice selective excitation was applied along one of the same dimensions. The intersection of the two orthogonal planes defined a column of unsuppressed, excited magnetization. Following this magnetization preparation, a frequency encoding gradient along the direction of the column encoded spatial information during readout. The gradient used a “flyback” k-space trajectory, where data were acquired only during the flat-top portion of the positive lobe (i.e., traversal of k-space lines in a single direction). The negative rewind lobes were designed to rephase magnetization as quickly as possible within the slew-rate hardware limit of the imaging gradients. Acquiring k-space lines in a single direction avoids errors that can occur when alternating directions, caused by slight asymmetries in positive and negative gradient waveforms.

The dense echo sampling provided by the MECV pulse sequence motivates a detailed analysis of multi-echo combination methods and the specific CNR optimizations available for this type of data. This investigation is presented in Chapter 3.

1.6 Parallel Imaging

The prototype MECV sequence warranted further development, because a single column excitation is not sufficiently flexible. One option worth exploring is to use “parallel
Figure 1.1: Pulse sequence diagram of the MECV pulse sequence. (a) Conceptual diagram indicating the components of outer volume saturation (OVS) in three spatial dimensions, slice-selective excitation to improve spatial localization, and subsequent readout providing a column of coarse voxels. (b) Outer volume very selective saturation (VSS) and 90° slice selection RF waveforms, and gradient waveforms in the x-, y- and z-directions. (c) Excitation and data acquisition portion of the pulse sequence showing flyback gradient echo train (modified from [98]).
imaging” principles to provide rapid fMRI acquisitions from a small number of coarse voxels placed arbitrarily in space. A brief discussion of parallel imaging principles follows to explain the attractive features of such an approach. As mentioned in section 1.3.3, the receive coils in MRI are used to measure signal induced by magnetization precessing in the transverse plane. In conventional 2D Fourier transform imaging, receive coils do not normally provide spatially resolved information, because the signals measured by each coil are integrated over the entire imaging volume (see 1.3). Parallel imaging techniques like SENSE [102], or SMASH [103] and GRAPPA [104], however, have been able to use coil sensitivity information to reduce the amount of data acquisition required in k-space for spatial encoding and subsequent image reconstruction. This reduction enables smaller TR values and can greatly improve temporal resolution in fMRI. In general, parallel imaging methods can be considered in a linear system framework [105], which is briefly described here. Because the DFT is a linear transform operating on a finite dimensional space (i.e., only a finite number of k-space samples are acquired), Fourier encoding of MRI data can be considered in a matrix formulation:

\[ y = Ex \]  

where \( y \) is a vector of all the k-space data, \( x \) is a vector containing the spatial magnetization data, and \( E \) is an encoding matrix, where in this case each row represents a spatial distribution of phases corresponding to a particular k-space location. The number of columns in \( E \) is the same as the number of elements in \( x \), and the number of rows (or encoding steps) in \( E \) is equal to the number of elements in \( y \). For each row in \( E \), the complex magnetization is multiplied at each location by a phase modulation, then summed together and placed in the appropriate location in \( y \). This is equivalent to a discretized version of equation 1.12, again neglecting coil sensitivities for the moment. Each element of \( E \) is defined as:

\[ e_{ij} = \exp(-2\pi i \vec{k}_i \cdot \vec{x}_j) \]  

where \( \vec{k}_i \) corresponds to the \( i^{th} \) k-space location and \( \vec{x}_j \) corresponds to the \( j^{th} \) image voxel.

The matrix equation 1.25 is presented as a forward problem, but the vector \( x \) of voxel magnetizations is actually the quantity to be determined (reconstructed) from the k-space data \( y \). After collection of all the data in \( y \), the image \( x \) can be determined by left multiplying \( y \) with the inverse of \( E \), \( E^{-1} \). For \( E \) to be directly invertible, it must be square (i.e., \( i = j \)) and full rank (each encoding step must be linearly independent
of all others). Fourier basis functions satisfy the latter requirement, as they form an orthonormal basis set. Inverting the matrix $E$ to solve for $x$ is equivalent to performing an inverse discrete Fourier transform in this framework:

$$x = E^{-1}y$$

(1.27)

This linear system formulation suggests that any basis set that spans the voxel space can also be used to encode spatial information, given an encoding strategy that can be physically realized, and that $E^{-1}$ can be determined. In parallel imaging, the spatial pattern of coil sensitivities is used to collect additional projections of the magnetization, providing a portion of the information in $E$ and reducing the number of gradient encoding steps needed in k-space, resulting in decreased scan time.

In more detail, parallel imaging employs a mix of coil and Fourier encoded data. The acceleration factor dictates what proportion of the Fourier encoding matrix is replaced by coil sensitivity encoding rows. For example, an acceleration factor of 3 means that only a third of full k-space is acquired by gradient encoding rows of $E$ (reducing scan time by a factor of 3). The remaining two-thirds of the missing information is synthesized by the coil encoding information. The SENSE method, for example, uses the incomplete k-space data to reconstruct images from each coil, where each image is corrupted by aliasing (overlapping image regions) artifacts caused by the effective under-sampling of k-space. The aliased images contain different information according to the sensitivity profiles of the coil they were produced from, where each coil sensitivity profile provides a different weighting of the underlying magnetization data. To remove aliasing from the images, the coil sensitivity information is used to invert a second linear system, producing the final full image. The two step reconstruction process in SENSE differs from the approach taken in SMASH and GRAPPA, in which the missing k-space data are synthesized directly from the measured k-space data from each coil, and the inverse DFT occurs as a final step, instead of the first. Without going into mathematical detail, these methods fill in the missing k-space encoding rows by computing linear combinations of the acquired k-space lines, given that the data from each coil are modulated by different spatial coil sensitivity profiles. The exact method of the determination of the weights for these linear combinations, and whether additional coil sensitivity calibration data are used distinguishes SMASH, GRAPPA and other variations of these methods from one another.

The number of independent degrees of freedom provided by the different coil sensitivities typically limits the achievable acceleration factors. For example, in the SENSE reconstruction problem, a reduction factor of 3 produces the same factor of aliasing.
To remove this aliasing, at least 3 linearly independent coil projections are needed to ensure the inverse problem is well-posed (i.e. a stable, unique solution exists). With multi-channel head coils providing up to 32 different coil elements, these acceleration factors are easily supported. However, the potential for noise amplification places a practical limit on the acceleration that can be achieved. The noise amplification depends on the precise structure of $E$ and in SENSE reconstruction, for example, the precise structure of the coil encoding matrix. The noise amplification is typically quantified by a spatially varying measure called the geometry factor, or g-factor [102], that generally increases with increasing acceleration factors. Similar limitations exist for the SMASH and GRAPPA methods, although the noise amplification behaviour is more complex. In standard applications, noise amplification typically restrict acceleration factors to the range of $2 - 4$, and significant amounts of k-space are still acquired through gradient encoding.

One important observation that follows from this formulation is the idea that by limiting the spatial dimensionality, all the spatial information contained in the image may be captured by the degrees of freedom provided by coil sensitivities, assuming a sufficient number of available coils. With some means to constrain the number of source voxels, it can become possible to encode all available spatial data using multi-channel coil projections without requiring any gradient encoding steps. This idea forms the basis for the constrained source space imaging (CSSI) work presented in Chapter 4.

1.7 Hypotheses and Thesis Outline

This thesis focuses on both the application and development of methods for investigating fMRI NF. This two-pronged approach to fMRI NF development is expected to provide insight into NF methodology and efficacy, while simultaneously working towards useful alternatives to standard EPI acquisitions in fMRI NF with ROI-targeted, high-temporal resolution, multi-echo acquisitions.

Chapter Two investigates the hypothesis that fMRI NF using kinesthetic motor imagery facilitates direct self-regulation of BOLD responses in primary motor regions, and investigates the brain activity that must be engaged to support NF training. This work, performed with standard EPI acquisition, also addresses questions of subject response variability to NF training, and laterality interactions between left and right primary motor cortex, analyzed using the PLS technique.

Chapters Three and Four explore the development of strategies for improving fMRI data quality and data acquisition methods to support future NF studies. The hypoth-
esis for Chapter Three is that the CNR of multi-echo fMRI data can be significantly increased with dense sampling and knowledge of the particular noise conditions present during acquisition, through use of appropriate multi-echo weighting methods. The dense multi-echo sampling provided by the MECV sequence is analyzed using existing and new methods for multi-echo data analysis. The MECV data are characterized as a function of acquisition parameters and noise properties, and CNR gains are compared to the CNR levels obtained in traditional acquisitions.

Chapter Four tests the hypothesis that it is possible to generate high quality BOLD fMRI data at sub-second temporal resolution from multiple coarse voxels without gradient encoding, using a purely coil encoded acquisition. The CSSI technique improves upon the MECV sequence by including more flexibility in ROI placement through novel source constraint methods and increases achievable temporal resolution using parallel imaging. The spatial encoding theory and development of a proof-of-principle pulse sequence are described, and the resulting BOLD measurement capabilities are validated in a simple hand motor task.

Finally, Chapter Five describes the future directions of fMRI NF including applications to stroke rehabilitation, and future work that could be undertaken based specifically on the thesis results.
Chapter 2

Investigation of fMRI
Neurofeedback of Differential Primary Motor Cortex Activity using Kinesthethic Motor Imagery

by Mark Chiew, Stephen M. LaConte, and Simon J. Graham

2.1 Introduction

Functional magnetic resonance imaging (fMRI) has become a viable technique for investigating how individuals can regulate their brain activity. Real-time fMRI (rt-fMRI) enables measurements and analyses of blood oxygenation level dependent (BOLD) signals spatially localized on the scale of millimetres to centimetres [106, 107] with a temporal resolution of approximately seconds or less. These signals can then be presented in the form of sensory stimuli for the subject to regulate, in a biofeedback process that is often termed neurofeedback (NF). Although it is possible to derive feedback signals using whole brain analysis methods like support vector machine classification and other multivariate supervised learning approaches [51, 108, 109], most studies to date have involved NF of signals from localized regions of interest (ROIs). Work using ROI-based NF has targeted diverse brain regions involved in emotion [45, 43, 42, 46, 44, 47], pain [110], audition [49, 111, 48], and language [50]. In these reports, there have been overt behavioural manifestations of NF training, such as changes in emotional state or the sensation of
pain, which have potential medical and therapeutic importance [112].

There have also been a number of NF studies investigating the motor system, with overt hand movement [37] and with motor imagery [113, 38, 114, 40]. Neurofeedback methods using motor imagery may be potentially useful to enhance motor rehabilitation of stroke or other physical disabilities [115]. For example, one study has found evidence for regional enhancement of BOLD activation using motor imagery NF [113], compared to a control group that received sham NF. Such an approach could potentially be used to enhance neuronal activity from damaged regions of the brain, improving stroke recovery. Others have improved motor imagery NF methodology with the addition of instrumental conditioning [38] and selection of optimal feedback presentation schemes (Johnson et al., 2010) to maximize BOLD signals in the targeted regions after NF training. The longer-term effects of imagery-mediated fMRI NF have also been investigated [114]. Importantly, this study showed that a single session of fMRI NF involving motor imagery, followed by a two-week period of self-practice, enabled healthy individuals to consolidate and sustain elevated activity levels in brain regions associated with motor skill learning.

Despite the success of these NF studies, they should be viewed as preliminary. For example, brain and motor behaviour changes observed in response to NF training need to be evaluated not only in the context of the individuals that respond to training, but also the non-responders. It has been commonly reported in past studies that not all participants were able to self-regulate successfully [38, 114, 40], although the neural differences between responders and non-responders remains poorly understood. In the absence of NF, motor imagery has been reported to elicit heterogenous brain responses across subjects [116]. Additionally, only one study has attempted to characterize the impact of motor imagery NF training in a behavioural test of overt motor function [38]. As a last example, although the neural mechanisms underlying NF have been initially assessed and are thought to require a cortico-basal ganglia-thalamic circuit [16, 114], different NF applications will likely engage slightly different networks of regions [117], and a detailed investigation of the brain networks involved in successful NF of motor imagery signals still remains to be undertaken.

The present study focuses on fMRI NF of the hand motor system using an ROI-based method targeting the primary motor cortex (M1), similar to the work of Bray et al. [38], but with some notable design differences. Bray et al. suggested that subjects tended towards performing kinesthetic motor imagery (kMI) during their NF study; here, kMI is used explicitly to access the motor system because a major topic of interest in the laboratory is the application of fMRI to enhance stroke recovery through optimization of physical rehabilitation methods. Studies have shown that the brain regions involved
in kMI resemble those for overt motor response more closely than in the case of visual motor imagery (vMI) [118]. As kMI therapy has potential to improve stroke recovery outcome [119] it is of interest, therefore, to explore the initial hypothesis that fMRI NF training in young healthy adults can enhance the brain activity associated with kMI. This represents an early step toward possibly using fMRI NF in the future to enhance the ability to perform kMI, stimulate neurons in the motor system, and thereby improve motor recovery in stroke patients.

The primary focus of this paper is the exploration of the distributed networks and brain responses to NF involving kMI, through a post-hoc (offline) analysis of the fMRI data using the partial least squares (PLS) method [91]. This multivariate approach is novel in the fMRI NF literature, as all previous ROI-based studies have mapped brain activity based on the general linear model (GLM) approach [120]. The resulting networks of brain activity generated by PLS are expected to be consistent with the networks previously reported in the literature for NF [16] and for NF with motor imagery [113, 38, 114, 40], while also accounting for response variability in kMI and NF across participants.

A secondary objective of this work is the characterization of inter-hemispheric interactions between the dominant and non-dominant M1 ROIs, while using a laterality index as the NF signal of interest. This is also novel in the NF literature and has relevance to the use of kMI for stroke recovery, considering cases in which the stroke lesion impacts either the dominant or non-dominant hand. Based on the small behavioural literature on kMI and lateralization [121] it is of interest to explore the hypothesis that kMI NF relating to the non-dominant hand is less effective than that for the dominant hand in right-handed subjects, and how dominant/non-dominant M1 interactions modulate the NF signal.

### 2.2 Methods

#### 2.2.1 Experimental Overview

Subjects first performed a functional localizer task designed to identify ROIs over the left and right M1 regions involved in both overt and imagined movement. These ROIs served as the subsequent signal sources for kMI NF involving either the dominant or non-dominant hand. During the NF training, consisting of 4 experimental runs each lasting 9 minutes, subjects attempted to maximize a specific activation laterality (either left or right) based on fMRI signals from both ROIs during kMI of the hand, assisted by a real-time visual feedback display.
2.2.2 Subjects

Eighteen young, healthy, right-handed adult subjects participated with informed consent and with the approval of the Research Ethics Board at Baycrest Hospital, Toronto. To control for practice effects and assess responses to feedback information, subjects were split into two groups: 13 subjects in the experimental group (27 ± 3 years, 7 male) received true NF, whereas 5 subjects in the control group (24 ± 3 years, 2 male) received sham NF. The sham NF was yoked to feedback from a randomly chosen subject in the NF group. The control group treatment was identical to that of the NF group in every other respect, allowing for a direct comparison between subjects who received relevant feedback and those whose feedback was independent of their brain activity.

2.2.3 Imaging

Imaging was performed on a 3.0 T Magnetom TIM Trio system (VB15 software, Siemens Healthcare, Erlangen, Germany) using a 32-channel phased array head coil. Structural imaging was performed using a T1-weighted 3D MPRAGE sequence, at 1 x 1 x 1 mm\(^3\) isotropic resolution. All fMRI scans were performed using a modified 16 slice (5mm) gradient echo T\(^*\)-weighted echo-planar imaging (EPI) acquisition, with 3 x 3 mm\(^2\) in-plane resolution, 64 x 64 matrix, 30 ms TE and 1 s TR. Physiological recording of respiratory and cardiac signals was performed for all fMRI runs using a respiratory bellows and a pulse oximeter, respectively.

2.2.4 Real-Time Setup

The Siemens image reconstruction software was modified to provide real-time data transfer to a computer running AFNI [122] on Scientific Linux (www.scientificlinux.org) over a local network connection. The AFNI computer received one multi-slice, volumetric set of brain image data from the scanner immediately after each TR. In the initial functional localizer phase of the experiment, the AFNI computer was used to perform a rapid, scripted analysis using the general linear model (GLM) approach to produce statistical parametric maps identifying subject-specific regions of brain activity suitable for NF. The localizer experiment employed a simple blocked design alternating 15 s of rest, with 15 s of bilateral hand clenching, left hand (LH) imagery, and right hand (RH) imagery respectively, for a total of 300 s. The AFNI computer received the localizer images immediately, and the scripted GLM analysis produced parametric maps identifying regions most active across both the overt movement and motor imagery tasks. Two 5 x 5 x
2 voxel (15 x 15 x 10 mm³) ROI masks were manually defined over left and right M1 locations, centred on the M1 regions with the maximum r² value in the full F-statistic parametric maps. M1 was targeted due to its ease of location and principal role in motor action, and because potential NF applications in recovery of motor function after stroke may target this region. The ROIs were made large enough to capture the entire hand motor area in all subjects.

During subsequent NF experiments, mean BOLD signal amplitudes were calculated for each ROI using the subject-specific masks defined from the localizer experiment. A separate stimulus computer running Windows XP received these calculated values from the AFNI computer with 300 ms latency from acquisition, using a custom data server built with Python and real-time AFNI protocols. Stimuli were then calculated and rendered graphically using the VisionEgg python library [123], then presented to the subjects using an LCD projector, projection screen, and a mirror mounted on the head coil.

### 2.2.5 NF Experiment

All subjects performed 4 sequential NF training runs, each separated by 1-2 min of rest. Each run consisted of 12 NF trials: 6 RH trials, and 6 LH trials, pseudorandomly ordered. A diagram of an idealized NF trial is illustrated in Fig. 2.1. Each trial lasted 45 s, consisting of: 20 s rest, cued with a fractal image and text; 5 s of NF cue represented by one of two fractal images; 15 s of real-time feedback; and 5 s of trial results. The NF cue was displayed for 5 s to accommodate the associated hemodynamic response, so that NF display began after BOLD onset. Cue images were balanced across subjects, representing RH and LH trials respectively, and remained constant throughout the experiment for each subject.

Subjects were carefully instructed prior to the onset of NF experiments. They were asked not to make any overt hand movements throughout, except when specifically instructed to do so (see Reaction Time Tests, below). When performing imagery, they were specifically instructed to avoid vMI techniques (seeing in the minds eye), and to focus only on kMI by imagining the execution and feeling of hand movements. Subjects all started with imagined hand clenching, although they were free to use any kMI strategy to increase the NF signal as long as the strategy was restricted to single hand movements. They were asked to perform kMI immediately on display of the cue and to sustain their performance throughout the NF period. They were not told which cue was associated with which type of trial; rather, they were asked to determine the correct associations
Figure 2.1: Example diagram of NF experiment following the functional localizer. Each subject performed four 9 min NF training runs and a pre- and post-reaction time test. Each NF run consists of twelve 45 s blocks, (6 RH and 6 LH trials each), pseudorandomly ordered. The 45 s block is made up of a 20 s rest period, a 5 s cue, a 15 s period of real-time NF and motor imagery, and a 5 s result (reward) display. The subjects earned 1 point for each successful trial, and earned nothing for each failed trial. The two reaction time tests consisted of 20 jittered trials, 5 for each combination of cue 1 x cue 2. Cue 1 was one of the 2 fractal cue images used during NF, and cue 2 indicated either R or L denoting a RH or LH finger response.
based on NF. The instructions were identical for both experimental and control subjects.

During the real-time feedback, subjects viewed a horizontal arrow. The length of the arrow was scaled every TR in proportion to the laterality index \( LI_n \), calculated as:

\[
LI_n = k \times \left( \frac{lROI_n}{lROI_{Rest}} - \frac{rROI_n}{rROI_{Rest}} \right)
\]

where the integer \( k = +1 \) for a RH trial, and \(-1\) for a LH trial, \( lROI_n \) and \( rROI_n \) indicate the BOLD signal amplitude in the left and right ROIs in the \( n \)th TR interval during kMI, respectively; and \( lROI_{Rest} \) and \( rROI_{Rest} \) are the mean BOLD signal amplitude during rest, respectively. This NF signal (a fractional signal difference) was used to control for global or non-specific activation changes, as well as to explore laterality-specific interactions. An additional vertical line was overlaid on the display, to provide subjects with a cumulative, time-averaged representation of the laterality index over the duration of the trial:

\[
LI = \frac{1}{N} \sum_{n=1}^{N} LI_n
\]

where \( n \) is the number of TR intervals from the beginning of the trial, and \( LI_n \) is the instantaneous value of LI calculated from Eq. 2.1. The direction of LI polarity (positive or negative) was visually presented such that the indicators moved right when RH activity was detected, and vice versa.

Subjects were asked to maximize the length of the instantaneous NF arrow once they had determined the cue associations, and trial performance was evaluated based on the average LI over the entire trial duration. The NF training employed an operant conditioning strategy, where trial success was dependent on the LI surpassing a threshold \( T \) that was invisible to the subject. The value of \( T \) was changed according to a conditioning schedule (Fig. 2.2), where 4 consecutive successful trials increased \( T \) to the smallest value from the previous 4 trials. After 4 consecutive failed trials, \( T \) decreased to the previous \( T \) value, to a minimum of 0. Subjects received points for each successful trial, and were asked to attain as many points possible. This measure of success was used solely for the purpose of accruing reward points in the conditioning procedure, and was not used as a measure of NF performance ability. The LI data were subsequently analyzed using a 3-factor mixed factorial ANOVA, with run (1-4) and hand (LH or RH) as the within-subject factors, and group as the between-subjects factor.
Figure 2.2: Flow chart of the instrumental conditioning reward schedule used to change the success thresholds. The threshold starts at 0, and after 4 consecutive above-threshold trials, a new threshold is set to be the smallest time averaged LI value from the 4 previous trials. The threshold decreases only after 4 consecutive below-threshold trials, and is set to be the previous threshold.
2.2.6 Reaction Time Tests

Two reaction time assessments were performed in the scanner, immediately pre- and post-NF to consider the impact of the NF conditioning cue associations, and the potential effect of the NF training on a simple overt motor behaviour test. Given a logistical requirement to conduct the experiment within a one hour time frame, the reaction time assessments were each undertaken in short, 3 min. intervals. The experiments were identical, each consisting of 20 time-jittered and pseudorandomly ordered trials of visually cued button press responses performed with the index finger. Two cues were used to prompt the subjects for each trial: an image cue appeared for 1.75 s, and a reaction cue displaying the letter R or L was displayed immediately after for 0.25 s, prompting the subjects to respond with their right or left hand respectively. Each test was composed of: 5 RH congruent, 5 RH incongruent, 5 LH congruent, and 5 LH incongruent trials. For congruent trials, the image cue was identical to the cue used in the NF training to perform kMI for the associated hand. For incongruent trials, the image cue opposed the NF association. Reaction times were measured using an 8-button fiber-optic response box system (Current Designs, Philadelphia, PA), recording button responses from the index finger of each hand timed from the onset of the reaction cue.

The reaction time data were analyzed using a 4-factor mixed factorial ANOVA, with time (pre- or post-training), hand (LH or RH), and cue-type (congruent or incongruent) as within-subject factors, and group (NF or control) as the between-subjects factor. Data were normalized using a log transform to meet normality conditions for parametric statistical testing.

2.2.7 Electromyography

Electromyography (EMG) was recorded for 9 subjects in the NF group to verify that no overt muscle activity occurred during imagery. The recordings were performed with an fMRI-compatible EEG system (BrainAmp ExG MR, Brain Products, Munich, Germany), using differential electrodes placed on the extensor carpi radialis longus muscle of the right forearm. Recordings from 4 subjects in the NF group and the subjects in the control group were not possible due to equipment availability. All subjects were also asked to report any overt movement that occurred during NF. The EMG time courses were analysed by comparing the RMS voltage values for the rest periods and the NF periods using planned paired t-tests, after MRI gradient artifact removal using the BrainAmp Analyzer 2 software (version 2.01, Brain Products, Munich, Germany).
2.2.8 Post-experiment

Immediately after the fMRI session, each subject was debriefed regarding their ability to determine the NF conditioning cue associations, and were asked to report the degree of engagement they felt with the feedback signal during NF trials. Control subjects were also asked whether they perceived that the NF signal was a sham. Several months after the experiment, subjects were assessed using the MIQ-RS questionnaire for motor imagery [124] to assess baseline ability to perform kMI.

2.2.9 fMRI Data Analysis

The fMRI data were pre-processed using the AFNI software package to perform rigid body motion correction, physiological noise correction, and spatial smoothing (6 mm Gaussian kernel). The individual subject data were then spatially normalized to the Montreal Neurological Institute (MNI) template for group comparison.

Brain activation maps were generated using PLS, a multivariate method for determining spatial patterns or networks in brain activity that maximizes covariances between neuroimaging data and external measures. The external measures can include task design contrasts (task-PLS), external behavioural measures (behavioural-PLS), or fMRI signals from seed voxels (seed-PLS) [91]. Latent variables (LVs) are output from a singular value decomposition of the covariance matrix created by cross-covarying the imaging data with the external measures. These LVs are similar to parametric maps output from traditional GLM analysis, except that voxel saliences or weights replace model estimates, and bootstrap ratios replace t-values or z-scores. The LVs capture networks of activity spread across the entire brain. Often the PLS output contains a large number of LVs, and only the most interesting and most significant are retained for analysis. Statistical significance and stability are assessed using permutation tests and bootstrap resampling. Bootstrap ratios for each voxel are calculated as the voxel salience divided by the standard error estimated from the bootstrap resampling.

In the present work, both task- and behavioural-PLS were used to analyze the fMRI data. Task-PLS was used to examine various group and task contrasts, and behavioural-PLS was used to explore whether consistent brain patterns were correlated with task performance. Brain scores were used to assess the degree of expression of a particular LV pattern by computing the inner product of the salience values with the mean BOLD data across conditions. In all analyses, 500 permutations of condition labels were used, and 80-100 bootstrap resamples, depending on the group sizes. Activation maps were thresholded at an absolute bootstrap ratio greater than 3, corresponding approximately to
99% confidence intervals. A 4 s response lag was used in the experimental onset timing to accommodate for the hemodynamic response delay. The PLS data matrices were created using the block design approach, where each 45 s trial was split into 4 (of 6 possible) conditions: rest, cue (LH or RH), NF (LH or RH) and result, with their respective durations outlined above. The data were averaged within each condition and across all trials to produce mean values for each condition, which were then averaged across subjects in each group and mean-centred (task-PLS) or correlated with a performance measure (behavioural-PLS) prior to the singular value decomposition.

2.3 Results

2.3.1 EMG

No significant difference in muscle activity was found between rest and NF conditions across all tested subjects: rest = 52.0 ± 38.7 uV, NF = 78.0 ± 74.2 uV (mean ± standard deviation, p > 0.3). Manual inspection of the EMG data revealed 5/9 subjects showed no visible muscle activity during NF periods, while 4 subjects showed some visible evidence of sparse spikes during at least one NF period, defined as any signal > 200 uV in amplitude. None of these subjects showed more than 6 spikes over the 4 runs and none lasted more than 500 ms in duration. The spikes were likely due to accidental movement, as no subjects reported any overt hand movement during the trials. In comparison, the average EMG voltage recorded during the reaction time tests was 158.3 ± 127.5 uV, significantly greater (p < 0.05, corrected) than the recorded rest or NF EMG signal amplitudes.

2.3.2 ROI Masks

Fig. 2.3 shows an axial slice through the group-averaged ROI mask regions transformed to MNI space. The regions of maximum overlap across subjects were determined by transforming the rectangular ROI masks into MNI space and averaging, and were centred at MNI coordinates: (-36, -28, 53) and (40, -27, 55) for the left and right ROIs, respectively.

2.3.3 Reaction Time

The results of the 4-factor ANOVA using the experimental and control group showed only a significant main effect of the hand factor (F1,16 = 8.99, p < 0.01), with the RH
Figure 2.3: A single axial slice of the group averaged ROI masks showing the left and right primary motor cortex overlaid on the group averaged structural image (MNI z coordinate=54mm). The averaged ROI mask image shows the percentage of overlap across subjects, and is thresholded to show only regions that overlap between 2 and 18 subjects (5% to 100% overlap respectively). ROIs appear to be well localized to the hand-motor regions on the pre-central gyrus.
responses faster than the LH responses. No other main effects or interactions achieved significance, including any effects with the time or cue-type factors.

2.3.4 NF Behaviour, LIs, and Thresholds

All 13 NF group subjects and 4 of 5 control subjects were able to identify the correct cue-trial type relationships. One subject in the control group was unsure, due to the perceived erratic behaviour of the feedback display, and none of the control subjects were aware that they received sham feedback during the experiment. In post-hoc assessment of baseline motor imagery ability using the MIQ-RS, attrition led to responses from only 6 out of 13 NF group subjects and 3 out of 5 control subjects. From the data available, the kinesthetic scores were similar within and across groups: $5.52 \pm 0.72$ (mean $\pm$ standard deviation) for the NF group, and $5.62 \pm 0.44$ for the control group. No significant relationships were found between NF performance (see below) and MIQ-RS scores, nor was any relationship found between NF performance and subject engagement.

Linear regression tests on the NF threshold $T$ vs. trial number in the NF group showed significant positive slopes for LH trials ($r = 0.27$, $p < 0.01$) and RH trials ($r = 0.18$, $p < 0.01$) and no significant findings for the control group ($p > 0.05$) (Fig. 2.4). Additionally, linear regressions were performed on the mean number of rewarded trials...
Figure 2.5: Scatter plot of the number of good LH trials against the number of good RH trials, where good denotes that BOLD signal during the NF duration was statistically significantly different from the baseline signal. The difference was required to be a signal increase in the contra-lateral ROI and/or a signal decrease in the ipsilateral ROI. The dashed lines mark the upper bounds of the control subjects’ performance and can be used to separate subjects into 2 groups. Twelve subjects (7 poor NF responders and by definition the 5 control subjects) were below threshold, whereas 6 NF subjects (good NF responders) exceeded the thresholds. Two NF subjects were successful in LH trials only, 1 in RH trials only, and 3 were successful in both LH and RH trials.

in the NF group by run for RH trials (3.2, 2.8, 3.2, 2.5) and for LH trials (3.8, 3.3, 2.4, 3.2). No significant change was measured in the number of RH rewarded trials (p=0.37) or LH rewarded trials (p=0.11). These analyses indicate that T increased without a drop in the number of rewards (i.e. overall, subjects performed better over time).

A 3-factor mixed factorial ANOVA for the LI values showed a significant interaction of group x run number (F3,48 = 3.59, p = 0.02), suggesting the presence of a training effect with NF and not with sham NF. No other significant main effects (group, run, hand) or interactions were found.

These results were subsequently explored further to assess inter-subject variability. All trials from each subject were tested for individual significance using an independent samples t-test (p < 0.05) of the BOLD signals from each ROI during the 15 s of NF against the corresponding 20 s of rest data. The NF performance for a trial was deemed good if one of the following three scenarios occurred: the target ROI mean was significantly increased without any change in the opposite ROI; the opposite ROI significantly decreased without any change in the target ROI; or if both the target ROI increased and
Figure 2.6: Group-averaged laterality index (LI) values by run for RH (top) and LH (bottom) trials, for good responders, poor responders, and controls. Error bars denote standard error of the mean.

the opposite ROI decreased simultaneously. Trials that did not meet the above conditions were labelled poor. Fig. 2.5 is a scatter plot of the number of good LH trials against good RH trials, indicating considerable variability in NF performance across all subjects. A threshold was set at 25% LH or RH trials to separate the NF group into good NF and poor NF responders based on the upper limit of performance for the control subjects. This resulted in 5 good responders in LH trials, and 4 good responders in RH trials, with 3 subjects above both LH and RH thresholds.

Fig. 2.6 shows the LI values split by the new groupings, averaged across subject by runs, for RH and LH trials separately. The results of the 3-factor ANOVA showed 2 strong significant effects: a main effect of group (good NF, poor NF, control) ($F_{2,12} = 19.42, p < 0.01$); and an interaction of group x run ($F_{6,36} = 3.41, p < 0.01$). The group x run interaction indicates that only the good responder group showed increased LI over time, whereas the poor and control subject data consistently showed LI values
close to 0. No main effect or interaction involving the hand factor achieved significance (p > 0.10), although LI values for poor responders in RH trials show a slight trend that decreased over time. Planned t-contrasts of the LI values of the good NF group against the poor NF and control groups indicate that the good NF group LI values were higher than those for the poor NF and control groups in all the RH runs and runs 2 and 3 of the LH trials, at a significance level of p < 0.05 (Bonferroni corrected). Additionally, a simple comparison of the number of rewards per group indicated a significant difference for RH trials (p < 0.01), although no significant difference was found in LH trials (p > 0.2), and no significant changes were found in the number of rewards across runs.

A breakdown of BOLD activity in the left and right ROIs for the good and poor responder NF groups is shown in Fig. 2.7. For the good responder group, it is evident that the largely bilateral symmetry in activation between the left and right ROIs in run 1 gave way to more unilateral activation asymmetry between ROIs in runs 2-4. In RH trials, negative activation or suppression of the ipsilateral left ROI appeared to be the driving effect of the positive LI in runs 2-4, and vice versa for LH trials. No such pattern was observed in the data for the poor responder group, where BOLD percent signal change was mildly suppressed or near 0 bilaterally across runs. A 3-factor mixed factorial ANOVA with factors of group, run and side (dominant vs. non-dominant) and for RH and LH trials separately indicated that significant interactions of group x side (p < 0.01) and group x side x run (p < 0.05) were present in RH trials, and just missed significance in LH trials (p = 0.081 and p = 0.057 respectively). A post-hoc assessment of activity in other motor regions such as the supplementary motor area (SMA) and left and right premotor areas for NF related changes yielded no consistent patterns of activation change, indicating that these results are specific to M1.

2.3.5 Behavioural PLS

To investigate the brain activation mediating the distinct performance differences between good and poor responders, behavioural PLS was performed using the number of good trials as the measure of NF performance. Analyses were performed for the entire NF group without including the control group, considering the performance effects shown in Figs. 2.4-2.7, and that behavioural PLS of only the control group showed no behavioural LVs (bLVs) covarying significantly with the behavioural measure (p > 0.4). In the NF group, 1 significant bLV was found (bLV1, p = 0.02, 66.6% cross-block covariance), and both LH and RH conditions were significantly correlated with NF performance (r = 0.42 and r = 0.81, respectively). The behavioural PLS validated the behavioural
Figure 2.7: Mean percent BOLD signal change for each ROI, averaged across subjects and within runs. Graphs on the left show data from good responders, and on the right show poor responders. The top and bottom rows reflect data from RH and LH trials respectively. Here the LH-ROI refers to the right M1, and the RH-ROI refers to the left M1. Error bars denote standard error of the mean.
classification undertaken in Fig. 2.5, confirming that there are distinct brain differences in NF conditions across the performance spectrum. The activation map and brain score scatter plots for bLV1 are shown in Fig. 2.8, showing regions including the bilateral insula, basal ganglia, thalamus, anterior cingulate (AC) and cingulate gyrus, left precentral gyrus, bilateral middle frontal gyrus (MFG), right supramarginal gyrus, left superior parietal lobule and bilateral superior frontal gyrus (SFG).

2.3.6 Task PLS

To investigate these differences further with the new group classification, task PLS was performed on the data across all conditions, separating the subjects into 3 groups as above: 6 good NF responders, 7 poor NF responders, and 5 control subjects. Although the group sizes for this analysis were small, it produced a number of interesting contrasts.
Three significant task LVs (tLVs) were found: tLV1 \((p < 0.001, 66.5\% \text{ cross-block covariance})\) highlighting NF vs. Rest contrast, tLV2 \((p < 0.001, 17.0\% \text{ cross-block covariance})\) highlighting a Cue vs. Rest contrast, and tLV3 \((p = 0.034, 6.3\% \text{ cross-block covariance})\) showing a group contrast between the good responders and the control group during NF conditions (poor responders did not express tLV3, with near zero brain scores). In the context of the present work, tLV1 and tLV3 are of primary interest.

The spatial activation map for the most predominant and pertinent latent variable, tLV1, is shown in Fig. 2.9, with bilateral activation of the anterior insula, medial frontal gyrus, bilateral middle temporal gyrus (MTG), thalamus, basal ganglia (putamen, caudate, pallidum), bilateral premotor, SMA, left SFG and bilateral inferior and superior parietal lobules (IPL/SPL). Significant clusters for tLV1 and tLV3 are listed in Tables 2.1 and 2.2. In comparison to tLV1, very few brain regions were associated with tLV3: left AC and left superior frontal gyrus were more active for good NF responders, whereas right middle frontal gyrus was more active for controls. For brevity, tLV3 activation
### Table 2.1: Significant clusters (>15 voxels) for tLV1.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI-x</th>
<th>MNI-y</th>
<th>MNI-z</th>
<th>Peak BSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>tLV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More active during NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle frontal gyrus-R</td>
<td>39</td>
<td>37</td>
<td>31</td>
<td>-9.6</td>
</tr>
<tr>
<td>Premotor cortex -L</td>
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<td>-7</td>
<td>61</td>
<td>-9.6</td>
</tr>
<tr>
<td>Premotor cortex -R</td>
<td>31</td>
<td>-8</td>
<td>59</td>
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<tr>
<td>Supplementary motor area</td>
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<td>0</td>
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<td>46</td>
<td>-13.1</td>
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<td>Middle temporal gyrus-R</td>
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<td>-6</td>
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<td>Middle temporal gyrus-L</td>
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<td>-12.6</td>
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<td>Angular gyrus-L</td>
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### Table 2.2: Significant clusters (>15 voxels) for tLV3.

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<th>MNI-y</th>
<th>MNI-z</th>
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<td>tLV3</td>
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<tr>
<td>More active during NF for good responders</td>
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<td></td>
</tr>
<tr>
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<td>26</td>
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</tr>
<tr>
<td>Superior frontal gyrus-L</td>
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<td>42</td>
<td>21</td>
<td>-5.6</td>
</tr>
<tr>
<td>More active during NF for controls</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus-R</td>
<td>53</td>
<td>-58</td>
<td>-4</td>
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</table>
maps and design scores are not shown.

2.4 Discussion

This study investigated the brain and behavioural responses to fMRI NF training using kMI over a training period of 40 minutes. The study, which reports findings that are largely consistent with the previous literature, is the first to explore brain activity in relation to variable inter-subject response during NF training, and to explore how differential feedback signals from the dominant and non-dominant M1 behave in response to kMI and NF.

A key outcome of the study was that the statistically significant effects of fMRI NF, found on average between the NF and control groups, were driven by a subset of the NF group based on both performance and brain activity. It is evident from the behavioural PLS results that a network of brain regions was engaged in proportion to NF performance (number of good trials), with approximately half of the NF group showing poor performance (0 to 6 good trials), and half showing a range of performance enhancement resulting from the NF training (approximately 7 to 20 good trials, out of a maximum of 24). The results of the behavioural PLS justify the approach initially undertaken, based on behaviour, to classify individuals in the NF group into two categories (good and poor responders), from which categorized BOLD characteristics and task-PLS results naturally followed. Although the classification thresholds were chosen on visual inspection, they were conservatively chosen from the standpoint that all poor responders in the NF group were identified as having performance similar to that of the controls. It is unlikely that slight readjustment of the classification thresholds would markedly change interpretation of the study results.

There is much evidence in the previous literature for a heterogeneous response to motor imagery NF in young healthy subjects: Bray et al. reported only 17/26 subjects meeting a performance criteria of at least 5 successful trials in the last training session [38]; Yoo et al. reported 10/11 experimental subjects achieving the desired upregulation threshold, although 4/11 control subjects also surpassed the threshold during the experiment [114]; Johnson et al. reported 4/8 and 2/10 subjects significantly increasing activation during intermittent and continuous NF respectively, with 4/10 subjects performing significantly worse [40]. It is difficult to draw any consensus from these data without consistent criteria for NF success or what constitutes the NF signal, yet these reports (and the current work) suggest that only a subset of the population is capable of responding to NF training of BOLD activity using motor imagery.
The other objective of this work was to study the interaction between the left and right M1 ROIs in response to NF training. In both RH and LH trials, the targeted kMI performance (enhanced laterality of brain activity) in good responders was driven not by up-regulation of the contralateral M1 ROI, but rather by suppression (relative to the rest condition) of the ipsilateral M1 activity. All subjects received the same instructions to maximize the feedback signal using any hand imagery strategy, and subjects were not aware that the signal reflected a laterality index. The observed results are consistent with reported findings of suppressed ipsilateral M1 activity in a study of dynamic inter-hemispheric interactions during unilateral hand movement [125], and are similar to the top-down inter-hemispheric sensory gating effects observed in studies of somatosensation [126].

Previous studies of laterality and motor imagery have shown ipsilateral activations to be present during unilateral imagery[127]. In a post-hoc analysis, deCharms et al. found no statistically significant change in activation of an ipsilateral M1 ROI [113], although the ipsilateral ROI was not directly included in the NF. Bray et al. however, observed signal decreases in the non-rewarded ROIs (foot ROI during hand trials and vice versa), where the signal difference between the ROIs was directly acted upon by subjects. This is consistent with the results presented here, and lends support to the claim that use of a laterality signal for differential NF engages additional covert associative learning mechanisms responsible for signal suppression [38]. Other evidence indicates that suppression of ipsilateral M1 enhances motor skill learning [128]. Collectively, these findings support continued investigation of differential ROI feedback signals for enacting brain and behavioural changes.

An effect of lateralization was expected to be observed with poorer NF performance for LH kMI, given the right handed subject group. There were some trends visible in the resulting data, although no statistically significant results: the LI values averaged slightly higher in RH trials than for LH trials in the good responder group, and the ROI data suggested that stronger ipsilateral suppression in RH trials drove this increase. One report suggests that suppression of ipsilateral M1 is stronger in RH movement than LH movement for right-handed subjects [129], supporting the observed trends. The lack of statistically significant findings in the present study either result from subject response variability masking the underlying effect, or from no effect being present. If the latter scenario is correct, then important implications exist for future application of NF to stroke rehabilitation. Without a lateralization constraint, potential candidates for NF training can be selected regardless of whether the stroke occurred near the dominant or non-dominant motor cortex. If handedness does modulate NF ability, however, patients with
strokes occurring near the dominant hand motor cortex would potentially be preferential candidates for NF training. Further study clearly needs to be done to address this question, particularly with a left-handed subject group to fully characterize the effects of handedness.

Looking at brain activation results extending beyond the M1 ROIs, the first LV of the task PLS (tLV1) produced a NF vs. Rest contrast, and showed an expected pattern of activity in motor control regions and self-awareness regions elicited by the motor imagery NF task. Activation of basal ganglia structures, thalamus, and cortical motor regions suggest engagement of the cortico-basal ganglia-thalamic circuits previously reported to be important in successful NF [16]. Strong engagement of parietal cortex, premotor and SMA are indicative of kMI [118], whereas activation of the right anterior insula and AC have been linked to interoception, or awareness of internal state [130]. The regions more active during rest likely reflect the default mode network, including the posterior cingulate, lateral parietal (angular gyrus) and superior frontal activations [131].

Interestingly, statistically significant activity in the M1 ROI regions was not observed in tLV1. There is evidence in the literature that M1 activity can be much less relative to SMA and pre-motor activity during motor imagery [132, 115], although the literature is conflicting in this respect [133]. Given that evidence of M1 suppression was observed in the ROI data analysis, one might have expected to observe M1 ROIs more active during rest. This may not have been observed for tLV1 because of the variability in subject response, as discussed above, where M1 ROI activity was inconsistently activated (or suppressed) across subjects and trials. The ROI results and the behavioural PLS results, which classified performance based on significance measures derived from the M1 ROI signals, leave little doubt that both M1 regions were involved in the NF task, even if they were not depicted in tLV1.

The behavioural PLS results identified brain regions that were significantly correlated with performance during the NF task. As might be expected, the activation map for bLV1 substantially overlapped bilaterally with that for tLV1, particularly in the insula, basal ganglia, thalamus, MFG and premotor cortex. The overlap confirms that NF success was mediated through engagement of regions already involved in the NF task, and not a separate mediating network. Additionally, several regions expressed in bLV1 coincide with the task positive network (TPN), a common set of regions activated during tasks requiring attention modulation [131]. These regions include the frontal eye fields (premotor), insula and dorsolateral prefrontal areas. This observation suggests that expression of the TPN is positively correlated with successful NF, and that expression of the TPN may reflect subject engagement in the NF training. Empirically, TPN expression represents
a strong marker for NF performance in RH trials with 65.6% explained variance, and to a lesser extent in LH trials with 17.6% explained variance. Although this study did not control for the effects of attention, evidence for co-expression of attentional networks during NF possibly indicates that attentional processes are a major factor mediating NF performance. This is supported by the fact that the difference in the number of rewards given between good and poor responders for RH trials is constant with time, and apparent even in the first run, indicating that success cannot be attributed to learning since the difference in performance was evident from the onset of the experiment. Because no significant differences were found in the number of rewards given between groups in LH trials, however, the behaviour of all good responders cannot be explained solely by an attentional effect of having more rewards. Future work could be undertaken to assess the underlying causal linkage of TPN expression and NF performance, and a deeper exploration into other factors contributing to performance variation.

The tLV3 results account for much less of the explained covariance (6.3% versus 66.5% for tLV1), but are of interest nevertheless because they highlight brain regions that were significantly different in the good responder group compared to the control group during the NF trials. To date, only two studies employing sham feedback control groups have looked at group differences in brain activity, both using a GLM analysis [114, 40]. In the present work, left lateralized AC and SFG were found to be significantly more active in the good responder group, compared to increased right MTG activation in the control group. Both the AC and SFG have been implicated in studies of general feedback processing [134], with both responding more to positive feedback, and the left SFG also sensitive to feedback validity. Response variability, particularly across good responders in the NF group, may account for the sparse pattern of brain activity observed in tLV3.

In comparison, Yoo et al. [114] found left pre-central gyrus, bilateral post-central gyrus, right MTG and right parahippocampal gyrus activation in an experimental > control contrast, and right medial frontal gyrus, right inferior parietal lobule, left cuneus and bilateral precuneus in the control > experimental contrast. Interestingly, Johnson et al. [40] did not find any significant activation in an experimental > control contrast, but did find activation in the control > experimental contrast, including the right MTG reported here. The lack of strong consensus between these studies and the tLV3 results of the present study may be due to differences in experiment design and the particular aspect of brain activity chosen for NF training, and in the details of the training procedure.

In the simple reaction time analysis, the significant main effect of hand (indicating subjects reacted faster in RH trials compared to LH trials) is an expected result given that subjects were all RH dominant. The lack of any significant main or interaction effects for
the group factor suggests that the NF training did not affect visuomotor response times over the duration tested, but it should also be acknowledged that the number of reaction time trials was rather low in this experiment (5 per condition per hand, 40 total), limiting statistical power to detect changes. Further studies specifically investigating the effect of NF training on overt motor performance will be necessary to provide a more conclusive picture of NF training effects.

Future directions for NF investigation include analyses to determine predictors for NF success, toward improving NF technology for responders and the exclusion of non-responders. One potential target for the selection process could involve expression of the TPN as found in this work. Adoption of whole brain classification approaches [135] may prove advantageous in targeting entire networks of regions, and for enhancing overall NF efficacy. Future work may also include investigation of NF ROIs in non-primary motor regions involved in motor learning and skill acquisition [136], or use of more sophisticated methods for calculating real-time BOLD estimates [137], which may lead to more sensitive and robust feedback measures. Alternative feedback signals may also be of interest, including targeting BOLD signal variance measures [138] instead of the commonly employed mean BOLD measures.

Lastly, NF might potentially be used in the long term as an aid in learning to perform kMI more effectively for use in imagery therapy to promote stroke recovery [119, 115, 139]. For example, NF could potentially be used to train individuals to perform kMI over vMI by rewarding increased activity in primary motor regions and decreased activity in primary visual areas. Alternatively, NF training could be used potentially to identify those who can perform kMI well, distinguishing them as candidates for imagery-based therapeutic intervention. We anticipate that some of the above issues will be topics of future investigation in our laboratory.
Chapter 3

BOLD Contrast and Noise
Characteristics of Densely Sampled Multi-Echo fMRI Data

by Mark Chiew and Simon J. Graham

3.1 Introduction

Use of $T_2^*$-weighted functional MRI (fMRI) techniques for studying brain biophysics and other neuroscience applications is now widespread. Although single shot, 2D multi-slice $T_2^*$ weighted acquisitions including gradient echo-planar imaging (EPI) [86, 140, 141] and spiral imaging [142, 143] are the predominant fMRI implementations at 1.5 - 3.0 T, this paper relates to a slightly different data acquisition strategy: use of multi-echo acquisition and methods to combine echo signals to improve blood oxygenation level dependent (BOLD) contrast. Rationalized below, the present work provides a generalized analytic framework for interpretation of existing multi-echo weighting methods in different noise conditions, adding to the existing literature on the subject.

Multi-echo imaging takes two or more traversals through the K-space origin at various echo times (TE) during the same excitation, providing improved sampling of the $T_2^*$ decay curve for each voxel and repetition time (TR). A variety of choices exist for multi-echo acquisition, such as: point resolved spectroscopy (PRESS) [101], echo-planar spectroscopic imaging (EPSI) [144, 145], proton EPSI (PEPSI) [100], multi-echo EPI [146], spi-
ral in/out imaging [147], and multi-echo radial imaging [148]. In the past, these imaging methods have been used in applications such as MR spectroscopy [101, 144, 145], dual-contrast imaging [149], motion and susceptibility artefact correction [96, 150, 151, 152], and relaxometry [153, 154, 155]. More recently, multi-echo imaging has emerged as a tool of choice in real-time fMRI applications [150, 153, 156, 45] to increase BOLD contrast in the presence of contrast-to-noise ratio (CNR) reductions associated with real-time processing constraints, such as limited image pre-processing and producing brain maps from time series data of reduced length.

Recently, a multi-echo coarse voxel (MECV) pulse sequence has been developed [98], similar to a line-scan EPSI [157], specifically for fast multi-echo imaging in real-time fMRI. This acquisition uses outer volume saturation to localize a column of magnetization, from which multiple $T_2^*$ weighted readouts per excitation are obtained at coarse voxel locations using an asymmetric gradient echo train. This MECV sequence is optimized for applications that can sacrifice spatial resolution throughout the entire brain volume for a single columnar field-of-view of coarse voxels with dense sampling of $T_2^*$ decay curves (256 echoes per voxel per TR). Because the sequence provides rapid data acquisition and reconstruction of brain activity, MECV acquisitions have potential utility in fMRI neurofeedback - a research method whereby individuals learn to control their brain activity during fMRI sessions. Detailed investigation of neurofeedback using fMRI is important for the development of new therapies targeting various neurodisabilities, and for the development of brain computer interfaces [117]. Secondly, the MECV sequence can provide detailed sampling of the BOLD hemodynamic response, enabling basic neuroscience studies of the temporal latency between responses from different brain regions [158].

In the fMRI era, Hennig et al. first demonstrated the superior CNR provided by multi-echo point resolved spectroscopy (PRESS) compared to conventional single echo acquisitions [101] and multi-echo EPI was used by Speck et al. to assess BOLD activation via $T_2^*$ parameter mapping [149]. However, evidence has shown that parameter fitting of the change in relaxation rate $\Delta R_2^*$ ($R_2^* = 1/ T_2^*$) provided less BOLD contrast than combining echoes using weighted summation [159]. Posse et al. introduced a method for combining multi-echo turbo-PEPSI data using weights proportional to the expected BOLD contrast as a function of echo time [100], whereas Poser et al. developed a method for weighting each echo in proportion to its expected CNR [97]. Recently, multivariate source extraction techniques, including principal component analysis (PCA) have been explored for estimation of BOLD contrast in multi-echo signals [160].

When considering the different multi-echo weighting methods, the existing literature
Chapter 3. BOLD Contrast of Multi-Echo fMRI

Figure 3.1: BOLD contrast fundamentals a) Exaggerated normalized signal decay curves for active (solid circles) and rest (open circles) conditions, characterized by different $T^*$ values. b) Normalized signal difference difference $\Delta S$ for active and rest exponentials plotted against TE. $\Delta S$ reaches a maximum at TE approximately the mean $T^*$ value between both states.
provides guidance in the context of the limited multi-echo acquisitions achievable with single-shot EPI and spiral readouts, and TE-independent Gaussian noise. However, several of the pulse sequence approaches mentioned above provide significantly improved sampling of $T_2^*$ decay curves by trading spatial resolution for temporal resolution. Furthermore, it has long been known that the noise in fMRI data is not purely independent white Gaussian noise [161], but exhibits additional components intrinsically related to the BOLD signal and other physiological fluctuations. Multi-echo fMRI methods are susceptible to the same effects to differing degrees, depending on implementation. Some theoretical frameworks have been proposed to model TE-dependent noise variance [82, 162] and temporal autocorrelations [88]. Additionally, previous work has shown that noise characteristics are dependent on voxel sizes [163, 98], suggesting that a comprehensive treatment requires the exploration of more general noise conditions.

Consequently, new theoretical and numerical simulation work has been conducted using pertinent noise models to characterize and evaluate multi-echo weighting methods more broadly as a function of echo sampling and noise. The theoretical framework naturally leads to the development of a new echo weighting method: echo weights that increase linearly with TE value. Data-driven approaches are also considered to define echo weights, using a modified PCA technique to compare with the model-based echo weighting schemes. Example fMRI data acquired using the MECV pulse sequence are used to validate the predictions of theory and simulation results in real conditions at 1.5 T and 3.0 T. The practical implications of this work for multi-echo fMRI data acquisition and analysis are subsequently discussed.

3.2 Theory

3.2.1 BOLD Contrast and Multi-Echo Data

The BOLD contrast mechanism is a complex function of multiple neurophysiological parameters that relate neuronal activity and metabolic changes in blood oxygenation, blood flow and volume within the cerebral vasculature and MRI parameters [164]. The net result is decreased paramagnetic deoxyhemoglobin in the capillaries and draining vasculature near the active neuronal population, approximately 4-6 s after the onset of activity, reducing the local magnetic field inhomogeneity in comparison to a basal neuronal condition. The associated positive BOLD effect is characterized by a very small increase in $T_2^*$ value (or an associated decrease in $R_2^*$), quantified as an increase in MR signal magnitude at the measured echo time (TE) value (Fig. 3.1a). The BOLD contrast
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\[ \Delta S \text{ is explicitly defined as the difference between MR signal magnitude in active and rest conditions, as shown in Fig. 3.1b, according to:} \]

\[ \Delta S \approx \frac{d}{dR^2} S \cdot dR^2 = S_0 \cdot TE \cdot \Delta R^2 \cdot e^{-TE/T^2}, \]

(3.1)

where \( S_0 \) is the initial signal amplitude. For convenience, the negative sign is omitted as only positive BOLD responses are considered here, and \( \Delta R^2 \) is taken to mean absolute change. For single-echo acquisitions, choice of TE as the mean \( T^2 \) across active and rest conditions maximizes \( \Delta S \) \cite{100}. As shown in Fig. 3.1b however, a wide range of TEs exhibit substantial BOLD contrast, with the full width at half maximum (FWHM) ranging from approximately 0.25 \( \cdot T^2 \) to 2.75 \( \cdot T^2 \) (FWHM \( \approx \) 2.5 \( \cdot T^2 \)).

Multi-echo data collection allows extraction of increased BOLD signal contrast information by sampling the \( T^2 \) decay at multiple TEs and then maximizing the signal difference between active and rest conditions by combining the echo signals using weighted summation. Consider the multi-echo data set as a matrix \( X \) with \( m \) rows (number of measurements occurring at TR intervals) and \( n \) columns (number of echoes). Each row represents a sampled \( T^2 \) decay, and each column is a different \( T^2 \)-weighted time-series. To produce a single \( mx1 \) output time-series, \( X \) can be multiplied by an \( nx1 \) vector \( w \) in the matrix equation

\[ v = Xw, \]

(3.2)

where the vector \( v \) is the output time-series and the vector \( w \) defines the weights for each echo time in the summation.

It is natural to seek the optimal \( w \) in an attempt to maximize BOLD contrast quantified by the CNR of the time-series vector \( v \). One possible choice, for example, is to set \( w \) equal to the unity vector 1. If each column in \( X \) represented an independent measurement, then this selection for \( w \) would provide the same benefit as simple signal averaging of \( N \) measurements for a \( \sqrt{N} \) signal to noise ratio increase in the case of Gaussian white noise. However, for multi-echo fMRI data the columns in \( X \) are not independent (correlations exist in the signal and the noise), and the net benefit of simply summing \( N \) echo signals is much lower than \( \sqrt{N} \), nor does it necessarily monotonically increase with \( N \). Consequently other choices for \( w \) must be considered.

3.2.2 Model-Based Weighted Summation

Additional weighting methods can be derived analytically based on the BOLD signal model defined above, and the experimentally validated fMRI physiological noise model
developed by Kruger et al. [82]. This simple model identifies three different noise sources that corrupt fMRI signals, characterizing the sources by their temporal standard deviations: TE independent thermal white noise \( \sigma_0 \); non-BOLD physiological noise that is proportional to fMRI signal, \( \sigma_{NB} \propto S_n \); and BOLD-like physiological noise that is proportional to BOLD-related signal change \( \sigma_B \propto \Delta S_n \).

In the following definitions, let \( \{TE_n\} \) be the set of \( N \) measured echo times, \( \{S_n\} \) the signal magnitudes evaluated over \( \{TE_n\} \), and \( w_n \) the elements of the weighting vector \( w \). Normalization factors are omitted for clarity, where each \( w \) is normalized by \( 1/\Sigma w^2 \). In this analysis only sets of equally spaced TEs are considered, such that \( \{TE_n\} = \{n\Delta t\} \) with an echo spacing of \( \Delta t \). When considering the BOLD contrast achievable with different weighting methods, it is useful to calculate the relative CNR increase of each method with respect to the CNR of a conventional single echo signal. For a single echo signal with \( TE = T2^* \), CNR can be calculated as:

\[
CNR_{\text{single}} = \frac{\Delta S}{\sigma} \approx \frac{S \cdot TE \cdot \Delta R^2}{\sigma} = \frac{S_0 \cdot T2^* \cdot \Delta R^2}{\sigma \cdot e},
\]

where \( \sigma \) is defined as the temporal standard deviation as measured during the basal state. For multi-echo signals, the expression for CNR becomes a ratio of sums:

\[
CNR_{ME} = \frac{\sum_{n=1}^{N} w_n \cdot \Delta S_n}{\sqrt{\sum_{n=1}^{N} w_n^2 \cdot \sigma^2(n)}} \approx \frac{\sum_{n=1}^{N} n \cdot w_n \cdot S_n}{\sqrt{\sum_{n=1}^{N} w_n^2 \cdot \sigma^2(n)}},
\]

where the numerator is the sum weighted signal difference, and the denominator represents the total weighted standard deviation, added in quadrature. The relative CNR value is simply the ratio \( CNR_{ME}/CNR_{\text{single}} \):

\[
rCNR = \frac{\Delta t \cdot \sigma(T2^*) \cdot e}{T2^*} \cdot \frac{\sum_{n=1}^{N} n \cdot w_n \cdot e^{-n\Delta t/T2^*}}{\sqrt{\sum_{n=1}^{N} w_n^2 \cdot \sigma^2(n)}}.
\]

where \( \sigma(T2^*) \) is the temporal standard deviation evaluated at \( TE = T2^* \).

Equations for rCNR are subsequently given for several echo weighting methods:

1. Simple weighting is the naive averaging scheme described above, in which all echoes are weighted equally and summed. That is, \( w_n = 1 \) for all \( n \), and:
2. The $T2^*$ weighted summation method [100] weights each echo by its expected BOLD contrast contribution, omitting the scaling factors in Eq. 3.1:

$$w_{T2^*}(n) = TE_n \cdot e^{-TE_n/T2^*} = n \cdot \Delta t \cdot e^{-n\Delta t/T2^*},$$

$$r\text{CNR}_{T2^*} = \frac{\Delta t \cdot \sigma(T2^*) \cdot e}{T2^*} \cdot \frac{\sum_{n=1}^{N} n^2 \cdot e^{-2n\Delta t/T2^*}}{\sqrt{\sum_{n=1}^{N} n^2 \cdot e^{-2n\Delta t/T2^*} \cdot \sigma^2(n)}}. \quad (3.8)$$

3. The CNR weighting method [97] weights echoes by the expected CNR contribution as measured by an additional multi-echo acquisition of the basal state (i.e. no behavioural task). Given a basal multi-echo dataset with a temporal signal-to-noise ratio of $\Psi_n$ for the nth echo, the CNR per echo can be calculated as:

$$w_{\text{CNR}}(n) = \frac{\Delta S}{\sigma} \propto \frac{TE_n \cdot S_n}{\sigma} = n \cdot \Delta t \cdot \frac{S_n}{\sigma} = n \cdot \Delta t \cdot \Psi_n.$$  

The CNR sum becomes:

$$r\text{CNR}_{\text{CNR}} = \frac{\Delta t \cdot \sigma(T2^*) \cdot e}{T2^*} \cdot \frac{\sum_{n=1}^{N} n^2 \cdot \Psi_n \cdot e^{-n\Delta t/T2^*}}{\sqrt{\sum_{n=1}^{N} n^2 \cdot \Psi_n^2 \cdot \sigma^2(n)}}. \quad (3.10)$$

Inspection of Eq. 3.9 shows that $\Psi$ and $w_{\text{CNR}}$ will take on a different form depending on the specific form of $\sigma$, analogous to a matched filter. With BOLD-like physiological noise $\sigma = \sigma_B = c_1 \cdot \Delta S$, it is apparent that $w_{\text{CNR}}$ becomes constant, reducing to the special case of $w_{\text{simple}}$. Similarly, in purely TE-independent Gaussian noise conditions $\sigma = \sigma_0$, $w_{\text{CNR}}$ is equivalent to $\text{TE} \cdot \text{S}$ (i.e., $w_{T2^*}$). This equivalence was observed in the initial development of the CNR weighting method [97]. The previous echo weighting methods were developed without consideration of fMRI noise characteristics, and their equivalence to CNR weights in particular noise conditions within the Krueger model is
noted post hoc. Extending this approach, however, there is one situation within the Kruger model for which an echo weighting scheme has not been previously developed.

4. The linear weighting method utilizes weights that increase in linear proportion to the TE value:

\[ w_{\text{Linear}}(n) = TE_n = n \Delta t, \]  

\[ r_{\text{CNRLinear}} = \frac{\Delta t \cdot \sigma(T_{2*})}{T_{2*}} \cdot \sqrt{\sum_{n=1}^{N} n^2 \cdot e^{-n\Delta t/T_{2*}}} . \]  

This definition is identical to the CNR weighting definition in the case where \( \sigma = \sigma_{NB} = c_2 \cdot S \), and completes the symmetry observed in the model framework with respect to the equivalence of \( w_{\text{CNR}} \) to \( w_{\text{Simple}}, \) \( w_{T_{2*}}, \) and \( w_{\text{Linear}} \) in \( \sigma_B, \sigma_0, \) and \( \sigma_{NB} \) noise conditions respectively. Although Eq. 3.5 can be used to predict rCNR behaviour in all echo weighting and noise scenarios, the derived analytical expressions do not have simple forms. Consequently CNR dependencies following from Eq. 3.5 are plotted in Fig. 3.2 for visual interpretation (see Results).

### 3.2.3 Data Driven PCA Weighted Summation

The weighting methods and their CNR characteristics described in the previous section are derived from models of signal and noise behaviour in fMRI. Alternatively, it is also useful to consider data-driven approaches to defining echo weights, whereby the weights are derived from specific fMRI experiments. Such approaches are likely to be robust in cases where model assumptions do not hold (e.g. \( T_{2*} \) decay is not monoexponential or varies throughout the brain), when time constraints preclude additional experiments to ascertain model parameters (e.g. noise assessments for the CNR weighting method), or when the multivariate nature of the time-series data is large (e.g. \( T_{2*} \) decay is densely sampled).

For specific comparison with the model-based weighting methods, a method based on PCA is developed. The PCA approach defines an alternate basis set for multivariate data by identifying orthogonal directions of maximal variance across the space defined by the variables. Returning to Eq. 3.2, the output time-series \( v \) can be re-interpreted as a dimensionality reduction along the echo dimensions of \( X \), where the echoes are projected onto a single dimensional subspace defined by the basis vector \( w \). Thus, PCA is used
Figure 3.2: Theoretical BOLD contrast gain (rCNR) using four model-based methods for multi-echo signal weighting at Δt = 1 ms. Four noise conditions are plotted (a) $\sigma_0$ noise only, (b) $\sigma_B$ noise, (c) $\sigma_{NB}$ noise, and (d) combined $\sigma_{0+B+NB}$ noise. Horizontal axes display the sampling window $TE_{\text{max}}$ normalized by $T2^*$. Vertical axes labels show rCNR for $T2^* = 50$ ms, although curve shapes are valid for all $T2^*$. 
Figure 3.3: Theoretical rCNR dependence on echo spacing $\Delta t$ in the $\sigma_{0+B+N_B}$ noise condition for $TE_{max} = 150$ ms ($3 \cdot T2^*$). Open circles indicate $T2^*$ weighted data, and open squares indicate CNR weighted data. Solid and dashed lines plot $1/\sqrt{\Delta t}$ model curves through the data. The error between the calculated values and the model curves are only evident at large $\Delta t$ ($r^2 > 0.99$).

to identify the projection $w$ from the principal component vectors, giving most weight to those echoes that contribute most to BOLD fluctuation under the assumption that task-related BOLD signal variance is the primary coherent variance source in the data. The PCA algorithm is described in the Appendix.

The output of the PCA weighting algorithm is not easily described in a closed form due to its statistical nature. Consequently, performance of this method is evaluated only by simulation and experiment.

3.3 Methods

3.3.1 Monte Carlo Simulations

To examine the rCNR behaviour of the different weighting schemes in more detail, Monte Carlo methods were developed to simulate fMRI signals from a single voxel of interest using MATLAB (The MathWorks, Inc., Natick MA, USA). Complementary to the ideal behaviour predicted theoretically (Eqs. 3.6,3.8,3.10,3.12), simulation parameters were defined for practical conditions, better reflecting experimental data. This included dependence of $\sigma_0$ on sampling density and the addition of physiologically mediated noise
Simulated gray matter R2* values were modulated with a boxcar waveform representing a block design consisting of alternative active and basal conditions of 20 s duration for 5 repetitions and a total of 200 time points (simulated TR = 1000 ms). The boxcar waveform was additionally convolved with a canonical hemodynamic response function (HRF) consisting of a sum of gamma variate functions [165], with parameterization following from the motor response HRF described by Glover [166]. Although in the linear approximation rCNR is largely independent of ΔR2* as long as it is small, a conservative value of |ΔR2*| = 0.29s\(^{-1}\) was used following from prior fMRI simulations of primary motor cortex activity [167]. A random Gaussian noise distribution was generated with TE-dependent variance modulated by \(\sigma^2 = a \cdot \sigma_0^2 + b \cdot \sigma_B^2 + c \cdot \sigma_{NB}^2\). The binary coefficients \(a, b\) and \(c\) were adjusted to produce 4 different noise conditions: Setting \([abc] = [100]\) produced \(\sigma^2 = \sigma_0^2\), \([010]\) and \([001]\) produced the \(\sigma_B\) and \(\sigma_{NB}\) conditions respectively, and \([111]\) produced the \(\sigma_{0+B+NB}\) condition. Values of \(\sigma_0 = 0.21\), \(\sigma_B = 0.53\), and \(\sigma_{NB} = 0.21\) (expressed as percentage of \(\text{S}_0\)) at TE = 30 ms were taken from Kruger et al. [82] for a 3.0 T MRI system to represent a general case, and variances at all other TEs were calculated accordingly.

The \(\sigma_0\) parameter depended on \(\Delta t\) by a factor of \(1/\sqrt{\Delta t}\) to model explicitly the signal-to-noise ratio changes accompanying simulated bandwidth adjustments [159]. Following the observations of others, an autoregressive AR(1) process with coefficient 0.5 was then used to generate successive samples in the noise time-series (TR dimension) [88]. To model a similar effect within the TE dimension, convolution with a Gaussian kernel of varying widths was used to induce inter-echo correlations. The Gaussian convolution suppresses high frequency fluctuations across echoes, and enhances correlation between echo time-series, in a neighbourhood determined by the width of the kernel. This method produced the diagonalized correlation matrix observed in Fig. 3.4, and was judged to be a good simple first-order approximation to actual correlations observed in real data. Normally distributed random numbers were generated using the MATLAB randn function. For each noisy, active time series, an additional simulated basal time series dataset was created, without the R2* modulation, which was required for evaluation of the CNR weighting method.

Simulations were performed using 1000 iterations for each set of experimental parameters tested, and the mean rCNR values reported. Different sampling densities were investigated using \(\Delta t = 1, 2, 3, 5, 6, 10, 15, 25, 30\) and 50 ms, with \(T E_{\text{max}} = 250\) ms. The noise correlation index was also varied at \(\Delta t = 1\) ms, parameterized by Gaussian kernel width (\(\sigma_{\text{CORR}}\)) values of 1, 5 and 10 ms.
The simulated datasets were processed in MATLAB using each of the weighting methods, yielding BOLD time-series vectors which were then compared using rCNR. The CNR was defined as $\Delta S/\sigma$, and was calculated using the general linear model framework (GLM) [87] as $\beta/\sigma_r$ where $\beta$ is the model regression coefficient and $\sigma_r$ is the standard deviation of the residuals. The model regressor was defined using the convolved box-car waveform and HRF described above. The rCNR was computed by normalizing the multi-echo CNR by the CNR of a single-echo time series at $TE = 50$ ms.

Aggregate noise correlations were also assessed using a “total correlation index”:

$$TCI = \frac{1}{N^2 - N} \left( \sum_{i,j} r_{ij} - N \right)$$  \hspace{1cm} (3.13)

where $r_{ij}$ are the elements of the noise correlation matrix $R$ and $N$ is the number of echoes. This produced an index that was 0 for a completely uncorrelated (identity) matrix, and 1 for a completely correlated matrix. When correlations are small, a simple relationship between TCI values and $\sigma_{CORR}$ values can be obtained for the simulation data by linear regression. For experimental data, only TCI values can be calculated directly, but $\sigma_{CORR}$ values can be estimated based on the linear regression parameters.

### 3.3.2 Experiments

Two sets of experimental data were evaluated in this work to provide a specific validation of the Monte Carlo simulations. Experiment A was performed on a 1.5T Signa MRI system (16 channel HDX, GE Healthcare, Milwaukee, USA) at Sunnybrook Health Sciences Centre, Toronto, using a quadrature birdcage head coil. Experiment B was performed on a 3.0T Magnetom TIM Trio system (VB15 software, Siemens Healthcare, Erlangen, Germany) at Baycrest Hospital, Toronto, using a 32-channel phased array head coil. Subjects gave informed consent to participate and all experimental data were collected with approval of the Research Ethics Boards at both hospitals, respectively.

Experiment A was conducted in 5 young, healthy right handed subjects (4 male) using the MECV pulse sequence with 20 runs acquired in total. A single linear column of 32 voxels ($5 \times 20 \times 20 \text{ mm}^3$, approximately 30-40 x larger than typical fMRI voxels) was prescribed left to right over both primary motor cortices, guided by a T1-weighted fast spoiled gradient echo anatomical image and whole brain spiral in/out functional localizer performed prior to MECV data acquisition. The MECV data were acquired at TR = 1000 ms with 200 time points, and 256 echoes were collected per voxel per TR at an echo spacing of 1.024 ms (readout bandwidth = 62.5 kHz). Subjects performed a simple hand
Figure 3.4: Correlation matrices for multi-echo datasets (black = 0, white = 1). Experimental data in basal conditions acquired with (a) a flip angle of 0 degrees showing uncorrelated noise; and (b) a flip angle of 42 degrees showing large noise correlations between echoes. Analogous matrices are shown for simulated noise data with (c) low ($\sigma_{CORR} = 1$ ms, TCI = 0.01) and (d) high ($\sigma_{CORR} = 20$ ms, TCI = 0.28) echo correlations.
Figure 3.5: Monte Carlo simulation results for 1 ms echo spacing with low noise correlation in the TE dimension produced by $\sigma_{\text{CORR}} = 1$ ms: (a) $\sigma_0$ noise only, (b) $\sigma_B$ noise, (c) $\sigma_{NB}$ noise, and (d) combined $\sigma_{0+B+NB}$ noise. Graphs represent the mean values of 1000 noise records. Vertical axes report rCNR with the CNR of a single-echo time series at TE = 50 ms as the normalization factor. Horizontal axes are identical to those used in Fig. 3.2.

clenching task using the same boxcar design described above, and single voxel regions of interest over primary motor cortex were determined by the peak cross correlation coefficient with respect to the reference boxcar waveform. In place of additional resting scans for computation of CNR weights, resting condition variances were estimated from a retrospectively reconstructed rest dataset, through concatenation of rest periods in the fMRI data. Rest blocks were truncated to avoid residual task-related variance (only the last 15 time points were used in each rest block), and time-series data were detrended using a first order polynomial prior to concatenation to avoid block-to-block variance. Noise data for the correlation estimates were computed from the residuals of column-wise regression of the data matrix with the HRF convolved task waveform.

Experiment B aims to complement the results from Experiment A by explicitly determining physiological noise model coefficients associated with the multi-echo data. A single left handed subject performed bilateral hand clenching, using the same boxcar de-
sign, scan geometry, and voxel localization procedure over the right primary motor cortex with the MECV sequence as described for Experiment A. All scans were acquired at TR = 500 ms for 400 time points. Eight resting fMRI and 4 block design fMRI acquisitions were performed, with slight differences in echo spacing (1.0 ms) and readout bandwidth (78.1 kHz) arising from an alternate implementation of the MECV pulse sequence which sampled during both positive and negative readout gradient lobes instead of the flyback gradients [168] used for Experiment A. The resting fMRI data were acquired at TR = 500 ms for 100 time points, comprising 2 sets of 4 flip angles: 0, 19, 42 and 90 degrees corresponding to 0%, 29%, 42% and 30% of the ideal fully relaxed maximum $S_0$. These data were used to compute the physiological noise model parameters defining $\sigma_0$, $\sigma_B$ and $\sigma_{NB}$. It should be noted that previous studies estimating the physiological noise parameters at 3.0 T [82, 163] utilized a larger TR value (3000 ms) to provide signals sampling the range from 0 to $S_0$ more completely. However, rapid temporal sampling is a key feature that typifies the MECV sequence. The decision to retain this feature in the experimental data, while reducing the range of $S_0$ sampled, has the primary effect of slightly increasing the error in estimating $\sigma_0$. Estimations of $\sigma_B$ and $\sigma_{NB}$ are independent of TR. Lastly, one of the datasets acquired at 90 degree flip angle was used as rest data for the CNR weighting method.

3.4 Results

3.4.1 Theory and Monte Carlo Simulations

According to the expressions derived from Eq. 3.5, Fig. 3.2 shows theoretical rCNR plots for model-based echo weighting methods in the different noise conditions investigated at an echo spacing of $\Delta t = 1$ ms. No temporal correlations in noise are assumed. These results can be viewed as the rCNR behaviour obtained by a set of increasing echo train windows sampling the $T_2^*$ decay at $\Delta t$ increments, up to some $TE_{max}$. For more generalized interpretation, rCNR values are plotted according to the normalized variable $TE_{max}/T_2^*$. The shape of the curves are independent of $T_2^*$, and only depend on $TE_{max}/T_2^*$. However, the absolute rCNR values need to be scaled by the corresponding difference in the effective echo spacing, or echo spacing normalized to $T_2^*$, with a scale factor of $\sqrt{T_2^{*1}/T_2^{*2}}$ (where $T_2^{*1} > T_2^{*2}$). Fig. 3.2 was scaled to show rCNR values at the physiologically realistic $T_2^* = 50$ ms.

In general, the curves increase from the origin towards a maximum, and either asymptotically approach this maximum or decrease back towards 0, depending on the weighting
method and the noise condition. As $TE_{\text{max}}$ becomes large with respect to $T2^*$, only the simple and linear weighting methods show rCNR reductions, while the $T2^*$ and CNR weighting methods monotonically increase. As predicted, the CNR weighting method produces weights identical to $T2^*$ weights in the $\sigma_0$ noise condition, simple weights in the $\sigma_B$ noise condition, and linear weights in the $\sigma_{NB}$ noise condition, and is consequently robust for the range of $TE_{\text{max}}$ explored. However, Fig. 3.2d predicts only small differences between weighting methods in realistic noise conditions, and beyond approximately $TE_{\text{max}}/T2^* = 3$, rCNR shows little increase (approximately 10%). For the case of simple weighting, this result agrees with previous theoretical calculations [100].

Although the closed form theoretical expressions for rCNR versus echo spacing are analytically complex, exploring curves such as those shown in Fig. 3.2 for various $\Delta t$ values indicates that the dominant effect is a $1/\sqrt{\Delta t}$ dependence. Example log-log plots of rCNR versus $1/\sqrt{\Delta t}$ are shown in Fig. 3.3 for CNR- and $T2^*$-weighting methods in the $\sigma_{0+B+NB}$ noise case at $TE_{\text{max}} = 3 \cdot T2^*$. Linear regression (solid and dashed lines) shows
that the inverse square root dependence characterizes the theoretical results extremely well for the practical range of \( \Delta t \) examined, producing \( r^2 > 0.99 \) for all weighting methods. This result is expected, due to explicit modelling of bandwidth effects \( (\sigma_0 \propto 1/\sqrt{\Delta t}) \) in the Monte Carlo simulations.

To examine more practical conditions, the Monte Carlo simulations additionally modelled temporal correlations in the noise structure of the simulated data, as an autoregressive process in the TR domain and cross-correlations across echoes in the TE domain with a Gaussian kernel. For illustration purposes, Fig. 3.4 plots noise correlation matrices for 2 example datasets and 2 simulated datasets. Figs. 3.4a and 3.4b illustrate low (TCI = 0.04) and high (TCI = 0.38) echo correlations in the resting fMRI data from Experiment B, and Figs. 3.4c and 3.4d show simulated noise correlations created with \( \sigma_{CORR} \) values of 1 ms and 20 ms respectively. Figs. 3.4a and 3.4c show correlation matrices very similar to scaled identity matrices, indicative of uncorrelated data. In contrast, Fig. 3.4b shows substantially increased correlations between echoes that occur close to one another in time, particularly for early echoes. This effect causes the diagonal features of the correlation matrix to “blur” and broaden, which is approximated in Fig. 3.4d using a relatively large \( \sigma_{CORR} \) value of 20 ms.

Two possible mechanisms for the elevated correlations at early echoes are head motion and off-resonance effects, both of which are not manifested in later echoes due to \( T2^* \) decay. Neither effect is modelled specifically in the the numerical simulations. Although Fig. 3.4d does not capture the larger correlations observed in the upper left quadrant of Fig 3.4b, nevertheless the blurring along the diagonal shown in Fig. 3.4d is similar to that shown in Fig. 3.4b and provides rCNR values that are in reasonable agreement with those achieved with experimental data (see below). For small TCI (< 0.20), the equivalent \( \sigma_{CORR} \) was found to be proportional to TCI with constant 71.9 ms\(^{-1}\).

Simulated mean rCNR vs. \( T_{E_{max}}/T2^* \) at \( \Delta t = 1 \) ms is plotted in Figs. 3.5 and 3.6 for \( \sigma_{CORR} \) values of 1 and 5 ms, respectively, with the PCA weighting method included. Similarities in the shape of the simulated and theoretical curves (Fig. 3.2) are immediately evident, with correspondence within a scale factor. Data for the CNR weighting method again show equivalent rCNR dependency to each of the other model-based weighting methods in a specific fMRI noise condition. In Fig. 3.5, the PCA weighting method works equivalently well to CNR weighting and \( T2^* \) weighting under \( \sigma_0 \) noise conditions and comparably well in the \( \sigma_{0+B+NB} \) conditions, although with slightly less rCNR at large values of \( T_{E_{max}} \). In Fig. 3.6, the PCA weighting method shows most sensitivity to significant noise correlations in the TE domain, with the maximum rCNR substantially reduced in comparison with the other weighting methods in the presence of \( \sigma_B, \sigma_{NB} \), and
Figure 3.7: Log-log plot of simulated rCNR vs $\sigma_{CORR}$, for CNR and PCA weighted data, in the simulated $\sigma_{0+B+NB}$ noise condition. Simulation parameters used were $\Delta t = 1$ ms, $T_{E_{max}} = 150$ ms, and 1000 noise samples at each data point. The open circles and solid line plot the CNR weighted data and the $\sigma^{z}_{CORR}$ model fit with ($x = -0.48$, $r^2 > 0.99$) for the CNR weighted data, respectively; and the squares and dashed line plot the PCA weighted data and model ($x = -0.52$, $r^2 = 0.97$).

Considering these noise correlations in somewhat more detail, the correlation between the noise at different TE values can be thought of as reducing the signal averaging benefit that was originally expected from densely sampled $T2^*$ decay curves. The effective sampling density is reduced by the factor $(\sigma_{CORR}/\Delta t)$, and consequently the logical first-order assumption is that rCNR gain should follow a $1/\sqrt{\sigma_{CORR}}$ dependence. Fig. 3.7 illustrates a log-log plot of rCNR in the $\sigma_{0+B+NB}$ noise case with $\Delta t = 1$ ms and $T_{E_{max}} = 150$ ms, generated using CNR- and PCA-weighting methods, versus $\sigma_{CORR}$. An inverse correlation between log(rCNR) and log($\sigma_{CORR}$) is clearly observable for both echo weighting methods, with estimated slopes of $-0.48 \pm 0.07$ ($p = 0.0011$) and $-0.52 \pm 0.29$ ($p = 0.0167$) obtained by linear regression, respectively. These estimates are quoted with 95% confidence intervals calculated from t-tests on regression coefficients, and indicate that resultant slopes are not significantly different from one another and not significantly different from the predicted value of -0.5. The other model-based methods show similar dependencies to that of the CNR-weighting method across the noise conditions.

Fig. 3.8 shows log-log plots of rCNR versus echo spacing $\Delta t$ at $T_{E_{max}} = 150$ ms, for $\sigma_{CORR} = 1$, 5, 10, and 20 ms. Although rCNR still decreases monotonically with
Table 3.1: Mean rCNR results across Experiment A (N=5)

<table>
<thead>
<tr>
<th>Weighting Type</th>
<th>rCNR ± standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>1.00</td>
</tr>
<tr>
<td>Simple</td>
<td>2.49 ± 0.39</td>
</tr>
<tr>
<td>Linear</td>
<td>3.49 ± 0.49</td>
</tr>
<tr>
<td>$T2^*$</td>
<td>2.99 ± 0.41</td>
</tr>
<tr>
<td>CNR</td>
<td>3.27 ± 0.40</td>
</tr>
<tr>
<td>PCA</td>
<td>3.37 ± 0.43</td>
</tr>
</tbody>
</table>

decreasing sampling density, the $\Delta t$ dependence is now more complex than presented theoretically in Fig. 3.3. Fig 3.8a shows data and the $\Delta t^x$ model fits obtained by linear regression (mean ± 95% confidence interval) for CNR ($x = -0.47±0.01$) and PCA ($x = -0.48±0.05$) weighting methods. The data and analogous fit parameters for the other weighting methods: simple ($x = -0.46±0.01$), linear ($x = -0.47±0.01$), and $T2^*$ ($x = -0.46±0.02$) are not shown for clarity, but have similar dependencies. The results of all regressions were highly significant, with $p < 0.001$. For Figs. 3.8b-d, the fitted lines are unchanged to illustrate the deviation of rCNR as $\sigma_{CORR}$ is increased. The essential feature of these plots is that the combined effect of increased echo spacing and increased $\sigma_{CORR}$ values rapidly reduces rCNR benefits to a minimum value, not surprisingly similar to the CNR obtainable with a single echo. The effect of increasing $\sigma_{CORR}$ is to shift the rCNR lower in the vertical direction, such that smaller and smaller echo spacings are required to achieve substantial rCNR benefits. In the extreme case, a $\sigma_{CORR}$ value of 20 ms is sufficient to remove nearly all contrast benefits of densely sampling a $T2^*$ decay curve with an echo spacing of 1 ms. Inspection of the plots suggests that the rCNR minimum is achieved when $\Delta t \cdot \sigma_{CORR} \geq 100 \text{ ms}^2$.

3.4.2 Experiment A

Table 3.1 shows the mean rCNR results of Experiment A (mean ± standard error). In this case, all weighting methods provide significant contrast gains when compared to a single echo time-series ($p \leq 0.01$, Bonferroni corrected for multiple comparisons), although none were statistically significantly different from each other. Inspection of the rCNR means indicated a trend that the linear, CNR-and PCA-weighting methods provided the largest contrast enhancement, whereas the simple- and $T2^*$-weighting methods performed slightly less well in comparison. The performance of the linear and CNR methods possibly suggests that the data exhibited large amounts of $\sigma_{NB}$ noise, although...
Figure 3.8: Simulated rCNR vs. echo spacing $\Delta t$ for $\sigma_{\text{CORR}}$ of a) 1 ms; b) 5 ms; c) 10 ms; and d) 20 ms in the $\sigma_{0+B+N_B}$ noise case, shown on a log-log scale. Open circles plot simulated CNR weighted data, and squares denote PCA weighted data. Solid and dashed lines represent $\Delta t^x$ fits for the CNR ($x = -0.47, r^2 > 0.99$) and PCA ($x = -0.48, r^2 = 0.98$) weighted methods at $\sigma_{\text{CORR}} = 1$ ms kernel data respectively. The plots show the effect of increasing noise correlations on rCNR as a function of $\Delta t$, where the benefits afforded by multi-echo fMRI are only maintained at small echo spacings if the noise correlations in the TE dimension become pronounced.
Table 3.2: Mean rCNR results across Experiment B (N=1)

<table>
<thead>
<tr>
<th>Weighting Type</th>
<th>rCNR ± standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>1.00</td>
</tr>
<tr>
<td>Simple</td>
<td>1.68 ± 0.06</td>
</tr>
<tr>
<td>Linear</td>
<td>2.79 ± 0.21</td>
</tr>
<tr>
<td>$T^2*$</td>
<td>1.48 ± 0.05</td>
</tr>
<tr>
<td>CNR</td>
<td>2.75 ± 0.22</td>
</tr>
<tr>
<td>PCA</td>
<td>4.49 ± 0.89</td>
</tr>
</tbody>
</table>

insufficient data were collected in Experiment A to establish this with certainty. The deviations of the rCNR means, however, reflect the substantial heterogeneity in signal and noise characteristics across subjects in this inter-subject comparison.

The log-log scatter plot in Fig. 3.9 shows the rCNR values for the CNR and PCA weighted methods for each of the 20 datasets in Experiment A against the estimated noise correlation in the TE domain as calculated from TCI values. The models were fit to the data for both weighting methods using linear regression, producing (mean ± 95% CI) $x = -0.55 ± 0.23$ ($p < 0.001$) for the CNR weighted data and $x = -0.57 ± 0.26$ ($p < 0.001$) for the PCA weighted data.

3.4.3 Experiment B

Table 3.2 displays the results for Experiment B, exploring a single subject in more detail, showing the mean rCNR (± standard error). In this individual case, the PCA weighting method produced the highest gain within experimental error. As in Experiment A, all weighting methods produced an output CNR significantly greater than the single echo time-series ($p \leq 0.005$, Bonferroni corrected) and the linear and CNR weights produced the highest mean gain in relation to the other model-based techniques. Given the results of Experiment A, a planned comparison of the mean rCNR of the PCA-, CNR- and linear-weighting methods against the simple and $T^2*$ methods showed significant difference ($p < 0.02$), supporting the possibility that data were acquired with large amounts of $\sigma_{NB}$ noise. To confirm this hypothesis, analysis of the resting data for this subject revealed physiological noise model parameters of $\sigma_0 = 0.30 ± 0.19$, $\sigma_{NB} = 0.73 ± 0.20$, and $\sigma_B = 0.46 ± 0.01$ (expressed as %$S_0$ at TE = 50 ms, ± standard error). The $\sigma_{NB}$ estimates were approximately 1.6 and 2.4 times larger than the $\sigma_B$ and $\sigma_0$ estimates respectively, consistent with expectations.
Figure 3.9: Log-log Scatter plot of rCNR values vs. TCI for all scans in Experiment A. Open circles indicate CNR weighted data, and crosses denote PCA weighted data (trends for other weighting methods are similar). The $TCI^2$ model fits to the CNR weighted data (solid line, $x = -0.55$) and the PCA weighted data (dashed line, $x = -0.57$) are both significant with $p < 0.05$. Estimated $\sigma_{CORR}$ values are also shown in the horizontal axis based on the linear relationship observed between TCI and $\sigma_{CORR}$ values obtained by numerical simulation.

3.5 Discussion

The analyses reported here extend the theoretical [159] and experimental [100, 97, 160] investigations of multi-echo fMRI contrast enhancement by exploring a variety of echo weighting methods under high echo sampling density conditions. Use of the MECV pulse sequence allowed for up to 256 echoes at $\Delta t = 1$ ms, whereas previous analyses involved tens of echoes spaced at 10-20 ms. Additionally, explicit inclusion of TE-dependent noise variances as well as noise correlations in the TE and TR dimensions allowed meaningful comparison of theory, simulations, and experiments in this dense sampling regime. The analytical expressions presented in the Theory section derived from models of fMRI signal and physiological noise convey the complex dependence of rCNR on the weighting methods and noise characteristics, and on signal and measurement parameters such as $R2^*$, $\Delta t$, and $N$ ($TE_{max} = N \cdot \Delta t$). The derived rCNR values are independent of $\Delta R2^*$ (under the assumption that it is small) and $S_0$. Theoretical and simulation results indicate that the achievable rCNR is close to the asymptotic value at approximately $TE_{max} \approx 3 \cdot T2^*$ in the physiologically relevant $\sigma_{0+B+N_B}$ noise case, with marginal gains obtained at larger sampling windows. This suggests a rule of thumb for the preferred sampling window: $TE_{max} \approx 180$ ms at 1.5 T and 150 ms at 3.0 T if the precise noise characteristics are unknown. This result is consistent with the analytical result of $3.2 \cdot T2^*$ obtained by
Posse et al. for the simple weighting case [100].

It is important to emphasize that these recommendations are based primarily on the combined noise conditions (i.e., $\sigma_{0+B+NB}$). Although theory and simulations have been provided that treat the various noise components in isolation, rCNR curves for the $\sigma_B$ and $\sigma_{NB}$ noise cannot be observed in isolation experimentally over the entire echo sampling window, and should not be over-interpreted. In the $\sigma_B$ case, no noise contribution is provided at small TE values. In both cases, noise contributions tend to zero as TE increases, indicating that $\sigma_0$ noise is dominant at large echo times. This explains why, in Figs. 3.2c, 3.5c, and 3.6c, the apparent large increases in rCNR exhibited by CNR weighting and linear weighting for large sampling windows are not apparent in the respective net rCNR curves which account for all noise sources in combination (Figs. 3.2d, 3.5d and 3.6d, respectively). Figs. 3.2d, 3.5d, and 3.6d also indicate that there are not large differences between rCNR obtained with each of the model-based methods. This observation notwithstanding, the same figures also show that CNR weighting provides the best rCNR irrespective of noise characteristics. Weighting each echo time-series by $\Delta S/\sigma$, instead of simply $\Delta S$, generalizes the $T^*_2$ weighting method by reducing weights by their estimated noise content.

The CNR weights reduce to $T^*_2$, simple or linear weights in the presence of $\sigma_0$, $\sigma_B$ and $\sigma_{NB}$ noise respectively. This produces weights that are adaptively optimal given the noise environment, compared to the fixed definitions used in the simple, linear and $T^*_2$ weighting cases. However, these positive attributes need to be placed in appropriate, practical context. Simulation results (not shown) suggest that the presence of non-monoexponential decay or other non-idealities can artificially inflate the SNR estimate used to define the CNR weights, resulting in rCNR reductions below what is achievable in the ideal case. For example, because CNR and linear weighting methods include terms proportional to TE in their weight definitions, derived by assuming that signals decay exponentially with respect to $T^*_2$, the effect of any non-BOLD signal decay or baseline signal at long TE is inappropriately amplified. In comparison, the $T^*_2$ method does not suffer from this effect. The requirement of a separate resting fMRI scan, or at the very least an additional set of volumes prepended to a scan is a further limitation of the CNR weighting method. Factors such as cumulative motion effects and scan-to-scan variability over the course of an experimental session can potentially diminish the validity of an initial CNR estimate provided from resting fMRI data. These are likely to be small concerns in practice, given that approximately one minute of preliminary scanning is sufficient for reliable CNR-weight estimation. Nevertheless, a robust technique that provides CNR weighting in the presence of experimental non-idealities, without requiring
resting fMRI data would be useful.

Evaluation of the data driven PCA weighting method also revealed robust rCNR curves in simulations, under $\sigma_{0+B+NB}$ noise conditions when echo spacing and noise correlations between echoes were small (Fig. 3.5) and, importantly, in two sets of experimental data (Tables 3.1, 3.2). These observations suggest that, contrary to investigations in low sampling density regimes [160], statistical methods like PCA are viable for BOLD contrast extraction under certain conditions. The performance of the PCA method depends on the pre-processing choices made, and the principal component selection algorithm (see Appendix). The particular choices made in this manuscript reflect best-case performance for the PCA weighting method, and were chosen based on an initial trial-and-error testing period to provide a fair base-case comparison between the different weighting methods. The data obtained in Experiment B may be an example of BOLD fMRI signals that are not well modelled by the theory outlined in Eqs. 3.1-3.12, and that rCNR is achieved better by using a data-driven technique for the specific subject under study. The departure from theory could arise either in terms of signal or noise, and may include non-constant brain activity over the course of the experiment (habituation or cognitive effects), or an analogous temporal evolution of noise parameters in the model of Kruger et al. [82] (for example, the non-BOLD noise component). Consistent with this argument, the rCNR results for linear, $T2^*$, and CNR weighting are all substantially lower than that for PCA for the particular data set in question. In Experiment A, the various weighting methods show much better agreement.

As a consequence of the present work, well-founded estimates for the appropriate echo sampling density ($\Delta t < 5$ ms and $TE_{\text{max}}/T2^* \approx 3$) and tolerable noise correlations across echoes ($\sigma_{\text{CORR}} < 10$ ms) have been determined.

Irrespective of echo weighting method, theory and simulation both showed that the CNR gain from multi-echo fMRI is proportional to $1/\sqrt{\Delta t}$ in the absence of significant noise correlations in the TE domain (Figs. 3.3 and 3.8). As such noise correlations increase, the rCNR enhancement provided by higher echo sampling density (lower $\Delta t$) is attenuated, to a global asymptotic lower limit, reached when all echoes are 100% correlated, similar to performing fMRI based on a single echo. This finding is consistent with previous reported observations [159]. It is unreasonable to expect that the equivalent TE value in this condition equals $T2^*$, which explains why the baseline rCNR values obtained in Fig. 3.8 fall below unity. In addition, simulations predicted a $1/\sqrt{\sigma_{\text{CORR}}}$ dependence of rCNR characterizing the effect of noise correlation across echoes in high sampling density regimes (Fig. 3.7), which fit the experimental data well, assuming a linear relation between $\sigma_{\text{CORR}}$ and TCI (Fig. 3.9). Collectively, these results indicate
that $r\text{CNR} \propto \frac{1}{\sqrt{\Delta t \cdot \sigma_{\text{CORR}}}}$, as long as both $\Delta t$ and $\sigma_{\text{CORR}}$ are small, and approaches a lower bound as either is increased (Fig. 3.8). More concretely,

$$r\text{CNR} = \begin{cases} \frac{\alpha}{\sqrt{\Delta t \cdot \sigma_{\text{CORR}}}} & \text{if } \Delta t \cdot \sigma_{\text{CORR}} < \gamma \\ \beta & \text{otherwise} \end{cases}$$ (3.14)

where $\alpha$ is factor encompassing all other contributing factors to $r\text{CNR}$, $\beta$ is the $r\text{CNR}$ lower bound, and $\gamma$ is the $\Delta t \cdot \sigma_{\text{CORR}}$ threshold, found here to be approximately 100 ms$^2$.

The combined effect of $\Delta t$ and $\sigma_{\text{CORR}}$ on $r\text{CNR}$ has important implications for the utility of multi-echo fMRI. First, even with very densely sampled $T2^*$ decay curves, (e.g. 1 ms, as provided by the MECV sequence) $r\text{CNR}$ values are likely to be much less than predicted by simple theory, due to the presence of noise correlations in the TE dimension. For example, the maximum $r\text{CNR}$ value achieved in Fig. 3.2d for CNR weighting of data acquired with $\Delta t = 1$ ms is approximately 12. In Fig. 3.8, $\sigma_{\text{CORR}}$ values of 1 and 5 ms reduce the $r\text{CNR}$ value to 6 and 2.5 respectively. Second, $r\text{CNR}$ values of 2.5 or less, corresponding to $\sigma_{\text{CORR}} >$ approximately 10 ms, were frequently observed in the results for Experiment A (Fig. 3.9). These noise correlations appear to be highly subject-dependent and as a consequence, substantial $r\text{CNR}$ benefits are obtained in some subjects, but not others. The presence of strong TE dimension correlations is consistent with the short echo spacings provided by the MECV sequence, in contrast to the low correlations observed in more sparsely sampled data [99].

Given that the log($r\text{CNR}$) versus log($\sigma_{\text{CORR}}$) dependence in Fig. 3.9 is inversely proportional with $r^2$ values of 0.58 and 0.53 for the CNR and PCA weighting methods respectively, it is very likely the dominant contribution to the variation in the mean $r\text{CNR}$ values reported in Table 3.1. From a different perspective, the variations reported in Experiment A could arise from inter-subject differences in BOLD signal amplitude ($r\text{CNR}$ is independent of $\Delta R2^*$ only when $\Delta R2^*$ is very small); in the relative proportions of $\sigma_0$, $\sigma_B$, and $\sigma_{NB}$ noise; or in the amplitude of a specific noise component. Although the first two effects undoubtedly are contributing factors in Table 3.1, there is additional evidence that the last effect is very important. The trend indicating that linear weighting provides improved $r\text{CNR}$ over other echo weighting methods in Experiment A suggests a predominant $\sigma_{NB}$ contribution. Although PCA weighting provided the largest $r\text{CNR}$ benefit for the single subject investigated at 3.0 T (Experiment B), linear weights provided the next largest benefit. Explicit noise modelling for Experiment B also indicated that the $\sigma_{NB}$ magnitude was larger than each of the $\sigma_0$ and $\sigma_B$ values by approximately a factor of two, which is consistent with multi-echo signal behaviour in large, coarse voxels shown in a previous study of the MECV sequence [98]. While the voxel size investigated
was much larger than those previously investigated [163] (2000 mm$^3$ vs. 75 mm$^3$), the data are consistent in showing dominant physiological components. Additionally, the same study showed that at large voxel volumes, differences in tSNR across field strengths disappeared, suggesting that the CNR comparison presented may not strongly depend on field strength. Lastly, the matrix for experimental data with TE noise correlations (Fig. 3.4b) exhibited the strongest correlations at early echoes, i.e. where $\sigma_{NB}$ contributions are the largest. Possible reasons for large $\sigma_{NB}$ contributions in MECV data include shot-to-shot variability, partial voluming effects due to head motion, and resonant offset effects related to $T2^*$ data collection in large voxels, exacerbated by head motion or respiration. Although these effects are not directly related to the BOLD signal biophysics of interest reducing the $\sigma_{NB}$ contribution in MECV data is an issue worthy of future research.

The investigation of field strength dependent differences in rCNR obtained by different echo weighting techniques was not practically achievable in this study. Experiment B was performed on a single subject and enabled a detailed empirical estimation of noise characteristics in MECV data. Such characterization was not possible in Experiment A due to time constraints. In addition, Experiment B was also implemented on a different MRI software platform with a slightly different pulse sequence implementation of the MECV method than was used for Experiment A. Nevertheless, a comparison across field strengths would be an interesting topic of future research and may be the subject of future work.

Although initial work (unpublished) suggested that rCNR was unchanged after a RETROICOR [84] physiologic motion correction, it may be possible in the future to improve data acquisition and processing strategies to reduce the effect of $\sigma_{NB}$ noise in MECV data, or other techniques that provide densely sampled $T2^*$ decays. More sophisticated implementations of the PCA method were not explored here, and future work can probe it in this densely sampled context, along with other multivariate methods [160]. In addition, the effects of non-uniform echo spacing and dependencies due to magnetic field strength were not considered in detail here. Opportunities remain for investigating and exploiting the influence of these issues on echo-weighting strategies in densely sampled fMRI. We are optimistic that with further technique development, ultimately it will be possible to improve the CNR gains currently observed experimentally toward theoretical limits, particularly to expand real-time fMRI applications.
3.6 Appendix

The algorithm for finding \( w \) follows a typical PCA dimensionality reduction process, with additional steps that are important for the specific fMRI application: a “pruning” process, where certain echoes are removed from the analysis, and a process for choosing the final principal component using a selection heuristic.

(i) Linearly detrend the columns in \( X \)

(ii) Compute the sample correlation matrix \( R \) (i.e. normalized covariance matrix):

\[
 r_{ij} = \frac{1}{M-1} \sum_{m=1}^{M} \frac{x_{mi} \cdot x_{mj}}{\sigma_{ii} \cdot \sigma_{jj}}, \tag{A1}
\]

where \( r_{ij} \) are the elements of \( R \), \( M \) is the total number of TR time points, the \( x_{mi} \) are the \( m \)th element from the \( i \)th mean subtracted column, and the \( \sigma_{ii} \) are standard deviations from the \( i \)th column.

(iii) Find the squared correlation coefficients of each echo with the first echo (i.e. \( r_{11}^2 \)), and remove all echoes that satisfy \( r_{11}^2 > T \) for some correlation threshold \( T \) (e.g. 0.05) from \( X \), to form \( X^* \)

(iv) Take the sample covariance matrix \( C \) from \( X^* \), and determine its eigen-decomposition \( C = PDP^{-1} \)

(v) For each of the first \( L \) principal components \( p_i \) (sorted by maximum variance), compute the squared sum of its coefficients, \( S = (\Sigma p_i)^2 \)

(vi) Let \( w \) be the principal component that maximizes \( S \)

Steps (i) and (iv) provide the core PCA functionality, whereas steps (ii), (iii), (v) and (vi) are specific to multi-echo fMRI. Steps (ii) and (iii) ensure that echoes that are highly correlated with those for the first echo are not included in the subsequent PCA. This assumes that \( TE_1 \ll T2^* \), and that early echoes (e.g. \( TE = 1 \text{ ms} \)) contain little BOLD contrast information but instead reflect noise variance due to motion, shot-to-shot variations and \( T1 \) fluctuation. Removing these data helps ensure that the principal component subsequently obtained is not biased towards non-BOLD signal changes. Step (v) and (vi) implement the selection heuristic, selecting the principal component vector with the greatest sum of coefficients squared, maximizing \( (w \cdot 1)^2 \). Considering the elements of \( w \) as a time-dependent waveform, the sum of coefficients squared value is equivalent to
the sum of the autocorrelation coefficients of \( w \), which is a measure of the degree of self similarity of \( w \). For white noise, the autocorrelation coefficients will approximate a delta function, maximal at a lag of 0, and diminishingly small everywhere else. Selecting the vector with maximum sum of autocorrelation coefficients avoids principal components that contain appreciable random noise, and also avoids pathological cases where significantly high noise variance is concentrated in a small number of echoes resulting in a highly ranked yet undesirable principal component.
Chapter 4

Constrained Source Space Imaging (CSSI): Application to Fast, Region-based Functional MRI

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4.1 Introduction

Typical functional magnetic resonance imaging (fMRI) methods sample the blood oxygen level dependent (BOLD) signal at 1-2 s intervals, for spatially encoded information from most or all of the brain. For many fMRI applications, this temporal resolution suffices because the relatively sluggish hemodynamic BOLD signal responses are well sampled. There are, however, reasons to develop fMRI methods that have much faster sampling.

For example, BOLD fMRI data are often contaminated by other physiological signals. Respiratory fluctuations and pulsatility arising from the cardiac cycle are sources of artifact that have been well identified [161]. Because the associated frequency content of respiratory and cardiac fluctuations can vary over time, both may be undersampled by typical fMRI time series data collection. Typical fundamental frequencies are \( \sim 0.25 \) Hz for respiration, and \( \sim 1 \) Hz for cardiac pulsation. In particular, the latter signal becomes aliased in fMRI data from typical sampling rates of 0.5 - 1 Hz that do not satisfy the Nyquist sampling criterion. At sampling rates > 2 Hz, both physiological signals are generally unaliased and more easily removed via filtering or regression, although higher harmonics of these signals may still be aliased.
Increased sampling rates also facilitate certain specific fMRI applications, such as detailed characterization of the BOLD hemodynamic response function (HRF), particularly when probing transient features such as the initial dip [164]; precise determination of the onset of BOLD responses in different brain regions, for mental chronometry investigations [158]; and improved determination of temporal correlations between brain regions in resting-state fMRI data. Lastly, the increasing application of fMRI at ultra-high field strengths such as 7T necessitates faster k-space readouts and more rapid sampling of T2* decay, to mitigate the image distortion and signal loss produced by increased magnetic field non-uniformity and reduced T2* values in biological tissues.

Various options have been explored for increasing fMRI temporal resolution. In particular, parallel image reconstruction methods use the spatial variation in coil sensitivity with multi-channel receiver coil arrays to eliminate time spent using imaging gradients to encode k-space, reducing the repetition time (TR). Parallel imaging can be performed in conjunction with other time-saving acquisition strategies to enhance temporal sampling rates, such as the multiplexed echo planar imaging (EPI) approach [169] that combines slice multiplexing [170] with simultaneous image refocusing [171] for a 4x3 acceleration factor to achieve temporal sampling at TR = 546 ms over the entire brain. Alternately, simultaneous multi-slice EPI acquisitions have recently been combined with CAIPIRINHA field-of-view shifting [172] for improved parallel imaging in sub-second whole-brain acquisitions [173].

Parallel imaging strategies can be applied more aggressively for even greater sampling rates. In one demonstration of the MR-encephalography (MREG) technique [174], no spatial encoding using imaging gradients was applied, with data projected only onto the coil sensor space. In the first demonstration of inverse imaging (InI) [175] and other examples of MREG, entire spatial dimensions of gradient encoding were eliminated by relying on multi-channel coil sensitivity information. In these cases, the coil sensitivity information was used to solve a linear system that was massively underdetermined, similar to the reconstruction in SENSE [102] and k-t SENSE [176] parallel imaging. The initial MREG approach allowed TR values as low as 50 ms (with an image prior needed for reconstruction), and the first InI approach combined with a PRESTO acquisition [177] enabled a TR of 20 ms. Both methods were demonstrated initially in a single slice and have large spatial point spread functions as a consequence of trading spatial resolution for temporal resolution.

Both the MREG and InI methods have undergone further enhancement, providing whole brain data sampling at a TR of 100 ms. The MREG technique has been extended to include additional non-Cartesian gradient projections to enhance data reconstruction.
using the COBRA method [178], providing whole brain data sampling using 3D gradient trajectories [179]. The InI method included k-space reconstruction algorithms [180] analogous to GRAPPA parallel imaging methods [104], and beamformer solutions to the inverse problem [181, 182]. Both methods however, still pay significant spatial resolution trade-offs for such sampling rates.

Additionally, although the temporal resolution of these methods is greatly enhanced while still accommodating whole-brain coverage, a practical limit is imposed by the available signal to noise ratio (SNR). In the case of conventional gradient encoding, SNR is proportional to the square root of the acquisition time, whereas in parallel imaging schemes, SNR can also be limited by well known g-factor penalties imposed by multi-channel receiver coil geometry. In both cases, multi-echo fMRI methods are available that can potentially increase the contrast-to-noise ratio (CNR) of BOLD signals by acquiring and strategically combining multiple images at various echo times during a single RF excitation [100]. At present, three multi-echo methods are available: weighted summation methods [100, 97]; model fitting methods [149]; and multivariate methods [160]. The reported gains in CNR support the use of such approaches to enhance BOLD signal contrast in the case of accelerated acquisitions, although to date they have not been widely adopted.

Here, a new method called constrained source space imaging (CSSI) is proposed for collecting densely sampled fMRI time-series data across a set of distinct regions at low TR values, using coil sensitivity encoding. The CSSI method uses radiofrequency (RF) selective excitation of multiple, arbitrarily located regions of interest (ROIs) to constrain the number of signal sources, after which direct spatial encoding of the magnetization at known source locations is achieved using coil sensitivity information only. Neither additional image priors [176] (other than coil sensitivity information) nor tools for solving underdetermined systems, such as beamforming [181] or regularization [178] are required for spatial encoding. The CSSI method also includes a densely sampled, T2*-weighted decay acquired in the absence of imaging gradients, from which the data samples are combined, increasing BOLD contrast and offsetting the noise amplification introduced by parallel imaging reconstruction.

The CSSI method can apply to any fMRI experiment involving a priori determined ROIs that requires time-series data at high temporal resolutions, such as modelling hemodynamics in specific regions [164], mental chronometry [158], network-specific functional connectivity analyses [183], or ROI-based real-time fMRI neurofeedback [184]. The CSSI method is also potentially applicable to measuring signals weighted by other MRI contrast parameters (e.g. T1 or T2 relaxation times) with suitable pulse sequence modification.
The present work describes the CSSI concept, and provides a proof-of-principle demonstration whereby fMRI data are acquired in a 4-voxel experiment using a 32-channel head coil [56]. The method is applied to a simple fMRI motor task, demonstrating the ability to record temporally resolved BOLD hemodynamic response data from ROIs in cortical motor areas. These results are subsequently discussed from the standpoint of improving the CSSI method in the future.

4.2 Theory

Parallel imaging methods shorten imaging time by reducing the amount of spatial encoding required from imaging gradients for full image reconstruction. To summarize parallel imaging theory, spatial encoding is viewed as a linear system [105]:

\[ k = Ex \]

where the vector \( k \) (of length \( M \)) represents the serialized complex k-space values, the vector \( x \) (of length \( N \)) represents the serialized complex voxel magnetization values, and the rows in the \( M \times N \) encoding matrix \( E \) correspond to the set of spatially varying phase modulations required to produce each k-space value. In normal Cartesian Fourier encoding, \( E \) corresponds to the forward Discrete Fourier Transform (DFT), and the image matrix size \( N \) and the k-space matrix size \( M \) are equal. This ensures that \( E \) is an invertible, square orthonormal matrix, where the inverse \( E^{-1} \) is the inverse DFT. The general extension of this description is that any invertible linear transform may serve as a spatial encoding matrix.

Next, consider the ideal case of independent multi-channel receiver coils, with each coil element receiving different information via a different coil sensitivity projection, multiplying the total number of encoding matrix rows by the number of coil elements available. With \( L > 1 \) coil elements, this produces an overdetermined linear system in the complete Cartesian Fourier encoding regime, with \( L^*M > N \) rows, assuming that the coil elements produce linearly independent effects on the signal. Removing some rows \( M \) (while maintaining \( L^*M \geq N \) and ensuring that \( E^{-1} \) is realizable) reduces the time spent gradient encoding, and thus the total imaging time. The extra rows due to \( L \) are acquired in parallel based on coil spatial sensitivity at no extra time penalty. For example, with 2 ideal coils, half of the gradient encoding steps can be removed, resulting in \( 2^*(M/2) = N \) rows, producing an encoding scheme with an acceleration factor of 2.

At one extreme, when \( L \) is large and \( N \) is small, data acquisition only at the k-space
origin (M=1, or no gradient encoding) may be sufficient to maintain the \( L \geq N \) inequality, keeping the linear system in a uniquely-determined or over-determined state. In this case, which can be achieved using RF selective excitation to localize N voxels, all subsequent spatial encoding is performed in parallel, and all data are acquired at the k-space origin, for optimal tracking of changes in tissue signal contrast. As there is no gradient encoding to traverse k-space, dense temporal sampling of a T2*-weighted signal decay can be used to generate a net BOLD signal. These concepts are explained in further detail below.

Elaborating on Eq. 4.1, given L coils and N single voxel ROIs each defined by the volumes \( V_n \), the equation for the baseband signal measured at the \( l^{th} \) coil element, \( s_l \), is given by:

\[
s_l(t) = \sum_{n=1}^{N} \int_{V_n} \Phi_l(r)m(r)e^{-i\gamma \Delta B(r)t}e^{-t/T2(r)}dV_n + \epsilon_l(t) \tag{4.2}\]

where \( \Phi_l(r) \) is the complex sensitivity of the \( l^{th} \) coil element (both magnitude and phase), \( m(r) \) is the magnetization, \( \gamma \Delta B(r) \) is the off resonance effect of magnetic field inhomogeneity, \( T2(r) \) is the position-dependent T2 decay constant, \( \epsilon_l(t) \) is a zero-mean noise term for the \( l^{th} \) coil, and \( t \) denotes time along the sampled signal decay. The \( \gamma \Delta B(r) \) and \( T2(r) \) factors both contribute to the measured voxel T2* decay coming from intrinsic decay and intra-voxel dephasing effects. The sum over the N voxel elements assumes that the integral of \( m(r) \) is zero outside the voxel volumes. An additional assumption is made to linearize this system of equations, namely that \( \Phi_l \) is constant inside each ROI volume. Thus:

\[
s_l(t) = \sum_{n=1}^{N} \Phi_{l,n} \int_{V_n} m(r)e^{-i\gamma \Delta B(r)t}e^{-t/T2(r)}dV_n + \epsilon_l(t) \tag{4.3}\]

If we then define:

\[
x_n(t) = \int_{V_n} m(r)e^{-i\gamma \Delta B(r)t}e^{-t/T2(r)}dV_n \tag{4.4}\]

then the linear system becomes analogous to Eq. 4.1:

\[
s(t) = \Phi x(t) + \epsilon(t) \tag{4.5}\]

where the elements of \( \Phi \) (analogous to E), \( \Phi_{l,n} \) correspond to the complex coil sensitivity measured by the \( l^{th} \) coil element at the \( n^{th} \) ROI location, and \( x_n(t) \) are the individual complex voxel signals corresponding to each ROI.

Eq. 4.5 can be solved in a number of approaches. The simplest uses the Moore-
Penrose pseudoinverse of the encoding matrix to find the least squares solution to the system. Because this formulation of the encoding matrix is independent of time, the inversion can be performed once and applied successively to each point in the t-domain, and every subsequent measurement in the time-series:

\[
\hat{x}(TR_p; t) = (\Phi^*\Phi)^{-1}\Phi^*s(TR_p; t)
\]  

(4.6)

where \(\hat{x}\) is the vector of estimated complex voxel magnetizations, \(TR_p\) denotes the index of the \(p\)th measurement repetition, and \(\Phi^*\) is the conjugate transpose of the encoding matrix. This direct inversion process is exactly the weak reconstruction approach without SNR optimization outlined in the original description of the SENSE method of parallel imaging with Cartesian under sampling [102].

Alternatively, the overdetermined system can be solved using a weighted least squares approach. One useful scheme, that is also time independent, weights the minimized residuals with the inverse of the coil noise covariance matrix:

\[
\hat{x}(t) = [(\Phi^*W^{-1}\Phi)^{-1}\Phi^*(t)W^{-1}]s(t)
\]  

(4.7)

where the symmetric elements of \(W\), \(w_{l1,l2}\), can be estimated by the following generalized expression for covariance of complex signals, where \(T\) is the number of noise samples collected:

\[
w_{l1,l2} = \frac{1}{T-1}\sum_{t=1}^{T}(\epsilon_{l1}^*(t) - \overline{\epsilon_{l1}})(\epsilon_{l2}(t) - \overline{\epsilon_{l2}})
\]  

(4.8)

Eq. 4.7 is equivalent to the weak reconstruction with SNR optimization in the SENSE imaging formulation [102]. The inherent low dimensionality of the constrained source space ensures that the matrix inversions in Eq. 4.7 can be performed near instantaneously with modern computer hardware, suitable for real-time reconstruction if required.

The CSSI approach thus provides spatial selectivity much as in a single voxel MR spectroscopy experiment, except that coil sensitivity encoding is used to acquire \(T2^*\) decay data from a small number of arbitrarily located voxels simultaneously. Time series data can then be generated from the series of decays from each voxel to produce robust, real-time measurements of BOLD signal changes (see below).

Intrinsic thermal noise penalties due to coil geometry can be calculated for this reconstruction process as a function of the coil noise covariance and the sensitivity encoding.
matrix, according to the definition of g-factor [102]:

\[
g(n) = \frac{\sigma_{0,red}(n)}{\sigma_{0,full}(n)} = \sqrt{(\Phi^*W^{-1}\Phi)^{-1}_{n,n}(\Phi^*W^{-1}\Phi)_{n,n}}
\] (4.9)

where \(\sigma_{0,CSSI}\) and \(\sigma_0\) denote the temporal standard deviation (i.e. of time series data at TR increments) of intrinsic noise components for the nth voxel reconstructed by CSSI and acquired using single voxel excitation and readout, respectively. The total increase in noise for CSSI reconstruction, \(\sigma_{CSSI}\), in relation to that for single voxel measurements, \(\sigma\), can be determined by combining a physiological noise model for fMRI data [82] with g-factor losses [185]:

\[
\frac{\sigma_{CSSI}}{\sigma}(n) = \sqrt{\frac{g^2\sigma_0^2 + \sigma_P^2}{\sigma_0^2 + \sigma_P^2}}
\] (4.10)

where \(\sigma_P\) reflects signal- and t-dependent physiological noise that is present in addition to intrinsic or electronic noise. From Eq. 4.10, it is evident that the total noise amplification in CSSI data depends not only on the coil geometry, but also strongly on the magnitude of the physiological noise component. If intrinsic noise dominates (\(\sigma_0 >> \sigma_P\)), then the noise amplification approaches \(g\), whereas if physiological noise dominates (\(\sigma_P >> \sigma_0\)), the amplification becomes negligible. In CSSI-fMRI, particularly with larger voxels, physiological noise can contribute substantially if not dominantly [163], which may enable use of high acceleration factors without substantial noise penalty from g-factor effects. As an aside, it should also be noted that in comparison to traditional SENSE with Cartesian undersampling, CSSI does not involve k-space sampling for spatial encoding during data acquisition. As a consequence, no \(\sqrt{R}\) acceleration factor penalty is incurred, where \(R\) represents the acceleration factor, or the number of aliased voxels. The coil geometry factor provides the only penalty. Although high acceleration may be possible, another perspective on this issue is that each sample at a given t-value, \(\hat{x}(t)\), will be very noisy due to high sampling bandwidth. Useful counterbalances are that the CSSI method is intended for use with coarse voxels (thus reducing the impact of intrinsic noise), and that SNR reductions can be mitigated by weighting densely sampled T2* decay data in an appropriate linear combination to achieve a robust metric of BOLD contrast at each TR value. In addition, densely sampled T2* decays provide other measures that can improve BOLD signal fidelity through suitable processing, such as motion estimates [96], physiological noise estimates [82] and respiratory fluctuation estimates [174].
Figure 4.1: (a) Modified STEAM pulse sequence diagram, where RF1 and RF3 excitations are dual-band pulses. The sequence measures densely sampled T2* decay data from 4 coarse voxels simultaneously. Shaded gradients are crusher gradients, and unshaded gradients are slice-select gradients. Optional Gx and Gy gradient waveforms (inside the dashed box) provide 2D Cartesian Fourier imaging (2DFT) to confirm voxel localization. (b) Slice profile directions showing selectivity from the RF excitations in (a). In this example, RF1 and RF3 are selective in the left-right and up-down directions respectively, and RF2 is selective in the plane of the page. The four intersecting regions form the localized voxels.

4.3 Methods

4.3.1 ROI Localization

As a proof of concept, a modified STEAM (stimulated echo acquisition mode) localization scheme (Fig. 4.1) was used to implement the CSSI method with 4 voxels as rectangular prisms, and with the 4 voxel positions restricted to the vertices of an arbitrarily sized and positioned rectangle. A standard STEAM sequence was modified such that the first and third radiofrequency (RF) pulses were dual-band, exciting and refocusing spins in 2 parallel slices with user-controlled widths and separation defined by the RF bandwidth and gradient magnitudes. The first RF pulse provided localization in the x-direction, and the third in the y-direction, and the intersecting regions of these orthogonal pairs of slices defined the voxel locations as columns. The 2nd RF pulse, selecting a slice perpendicular to the columns, provided localization in the z-direction. All RF pulses were amplitude modulated with a sinc envelope, with durations of 2.56 ms for the second pulse, and 3.84 ms for the first and third pulses. Crusher gradients were played after the third RF pulse to eliminate all transverse magnetization from the subsequent free induction decay, and a balanced pre-focusing pair of gradients were placed after the first RF pulse, to ensure proper refocusing in the desired voxels. A large z-direction crusher was placed in the TM
period to eliminate all other echo refocusing pathways, providing voxels localized solely by the stimulated echo formation.

In the prototype implementation, 90° flip angles were used for each of the RF pulses, and TR = 250 ms was chosen due to the large flip angles used. STEAM timing parameters \( TM = 5.0 \text{ ms} \) and \( TE = 12 \text{ ms} \) were chosen to minimize signal losses due to T1 and T2 decay. The data acquisition began \((t=0)\) at \( TE/2 \) after the third RF pulse (the stimulated echo maximum) sampling the subsequent exponential \( T2^* \) decay. The \( T2^* \) decay data were sampled with 1024 points at 10.24 kHz acquisition bandwidth (100 ms readout time), and the ROIs were chosen to be \( 10 \times 10 \times 10 \text{ mm}^3 \) cubic voxels. As an additional modification, a variant of the pulse sequence was implemented with imaging gradients for standard a 2D Cartesian k-space readout, used for validation of the voxel selectivity and placement.

### 4.3.2 Coil Encoding Matrix

To identify precisely the relative magnitude and phase factors of the coil sensitivities \( \Phi_{ln} \) associated with \( l \)th coil on the \( n \)th ROI, single voxel calibration data were acquired from each of the 4 ROIs in turn, using a conventional single voxel STEAM acquisition with imaging parameters identical to the dual-band STEAM. To determine \( \Phi_{ln} \) with sufficient accuracy, 32 \( T2^* \) decay measurements were made of each ROI (taking approximately 30 s total), from which the last 24 measurements were subsequently averaged, to avoid bias from dynamic equilibrium effects. The phase at the stimulated echo maximum was estimated by simple least squares linear fitting of the \( t = 0 \) intercept of the complex signal phase as it evolved from \( t = 0 \) to 20 ms, with phase unwrapping performed as required. The magnitude estimates at the stimulated echo maximum were taken as the average magnitude at \( t=0 \) and normalized by the root mean square value across all coils for each ROI. This procedure is sufficient for proof-of-principle fMRI experiments as \( T2^* \) changes within each ROI are of interest here, as indicated below. Future implementations may require more sophisticated procedures to separate \( m(r) \) and \( \Phi(r) \) terms. The coil noise covariance was estimated using Eq. 4.8, with the noise time-series of each coil estimated from 24 measurements of the 1024th data point in the \( T2^* \) decay, acquired approximately 100 ms after the peak of the stimulated echo.

### 4.3.3 Imaging and Reconstruction Validation

All experiments were performed on a research dedicated 3T Siemens TIM Trio (VB17 software, Siemens Healthcare, Erlangen, Germany) using a 32 channel head coil [56].
In preliminary experiments, the spatial localization provided by the dual-band STEAM sequence was assessed by imaging a cylindrical, plastic bottle phantom (1.9 L, 5 g NaCl, 3.75 g NiSO4 x 6H2O per 1000 g water) using the optional 2DFT gradient encoding module at 1 x 1 mm\(^2\) in-plane resolution and 10 mm slice thickness. The mean signal intensity was evaluated for each of the voxels and compared to the mean signal in a large background region. The spatial profile of each voxel was investigated by measuring the width of the magnetization transition band from 5% to 95% of the maximum value. Full-width at half maximum (FWHM) values were also calculated for the voxels.

Because CSSI does not utilize k-space encoding with imaging gradients during data acquisition, all voxels are aliased on top of one another irrespective of their position in space. In this prototype implementation, with voxels positioned on a Cartesian grid, there are similarities to a SENSE reconstruction with 2 by 2 acceleration and 4-fold aliasing. The ability of the data reconstruction to separate and correctly assign T2* decay signals to the appropriate voxels was assessed using the root-mean square error (RMSE) of the T2* decays produced by CSSI compared to the individually acquired decays from the calibration STEAM experiments, normalized to the signal maxima. This assessment was made from in vivo data collected in the fMRI validation experiment (see below). Data were averaged across 40 time points from the last 10 s of CSSI time series data acquisition, and across 24 time points from the calibration STEAM data.

4.3.4 fMRI Validation

A series of fMRI measurements were undertaken to validate the CSSI approach using the 4 voxel dual-band STEAM prototype. Each run was preceded by a 30 s calibration STEAM acquisition for coil sensitivity mapping, to account for potential shifts in head position between runs. Initially, T1-weighted anatomical MRI was performed with an axial, 1 mm\(^3\) isotropic 3D MPRAGE sequence (TR/TI/TE = 2000 ms/1100 ms/2.8 ms, flip angle = 9°, 6/8 phase partial Fourier). The voxels were positioned manually using the anatomical image data by an individual experienced with localizing functional neuroanatomy (M.C) such that two of the voxels were located over the primary motor cortex (M1) and the supplementary motor area (SMA) in the dominant, contralateral hemisphere. The other two voxel positions were fixed by the positioning of the SMA and M1 voxels, and did not localize to regions involved in motor control, and consequently were not anticipated to exhibit fMRI signals of brain activity. Voxel placement was confirmed once using the modified STEAM prototype with the addition of 2DFT gradient encoding module.

Subsequently, a simple visually cued motor task was used to assess BOLD responses in
Chapter 4. Constrained Source Space Imaging

the contralateral M1 and SMA. Six young healthy adult subjects (5 right-handed, 1 left-handed) were scanned with informed consent at Baycrest Hospital. In the experiment, each subject performed six runs of CSSI-fMRI, each lasting 320 s in duration, consisting of ten trials lasting 30 s each, for a total of 60 trials per subject. Rest periods of 10 s were included at the beginning and end of each run to allow the magnetization to reach equilibrium and for measurement validation purposes, respectively. For each trial, subjects were required to move a cursor from one location to another by tapping a button with the index finger on their dominant hand within a 2 s duration. The task screen consisted of a yellow background with a black dot representing the cursor, and with green and red boxes denoting the start and end locations respectively. The task screen appeared at trial onset. During the inter-trial interval, subjects viewed a grey screen with a black central fixation cross.

4.3.5 Data Processing

The raw complex data were reconstructed using Eq. 4.7, and BOLD signal time-series data were ultimately produced from the magnitude data fitting the measured decays with a monoexponential model to produce T2* estimates [149]. Monoexponential fitting provided a simple method to combine all T2* decay samples into a robust metric with BOLD signal contrast. Other signal weighting methods [95] were investigated and produced similar results, not reported here for brevity.

The BOLD time series data were further processed to remove head motion artifacts by linear regression. The initial sample (t = 0) of each T2* decay, as estimated by the same mono-exponential fitting process above, provided a measure of the partial voluming, inflow, and spin-history effects from head motion, with little BOLD contrast [96]. Using these samples, motion effects were subsequently regressed from the T2* time series data using a sliding window approach, using linear regression coefficients estimated point-by-point over successive 10 s windows (40 points) centered on each time point. After this procedure, which was efficient at removing transient motion artifacts over a timescale of several seconds, two additional processing steps were performed to reduce slower spurious fluctuations in the data. Third-order polynomial regression was performed as is typical in fMRI analyses; in addition, time series data were investigated with and without low pass filtering (Hann window, 0.25 Hz cutoff frequency). Separately, first-order estimates of the rate of phase change in the complex T2* decay data were also calculated to produce frequency shift time-series [174] for investigation of respiratory fluctuations.

To evaluate the fMRI time-series data, Students t-statistics were calculated from the
BOLD time-series data for each voxel using general linear model estimates [120]. The M1 and SMA time-series were evaluated for significance, and for the CNR enhancement provided by the T2* fitting process. Because Students t-values are calculated as a ratio of the BOLD signal difference from baseline and an estimate of the standard error, they can be interpreted as indicators of CNR, particularly when the same number of data points are used.

4.3.6 Noise Analysis

To assess the SNR characteristics of this initial CSSI implementation, and the impact of multi-channel coil geometry effects, the intrinsic noise component $\sigma_0$ of the total noise variance was separated from the physiological noise component $\sigma_P$ with a least-squares fit of the established Kruger model [82] using the Levenberg-Marquardt algorithm. This was possible using the CSSI method without using multiple experiments with different flip angles, as undertaken by others [82], given that the T2* decay was very densely sampled. The last 40 time points of each run were used to estimate the time-dependent noise through subtraction of the mean signal decay, producing a noise measurement time-series for each sampled decay point. Physiological noise variances with decay-time dependence were computed from these noise time-series, which along with the mean signal decay estimate were used to estimate $\sigma_0$ and $\sigma_P$ from the noise model. Estimates of $\sigma_0$ were also made for each voxel in the single-voxel STEAM calibration data using 24 measurements in the same manner, and an experimental g-factor was produced for each voxel as a ratio of $\sigma_0$ from the CSSI and single-voxel data. The experimental g-factors were compared to the theoretical g-factors computed from Eq. 4.9, based on the encoding matrices and estimated coil noise covariance. In addition, the overall noise amplification in each voxel was computed from a ratio of the standard deviations of the CSSI and single-voxel data, evaluated at $t = 30$ ms.

4.4 Results

From the phantom validation experiments, the mean signal magnitude ($\pm$ standard deviation) measured inside the FWHM of the 4 voxels was $521.9 \pm 6.1$, whereas the mean signal magnitude taken in a $10 \times 10$ mm$^3$ ROI in the centre of the phantom was $0.9 \pm 0.8$, indicating negligible signal in regions outside the prescribed voxels. The FWHM and transition width values were measured after resampling to 0.1 mm resolution using linear interpolation, and were measured in both the x- and y-directions. The mean
Figure 4.2: Voxel localization achieved using the modified STEAM sequence from Fig. 4.1 overlaid on a T1 structural image. Voxels are labelled numerically clockwise, starting with the SMA voxel at the upper left.

FWHM value for all voxels was $10.8 \pm 0.1$ mm, and mean transition width was $3.8 \pm 0.2$ mm. Voxel centres were positioned in the image field-of-view to precision higher than the imaging resolution of 1 mm.

As expected, CSSI reconstruction using Eq. 4.7 yielded well distinguished T2* decays from each voxel. Fig. 4.3 shows example decays from a single subject, with good agreement between truth data as obtained by single voxel STEAM acquisitions (solid lines) and the CSSI reconstructed data (x and + symbols). For better visualization, the results for only voxels 1 (SMA) and 3 (M1) are shown, although the level of agreement for the other voxels is very similar. The overall RMSE observed between the true and CSSI reconstructed decay data across all subjects and voxels was $3.5 \pm 1.7 \%$, indicating good fidelity for the reconstruction.

The experimental and predicted g-factor values obtained for each subject are shown in Fig. 4.4a. Each data point represents one of four voxels from each subject, for a total of
Figure 4.3: CSSI reconstructed T2* decays compared to the true decays measured using a single voxel STEAM sequence. Data are shown from the SMA (voxel 1) and M1 (voxel 3) from 1 run of a representative subject. Only 2 of the 4 localized voxels are shown for clarity, although reconstruction fidelity is similar across all voxels.

Figure 4.4: Measured noise properties vs. theoretical g-factor noise amplification values for CSSI reconstruction, for each of the 4 voxels across all subjects. Each subject is represented by a different symbol, and error bars denote the standard error of the mean due to averaging across runs within each subject. Solid lines denote the line of identity. (a) Measured g-factors obtained by computing the intrinsic noise amplification only. (b) Measured SNR loss, evaluated by taking the ratio of total noise values between single voxel STEAM data and CSSI data, evaluated at $t = 30$ ms.
24 points. Data for different subjects are distinguished by different symbols. Error bars in both directions indicate the standard error of the mean across all runs. Most of the data points are clustered around or slightly above the line of identity (solid line). In this experiment, experimental g-factors were measured from 1.5 - 3.5, varying across voxel configurations and subjects, with greater inter-subject than intra-subject variability and a tendency for g-factor values to cluster across voxels for each individual subject. Fig. 4.4b shows the measured SNR loss (the ratio of SNR obtained by single voxel STEAM to that obtained by CSSI, at t = 30 ms) plotted against the predicted g-factors, as well as the line of identity. The g-factor provides an upper bound to the SNR loss, validating the relationship predicted by 4.10. Values clustered near the line of identity represent voxel data with predominantly intrinsic noise contributions, whereas the values further below the line of identity have increasingly dominant physiological noise contributions. The theoretical uncertainty of the measured SNR loss ratio was calculated to be 18.6%, based on the standard errors of the sample standard deviation measurements, which is reasonably consistent with the experimentally determined error bars.

A representative set of CSSI BOLD time series data produced by T2* parameter fitting is shown in Fig. 4.5 for all 4 voxels, for one run in a single subject. Raw, unfiltered data are shown in grey, and filtered data are shown in black, with only the first half of the run shown for clarity. Vertical lines indicate the stimulus onset for each trial. Only the SMA and M1 voxel show stimulus-dependent signal modulation, with a change in T2* value $\Delta T2^*$ on the order of 1 ms, and all voxels display physiological noise artifacts. Furthermore, voxel 4 (located along the posterior midline) shows considerable physiological noise-related variance, with respiratory fluctuations particularly visible in the raw data. It is evident that the physiological noise contribution depends on variations in voxel content and spatial position, as expected.

Fig. 4.6 shows the signal amplitude spectra from the raw data as shown in Fig. 4.5, quantifying the specific contributions of respiratory and cardiac noise fluctuations. Respiratory fluctuations (labeled R) concentrated about 0.25 Hz and cardiac fluctuations (labeled C) near 1.0 Hz are observed, with amplitude levels reflecting the fluctuations visible in Fig. 4.5. Voxels near the midline (1 and 4) show much higher cardiac noise than the more lateral voxels (2 and 3). The peaks at the task interval frequency of 0.03 Hz (labeled $f_0$) are also easily identified in the SMA and M1 voxel insets, along with components at the first and second harmonic ($f_1 = 0.06$ and $f_2 = 0.09$ Hz). It should be noted, however, that these signals likely contain contributions from respiratory volume fluctuations, which occur at about 0.03 Hz, and intrinsic resting BOLD signal fluctuations, which occur at frequencies less than 0.1 Hz [80].
Figure 4.5: T2* time-series data from a representative 4 voxel CSSI experiment in one subject. Vertical lines indicate the onset of individual trials of the motor task. Raw, unfiltered data are shown in light grey, and low pass filtered data are shown in black. Activation signals are readily observable in the SMA and M1 voxels (1 and 3), whereas voxels 2 and 4 exhibit spurious signal fluctuations only. Only the first 150 s of the run are shown for clarity.
Figure 4.6: Amplitude spectra (square root of the power spectra) for the raw data shown in Fig. 4.5. Peaks labelled R denote respiratory frequencies near 0.25 Hz. Peaks labeled C denote cardiac pulsatility near 1.0 Hz. The inset on voxels 1 (SMA) and 3 (M1) is a zoomed view highlighting the 0 - 0.3 Hz frequency range, with task frequency of 0.03 Hz denoted by $f_0$, and the first and second harmonic peaks denoted by $f_1$ and $f_2$ respectively.
Figure 4.7: Voxel frequency shift amplitude spectrum and frequency shift time series (inset) from voxel 3 (M1). The respiratory peak is evident near 0.25 Hz. There are no apparent peaks at the task fundamental frequency of 0.03 Hz or its harmonics, nor at the frequency of cardiac pulsation. An 80 s portion of the time series is shown for clarity.
Fig. 4.7 illustrates the results of a frequency shift time-series analysis for a single voxel in a representative subject. The amplitude spectrum and frequency shift time series (inset) are shown for voxel 3 (M1) of the data shown in Figs. 4.5 and 4.6. The frequency shift shows a dominant component of respiration producing up to ±2 Hz fluctuations in resonant frequency offset, (corresponding to observed magnetic field shifts of ±47 nT) due to susceptibility changes from the expansion and contraction of the lung cavity. Cardiac pulsatility is not as well captured in this measure, as expected. A visual comparison of the frequency shift spectrum with M1 (voxel 3) BOLD spectrum in Fig. 4.6 indicate a lack of task-related frequency enhancement, suggesting that the frequency shift data represent an intrinsic and voxel-specific, BOLD-free measure of respiration dominated physiological fluctuation.

Considering now the fMRI data over all subjects, only runs showing Students t-values > 2.576 corresponding to p < 0.05 (uncorrected) in a Students t-distribution with infinite degrees of freedom were considered to show activation. Two subjects had mean Students t-values in the (M1, SMA) voxels of (-1.52, -0.66) and (0.88, 2.46) respectively, suggesting errors in voxel placement. The remaining 4 subjects showed mean values of (13.11, 5.34), (14.85, 4.45), (10.48, 5.95) and (3.96, 4.01) respectively.

Averaged ∆T2* HRFs in the M1 and SMA voxels from the 4 remaining subjects are plotted in Fig. 4.8 (A-D) for 5 seconds prior to stimulus onset to 25 seconds post-stimulus after complete data processing, including low pass filtering for visual display. In all subjects, the HRF peaks at approximately 5 s post-stimulus. In subjects A-C, the ∆T2* is approximately 0.8 ms in M1, and somewhat smaller in the SMA (0.3 - 0.8 ms). In subject D, the SMA response is similar to the other 4 subjects, with a much smaller (but statistically significant) M1 response with peak ∆T2* of approximately 0.2 ms. One possible explanation for this finding is mis-placement of the M1 voxel, with large partial voluming effects suppressing the measured BOLD signal change. The ∆T2* SMA HRF for subject D also showed a strong initial dip in the response. During initial data processing it was observed that this transient was present in the data for other subjects and was effectively suppressed by the motion artifact regression. It is likely that this procedure was insufficient for removing this motion artifact for subject D.

4.5 Discussion

This work introduced the CSSI method, a novel imaging technique that enables multiple voxels to be densely sampled simultaneously during T2* decay and in the TR domain, with spatial encoding provided by RF selective excitation and coil sensitivity encoding. A
Figure 4.8: Averaged $\Delta T^2*$ HRFs in M1 (black) and SMA (grey) across 4 subjects (A-D), from 5 s pre-stimulus to 25 s post-stimulus. Onset of the stimulus occurred at $t = 0$, and error bars denote the standard error of the mean across 60 trials.
proof of concept implementation has successfully demonstrated the application of CSSI in a test phantom and in a simple fMRI experiment. The CSSI method is a natural extension of the one-voxel one-coil imaging approach introduced with the MREG technique by Hennig et al. [174], with an explicit, experimentally applied constraint in the source space (RF selective excitation) to ensure spatial localization of distinct source signals from multi-channel receiver coil data.

The proof-of-concept implementation of CSSI using a modified STEAM sequence successfully separated decay signals in space from 4 voxel sources, in the absence of any spatial encoding gradients during readout. CSSI experiments in a test phantom showed little signal leakage outside the prescribed voxels. In human subjects, CSSI data showed very good correspondence (approximately 3.5% RMSE) with T2* decays measured separately in each voxel.

It should also be considered that the CSSI data were measured about 5 min after the calibration step and measurement of T2* decays using single voxel STEAM. Because the CSSI and single voxel data were not measured simultaneously in subjects, some of the RMSE may be attributed to voxel misregistration errors due to movement, where excited voxels no longer coincided exactly with the prescribed voxel locations. The discrepancy may also reflect errors in characterizing the complex coil sensitivities from the calibration scans (e.g. from the assumption of constant coil sensitivities across the finite sized voxels), or bias due to non-zero sum residual background magnetization from imperfect selective excitation.

In a simple motor task, the CSSI method produced robust characterizations of the ΔT2* HRF in multiple brain regions. These experiments were well able to distinguish HRF features such as the amplitude, time-to-peak and overall shape, and may be a useful as a tool for fine characterization of hemodynamic responses for statistical modelling [70]. The Students t-values measured in 4/6 subjects ranged from 3.96 – 14.85, encompassing the peak t-values measured with one previous ultra-fast fMRI technique (5.8) [180], and falling just short of the values produced by others (around 15, see Fig. 6A in [182]). The t-values reported in the present work were produced with a proof-of-concept CSSI implementation. It is expected that with further CSSI pulse sequence development even better fMRI signal contrast will be achievable, with sensitivity to estimate features such as the HRF latency between brain regions.

In this study, the ΔT2* data showed adequately small motion susceptibility. Due to the modified STEAM localization used in this study, large drops in raw CSSI signals were observed co-incident with the onset of the experimental stimulus, most likely due to motion. When motion is present during the excitation, a mismatch in the amount of
gradient dephasing can occur between the first and last pair of crusher gradients, which then only partially refocus magnetization with a subsequent signal loss. Partial voluming effects and changing voxel content with motion may also account for some of the observed signal drop.

This problem is not expected to occur in future implementations of CSSI, as the dual-band STEAM sequence was only used for proof-of-concept to illustrate the basic theoretical principles and validity of the CSSI approach. The modified STEAM sequence provided a simple method for localizing 4 voxels by RF selective excitation, and should not be regarded as a practical platform for continued CSSI development.

Indeed, many aspects of the CSSI technique can be enhanced or optimized in the future, including the number, size, shape and placement of source voxels and optimized non-90° flip angles for fast excitation with the inclusion of spoiler gradients at faster TRs to prevent steady-state coherence effects. Parallel RF transmit techniques [186] can potentially be used to enable such optimizations, through design of 2D or 3D selective excitations for placing voxels independently in space. For example, one factor limiting SNR in the prototype CSSI implementation was the use of 90° flip angles implemented by the dual-band STEAM sequence, which restricted the TR to 250 ms to prevent extreme loss of signal due to low dynamic equilibrium magnetization. Using a parallel RF transmit approach, multi-dimensional RF selective excitation can be achieved closer to the optimal Ernst angle, facilitating a decrease in TR without substantially degrading SNR performance. Acquisitions with sub-100 ms TR at the Ernst angle can be accommodated with theoretically only a slight drop in steady-state magnetization compared to the 90° excitation at 250 ms presented here (e.g., 0.13M₀ for TR = 50 ms vs. 0.15M₀ for TR = 250 ms, assuming T₁ = 1500 ms in gray matter). This will also require a reduced time window for sampling T₂* decay, which is practical because the latter portions of the T₂* decay curve contribute progressively less to BOLD contrast enhancement in weighted multi-sampling strategies [95, 98]. Although parallel RF transmit technology is hardware intensive and not yet widely available, scientific and commercial interest continues to increase for applications at 3T and 7T, such that it may be feasible to study applicability to CSSI in the near term.

The CSSI technique provides several advantages for fast brain imaging where full brain coverage is unnecessary. First, potential concerns about noise amplification due to the parallel imaging component of CSSI reconstruction appear to less than for the case of static, anatomical MRI. This is because fMRI signals are often predominantly influenced by signal-dependent physiological fluctuations, rather than intrinsic, electronic noise. In parallel imaging, noise amplification is conventionally parameterized by g-factor values,
which relate solely to intrinsic noise. Consequently, elevated g-factors may not significantly impact the total measured noise when large physiological noise contributions are present. In this study it was found that g-factor noise amplification factors of approximately 1.5–3.5 were measured, whereas overall SNR reduction was measured to be in the range of 1.5–2.5 (i.e. 30% less impact). The exact SNR reduction level depends on the particular coil geometry factors, as well varying ratios of physiological and intrinsic noise, as discussed previously in EPI acquisitions [185].

Second, the densely sampled T2* decay readout used in CSSI is beneficial from several standpoints. Multi-sample weighting methods can be used to enhance CNR over single echo acquisitions, typically by factors of approximately 3-5 [95]. Detailed decay time-dependent signal information can be used to estimate motion and non-BOLD related signal fluctuations for nuisance regression [96], or to fit a physiological noise model [82], as successfully applied in this study. There is also excellent potential to measure very rapid T2* decay in regions with elevated magnetic field inhomogeneity, or at ultra-high magnetic fields, compared to what is achievable using a single echo EPI or spiral k-space readout. Additionally, the complex measured decays allow quantification of resonant frequency shifts to be quantified in each voxel, as a direct measure of respiratory effects, which can be useful for physiological noise modelling and removal.

Third, there may be some benefit associated with the absence of gradient encoding during readout. (The adoption of 3D selective excitation techniques, however, may require strenuous gradient use during RF excitation). Image artifacts characteristic of fast EPI or spiral k-space readouts, such as phase accumulation errors, Nyquist ghosting, and specific off-resonance or chemical shift artifacts, will not be present in CSSI data. Rather, artifact sources will manifest differently. For example, off-resonance effects were observed in the present work, as FIDs exhibited both real and imagery components (whereas FIDs with purely real components would be expected in the ideal case). Taking the magnitude of each FID helped to mitigate this effect and elevate T2* estimates.

Fourth, the CSSI method provides several advantages compared to simple sequential measurement of fMRI data from a series of single voxel measurements made at each different voxel of interest. The sequential approach can be undertaken in two simple ways: a) fMRI data can be collected in separate runs for each voxel, or b) using interleaving, whereby each time point is collected sequentially for each voxel. The ability to record fMRI data simultaneously over multiple voxels, as provided by the CSSI method, ensures that slowly varying temporal effects, such as learning, habituation, or modulations in focused attention, are captured consistently across all voxels during a single manifestation of performance on a behavioural task. This cannot be achieved by sequential
measurement a), which also has much potential for misregistration and partial voluming errors due to head motion. Sequential measurement approach b) is more robust than a), but the temporal resolution of fMRI data sampling is reduced by a factor equal to the number of voxels. Thus, the CSSI method is better suited to studying subtle temporal characteristics of fMRI signal responses.

Successful CSSI with minimal spatial encoding artifact will depend critically on the ability to select and localize multiple coarse voxels by RF selective excitation. The current proof-of-concept, which localized voxels using a dual-band STEAM sequence, placed low demands on the gradient hardware but provided limited voxel localization capability. A future implementation with parallel RF transmission would provide more flexible voxel localization using the excitation k-space approach in the small tip angle regime [187]. A previous demonstration using an 8-channel parallel RF transmission system further emphasizes this concept [188]. A low flip angle, 2D selective excitation achieved by a spiral k-space trajectory of 5 mm spatial resolution provided a set of spatially distinct rectangular ROIs, similar to those that might be used in CSSI. With gradient amplitudes of 35 mT/m, gradient slew rates of 150 T/m/s, and 4-fold acceleration, the total time necessary for excitation was 2.42 ms, producing a 2D excitation pattern with high correspondence to the target ROIs (correlation coefficient r = 0.88). The feasibility of directly exciting a set of prescribed voxels in 3D, as well as detailed considerations of power deposition, require further study but this example holds promise for beneficially combining parallel RF transmission technology with the CSSI method.

The utility of CSSI is limited in configurations where source voxels are very close together, which can lead to g-factors approaching infinity. Due to lack of k-space encoding, the CSSI method cannot adopt field-of-view shifting to solve this issue as used in CAIPIRINHA [172]. In a parallel RF transmit version of CSSI, however, it may be possible to tailor the phase of each voxel individually, imparting what is effectively an RF-induced modification to the effective coil sensitivities [189], for improved reconstruction in previously untenable voxel configurations. Much further exploration is needed to investigate the impact of the complex relationship between the number of coil channels L, the number of source voxels N, the voxel locations, and RF excitation selectivity on CSSI data.

Calibrations are required to determine the coil sensitivity encoding information prior to CSSI. Auto-calibration approaches like GRAPPA [104] cannot be applied here due to lack of k-space information. Furthermore, the constrained source approach requires strong a priori knowledge of the voxel locations in the brain. These can be provided in some cases by landmarks of functional neuroanatomy, or better using a functional
localizer fMRI experiment prior to CSSI, involving a behavioural task designed to activate the desired brain regions. It is likely that the use of a functional localizer would have improved CSSI data in the present experiment, as the fMRI results from at least one subject (subject D) suggested voxel mis-positioning. Mis-positioning could have occurred due to operator error, or inter-subject variability in functional neuroanatomy, which is known to be substantial [190]. In addition to helping ensure that voxel location and volume precisely coincide with regional brain activity, optimizing CNR [191], functional localizers are critical for ROI-based fMRI neurofeedback experiments, to provide optimal ROI geometry for real-time image processing [184].

The CSSI method can be easily extended to incorporate additional encoding techniques such as the COBRA technique [178], where arbitrary gradient projections can be added to the readout until the encoding matrix is well conditioned. With the inclusion of gradients, echo-shifting techniques may also be employed to further reduce the TR without impacting the TE needed for BOLD contrast [192]. The de-coupling of spatial encoding and data readout in the CSSI method lends flexibility to the types of contrast and applications that CSSI is capable of supporting, including the T2*-based fMRI presented here. With minor modifications for example, the CSSI method can be applied to multi-voxel spectroscopy without the need for Hadamard encoding [193], multi-voxel relaxometry or magnetic field measurements for gradient shim adjustments. Additional signal contrasts, such as combined T2 and T2* contrast can be developed with the use of refocusing spin echoes.

A novel method has been introduced for fast fMRI measurement of the BOLD response in a source constrained regime. Utility was demonstrated for cortical motor regions in a simple motor task, with more general potential for applications where fast and robust temporal sampling is useful in cases where the regions of interest are known a priori, such as in latency-resolved fMRI or mental chronometry [158], network-specific connectivity analyses [183], and real-time fMRI neurofeedback [95]. Further development and application of the CSSI technique will be a topic of future investigation in the laboratory.
Chapter 5

Conclusion

The continued interest in the development and application of magnetic resonance in science and medicine over the past 60 years highlights the power and flexibility of the technique. From its initial development in the early 1990s, fMRI has become an essential tool for localized, non-invasive, imaging of brain activity. The work presented in this thesis has focused on one particular application – the use of fMRI for neurofeedback to provide localized brain signals to train individuals to regulate their brain activity. What follows is a discussion of the outcomes of the main hypotheses and objectives of this thesis, as well as the implications and future directions stemming from this work.

5.1 Summary

Chapter 2 presented a study of the efficacy of fMRI NF using kinaesthetic motor imagery. The hypothesis that successful self-regulation of brain activity is possible under these experimental conditions was partially borne out, as a subset of young, healthy subjects was capable of responding to NF training. This work also highlighted inter-hemispheric interactions between the left and right M1 areas as subjects attempted to increase the laterality of their brain activity. Distributed brain activity was identified for successful NF engagement, namely task-positive network (TPN), including regions such as the frontal eye fields and the insula. Thus, the TPN may serve as a potential marker for predicting NF ability. This chapter provides a case for further development of fMRI NF into a future clinical tool for motor rehabilitation, and for improving upon basic fMRI NF methodological concerns such as subject selection.

Chapter 3 contained an investigation of multi-echo fMRI optimization in a dense sampling regime, using a combination of analytical modelling, Monte Carlo simulations, and human experiments. Hypothesizing that specific knowledge of the time series noise
can lead to better CNR optimization of multi-echo data, comparisons of various multi-echo combination methods in different noise regimes and sampling densities were carried out. The complex relationships between noise variance, noise correlation between echoes, multi-echo sampling rate, and echo combination methods were characterized, providing supporting evidence for the echo weighting method known as “CNR weighting”. This work also suggested that multi-echo weighting using PCA can be a viable alternative in dense sampling regimes, given an appropriate method for selecting the principal component that best reflects BOLD signals.

Finally, Chapter 4 reported on the development of a novel, fast fMRI acquisition scheme using the combination of parallel imaging and RF selective excitation to constrain the potential sources of magnetization to a small number of coarse voxels separated in space. The driving hypothesis for this work was that limiting the voxel source space would facilitate faster and more robust parallel imaging, using only multi-channel receive coil sensitivities for image reconstruction, without gradient encoding of data in k-space. The proof-of-concept demonstration successfully showed the feasibility of this idea by characterizing the BOLD responses in four coarse voxels during a simple motor task. Furthermore, the CSSI technique is not solely applicable to fMRI NF, and can be used for other applications such as improved fMRI measurements of signals within the nodes of a resting state functional network.

During the thesis work, a number of ancillary tools were created to assist in the completion of the research objectives. These tools may be useful for use in future, unrelated work in the Graham laboratory or by other researchers. One example is the development of a comprehensive real-time fMRI solution (with the assistance of Dr. Stephen LaConte) that links the MR image acquisition and reconstruction with computers that run neuroimaging software (e.g. AFNI) and visual stimulus display software (written in Python) in a flexible and accessible manner. With minor modification following a recent MRI system software upgrade at Baycrest Hospital, this real-time framework can be used to provide instantaneous measures of the BOLD response for any application, as well as to provide other real-time data such as 3D rotational and translational motion estimates, in numerical or graphical form. Additionally, the portions of the real-time framework not tied to the Siemens platform can be adopted for use in other MRI system environments, in conjunction with other real-time imaging solutions. One possible application of such a tool is in fMRI studies to assess brain-behavioural relationships in stroke patients in an exploratory fashion. Conceivably, with fMRI analysis performed rapidly during behavioural testing procedures, it would be possible to assess in individual patients how brain activity changes arise when tasks progress from those that are simple
for the patient, to those that are more challenging.

Secondly, a set of Python-based libraries for reading and manipulating “raw”, multi-channel imaging data from Siemens (VB15A and VB17A) MRI systems was developed to facilitate the pulse sequence development performed in Chapter 4. Access to the raw measurement data can be useful in pulse sequence development, and Python is a programming language that is well suited to data analysis, with a rich open source scientific computing community. Alternatively, the libraries provide options to output data in formats friendly to other popular scientific computing platforms (e.g. MATLAB).

5.2 Future Directions of NF in Stroke Recovery

Exploration of the use of fMRI for performing NF is still an area of ongoing interest, without a clear consensus on the choice of methodology. Furthermore, the clinical utility of the technique is still not yet well known, although numerous groups have been working with fMRI NF in a number of potential clinical domains. In this section, some thoughts are provided on the potential directions for future fMRI NF investigations based on the work in Chapter 2, directed towards the ultimate goal of identifying a role for fMRI NF in motor rehabilitation following stroke.

The first and most straightforward targets for future study are the heterogeneous response to NF training observed in the young healthy population, and identification of TPN activity as a marker for NF success. With the well known costs associated with MRI time, identifying a simple predictive measure of NF training receptivity would be useful in developing exclusion criteria to preclude the use of fMRI NF in patients who would not respond favourably. Such a measure must be either behavioural in origin or based on a brief fMRI experiment that could be added easily to an existing clinical MRI protocol. One potential solution is a “classifier” fMRI experiment combining a resting state component, and a task component where subjects are asked to perform a task based on interoceptive awareness, or continuous motor imagery. Since default mode network (a commonly identified network of regions expressed during rest) and TPN activity are believed to be anti-correlated [131], this experiment should measure default mode expression during the resting state, and suppression during the task, as well as expression of the TPN during the task, which could then be extracted and analyzed using PLS or other multivariate methods. For the purposes of evaluation, this brief scan could precede fMRI NF measurements similar to those presented in Chapter 2, in a study group large enough to build a confident predictive model of performance with respect to the TPN expression in the short classifier scan. This proposed experiment
also addresses some concerns from the results of Chapter 2, regarding the alternative possibility that elevated TPN expression during successful NF was purely a marker of sustained attention, and that successful subjects were better able to sustain attention to the task than the unsuccessful subjects over the successive 9 minute runs. If this possibility is true, the results of the proposed experiment would not show any predictive power for the classifier scan, assuming that fatigue or inattentiveness would not manifest in a shorter fMRI scan.

A second potential area for exploration departs from ROI-based NF through the use of whole-brain classification. Sometimes referred to as temporally adaptive brain state (TABS) fMRI [135], these approaches use the entire brain for brain state modification, thus avoiding issues of ROI selection and the need for functional localizer experiments. One interesting application of this technique can be described as a “brain mimicry” experiment. In this method, one group of subjects (e.g. healthy subjects) performs a task such as motor imagery, without NF, while whole brain fMRI data are collected. These data can be used as training data for a subsequent brain state classification experiment with a second group of subjects (e.g. stroke patients). The second group can undergo a typical NF experiment, except in this case, the feedback measure would be some scalar measure of overall brain state. Here, the goal of the experiment for the stroke patients would not be to maximize activity in any particular region, but rather to produce a brain state that is as close as possible to the state defined by the training data from the healthy group. A hypothesis can be put forward that the emulation of healthy brain states may facilitate the neurological, and associated physical recovery in stroke patients. Previous studies of TABS fMRI have focused on changing brain states within subjects, rather than between subjects. Furthermore, target “healthy” brain states might be generated based on current understanding of normal brain activation patterns, without the need for a healthy subject group.

The feasibility of this type of training can be easily tested in pilot fashion in a simple tandem fMRI experiment, with two subjects. For example, subject A performs finger tapping with either the right or left hand, while whole brain fMRI data are collected. Next, subject B performs a NF experiment with the data from subject A as the training set for the classifier. If subject B can successfully “guess” the hand used by subject A by manipulating their hand movements and related brain state, then the brain mimicry can be considered a success. Obvious practical considerations make this a non-trivial experiment to implement, particularly the normalization of brain anatomy across subjects to make inter-subject brain state classification viable. One solution to this is to “pre-warp” the training data spatially to the test subject anatomy, removing the need for
real-time normalization of the fMRI data. In addition, the whole-brain data collection requirement can be relaxed by identifying network nodes or ROIs that best capture the desired brain state, and performing an ROI-based acquisition such as CSSI. Classification algorithms do not require whole brain data, and can work well with data of reduced dimensionality provided by a source constrained method.

The work proposed in this section is still firmly focused on NF approaches to effect changes in brain activity, and to establish clinical relevance for motor rehabilitation applications, and more work is required to establish the link between brain activity changes and subsequent motor behaviour changes. In the long term, based on the success of such experiments, further work is also required to establish the efficacy of NF techniques in aged populations and stroke patients, who may have cognitive deficits associated with aging or stroke that prevent the successful application of NF. Finally, to have practical relevance, any fMRI NF-based therapy should ideally be either a single-session in length, or short enough to append to an existing MRI protocol. Because lasting changes are unlikely to result from a single session intervention, fMRI NF is more likely poised in a therapeutic priming role, in which subjects learn how to best perform imagery practice to facilitate brain activity change with the help of NF, and subsequently pursue practice at home or in another environment without the aid of real-time feedback. This type of approach has been investigated in the short-term, with some promising results [114]. It is also important to emphasize that although MRI is viewed as a costly, scarce healthcare resource, its judicious application in this context has the potential to offset that substantial cost by improving rehabilitation and reducing the socioeconomic burdens associated with long term disability.

5.3 Future Directions for Constrained Source Space Imaging

The initial proof-of-principle implementation of the CSSI technique was demonstrated in a simple fMRI application. The technique can be refined with a number of future improvements and modifications, for a range of applications as outlined in Chapter 4.5. In the following section, two example modifications to the CSSI technique are expanded: one to enhance its imaging capabilities, the other to adapt the technique for MR spectroscopic imaging.

First, the flexibility and SNR of the CSSI technique will likely be improved through the use of 3D tailored RF selective excitation pulses. Although multi-shot “excitation
k-space” strategies can be implemented on standard, single-channel transmit systems [194], these require long durations and strenuous gradient requirements and may not be suitable for fast imaging. The CSSI method would benefit greatly from parallel transmit technology, which employs techniques such as transmit SENSE [186] to accelerate the 2D or 3D excitation of magnetization using multiple, independent transmit channels [195] with reasonable RF pulse durations. This technology allows imaging to be performed selectively on arbitrary regions of interest, without the restriction of 90° flip angles in rectangular ROIs on a rectangular grid, as with the modified STEAM proof-of-principle design tested in Chapter 4. The ability to shape conformal ROIs to prevent structural or functional partial voluming would improve SNR [196], as would the ability to perform excitations with flip angles closer to the SNR-optimal Ernst angle.

Employing tailored RF excitations also introduces the possibility for separately customizing the excited magnetization phase in each voxel, which can produce improvements in reconstruction fidelity [189]. Briefly, this improvement comes by using the principles developed in the “virtual coil” parallel imaging technique [197] to include complex conjugate signal and sensitivity information (the “virtual coils”) in the encoding equation. One can consider the combined effect of magnetization phase and coil sensitivity to produce an equivalent complex, “effective” coil sensitivity. Normally receive coil sensitivities are fixed, and sensitivity encoding matrices are simply defined by voxel locations. The “effective” sensitivities however, can be customized by adjusting magnetization phases through excitation, thereby enabling the user optimization of the encoding matrix. This freedom can be used to minimize the parallel imaging g-factors, or to facilitate CSSI in untenable voxel configurations where the standard encoding problem would not be well posed.

There are some practical considerations that must be addressed with these modifications, including the ability to define ROI excitation profiles in real-time. Because fMRI ROIs are often defined by functional localizer experiments, pre-computed RF transmit amplitude modulations and gradient trajectories may not be applicable, and some interactive means of selecting or “painting” excitation ROIs in real time must be developed. With current technology, iteratively designed parallel transmit RF pulses can be calculated in approximately 1 minute [198], so it seems feasible to build an interactive user interface that can function in real-time or near real-time. Another practical consideration is intra-scan head motion, which can not only produce unwanted signal fluctuations, but offsets the imaging ROIs from the true locations of interest. At present, there is no possibility for retrospective correction in CSSI data as in whole brain acquisitions. Fortunately, the Graham laboratory has been developing prospective motion correction
techniques using an external optical tracking system [199], which would be very useful in preventing the localization errors and artifacts mentioned above. Work would have to be done to integrate the real-time position adjustments into a parallel transmit system. One final consideration is that parallel transmit requires specialized MRI system components that are not yet widely accessible, although first-party and third-party parallel transmit solutions are becoming increasingly available.

A different application of the CSSI technique is for simultaneous single voxel spectroscopy (SVS), which is a natural extension of single voxel spectroscopy using STEAM. In conventional magnetic resonance spectroscopic imaging (MRSI), spectra are localized in a coarse Cartesian grid in either 2D or 3D using appropriate phase encoding and RF slice selection, with scan durations proportional to the number of imaging voxels. With parallel imaging, MRSI can be accelerated to reduce the spatial encoding time, although even using state of the art approaches such as the PEPSI-SENSE technique [200], 32x32 voxel coverage of a plane still takes 16 s at 4x acceleration. The CSSI technique falls in between temporally resolved, single voxel coverage SVS methods, and the much slower, planar or volume coverage MRSI techniques. With the multi-voxel spatial coverage in CSSI, time-resolved spectra can be produced with the same repetition rate as SVS, and with expanded, albeit limited spatial coverage. This can be useful in applications where fast dynamic or functional spectroscopy is desired, such as in experiments monitoring dynamic concentrations of brain metabolites that is being explored at higher fields [201], or in dynamic mapping of absolute brain temperatures across multiple ROIs [202]. In addition, a robust CSSI implementation of multivoxel MRSI would avoid some of the aliasing problems associated with MRSI approaches that use k-space encoding methods [203].

Modification of the existing prototype to accommodate spectroscopy can include the addition of water suppression [204], which can be added prior to excitation. Additionally, if necessary, outer volume lipid suppression can be performed as part of the magnetization preparation stage. The readout duration and TR can easily be adjusted to acquire data with the desired spectral bandwidth and resolution, and TEs can be chosen to optimize metabolite contrast. Following FID separation, signals would undergo temporal Fourier transforms instead of BOLD signal estimation, although the data inversion step would be identical to that described in Chapter 4. The same practical issues remain as well, including susceptibility to motion and g-factor induced SNR losses. The motion correction scheme proposed for fMRI would apply to spectroscopy as well, although more care would be needed to account for position-related magnetic field inhomogeneities, possibly through improved shimming.
5.4 Integration of CSSI and NF

This thesis has presented an application of fMRI NF in young adults, and the development of techniques designed to facilitate and enhance the acquisition of fMRI data for NF applications. One important future direction is the integration of the CSSI technique with a NF experiment. Although this is possible with the CSSI prototype, inclusion of some of the proposed improvements to the CSSI sequence from the previous section may be prudent before attempting a NF experiment. The most important element would be the prospective head-motion correction, without which the BOLD signals would be highly contaminated with motion, providing an undesirable alternate mechanism for subjects to control their NF signals. The simple data reconstruction process lends itself to easy integration with the existing real-time fMRI data processing and stimulus display, requiring minor modifications to the MRI system image reconstruction code. The relatively coarse, rectangular voxels provided by the dual-band STEAM excitation are well suited for the large, rectangular ROIs typically used for NF signal calculation, although the proposed parallel transmit improvements would facilitate more flexible voxel placements and shapes. Real-time respiratory and cardiac artifact correction [205] and signal filtering approaches may also be necessary to improve the CNR of fMRI signals used in NF.

One interesting experiment would be to test the efficacy of NF using a CSSI acquisition compared to a standard, EPI acquisition. Faster and more robust BOLD estimates would facilitate many different kinds of NF experiments (e.g., incorporating signal latency), and may improve the fidelity of the NF signals, enhancing the ability of subjects to regulate their brain activity. The latter claim is not obvious, however, and this assertion should be tested. In fact, it may be that subjects perceive the underlying NF-related BOLD signals despite low sampling rates and noise, and that further optimization of CSSI BOLD data would produce diminishing returns. An experiment could test the dependence of NF success on the feedback signal update rate and CNR, and would complement existing studies that are looking towards optimizing feedback signal properties [40].

5.5 Final Remarks

Over the past 20 years, fMRI has grown from novelty to near ubiquity in neuroscience research. Continual improvements in fMRI capabilities and the development of new imaging methods are leading to drastic enhancements in spatial and temporal resolution, with many implications for the types of questions researchers are now able to address. In
this thesis, consideration of parallel imaging and multi-echo fMRI methods have led to the development of the CSSI technique, which will benefit from the growing adoption of parallel RF transmit technology. Recent developments have also furthered the progress toward using fMRI as a clinical tool, including the work in this thesis that explored the potential for fMRI in motor rehabilitation following stroke. As such, it will be interesting to see how fMRI will continue to grow and develop over the next 20 years.
Bibliography


