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#### ADVANCES IN IMAGE ACQUISITION AND FILTERING FOR MRI NEUROIMAGING AT 7 TESLA (Thesis format: Integrated Article)

by

Andrew Curtis

Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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## Abstract

Performing magnetic resonance imaging at high magnetic field strength promises many improvements over low fields that are of direct benefit in functional neuroimaging. This includes the possibility of improved signal-to-noise levels, and increased BOLD functional contrast and spatial specificity. However, human MRI at 7T and above suffers from unique engineering challenges that limit the achievable gains. In this thesis, three technological developments are introduced, all of which address separate issues associated with functional magnetic resonance neuroimaging at very high magnetic field strengths.

First, the image homogeneity problem is addressed by investigating methods of *RF shimming* — modifying the excitation portion of the MRI experiment for use with multichannel RF coils. It is demonstrated that in 2D MRI experiments, shimming on a slice-by slice basis allows utilization of an extra degree of freedom available from the slice dimension, resulting in significant gains in image homogeneity and reduced RF power requirements.

After acceptable images are available, we move to address complications of high field imaging that manifest in the fMRI time series. In the second paper, the increased physiological noise present in BOLD time series at high field is addressed with a unique data-driven noise regressor scheme based upon information in the phase component of the MRI signal. It is demonstrated that this method identifies and removes a significant portion of physiological signals, and performs as good or better than other popular data driven methods that use only the magnitude signal information.

Lastly, the BOLD phase signal is again leveraged to address the confounding role of veins in resting state BOLD fMRI experiments. The phase regressor technique (previously developed by Dr. Menon) is modified and applied to resting state fMRI to remove macro vascular contributions in the datasets, leading to changes in spatial extent and connectivity of common resting state networks on single subjects and at the group level.

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# Keywords

Magnetic resonance imaging, high field, functional imaging, phase, neuro imaging, radio frequency, transmit array, physiological noise

## **Co-Authorship Statement**

This thesis consists of three papers describing original research works, as chapters 2, 3, and 4 that are all co-authored. Contributions are described below.

Chapter 2: "Slice-by-slice B<sub>1</sub>+ shimming at 7T" has five contributing authors: AT Curtis, KM Gilbert, LM Klassen, JS Gati, and RS Menon. AC and RM devised the concept and experiments for validation. AC programmed the pulse sequence software, acquired and analyzed the data. LMK provided advice for pulse sequence implementation, and provided low level scanner library (PSG) modifications. KG developed the RF coils and contributed insight for analysis. JG provided scanning support and insight for analysis. AC and RM wrote the manuscript.

Chapter 3: "HighCor: A novel data-driven regressor identification method for BOLD fMRI" has two co-authors, AT Curtis and RS Menon. AC and RM devised the concept, experimental protocols, and analysis methodology. AC acquired and analyzed the data. AC and RM wrote the manuscript, and engaged in glorious battle with reviewers.

Chapter 4: "Phase based venous suppression in resting-state BOLD-fMRI" has three coauthors: AT Curtis, RM Hutchison, and RS Menon. AC and RM devised the concept. All three authors had input for the experimental methodology. AC performed data acquisition, processing and analysis. All three authors contributed to writing the manuscript.

## Acknowledgments

The work contained in this thesis is only a small view of a significant development effort by an amazing team of people. None of this research would have been possible without the support, guidance, and hard work of many individuals, all of whom I am grateful to have worked with and learned from.

First, the greatest thanks to my supervisor, Prof. Ravi Menon. Always insightful, rigorous, and critical, pushing for excellence in research, writing, and presentation – yet with a keen ability to keep the big picture in mind – Ravi stands as an excellent role model who has certainly helped me to become a better scientist. I will be ever grateful of his patience and support while researching ever another crazy idea.

I was fortunate to work with many exceptional scientists during my time at Western. Of these, Joe Gati, Martyn Klassen, Kyle Gilbert, Mohamed Abou-Khousa, David Rudko, and Matt Hutchison deserve particular mention for their contribution to my research. Thank you all for your input, encouragement, thought-provoking discussions, and for always having time for "one more quick question."

Lastly, I thank my friends and family, old and new, for their unwavering support of the lifelong student.

## List of Abbreviations

- B<sub>o</sub> Main (static) magnetic field strength
- B<sub>1</sub> Radio frequency magnetic field strength
- BOLD Blood oxygen level dependent
- CNR Contrast to noise ratio
- CSF cerebrospinal Fluid
- EPI Echo planar imaging
- fMRI Functional MRI
- GLM General linear model
- GM Gray Matter
- GRE Gradient recalled echo
- RF Radio frequency
- ROI region of interest
- SE Spin echo
- SNR Signal to noise ratio
- T2 Transverse relaxation rate
- T2\* Effective transverse relaxation rate
- TE Echo time
- TR Sequence repetition time
- WM White Matter

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## Preface

Magnetic resonance imaging, or MRI, is an incredibly versatile set of technologies that has had huge impact in diagnostic medicine, psychology, and neuroscience. The utility and popularity of MRI can be attributed to the wide variety of image contrasts that can be realized by changing the manner in which the MRI experiment is performed. MRI is a very safe imaging methodology, employing no ionizing radiation, and thus lends itself well to longitudinal studies and investigations of healthy volunteers. In the realm of neuroscience research, these properties make MRI particularly useful for investigating both structure and function of the brain.

The strength of the main magnetic field ( $B_0$  -- measured in Tesla) affects many of the imaging properties in MRI. Several important imaging parameters scale with the strength of the main magnetic field due to the underlying physics of the MRI experiment, and can result in distinct performance improvements in attainable image resolution and functional contrast. Specifically, image signal-to-noise ratio scales with the field strength, allowing for great improvements in image quality, differing contrast, and/or a reduction in scan times.

Clinically, 1.5 Tesla has become the incumbent standard with newer clinical systems transitioning to 3.0 Tesla. Even higher field strengths are available but are still very much in the research domain, mainly due to the technological challenges of imaging at high field. These challenges arise from several effects that also scale with magnetic field strength. Addressing some of these challenges for human neuroimaging is the focus of this thesis. In this work, all imaging is performed on a research-oriented 7.0 Tesla imaging system. Application work is focused on functional imaging of the brain, based heavily on BOLD fMRI -- techniques which will be described in more detail later in the background material.

This neuroimaging-focused system brings the promise of improved imaging resolution and sensitivity for functional imaging studies. As alluded to above, there are some benefits to performing MRI at high field strengths, however, these are tempered by several associated phenomena that make high field MRI very challenging. One such troubling effect arises from the wavelength of the radio-frequencies (RF) involved, resulting in non-uniformities

in the image brightness and contrast. Another confound arises from the increased levels of energy deposition, resulting in tissue heating and making high duty cycle, large flip angle sequences difficult to perform. Heightened sensitivity to magnetic field susceptibility gradients can lead to image distortions and greater contamination from physiological sources.

This thesis addresses three such confounds, proposing new methods to help mitigate their influence. They are (in order of exposition): image inhomogeneity due to RF wavelength effects, the increased contamination of physiological noise in fMRI, and the signal biasing effects of veins in resting state fMRI.

The following chapters are organized to explain these phenomena, and to provide background for the subsequent research papers.

**Chapter 1** contains an overview of the excitation phase of the MRI experiment. We review signal excitation in the context of the RF inhomogeneity artifacts present in human neuroimaging at 7 Tesla. This includes exploring the role of multi-channel RF coil arrays, methods for mapping of the transmit RF fields, and the role of multi-transmit technology for homogenizing the RF excitation and thus image contrast. The concept of RF shimming, the process of controlling these multi channel coil arrays to better control the RF excitation is also introduced, and the process we have developed for fast, robust day-to-day operation is reviewed. This groundwork is then leveraged to modulate the " $B_1$ + shim" for every excitation in the pulse sequence, allowing for marked improvements in homogeneity and power efficiency. This new work serves as background for the first research paper (Ch 2), which is fairly technical with minimal introduction of its own. Chapters 3 and 4, also introduced below, are more applied in nature and were published as methodology papers in NeuroImage. As such, they have significant amounts of self-contained introductory material for the reader.

**Chapter 2** presents a method for RF shimming for the ubiquitous multi-slice acquisitions used in MRI. It is demonstrated that in 2D MRI experiments, performing RF shimming on a slice-by slice basis allows utilization of an extra degree of freedom available from the slice

xv

dimension, resulting in significant gains in image homogeneity and reduced RF power requirements when compared to using fixed shim solutions for the whole brain. This contribution is published in *Magnetic Resonance in Medicine*.

**Chapter 3** describes a method for addressing one of the complications of high field imaging that manifest in the fMRI time series: the increased physiological noise present in BOLD time series at high field. This is addressed with a unique data-driven noise regressor scheme based upon information in the phase component of the MRI signal. It is demonstrated that this method identifies and removes a significant portion of physiological signals, and performs as well or better than other popular data driven methods that use only the magnitude signal information. This work is published in the journal *NeuroImage*.

**Chapter 4** presents a method for dealing with another complication of BOLD-fMRI at high field. Here, the BOLD phase signal is again leveraged to address the confounding role of veins in resting state experiments. The phase regressor technique is modified and applied to resting state fMRI to remove macro vascular contributions in the datasets, leading to changes in spatial extent and connectivity of common resting state networks on single subjects and at the group level. This work is published in the journal *NeuroImage*.

**Chapter 5** serves as a conclusion, summarizing major results and discussing continuing and future research questions.

The field of MRI is mature enough to have many excellent textbooks available. The background material presented in this thesis is not meant to provide an exhaustive nor complete description of MRI. For readers looking for additional detail, the author has found two texts particularly helpful: Haacke's *Magnetic Resonance Imaging: Physical Principles and Sequence Design*, and de Graff's *In Vivo NMR Spectroscopy*.

## 1. MRI Background

Magnetic resonance imaging is based on the nuclear magnetic resonance phenomenon. Atoms with a non-zero nuclear spin angular momentum--an intrinsic, quantized property--exhibit a magnetic moment and respond to externally applied magnetic fields, demonstrating a splitting in energy levels of the different spin states. In MRI the predominant nuclei of interest is the single proton in hydrogen, <sup>1</sup>H, a spin- $\frac{1}{2}$  particle, with quantized spin m<sub>s</sub>=  $\pm \frac{1}{2}$ .

Three magnetic fields are utilized to perform MR imaging. The strong static main field, B<sub>0</sub>, and two time-varying fields: the radiofrequency (RF), or B<sub>1</sub> field, responsible for signal excitation and reception, and the gradient fields used for spatial encoding of the image.

In the uniform external magnetic field produced by the MRI machine ( $B_o$ , oriented along the z-axis by definition), the proton nuclear magnetic moments lead to discretized energy values for the two spin states, sometimes referred to as spin-up and down, or parallel and anti-parallel. Parallel and anti-parallel configurations have slightly different a potential energies that scale with the external magnetic field strength and a characteristic scaling factor called the gyromagnetic ratio,  $\gamma/2\pi$ (42.57 MHz/T for Hydrogen). Given B<sub>o</sub> in the z direction, the energy levels E are:

$$E = -\mu \cdot B = -\mu_z \cdot B_z = -\gamma m_s \frac{h}{2\pi} B_0 = \mp \frac{1}{2} \gamma \hbar B_0.$$

There is then a small energy difference between the spin up and down states given by  $\Delta E = \hbar \omega_o$ . For an ensemble of spins, the drive to lower energy (ground state) is offset by the thermal energy of the system, resulting in an equilibrium where a surplus of the spin population is in the ground state, given by the Boltzmann distribution:

$$\Delta N = e^{\frac{-\Delta E}{k_B T}}$$

where  $k_B$  is the Boltzmann constant and T is the temperature of the system. It is this population excess that is the basis for signal in MRI. Summed over the population of spins in a sample, the magnetic moments add vector-wise, and the resultant is referred to as the *net* magnetization of the sample,  $M_0$ , with a magnitude:

$$M_0 = \frac{\rho_0 \gamma^2 \hbar^2 B_0}{4k_B T},$$

where  $\rho_0$  is the proton density. While NMR is fundamentally a quantum mechanical phenomenon, the behavior of the MRI experiment for hydrogen, when expressed in terms of the bulk magnetization behaves in a manner that is completely described by a classical vector model. At equilibrium,  $M_0$  is aligned parallel to  $B_0$ , the direction of which defines the *z* or *longitudinal* axis, and is normal to the *transverse*, or *x-y* plane. Once excited away from the z axis, these magnetic moments will precess about  $B_0$  at a frequency  $\omega_0 = \gamma B_0$ , called the Larmor frequency, roughly 300 MHz for hydrogen at 7 T. Only the component of the magnetization in the transverse plane generates detectable signal.

#### Excitation

In order to acquire signal for imaging, the bulk magnetization must first be excited away from equilibrium. Spin excitation is attained by application of a time-varying radiofrequency magnetic field, B<sub>1</sub>, at the Larmor frequency. Because the application of this B1 field is typically of a short duration, with a shaped envelope, it is commonly referred to as an RF *pulse*. The result of this RF pulse is the net magnetization vector experiencing a rotation, or flip, down into the transverse plane. The x and y -axes in the transverse plane are defined by the phase of the initial RF excitation pulse. The angle that the magnetization vector is rotated away from the z-axis is referred to as the flip angle,  $\alpha$ . For instance, a 90-degree flip angle about the x axis results in the magnetization vector being rotated completely from the z-axis down into the transverse plane, along the y axis.

The RF amplitude in Hz,  $\omega_1$  at a point in space, r, is controlled by two parameters, the driving amplitude, w, and the spatially varying local magnetic field produced by the transmitting element:

$$\omega_1(\mathbf{r}) = w\gamma B_1^+(\mathbf{r}).$$

For a constant RF pulse at the Larmor frequency of amplitude  $\omega_1 = \gamma B_1$  (ignoring the spatial behaviour for now) and duration  $\tau$ , the flip angle experienced by the magnetization vector is:

$$\alpha = \omega_1 \tau$$

More generically, for a pulse with a time varying envelope:

$$\alpha = \int_0^\tau \omega_1(t) dt$$

The system elements responsible for transmitting RF pulses and receiving the MRI signal are known as RF coils. These are typically resonant loop structures that are designed and tuned to be sensitive to the magnetic field fluctuations generated by spins at the Larmor frequency.

The magnetic fields generated by RF coils are vector valued in space, with their magnitude typically reported in micro-Tesla, and can be decomposed in terms of their x and y components:

$$\mathbf{B}_1 = B_x \boldsymbol{e}_x + B_y \boldsymbol{e}_y.$$

However, it is much more useful to express these fields in a circularly polarized basis with co- and anti- rotating basis vectors  $e_1$  and  $e_2$ . We can express:

$$\mathbf{B}_1 = B_1^+ \hat{\boldsymbol{e}}_1 + B_1^- \hat{\boldsymbol{e}}_2.$$

Here the scaling for the co-rotating and counter-rotating fields  $B_1$ + and  $B_1$ - can also be written in terms of the original Cartesian components:

$$B_1^+ = \frac{1}{2}(B_x + iB_y)$$
, and  
 $B_1^- = \frac{1}{2}(B_x - iB_y).$ 

These decompositions are useful because the co- and anti- rotating (or right and left polarized) components are recognized as being responsible for excitation during transmission, and reception of signal, respectively.

## **RF** Inhomogeneity

The simplest coil element in use in MRI is the venerable loop coil, a building block from which larger coil arrays may be constructed. An example of the transmit  $B_1$ + field distribution produced by a loop surface coil in the human head at 7 T is displayed in Figure 2-1. The B<sub>1</sub> field generated by such coil falls off very quickly, limiting the imaging region. As such, individual surface coils are rarely used for signal transmission, except in specialized circumstances. The spatially localized fields generated by surface loop coils have advantages when combining multiple loops to increase volume coverage. Such designs are commonly used for signal reception. Surface coils arrays designed for transmission exist and have been shown to provide some benefits versus volume transmitters in SAR and shaping of the transmitted RF field(1). Typically for whole brain imaging, *volume* coils -- RF coils that produce homogeneous fields over the entire imaging volume -- are utilized, one popular geometry being the birdcage design. In high-field human imaging these volume coils no longer produce uniform B1 fields owing to the RF inhomogeneity artifact. This effect is commonly referred to as a 'center brightening' artifact because of the typically larger signal intensity in the central regions of the brain in low flip angle gradient echo sequences. In the literature, this is also described by the equally confusing term *dielectric resonance*(2,3).



Figure 1-1 Surface Coil Transmit Profile

Sample profile of the magnitude of  $B_1$ + in an axial slice produced by a 15cm-diameter surface coil located over the visual area (approximate location shown) in the human head at 7T.

As an example of this effect, Figure 1-2 displays a gradient echo image acquired at 7 T using a whole head birdcage coil. For most imaging applications, the ideal RF coil for transmission would produce a  $B_1$ + field with uniform amplitude over the whole sample, to enable a homogeneous flip angle over the imaging region.

At higher field strengths, where the operational frequency of the MRI increases, the RF wavelength approaches the dimensions of the sample. The shortened wavelength leads to destructive interferences between the B<sub>1</sub> fields produced by the elements of the RF coil (loops in an array or rungs of a birdcage), resulting in spatially varying amplitude and phase of the resultant  $B_1$ + field(2,4,5). The non-uniform flip angles generated as a result lead to spatially varying signal and contrast in the acquired images. For example, regions experiencing excitation flip angles smaller or larger than expected can suffer from reduced signal levels, via under-flipping or magnetization saturation, respectively. The wavelength to object size ratio becomes problematic for human imaging of the torso at 3 T, and in the head at 7 T.



**Figure 1-2 7T Centre Brightening** 

Characteristic center brightening artifact demonstrated in an axial slice in the human head at 7T. Acquired with a birdcage head coil, RF interferences in the periphery of the brain lead to attenuation of the  $B_1$ + (circled). Addressing RF inhomogeneity is important. The base low-frequency image *intensity* variation is problematic although intensity variations can be inferred and corrected with post processing techniques (in much the same way that receive field normalization is performed). However, signal loss from under- or over-flipping cannot be recovered, and thus spatially alters the signal to noise ratio (SNR), reducing the SNR efficiency of any imaging.

Equally concerning are the image *contrast* variations between and within tissue types. As a result of the *B*<sub>1</sub>+ inhomogeneity, nearly all imaging sequences will have tissue contrast altered spatially either via imperfect RF refocusing effects, or from changes in the steady-state magnetization at the different effective flip angles. Spatially varying contrast changes can lead to significant problems for many applications -- from visual identification in diagnosis, to automated segmentations that rely on well-defined differences between tissue types. An example of this effect is demonstrated in Figure 1-3, where an axial slice from a typical T<sub>1</sub>-weighted anatomical dataset are shown side-by-side, one acquired from a 3 T scanner, with a comparable 7 T image to the right. Observable in the 7 T image are both the overall intensity variation (center brightening), as well as contrast effects from the imperfect excitation pulses -- contrast between grey and white matter is nearly lost in some locations. It should be noted that the use of an adiabatic inversion pulse in this example mitigates the contrast loss during magnetization preparation, and residual contrast effects are mainly from the excitation pulses in the readout.

Overall image intensity and contrast can also differ from what one might expect given a particular sequence parameter set, depending on how the mean flip angle is calibrated over a potentially wide  $B_1$ + distribution. RF inhomogeneity is also quite problematic for many quantitative imaging techniques (parametric mapping) that rely on a well-defined signal response to the applied RF pulses.

## B<sub>1</sub>+ Shimming

Several approaches for combating the inhomogeneity artifact are known. Softwarebased approaches are popular for their (relative) ease of implementation and low cost overhead.  $B_1$ + insensitive RF pulses like composite or adiabatic pulses can be designed and employed, but they are not applicable in all situations. For an overview refer to de Graff (6). Another important software approach is the design of gradient encoded RF pulses (typically known as 2D or 3D RF). These pulses are designed to spatially tailor the excitation response with the additional control available from gradient encoding. Implementation of 2D/3D RF for low flip angle excitation is fairly simple problem, but the method becomes significantly more complicated in high flip angle applications like inversion and/or refocusing pulses (7–10).



Figure 1-3 3T vs 7T Anatomical

T<sub>1</sub>-weighted MPRAGE acquired with a birdcage coil at 3 T (left) and 7 T (right) demonstrating spatial signal amplitude and contrast effects from the inhomogeneous transmit field.

Hardware approaches, in the form of multi-channel RF transmit coil arrays are also a promising option(1,2,11–15). In contrast to the typical situation in MRI where a

single volume coil is responsible for RF transmission (typically referred to as the body coil), transmit arrays consist of multiple independently controlled elements that are constructed such that the combined (vector) sum of the  $B_1$ + fields from all elements results in a more homogeneous excitation field. The size, shape, and number of elements in the array affect the combined spatial response of the array (16) with competing design goals of penetration depth, coverage, power efficiency, and element isolation. Design of such arrays was and continues to be the approach taken by our lab for the 7 T scanner. Such design problems have received significant attention from the group with myriad coil array geometries and construction methods having been developed and tested (13–15).



Figure 1-4 Birdcage (top) vs 12 Channel Tx-Array (bottom)

Use of multi transmit coil technology allows tailoring of the field profiles and partial correction of the RF inhomogeneity artifact.

Figure 1-4 demonstrates the difference between a birdcage and 12 channel surfacecoil transmit array in matched slices using a low flip angle gradient echo sequence. Increased receive signal intensity partially masks the center-brightening in the transmit array (Figure 1-4, bottom row), yet the RF inhomogeneity is still detectable as contrast variation within the images.

Such transmit arrays, designed for performance on a reference head/phantom, prove to be sensitive to the variation found when performing MRI on real subjects. Head shape, size and positing within the transmit array affect the performance, and as such, the  $B_1$ + profiles of each element and the overall  $B_1$ + homogeneity. Independent control of the driving amplitude and phase of each element at run time allows for further tuning of the RF excitation field on a per-subject (and even per-ROI) basis. This process is referred to as  $B_1$ + shimming.

When the spatial profiles of more than one transmit coil overlap, the field vectors add, resulting in a field that is a linear combination of those from each individual coil:

$$B_1^+(\vec{r}) = \sum_{i=0}^{nCoils} B_{1,i}^+(\vec{r}).$$

By individually controlling each coil element, the RF excitation field can be shaped. Options for driving a set of coils are varied; separate amplifiers per channel allow for scaling of the contributions of each element. The addition of phase shifters adds modulation of the spatial phase offset, and separate per-channel waveform generators enable modulation of the RF pulse shapes on a per-transmitter basis. The MRI platform used in this work has sixteen separate RF chains, enabling all of these capabilities for fine control of the transmitter channels.

Amplitude scaling and phase offset controls for each channel can be represented as complex-valued vector  $w \in \mathbb{C}^{1 \times nCoils}$ . By modulating the weights, the resultant summed excitation field at a given point in space, *r*, can be controlled:

$$B_1^+(w,r) = \sum_{i=0}^{nCoils} w_i B_{1,i}^+(r).$$

Solving the shimming problem involves selecting a weights vector to optimize some metric over a targeted region of interest (ROI) for imaging, typically a voxel, slice, or volume area, i.e. to homogenize  $B_1^+(r)$  for  $r \in \Omega_{ROI}$ . This process is depicted pictorially in Figure 1-5, which demonstrates the summation of many coil  $B_1$ + profiles in a single slice.

Constraints on the problem variables can be employed to aid in the solution. One particularly important concern at high field strengths is the *transmit efficiency*. We take a brief aside to explain this concept, and the related idea of specific absorption rate, or SAR. Given a single coil with some known  $B_1$ + at a point in space, a desired excitation flip angle for a fixed duration pulse can be achieved by scaling the amplitude of excitation.

Two problems arise from low  $B_1$ + efficiency. First, amplifiers have hard limits on the amount of output power that is able to be delivered to the RF coil. Second, and more problematic for human imaging, are the effects of tissue heating that occur. These transmit elements also generate electric fields in addition to the magnetic  $B_1$ + fields. The E fields interact with tissue and lead to energy deposition, in the form of tissue heating. A hard limit exists on the rate of tissue heating, and is called the specific absorption rate, or SAR, measured in W/kg.

Energy deposition is a strict constraint for high field imaging, and scales with the sample conductivity and the square of the electric field generated by the coil. Efficient transmit coil design, while outside the scope of this work, can be understood to involve maximizing the  $B_1$ + generated while minimizing the magnitude of the E field in the sample. In a multi-channel transmit coil, we are restricted by the designers on the absolute efficiency of each element, however, depending on how the array is driven the efficiency in practice can be greatly changed. To understand this concept, consider a region in a sample within the RF coil, where the  $B_1$ + field from each transmit element, when driven in isolation, is



Figure 1-5 *B*<sub>1</sub>+ Shimming

*Outer ring*: Magnitude images of relative  $B_1$ + for 14 selected channels of a cylindrical transmit array. The  $B_1$ + shimming process is to choose an amplitude and phase scaling for each channel to homogenize the summed field over the slice. *Centre*: Resultant  $B_1$ + distribution if fixed weights are used to align all channels only at the centre of the volume, mimicking the field pattern of a birdcage at high field, known as *circularly polarized* mode. Even though individual channels have significant amplitude in the periphery of the brain, destructive interference leads to vector cancellation and low resultant  $B_1$ +. Color range matches that in Figure 1-1: red=1 to blue=0.

non-zero. If we choose to drive the transmitters (by picking appropriate weights) such that the  $B_1$ + fields from all coils add constructively, we might expect to be near the peak efficiency for that region. On the other hand, were we to choose weights such that the  $B_1$ + field vectors almost totally cancel, very little  $B_1$ + will be generated even with large input power -- a very inefficient situation indeed. The E fields will likely not cancel, however (especially averaged over the sample) leading to tissue heating still occurring even in the absence of any spin excitation from  $B_1$ +.

Returning to the concept of shimming, it is apparent that tradeoffs must be made between the homogeneity of the  $B_1$ + shim solution over the sample, and the average amount of vector cancellation between elements. A uniform field that requires orders of magnitude more power for the same flip angle is nearly useless. This is demonstrated in Figure 1-6. Here, the same fast spin echo image was acquired on a phantom with two very different  $B_1$ + shim solutions, one near maximum average efficiency, and one near maximum achievable homogeneity (and low efficiency), as a result, the "homogeneous" solution requires nearly 11 dB more power for a matched excitation flip angle.

To help achieve solutions with a physically realizable transmit efficiencies, the sum of squares of the weights vector is constrained by a limit *L*. Constraints on peak scaling per channel can also be integrated via box bounds on the magnitude of the elements of *w*. We can then express the shimming procedure as a problem of the form:

 $\begin{array}{ll} \min & f_0(B_1^+(w,r)) \\ \text{subject to} & \|w\|^2 \leq L \end{array} \quad r \in \Omega_{ROI} \quad , \\ \end{array}$ 

where  $f_0$  is a metric to assess inhomogeneaity of the resultant  $B_1$ +. The choice of the metric is important and greatly affects the quality of shimming achievable (17), as well as the difficulty of solution.



Figure 1-6 Comparison of *B*<sub>1</sub>+ shim efficiency

Fast spin echo image of phantom with a 12 channel RF transmit array. Left: CP-mode, high efficiency B<sub>1</sub>+ shim. Right: Shimmed for maximum attainable uniformity. The uniform shim requires 11 dB more RF power, unsuitable for invivo applications.

Options for what would make a good objective  $f_0$  are easily theorized but tend to be difficult to implement from a practical perspective. For instance, high uniformity and efficiency are desired, so one might propose functions of the form  $f_0(x) = \text{mean}(x) / \text{stdev}(x)$ . At first pass this would seem like a reasonable choice – as a high mean  $B_1$ + provides efficiency while a low standard deviation implies some uniformity. In practice, such a metric is a very poor choice due to its highly nonlinear behaviour. In all works here, we choose a least squares fit to a predetermined smooth spatial distribution for  $B_1^+$ , details of which are given in Chapter 2. The spatial behaviour of the  $B_1$ + fields makes solving this problem interesting: the solution difficulty ranges from trivial (for a single point, there is a vector w that aligns all transmitters for total constructive interference at that point), to very complicated when trying to solve over large areas where many minima can exist. This solution difficulty results from the rather limited number of controls (w) for the large problem space, coupled with the overlapping spatial profiles of the transmit elements.

The degrees of freedom for shimming solutions can be increased any time we can subdivide the region of interest into more spatially localized areas. Fortunately, this occurs frequently in many MRI sequences: any 2D sequence inherently splits the data acquisition into slices of the otherwise 3D volume. By shaping the pattern for each slice individually, the shimming problem is simplified two-fold: by increasing the degrees of freedom, as mentioned before, and by reducing the spatial extent over which uniformity is required. This is precisely the approach taken in Chapter 2, which develops a framework for shimming on a per-slice basis for 2D acquisitions, and demonstrates its efficacy in terms of solution uniformity and efficiently. It should be noted that multiple spatially localized pulses are also used for other purposes: spatial saturation, fat saturation, and spin tagging for instance.

## B<sub>1</sub>+ Mapping

Before one can compute  $B_1$ + shim solutions, one must have knowledge of the  $B_1$ + fields generated by all coil elements in the transmit array. Measures of  $B_1$ + also allow for spatially localized flip angle calibrations. In the following, we review basics of  $B_1$ + mapping, and the method used for generating these maps over all coil elements in the transmit array.

 $B_1$ + Mapping sequences are a class of MRI protocols that relate the observed MRI signal to the underlying transmit field. One of the simplest approaches is the double angle method. Useful primary for pedagogical purposes, it generates a flip angle map from two separate fully-relaxed gradient echo acquisitions, M<sub>1</sub> and M<sub>2</sub>, at two prescribed flip angles  $\theta$  and  $2\theta$ . The local flip angle in any voxel can then simply be computed (18) as  $\alpha = \cos^{-1} \left(\frac{M_2}{2M_1}\right)$ . Knowledge of the flip angle distribution and transmitter calibration (pulse width and power) allows solving for  $B_1$ + from the relation  $\alpha = \gamma B_1 \tau$  (section 2.1). The double angle method is seldom used in practice because of the requirement for full relaxation of the magnetization in order to avoid bias from T<sub>1</sub> effects.

Research in  $B_1$ + measurement methods focus on either improving mapping accuracy or shortening the acquisition times (19–24). For practical mapping needed by multitransmit systems, finding methods that provide fast measurements with reasonable accuracy is key, as maps of the 3D distribution of  $B_1$ + are needed for each logical transmit channel, covering the entire volume of interest. For systems with high transmit channel counts (8, and 16 becoming more common), even relatively fast sequences at one minute per channel quickly become infeasible for use on every patient that is imaged.

To operate quickly, mapping schemes must overcome the  $T_1$  biasing effects to enable short repetition times. The acquisition of choice for mapping in this work is the Actual Flip angle Imaging (AFI) method(24). Like the double angle method, AFI uses an algebraic relationship between acquisitions to infer the local flip angle. AFI however is much faster, operating in a spoiled steady state. AFI uses two interleaved pulse-echo pairs measured with the same flip angle but different TRs. The signal ratio, r, between these two FIDs allows computation of an estimate of  $B_1$ + :

$$\alpha = \cos^{-1}\left(\frac{rn-1}{n-r}\right)$$

The sensitivity of the AFI mapping depends mainly on the tissue properties and the n parameter which relates the two TR values,  $TR_2 = n * TR_1$  (24,25). For reasonable TRs of 20ms and 100ms (n = 5), a 3D AFI sequence covering the brain would still require roughly a minute per channel for coarse resolution and full Cartesian sampling. While some have suggested moving to parallel imaging or faster sampling trajectories (EPI, stack of spirals, *etc.*), these bring their own challenges and are not employed in this work.

## Transmit Array B<sub>1</sub>+ Mapping

Mapping  $B_1$ + for transmit arrays poses additional difficulties that stem from requiring  $B_1$ + maps of each individual element in the array. While the entire array may allow imaging of the entire volume, each of these elements, usually small and localized, are not typically sensitive to the whole imaging volume. This means that when mapping these elements in isolation, a large range of  $B_1$ + is generated. When operating in a regime where areas close to the active element experience reasonable flip angles, distant regions will experience near zero flip angles. Signal to noise ratio in these regions will be very poor as a result, leading to errors in  $B_1$ + estimates far from the element in question. In a single coil scenario this is not of great concern, as a single surface coil would be positioned such that distant areas would typically not contain important anatomy. In a transmit array this is not the case, as regions with low sensitivity from one element may still be within the imaging volume, and sensitive to other elements, thus accurate knowledge of  $B_1$ + in these areas is important.

This large dynamic range in  $B_1$ + from each element (as seen in Figure 1-1) also affects the accuracy of the measurement in terms of residual T<sub>1</sub> bias -- regions experiencing vastly different flip angles will be biased differently, and not one-toone with flip angle. To address this dynamic range problem, coils are mapped not one at a time, but in linear combinations chosen for reasonable  $B_1$ + coverage(26). For a set of  $N_C$  coil elements in the array this encoding can be represented by a  $N_C * N_C$  matrix, E, where the measurements  $m_i$  in a given voxel are related to the underlying sensitivities  $B_1^+$  by:

$$m^T = EB_1^+$$

Then for each voxel, the original (individual) coil sensitivities can be recovered by simply inverting the encoding. Acquisition of one coil map at a time is equivalent to an identity encoding matrix. Using this approach, the modes that are mapped can be chosen to have reduced dynamic range or better coverage of the volume, thereby reducing systematic measurement errors.

Given that the relative phases and magnitude profiles of the transmit elements change with coil loading and between system reboots, a-priori determination of "best case" encoding is difficult. Instead, we choose the matrix of the discrete Fourier coefficients of size  $N_C * N_C$ , this has a condition number of 1, an easy analytic inverse, and produces significant variation in the spatial patterns generated by the superposition of transmit fields.

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## 2. Slice-by-slice B<sub>1</sub>+ Shimming

### Introduction

Human magnetic resonance imaging at high field strengths (>3 T) suffers from wellknown inhomogeneity artifacts due to wavelength interference effects of the radiofrequency (RF) fields in tissue. Depending on the field strength and anatomy being studied, these intensity variations can range from being relatively benign to being detrimental to the ability to perform diagnosis and quantification (1, 2).

Many methods exist for combating RF-transmit inhomogeneity that can be implemented on most imaging systems, including the use of adiabatic pulses(3), composite pulses(4), and 3D RF excitation(5, 6). Although requiring substantial additional hardware investment, multi-channel transmit coils are another demonstrated alternative for improving the homogeneity of the RF field, and can potentially be used with the previously mentioned methods. Promising developments have been made in the engineering of transmit coils with tailored  $B_{1^{+}}$ distributions, including shaping the transmit field (7); reducing coupling between coil elements (8, 9); providing better basis sets for modulating the RF field in all directions (10, 11); and creating load-insensitive coils (12). However, coil design alone is insufficient for producing highly uniform  $B_1^+$  distributions, and the independent modulation of the driving amplitudes and phases of the separate transmit elements (known as ' $B_1$ ' shimming') is required. Although  $B_1$ ' shimming can significantly improve homogeneity, at high field strengths the  $B_1^+$  fields that are produced prove to be a poor basis set for generating uniform images over the entire brain, leading to promising developments in multi-channel versions of composite (13) and multi-dimensional pulses (14, 15). In an effort to increase the number of degrees of freedom available for such field shaping, there has been a trend toward

larger numbers of transmit channels, mirroring the scaling of parallel receive architectures in the past decade.

This manuscript adopts a different approach; we exploit the extra degrees of freedom that are available when performing ubiquitous multi-slice MRI acquisitions, and we demonstrate that by shimming on a per-slice basis, gains can be achieved in  $B_1$ <sup>+</sup> performance. The utility of subdividing the volume into smaller regions of interest (ROIs), thereby producing simpler optimization problems, has been previously demonstrated in a simulation study by Mao et al. (16). They reduced the shim ROI from the whole head down to a single slice to yield shim solutions with a higher homogeneity. The primary aim of this manuscript is to experimentally evaluate the efficacy of this  $B_1$ <sup>+</sup> shimming technique and extend it to multi-slice acquisitions. The technique is then compared to conventional volumetric shimming methods, as they are the standard for the birdcage coils and fixed-phase multi-transmit arrays which are currently in common usage.

At high field, the  $B_1^+$  field pattern is dependent on the subject's geometry and position within the RF coil—this suggests a single shimming technique may not be suitable for all subjects. The secondary aim of this manuscript is therefore to evaluate the effect of implementing different shim targets in the slice-by-slice shimming technique.

### Methods

### Hardware

All imaging was performed on an Agilent 7T head-only MRI scanner (Agilent, Inc, Walnut Creek, CA) with an AC84 head gradient coil (Siemens, Erlangen, Germany). The Direct Drive console (Agilent Inc, Walnut Creek, CA) was configured for driving 16 transmit channels via individual waveform generators and 1-kW peak-power broadband amplifiers (2 x 7T1000M-8C, Communication Power Corporation, Hauppauge, New York), allowing real time control of RF amplitude and phase on a per-channel basis. System software was modified to support real-time modulation of  $B_1^+$  shims. Transmitted power was measured using a high dynamic range inhouse built power monitoring system that reported both forward and reflected individual-channel and combined-power levels.

A 15-channel transceive RF coil (described in Ref. (10)) was utilized in all experiments. The 15 channels are split into three rings in the longitudinal direction and mounted on a 27.9-cm-diameter cylindrical former. The superior and middle rings each contain six  $13.3 \times 8.9$  cm elements positioned symmetrically about the cylinder. Three additional channels covered the posterior half of the inferior ring. This arrangement yields a coil length of 13.7 cm and 19.9 cm at the anterior and posterior aspects, respectively. The coil was tuned and matched for an average head size and was not optimized on a per-subject basis.

All volunteers signed a written consent form for the study in accordance with the University of Western Ontario research ethics board. MATLAB (The Mathworks, Natnick, USA) and C were used for all data analysis and algorithm development.

# $B_1^+$ Mapping

 $B_1^+$  maps were acquired from five subjects of differing head size. The field of view (FOV) of each map was positioned identically with respect to the transmit coil and magnet isocenter. To have sufficient voxel counts to compute performance statistics, 3D maps were acquired with a 220 × 220 × 220 mm FOV and a matrix size of  $64 \times 64 \times 64$ .  $B_1^+$  mapping was performed with a multi-step hybrid mapping approach modified from Refs. (17, 18) as outlined below.

In the first step, low-resolution 3D FLASH volumes (TE/TR: 2.8/7.2 ms, BW: 531 Hz/px, nominal flip angle: 3°, slab thickness: 200 mm) were acquired for each transmit channel. Coils were not mapped one-at-a-time but in sets using a linear 'virtual array' combined driving mode consisting of the discreet Fourier transform matrix coefficients (equivalent to the 'Butler' matrix driving mode in (19)). At these low resolutions, flip angles of less than 3° were employed which helped to eliminate relaxation bias while still providing sufficient SNR for accurate measurement of RF phase. Assuming a small flip angle and negligible relaxation effects,  $B_1^+$  is linearly proportional to the received signal.

In the second step, the linear combinations of the measured  $B_1^+$  maps were separated into individual channels, and a  $B_1^+$  shim utilizing only the phase was calculated from the FLASH maps (see following section for description). Actual flip angle imaging (AFI) (20) with optimized RF and gradient spoiling (21) was then performed with all transmitters driven in the circularly polarized (CP)-volume mode (TE/TR/TR2: 2.8/20/100 ms, BW: 531 Hz/px, nominal flip angle: 70°, slab thickness: 200 mm). The relative  $B_1^+$  estimates from step one were then scaled by the measured flip-angle distribution, producing a set of calibrated  $B_1^+$  maps. To minimize effects of the RF pulse profile on the measurement, two different pulses were used for the two consecutive measurement steps, designed to have similar pass-band responses for their respective low and high flip-angle regimes.

At the acquired resolution,  $B_1^+$  maps of all 16 channels required approximately 15 minutes (7 minutes to acquire 3D FLASH maps and 8 minutes to acquire AFI maps); however, sufficient  $B_1^+$  maps can be obtained at lower resolution (6 × 6 × 6 mm voxels) in under 3 minutes.

### $B_1^+$ Shimming

The circularly polarized or geometric-phase driving mode was calculated from the  $B_1^+$  maps as the set of phases that led to constructive interference of all channels at the center of the coil volume (mid-brain). This is analogous to  $2\pi/n$  geometric phase splitting in an *n*-port cylindrically symmetric coil, mimicking the behaviour of the commonly used quadrature birdcage coil (22). We examined both the CP driving mode (CP-volume), as well as the scenario where the flip angle was adjusted on a per-slice basis to compensate for  $B_1^+$  falloff (CP-slice), as might be achievable with current generation clinical systems via scaling of the excitation flip angle by slice location. While it has been shown even at low field strengths that CP driving modes may not be ideal for the head (23), the CP mode provides a useful comparison to commonly found birdcage coils and fixed-phase multi-transmit arrays.

In addition to the CP mode, two shim optimizations were investigated: shimming to attain a power-efficient transmit field and shimming to produce a more uniform transmit field. To attain an 'efficient' field, the shim target, T, was set to the ideal non-interacting superposition of transmit maps (i.e., sum||  $B_1^+$ ||). To attain a more 'uniform' field, a 3D Gaussian was fit to the 'idealized' non-interacting sum of transmit maps, using a least squares regression, to minimize field fluctuations and impart prior knowledge of physically attainable, smooth, and typically lower SAR solutions (24). Fitting was performed with seven variables: an overall scaling factor, as well as the (x,y,z) center offset and (x,y,z) full-width half-maximum (FWHM) of the Gaussian profile. Shimming was performed by finding weights  $\alpha \in \mathbb{C}^n$  (where *n* is the number of transmit channels) that minimized a constrained-magnitude least-squares fit of the estimated  $B_1^+$  distribution to the target T, over the ROI, using the CP-volume mode as an initial parameter set:

$$\min \sum_{j \in ROI} \left\| \left| \sum_{c=1}^{n} \alpha_{c} B_{1,c,j}^{+} \right| - T_{j} \right\|^{2}.$$
(2-1)

Equation [2-1] was solved using the local variable exchange method discussed by Setsompop et al. (25). This method is used to reformulate Eq. [2-1] by introducing an auxiliary phase term,  $\phi$  (initially set to the CP-mode phase), and the complexvalued vector  $\Phi = \exp(i\phi)$ :

$$\min \sum_{j \in ROI} \left\| \sum_{c=1}^{n} \alpha_c B_{1c,j}^{+} - \Phi_j \mathbf{T}_j \right\|^2$$
(2-2)

and iteratively solving for  $\alpha$  then  $\phi$  until convergence is reached. The floating phase term is updated via  $\phi_j = \angle (\sum_{c=1}^n \alpha_c B_{1,c,j}^{+*})$ . This optimization process is performed on-line in several seconds.

### Comparison of Shim Solutions

In total, six shimming methods were compared: CP-volume, 'efficient' volume, 'uniform' volume, CP-slice, 'efficient' slice, and 'uniform' slice. Since 3D  $B_{1^+}$  maps were acquired over the entire brain volume,  $B_1^*$  shim solutions could be calculated over any arbitrary ROI. To compare different shim targets and to reduce coil geometry effects on the analysis, the  $B_{1^+}$  shims were calculated (i) over the entire  $220 \times 220 \times 220$  mm volume that was mapped and (ii) over three stacks of 44 slices. Each slice in the stack was 5-mm thick, thereby covering the same  $220 \times 220 \times 220$  mm volume (stacks were oriented in either the axial, sagittal, or coronal plane). After  $B_1^+$  shimming, transmit power levels were scaled such that the desired flip angle occurred at the 90<sup>th</sup> percentile of the predicted flip-angle distribution, an implementation practicality designed to avoid large regions of overflipping that could occur if the flip angle distributions were broad. To simplify the presentation of results, this 90<sup>th</sup> percentile was scaled to a nominal value of 1.0 in the  $B_1^+$  maps, which was then used to compare global worst-case SAR. Two metrics were employed to evaluate the quality of shim over each slice: (i) the standard deviation of the distribution of  $B_{1^+}$ , and (ii) the mean value of  $B_{1^+}$ . An ideal  $B_{1^+}$  field

distribution would have a standard deviation of zero and a mean value of one. To ensure a fair comparison, the results for the volume shims were calculated on a slice-by-slice basis (as comparing a single slice to an entire volume would bias measures of standard deviation).

#### Imaging

To visually demonstrate  $B_1^+$  shimming performance over the whole brain, a 2D fastspin-echo (FSE) image series was acquired in the sagittal orientation (FOV: 192 × 192 mm, matrix size: 256 × 256, number of slices: 8, slice thickness: 4 mm, slice gap: 20 mm, TR: 5 s, echo spacing: 10 ms, echoes per train: 16, center echo: 8, bandwidth: 390 Hz/px, TE (equivalent): 60 ms). FSE acquisitions were individually optimized over the identical slice prescriptions with the different algorithms. FSE images were chosen, instead of low flip-angle FLASH images, to cause  $B_1^+$ inhomogeneity effects to be more visually apparent.

### SAR Reporting

Only global worst-case SAR is considered in this manuscript, and is reported as the sum of squares of all transmitter weights summed over all slices in each volume. This is a conservative approach that assumes all forward power contributes to SAR; therefore, all relative SAR figures represent a worst-case upper bound.

		СР	Efficient	Uniform
Relative SAR				
Volume Shim		$1.00 \pm 0.03$	$1.04 \pm 0.03$	$1.40 \pm 0.04$
Slice Shim	(average <sup>a</sup> )	$1.21 \pm 0.04$	0.938 ± 0.01	$2.35 \pm 0.07$
	Axial	$1.57 \pm 0.07$	$1.18 \pm 0.02$	$2.20 \pm 0.04$
	Coronal	$1.04 \pm 0.03$	$0.801 \pm 0.005$	$2.42 \pm 0.14$
	Sagittal	$1.02 \pm 0.03$	$0.829 \pm 0.004$	$2.44 \pm 0.04$
Standard Deviation				
Volume Shim		0.175 ± 0.006	0.167 ± 0.006	$0.150 \pm 0.012$
Slice Shim	(average <sup>a</sup> )	0.185 ± 0.006	$0.147 \pm 0.011$	$0.129 \pm 0.012$
	Axial	0.155 ± 0.002	0.136 ± 0.003	$0.124 \pm 0.005$
	Coronal	$0.202 \pm 0.002$	$0.154 \pm 0.004$	$0.134 \pm 0.004$
	Sagittal	0.198 ± 0.002	0.150 ± 0.004	0.131 ± 0.003
Mean				
Volume Shim		0.720 ± 0.009	$0.731 \pm 0.012$	$0.770 \pm 0.014$
Slice Shim	(average <sup>a</sup> )	$0.762 \pm 0.007$	$0.812 \pm 0.014$	0.834 ± 0.016
	Axial	0.800 ± 0.003	$0.825 \pm 0.004$	$0.842 \pm 0.006$
	Coronal	$0.740 \pm 0.002$	0.802 ± 0.005	0.829 ± 0.005
	Sagittal	0.745 ± 0.002	0.808 ± 0.005	0.833 ± 0.004

 Table 2-1: Shim performance over the entire head.

<sup>a</sup> The average is calculated over the axial, coronal, and sagittal slice stacks.

## Results

Figure 2-1 displays SAR, standard deviation of  $B_1^+$ , and mean  $B_1^+$  by shim method when averaged over the entire brain (and all slice orientations and subjects) and normalized to the CP-volume mode. Although the relative difference in performance between each shimming method and the CP-volume mode may be coil dependent, Figure 2-1 provides the normalized values to better demonstrated overall trends. The corresponding absolute differences in slice-by-slice behaviours for each orientation are illustrated in Figure 2-2, with the numerical shim performance results presented in Table 2-1. The CP-volume mode had an inferior performance compared to the other shimming methods, with a standard deviation in  $B_1^+$  of nearly 18%, and a mean  $B_1^+$  of 0.72 ± 0.009 (an ideal  $B_1^+$  field would have a standard deviation of 0% and a mean of 1).

Volume shimming methods showed weak improvements overall, with the 'uniform' shims performing best with a  $B_1^+$  standard deviation of  $15 \pm 1.2\%$  and mean of  $0.770 \pm 0.014$ , at the cost of a 40.0  $\pm 5.2\%$  increase in relative SAR compared to the baseline CP-volume mode. The CP-slice method did not significantly affect the standard deviation of  $B_1^+$  compared to the CP-volume case (since the spatial distribution of  $B_1^+$  within any slice remains unchanged), yet was able to partially compensate for coil sensitivity falloff by scaling the transmit amplitudes from slice-to-slice. This behaviour is visible in Figure 2-2 (red trace) where the relative SAR changes with slice location. The resultant mean  $B_1^+$  over the slice stacks has a reduced variation compared to the CP-volume mode, as expected for slice-by-slice optimization. It is important to note that the mean  $B_1^+$  value is not uniform over the slices. This is a consequence of the scaling of transmit power (i.e., the 90<sup>th</sup> percentile of the  $B_1^+$  distribution is scaled to the desired flip angle, as explained in the Methods section) and the differing  $B_1^+$  distribution within each slice.



**Figure 2-1: Shim performance metrics** 

Global SAR, standard deviation of B<sub>1</sub><sup>+</sup>, and mean B<sub>1</sub><sup>+</sup>, averaged over the entire brain (and in all stack orientations), for the six shimming methods: 1) CP-volume, 2) CPslice, 3) 'efficient' volume, 4) 'efficient' slice, 5) 'uniform' volume, and 6) 'uniform' slice. All values have been normalized to the CP-volume mode. Error bars represent the standard error over subjects. Slice-by-slice shimming methods showed marked improvements over their volumetric counterparts. Averaged over the entire brain (and all three slice orientations), the 'efficient' shim resulted in a standard deviation of  $B_{1^+}$  of 14.7  $\pm$  1.1%, a mean  $B_{1^+}$  of 0.812  $\pm$  0.014, and relative global SAR reduction of 6.2  $\pm$  3.1%. The 'uniform' shim also resulted in significant differences: the standard deviation of  $B_{1^+}$  was further reduced to 12.9  $\pm$  1.2%, while the mean  $B_{1^+}$  improved to 0.834  $\pm$  0.016, at the expense of a 135  $\pm$  8% increase in relative SAR. These shimming methods proved robust (i.e., converged to acceptably smooth solutions with no field nulls) when imaging subjects with varying head sizes and when utilizing different RF coils (different RF-coil data not shown).

The coil amplitudes and phases for optimized shim solutions varied markedly with slice location across the head. The phase of an individual channel was observed to change over the entire range of  $0-360^{\circ}$  and mean amplitude by up to a factor of three (as realized in the case of the slice-by-slice 'uniform' shim—see also the traces in Figure 2-2). Two  $B_1^+$  distributions are displayed in Figure 2-3 that illustrate the large difference in optimized 'efficient' driving modes in coronal slices anterior and posterior in the head.

Figure 2-4 shows a sagittal stack of slices shimmed with all six methods. Of particular interest is the orthogonal re-slicing that demonstrates the increased homogeneity over the whole volume when  $B_1$ <sup>+</sup> shimming on a slice-by-slice basis (Figure 2-4.ii, rows e and f). The negligible difference between the 'efficient' and 'uniform' volume shimming methods in comparison to the CP-volume mode reflects the limited degrees of freedom available to influence the  $B_1$ <sup>+</sup> over the large head volume, even with 15 transmitters, due to the slowly varying nature of the  $B_1$ <sup>+</sup> fields providing a poor basis set.



Figure 2-2: Shim performance by slice location

Slice-by-slice global SAR (relative to CP-volume mode), standard deviation of  $B_1^+$ , and mean  $B_1^+$  in the axial, coronal, and sagittal orientations. Approximate slice locations are indicated in scout images (bottom row). Legend: *black:* CP-volume, *red:* CP-slice, *green:* 'efficient' volume, *teal:* 'uniform' volume, *blue:* 'efficient' slice, *purple:* 'uniform' slice.



Figure 2-3: Sample shimmed *B*<sub>1</sub><sup>+</sup> distributions

Representative  $B_1^*$  distributions for coronal slices (**a**) midway anterior and (**b**) midway posterior in the brain, when shimming with the 'efficient' slice-by-slice method. These  $B_1^*$  maps illustrate the large difference in shim solutions required for efficient excitation at different slice locations across the head. Green lines in the axial plane (right column) denote the slice locations over which shimming was performed.



Figure 2-4: Shim solutions for a sagittal stack of slices

Representative shim solutions for a sagittal stack of slices. (i) Sagittal views of resultant B<sub>1</sub><sup>+</sup> in each slice, and (ii) coronal re-slicing through slice centers to demonstrate through-plane behavior. Rows represent the six shimming methods:
(a) CP-volume, (b) CP-slice, (c) 'efficient' volume, (d) 'efficient' slice, (e) 'uniform' volume, (f) 'uniform' slice.

#### Imaging Results

Figure 2-5 presents representative slices from two FSE image series, acquired with the CP-volume (5.a) and 'efficient'-slice (5.b) shim solutions. The intensity variations correspond well with the spatial patterns in the predicted  $B_1$ <sup>+</sup> maps (Figure 2-4, rows a and d), even though the images were acquired from a different subject than the map data. Measured forward transmit power (10-s average), was approximately 1.1 W/kg and 0.94 W/kg for the CP-volume and 'efficient'-slice scans, corresponding to a 17% reduction in transmitted power. This reduction was within the predicted range of 21 ± 4% for the sagittal stack (Table 1).

## Discussion

At higher field strengths, shorter wavelengths result in different driving modes behaving more efficiently than the CP mode (1). In this study, the fact that simple scaling of the flip angle (CP-slice) yields significantly higher global SAR (21 ± 6%) for a minor improvement in the standard deviation of  $B_{1^+}$  (6 ± 5%) suggests that the CP-mode of this coil is non-optimal across the head. It has been shown that fixedphase volume transmission is not capable of producing a homogeneous transmit field over the whole brain even when using a close fitting elliptical coil (26), thus necessitating more sophisticated shimming methods or different coil geometries.

To address this problem, we assessed the  $B_1^+$  behaviour when shimming slice-byslice versus over a volume, while examining two of the infinitely many shim targets on the efficiency/uniformity tradeoff curve. The 'efficient' slice-by-slice shimming method provides improvements in the uniformity and standard deviation of  $B_1^+$  (as detailed in the Results section and in Figure 2-1), with a minor reduction in relative SAR. However, when examining the behaviour of this shimming method over individual slice stacks (Figure 2-2, blue trace and Table 2-1), it is observed that the relative SAR is significantly reduced in both the coronal and sagittal stacks (by 19.9  $\pm$  8.3% and 17.1  $\pm$  2.4%, respectively). The large increase in power scaling in the axial case (18.5  $\pm$  8.3%) is required to compensate for the sensitivity falloff of this relatively short RF coil, and masks this improvement when the stacks are averaged.

The 'uniform' slice-by-slice shimming method yields higher gains in uniformity (see Results) at the expense of a nearly 2.5-fold increase in required power. While the shim performance is similar across subjects, the power scaling behaviour is more variable (Figure 2-2, purple trace). This is most likely due to differences in coil loading between subjects that in turn affect phase and amplitude scaling. This behaviour is not as prominent with the 'efficient' shimming method, as these differences are inherently incorporated into the measured coil efficiencies of the shim target (sum||  $B_1^+$ ||).

### Through-slice Intensity and Phase

One caveat of modulating the RF transmission slice-to-slice is the consequent variation in through-slice intensity patterns when compared to a smoothly varying volume shim. While this can be corrected given the estimates of the  $B_1^+$  distribution (or with black box or model-based post-processing correction methods (27, 28)), the visible effects on image-to-image magnitude are small (see Figure 2-5, where the more conspicuous feature is the more homogeneous slice-to-slice intensity in (b)). A more problematic artifact is apparent when tracking through-slice phase. The non-smooth nature of phase variation through the volume could potentially confound unwrapping methods; however, this phase modulation can be corrected on a voxel-by-voxel basis by using the predicted shim maps.



Figure 2-5: Sample shimmed FSE data

Slices from a sagittal FSE acquisition with (**a**) CP-volume and (**b**) 'efficient' slice shim. Shimmed slices demonstrate more uniform images with improved excitation of the cerebellar regions and lower variation in slice-to-slice intensity.  $B_1$ <sup>+</sup> falloff from limited RF coil coverage occurs toward the superior aspect of the brain and inferior to the cerebellum. This is partially compensated by slice-by-slice shimming.

# Applications

Depending on the application of interest, slice-by-slice  $B_{1^+}$  shimming can be implemented to increase the uniformity and/or the power efficiency over the brain. In multi-slice acquisitions where differential measurements are recorded (such as BOLD fMRI or diffusion tensor imaging), high  $B_1^+$  uniformity is potentially of reduced importance, as transmit power is one of the key limitations to highresolution whole-brain coverage. Slice-by-slice shimming can be optimized for transmit efficiency to provide single-pulse excitations without additional gradient activity. Other high duty-cycle, steady-state acquisitions, such as SSFP and FSE, are candidates for slice-by-slice  $B_1^+$  shimming, since achieving phase coherence in refocusing trains via 3D RF pulses is difficult and lengthens the repetition time. As was demonstrated in Figure 2-5, slice-by-slice shimming is ideal for FSE imaging, which requires lower transmit power and improved homogeneity compared to the CP-volume mode. Slice-by-slice modulation of the  $B_1^{+}$  shims can also be integrated with other intelligent modulation schemes that have been suggested: such as alternating  $B_1^{+}$  shims on each excitation in a multi-shot acquisition to provide a reduction in SAR (as in (29)) and/or improved uniformity (30), or choosing shims tailored for specific RF pulses (31). It is expected that adiabatic, composite or 3D pulses used in conjunction with the smaller  $B_1^+$  distribution that results from sliceby-slice  $B_1^+$  shimming would have more relaxed design criteria an therefore lower SAR. This is an area for future investigation.

## Conclusions

We have demonstrated that by utilizing the additional degrees of freedom available in a multi-slice acquisition,  $B_1^+$  shim solutions over individual slices may be computed and applied in real-time acquisitions. Due to the nature of the RF interference patterns, shimming over smaller ROIs is a simpler optimization problem, a fact that is taken advantage of by shimming on each slice in a multi-slice acquisition. We hypothesize that the gains demonstrated in efficiency are a direct result of the CP mode being less than ideal for head geometries at high field, and hence more efficient  $B_{1^+}$  distributions can be created by modulating the shims based upon spatial location. The ubiquitous nature of multi-slice acquisitions makes this an attractive option when multi-transmit architectures are available. The benefit of slice-by-slice shimming manifests as improved RF performance on both ends of the transmit efficiency/uniformity spectrum when compared to fully volumetric shims.

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# HighCor: a novel data-driven regressor identification method for BOLD fMRI

# Introduction

Suppression of physiological and confound signals in BOLD fMRI is an important processing step, particularly at higher magnetic fields. It is possible to extract patterns of these signals for subsequent filtering directly from the datasets. Methods that do so are referred to as *data-driven* or intrinsic methods. These approaches typically rely on either pre-defined source regions (e.g. white matter or ventricles) or statistical measures to identify areas that are expected to contain confounding signals (sets of voxels, sometimes referred to as 'noise ROIs'). This paper introduces an alternative criterion for the selection of these reference voxels that has a strong *physical* basis as described below.

## Background: Physiological Noise

The potential of BOLD fMRI at higher magnetic fields is well known. The dual scaling of both image signal to noise (SNR) as well as BOLD contrast allows for potential improvements in activation detection levels, resolution, or scan time reductions (1). In practice, these theoretical benefits are tempered by the increased contribution of physiological noise which also scales with the MRI signal (2). This contamination results in the deviation of the linear relationship between image SNR and temporal SNR (3), meaning that improvements to base image SNR may not directly translate to temporal SNR.

Following the derivation by Kruger and Glover (2) and Triantafyllou *et al* (3), in any given voxel the total noise  $\sigma$ , can be modelled as being composed of independent thermal and physiological components:

$$\sigma = \sqrt{\sigma_o^2 + \sigma_p^2}.$$

This model is an approximation, limited by the fact that physiological noise is nonwhite (it contains strong frequency dependence) and non-stationary (the signals can change in time). Nevertheless, it is useful for illustrating behaviour as image noise scaling changes. The term 'physiological noise' is somewhat misleading, and it is important to remember that, by and large, these are real signals that are present in the data, as opposed to random fluctuations driven by a noise process, as is the case for thermal noise.

An estimate of the SNR of the time-course is given by the ratio of mean signal intensity,  $\overline{S}$ , to the noise level:

$$tSNR = \frac{\bar{S}}{\sqrt{\sigma_o^2 + \sigma_p^2}}.$$

Then the ratio of physiological to thermal noise directly relates the image SNR  $(SNR_o = \bar{S}/\sigma_o)$  to the temporal SNR (tSNR):

$$\frac{\sigma_p}{\sigma_o} = \sqrt{\left(\frac{\mathrm{SNR}_{\mathrm{o}}}{\mathrm{tSNR}}\right)^2 - 1} \,.$$

This relation leads to the troubling observation that even with high image SNR, the effective temporal SNR (and therefore the reliability of detecting BOLD-related signal changes) can be severely limited. In addition to merely reducing the effective temporal SNR, physiological noise is particularly problematic because it also introduces spatial and temporal correlations which influence resting state measures and GLM statistics (4,5).

Recent works by Vogh *et al* (6) and Hutton *et al* (7) confirm the notion that physiological noise reduction can vastly improve the performance of task-based BOLD fMRI in many cases. Although traditionally applied in resting state analyses and/or in studies focusing on particularly corrupted regions, such techniques become significantly more important for everyday use at 3 T and above where the physiological-to-thermal noise ratios are large at typical imaging resolutions (3). Physiological signal suppression can be achieved with several methods. Frequency based filtering can be effective in certain cases (8,9), but is difficult to implement in practice due to the typically slow sequence repetition times (TR) with respect to respiration and heart rates. Because of the significant temporal aliasing of these noise sources there is the potential for overlap with the BOLD signals of interest. External recordings of a subject's physiological parameters can be used to model the signal changes in a BOLD time-course and generate regressors with appropriately aliased frequency components. One example of this approach is the widely used RETROICOR (10).

As an alternative to external recording, data driven techniques attempt to derive regressors for physiological noise reduction from the dataset itself. Compared to external recording approaches, data driven techniques have the theoretical benefits of a) directly identifying aliased confound signals in a model-free manner, b) the convenience of not requiring extra monitoring equipment, and c) being applicable as a post-processing step. In the next section we review some data-driven component methods for filtering fMRI data.

#### PCA and ICA

Data reduction methods such as principal component analysis (PCA) and independent component analysis (ICA) are popular in the fMRI literature thanks to the fact that they are generally well understood, robust, and widely available as software tools. These methods have seen many uses in fMRI, from identifying activation in task-based and resting state fMRI (11) to de-noising applications (12), artifact identification (13–15), and physiological signal suppression (16). The robustness of these methods and quality of the component estimates rely heavily on the ability to segregate desired signal from background noise. There are two general approaches to this issue. One option is to take all voxels, perform the dimensionality reduction of choice, then attempt classification of the resultant components (12,14,17,18). This can be difficult thanks to the huge dataset sizes and inherently noisy signals. An alternative approach (and the one used in this paper), is to pare down the set of voxels used to generate the components thereby limiting analysis to only those regions containing (ideally) high fidelity measurements of the contaminating signals. Common examples are the masking of white matter and ventricles, or examining edge voxels for motion parameters.

Recently, it was demonstrated that voxels selected based upon a criteria of having unusually high temporal standard deviations (tSTD) can contain significant information about physiological confounding signals including respiration and cardiac-related fluctuations (16). They proposed a method for generating components based on these high tSTD voxels, *compcor* (*cc*), a promising data-driven alternative to external recording methods like the popular RETROICOR(10). The algorithm is simple: rank voxels by tSTD, group the voxels with the largest tSTD(typically the top 1-2%), and perform PCA to generate a small number of robust temporal signals for subsequent regression. Using datasets with high temporal sampling, the authors demonstrated that the frequency spectra of regressors generated from *compcor* included components that matched externallymonitored RETROICOR regressors very closely, with filtering performance that was on par or better in a sample of both BOLD and ASL fMRI runs.

Despite the promising filtering results and the convenience afforded by *compcor*, its adoption to general use has been slow. This may be because it is not immediately obvious that voxel selection on temporal standard deviation alone is sufficient to

capture many physiological signals of interest. Physiological noise is known to be non-white, so temporal standard deviation may not be a good classifier in all cases.

We propose a novel noise set selection criteria, *highcor*, which captures noise from voxels with very high correlation between their magnitude and phase time-courses. As described in the following section, many of the mechanisms that generate unwanted signal changes in BOLD magnitude data can be expected to also distort the local phase angle. Compared to thresholding voxels by tSTD, one might expect different voxels to be selected by this criteria, containing a different estimate of confound signals.

In this paper we introduce and investigate the utility of *highcor* for selection of noise reference voxels and benchmark against *compcor*, a method we see as being a particularly attractive for its performance characteristics, convenience, and its previous validation against RETROICOR.

## Methods

#### Phase changes and physiological noise

In static tissue, the measured magnitude and phase of a voxels bulk magnetization vector should be constant in time and measurements of these quantities temporally uncorrelated. Some factors that produce temporal phase changes (like motion) also give rise to signals in the magnitude time-course, which are precisely the confounds we seek to remove. At high field, signal changes associated with physiological noise have been shown to be more dominant in the phase spectra (19), and show a much stronger TE dependence and spatial specificity than in the magnitude time-course (20).

Coherent temporal phase changes in a BOLD fMRI voxel time-course occur for a limited number of reasons, which can be broken down into either large-scale or voxel-localized effects. Subject motion, cardiac and respiration-induced B<sub>0</sub> shift, as

well as drift from gradient heating are easily understood phenomenon that produce coherent phase changes over quite large distances (20): a shift in the main field leads to a different phase offset by the echo time.

While these types of phase changes are prominent, they do not directly induce significant BOLD-like  $T_2^*$  de-phasing in the magnitude because they are spatially coherent on a voxel length scale. Magnitude signal changes from this type of motion can occur if the voxel contents change and/or spin history effects arise. So while there is no direct relationship between the phase change at a voxel level and signal change in the magnitude time-course, there is a potential to measure correlated signal changes related to these 'large-scale' artifacts.

Temporal phase changes can also appear on a more spatially localized scale, driven by several processes that modulate the intra-voxel magnetic susceptibility. Changes in local tissue geometry produce coherent phase differences that originate mainly from cardio-respiratory pulsitility and flow effects (19). Stronger phase changes occur in voxels near large susceptibility gradients, such as air/bone/csf/tissue interfaces (21). Susceptibility changes can drive inter-voxel signal de-phasing leading to reduced  $T_2^*$  and are thus detectable in the magnitude signal. Such signals are also often seen in voxels around the rim of the brain or ventricles and arise from small head movements.

Changes in blood oxygenation levels produce well known susceptibility modulations, driven by changes in tissue metabolism, cerebral blood volume, and blood flow. Susceptibility differences between intra- and extra-vascular compartments modulate the effective  $T_2^*$  via the local de-phasing, and can also lead to coherent phase changes in some circumstances. Whether a coherent phase change occurs depends on the vascular structure within each voxel (22). In the case of the cortical vasculature the quasi-random organization of capillaries within capillary beds of the cortex generate mostly spatially incoherent phase changes,



Figure 3-1 Magnitude-phase correlation vs temporal standard deviation.

Scatter plot of absolute value of magnitude-phase correlation (x) vs temporal standard deviation (y) for all voxels in the fast TR dataset. Voxels selected by cc, hc, are indicated and represent the top 2% by each metric. The intersection of these amount to 12% of the selected voxels (0.17% of all voxels). Accompanying histograms describe the distributions along each axis. For visibility, histogram counts for cc and hc have been scaled by a factor of 50.

whereas regions with larger, more structured venuoles and veins generate coherent changes in the local magnetic field, resulting in measurable phase signals (22–24).

To summarize, temporally correlated magnitude and phase signals in GE-EPI BOLD fMRI in a given voxel arise from either scanner instabilities, motion, cardiorespiratory effects (bulk motion and localized pulsitility), or blood flow changes (BOLD effect in voxels with sizeable veins). For this reason, we hypothesize that confound signal can be isolated for subsequent filtering by focusing on voxels exhibiting high correlation between their magnitude and phase components.

Our algorithm can be stated simply:

- 1. For task based studies, ignore any voxel where the magnitude time-course is correlated with any column of the experimental design matrix (with a correlation threshold of |r| > 0.2 used in all examples herein)
- 2. For all remaining voxels: correlate the magnitude and phase time-course from each voxel (at zero time lag)
- 3. Generate a set of noise voxels by selecting the top x% (see below) by absolute value of the magnitude and phase correlation
- 4. Perform PCA on this set to generate noise regressors

The choice of how many voxels to retain for the noise voxel set requires a balance between selecting enough to sufficiently capture signal behaviour and limiting contamination from background measurement noise present in each time series. Inclusion of too many noisy voxels will lead to a much denser principle component spectrum, and can reduce the efficacy of the technique because PCA in general is not robust to outliers. Following the work of Behdazi (16), two percent of all voxels (after brain extraction) were selected, a threshold that was just over 2.5 standard deviations larger than the mean on a test dataset (matching the group study data used, specified below).

Similarly, the number of principal components to retain as regressors is an important factor; enough should be kept in order to represent all major confounding

signals. Conversely, retaining too many can be detrimental since components corresponding to smaller singular values can contain less information (and sometimes significant noise) which can lead to over-fitting and noise amplification, in addition to reducing total degrees of freedom for subsequent analysis. Principal components that explained up to 80% variance were retained.

It is important to note that we utilize the simple definition of linear (Pearson) correlation:

$$r_{xy} = \frac{\sum_{i} (x_{i} - \bar{x})(y_{i} - \bar{y})}{\sqrt{\sum_{i} (x_{i} - \bar{x})^{2} + \sum_{i} (y_{i} - \bar{y})^{2}}}$$

While perfectly linear relationships between magnitude and phase signal responses are unlikely. The robust performance observed can be attributed to the fact that we are only interested in those voxels at the very high end of the correlation scale.

#### MRI Hardware

All scanning was performed on a 7T head-only Direct Drive MRI scanner (Agilent) equipped with an AC84 head gradient and amplifier (Siemens). An in-house built coil system was used for signal transmission and reception consisting of a 23 channel conformal receive array nested in a 15 channel transmit-only elliptical coil, with each coil paddle individually driven by a 1 kW power amplifier (Communication Power Corp). B1+ mapping and shimming was performed to improve image homogeneity over the brain volume, using protocols as described in (25).

#### BOLD fMRI Data

Several sample data sets from healthy volunteers were acquired and analyzed. All volunteers provided informed consent for the study, in accordance with the research ethics board guidelines at the University of Western Ontario.
### Dataset 1

A very fast TR dataset (TR 0.15 s) was acquired on a single subject. The fast TR was chosen to be well above the Nyquist limit for sampling cardiac and respiratory related fluctuations (baseline and harmonics). Accurately measuring these signals without aliasing enabled study of the ability of the data-driven regressors to identify these confounds, and examine performance as the signals start to alias via artificial signal decimation experiments. To achieve this sampling rate, the slice count was limited to 3 axial slices spanning the brain with a 5 cm slice gap. Other EPI parameters were: 2.5 mm isotropic resolution, matrix: 96x96, ramp sampling, 300 kHz bandwidth, parallel imaging acceleration factor 3, TE: 20 ms, and a 20 degree flip angle – approximately the Ernst angle for grey matter at 7 T. GRAPPA was employed for all parallel imaging data reconstruction (26), with a default kernel size of 4 x 4. For EPI data, a fully sampled k-space reference was generated via a standard multi-shot pre-scan in order to estimate GRAPPA kernel weights.

Such fast TR sampling can lead to dynamic image intensity effects as steady-state is approached from the long  $T_1$  at 7 T. In spoiled gradient echo, these intensity changes would be only found in the magnitude, and as such could potentially bias measurements of both temporal standard deviations, and of correlation with the phase time courses. To mitigate these effects, 30 seconds of dummy volumes were acquired (and discarded). Inflowing spins from important physiological sources (CSF and arteries) will also have different magnitude signal behaviour at these fast TRs compared to more typical TR values.

#### Dataset 2

In order to investigate the applicability of this technique to more typical fMRI acquisitions, task based whole-brain BOLD GE-EPI data were acquired on six volunteers. The EPI acquisition had the following parameters: 2.5 mm isotropic, 240x200 mm field of view (96x80 matrix size), ramp sampling, 300 kHz bandwidth, parallel imaging acceleration factor of 3, TR: 2 s, TE: 22 ms, 48 slices, a 60 degree flip angle, and fat saturation. In order to generate robust activation, an anti-saccade task was chosen as the functional paradigm (27). Briefly: the paradigm was implemented in 18 s blocks of random left-right anti-saccades each of 3s duration, followed by 18 s of rest fixating on a centre target. The 36s task-rest block was repeated 5 times per run. A total of six functional runs were acquired per volunteer. A T<sub>1</sub>-weighted anatomical MPRAGE was also acquired for each subject, with the following parameters: TR 8 ms, TE 3 ms, TI 1.35 s, BW 50 kHz, matrix size 220x220x150, 1 mm isotropic resolution, with a parallel imaging reduction factor of 2 in phase x 2 in slice, and a fully sampled region of 64x44 reference lines about the centre of kspace, for an effective acceleration of 2.4. For improved visualization of small scale effects, an additional fMRI run was acquired on one subject at a higher resolution: 1x1 mm in-plane x 2 mm slice thickness, 220x192 mm field of view (220x192 matrix size), ramp sampling, 625 kHz bandwidth, acceleration factor 4, TR: 3 s, TE: 27 ms, 50 slices, and a 70 degree flip angle.

#### Software

Data processing and analysis was carried out in python and MATLAB (The Mathworks, Natnick NJ). The nipype package (28) was used for constructing and automating processing pipelines, which leveraged python and MATLAB code for the regressor generation and the FSL suite (29) for all other processing tasks. Freesurfer tools (30) were employed for brain segmentation.

## **Processing Pipeline**

The EPI data were reconstructed into complex-valued image series for each receiver coil, and combined into a single complex-valued volume. After combination, the complex time-course was split into its constituent magnitude and phase components for post-processing, since there are a lack of available software tools for typical fMRI processing of complex valued image series. Additionally, most such image processing tools (motion correction, brain extraction, etc) for fMRI are designed with assumptions about the image values and contrast present in magnitude EPI data. The magnitude processing proceeded as 'normal' through FSL tools (29) for de-trending via high pass filtering, motion correction, and brain extraction. In the phase data, large phase jumps were first removed by temporally unwrapping the phase of each voxel, followed by linear de-trending, then conversion to delta-phase time-courses (by subtracting the phase of the first volume). High pass filtering matching the magnitude data was then preformed to remove residual very-low-frequency trends. Motion correction as calculated from the magnitude data was then applied to the phase time-course.

Regressors were generated via *compcor* or *highcor* algorithms in python. The identified regressors were removed (with fsl\_regfilt). Preliminary data suggested application of *compcor* regressors on data already filtered with *highcor* could lead to additional gains in noise reduction. As such, this combination of regressors was included to investigate if residual physiological noise in the dataset was identifiable.

# **Frequency Analysis**

Examination of the frequency content of the selected noise voxels, regressors, and even the entire datasets pre- and post-filtering can yield insight into the physiological signals present. All frequency spectra were generated via a multi-taper method using the time series tools in the nipy toolkit.

### Aliasing and Decimation

Because of concerns with aliasing potentially affecting measurements of tSTD and magnitude-phase correlation, a decimation study was first performed to investigate the behaviour of these data driven techniques as TR lengthens. In order to better utilize all sampled data points, rather than simply low pass filtering, regressors were generated with *compcor* and *highcor* from under-sampled versions of the fast

TR data, as follows. Fast TR time series data were decimated by integer factors *n* from 2 ... 20, by taking every *n*th point. At each under-sampling factor, the decimation was repeated by shifting the starting time point until all data were used (for example, at a factor of 2, we first take points (0,2,4, ...) then (1,3,5, ...), yielding 2 different time series). Regressors generated from these undersampled datasets can then be compared across the decimation repetitions, and between decimation rates. To do so, regressors were generated with *cc* and *hc* and power spectra were calculated for all repetitions of regressors at every decimation rate.

To serve as reference for the aliased confound signals, the *compcor* and *highcor* regressors generated from the fully sampled dataset were also down sampled to matched sampling rates. The difference in regressor frequency content between the directly down sampled reference regressors and those generated from the decimated datasets was then computed. The voxel locations identified as part of the noise set were also recorded for each under-sampling factor.

#### **Performance Metrics**

Regressor performance was assessed by measuring temporal standard deviation of GLM residuals for all 36 functional runs in dataset 2. Total tSTD of all voxels within each subject's brain mask was measured and compared to the unfiltered datasets. tSTD changes were also measured by tissue type (cortex, white matter, and ventricles), using Freesurfer segmentations of the anatomical MPRAGE images, transformed into the EPI image space. For this step, any voxels demonstrating partial voluming between tissue classes were discarded. Temporal SNR behaviour (tSNR) was also measured in matching ROIs, and was calculated by dividing the mean image intensity by the temporal standard deviation for each voxel.

While changes in activation following filtering is not a good metric for comparing methods, it provides a check that task signals are not being removed as a side-effect of processing. Since large amounts of signal variance can be removed, picking improper signals for filtering, having noisy regressors, or over fitting due to too large of a regressor count can all serve to confound detection of task signal. To ensure some spatial smoothness for clustering, all GLM analyses used Gaussian isotropic blurring (2 mm FWHM) and also included motion estimates as confound variables, correction for temporal autocorrelations, and employed clustering with a cluster z-threshold of 2.0. Processing for the high resolution dataset was identical save for blurring, where only a small 1 mm FWHM kernel was employed.

Subject-specific functional ROIs were generated prior to analysis (using the unfiltered datasets) by performing a group average GLM for each subject that combined together all functional runs, in order to identify areas expressing reliable response to task. A much larger Gaussian blurring kernel of 5 mm FWHM was employed for this analysis. Blurring with a large kernel was employed for the dual purpose of suppressing effects of background (thermal) noise, and for growing and smoothing the region somewhat to create a small neighborhood around the clusters. Since a major motivation for removal of physiological noise is the potential for improved detection of task activation, changes in z-statistics post-filtering were measured by recording mean z-scores and counts of voxels passing threshold (z > 3.0) restricted to the pre-defined functional regions of interest. Differences between the measured metrics by filtering treatment were assessed with two-tailed paired difference t-tests with a nominal significance threshold of  $\alpha = 0.05$ , conservatively corrected for multiple comparisons via Bonferroni correction. The tSTD and activation metrics were converted to percent change versus the unfiltered data for visual display, and tSNR is reported compared to the baseline (unfiltered) levels.

# Results

### Fast TR Data

It was hypothesized that the physical mechanisms that lead to temporally correlated magnitude and phase would result in the identification of different voxels than those selected using tSTD. Figure 3-1 displays a scatter plot of tSTD vs magnitude-phase correlation coefficient for all voxels in dataset 1. Voxels passing threshold for inclusion in the confound reference set are indicated, as is the intersection (voxels



Figure 3-2 Multi-taper PSD of regressor sets.

Summed multi-taper power spectral density (PSD) of regressor sets. Traces represent: *cc- compcor*, *hc*- highcor, and *cc*(post) - calculation of *cc* regressors on data already filtered by *hc* regressors. The existence of frequency peaks in the cc-

post regressors that match those in the *hc* regressor set indicate incomplete filtering of these frequency components, leading to a potential for further reductions. Note that the scale of features in these principle components are not necessarily indicative of their relative scale in the datasets, see Figure 3-3. For reference, the power spectra of regressors generated from a random selection of voxels is also displayed, which fails to classify many important features.

identified by both criteria), amounting to 12 % of the selected voxels in this example. An important observation is that many voxels with high magnitude-phase correlations do not necessarily exhibit large temporal standard deviations. This could be indicative of signals with lower peak-to-peak variations, and/or signals with larger but temporally sparse spikes. From these voxel sets, 5 PCs generated via *cc* were required to reach 80% of the explained variance, and 7 PCs were required from the *hc* voxel set.

Despite the differences in the locations of the sets of selected voxels, the frequency envelope of the regressors was surprisingly similar (see Figure 3-2), yet *hc* regressors were found to contain some additional frequency peaks. Large signal sources at frequencies that are suggestive of respiratory and cardiac motion are visible in both *hc* and *cc* regressors, with *hc* appearing to capture relatively more respiration effects, whereas *cc* appears more sensitive to the cardiac-related peak at 0.8Hz. Small differences in the high frequency multiples of the cardiac signal are detectable between *hc* and *cc*. In addition, changes in the noise floor are also present in the log plot, but these are small in absolute scale ( $\approx 0.15$  % versus 0.3% of max). For reference, Figure 3-2 also displays a regressor set generated from randomly chosen voxels. The noise floor is high and few peaks are easily discernible, illustrating the importance of a good voxel reference set. Figure 3-3 shows frequency spectra aggregated from all voxels in this dataset before and after filtering. It was observed that lower frequency contributions and signals at respiratory frequencies were greatly reduced after one pass of filtering with *cc* or *hc* regressors, whereas cardiac related signals were only partially attenuated. Interestingly, *cc* regressors generated from the *hc* filtered dataset (Figure 3-2, red line) retain nearly all frequency peaks,



Figure 3-3 PSD pre- and post- regression.

Multi-taper power spectral estimates of the fast-TR time series before and after regression, summed over all voxels. The flat baseline in the log plot is indicative of the thermal noise background. Respiratory noise (peak around 0.2 Hz) is almost completely removed by all methods, whereas cardiac related signals (0.75 Hz and higher multiples) are only partially attenuated, and benefit from multiple filtering passes (hc+cc).



#### Figure 3-4 Multi-taper power spectra of decimated regressors

Multi-taper power spectra of regressors calculated from decimated versions of the fast TR dataset, averaged over all repetitions (see Methods section). Error bars indicate standard deviation across repetitions. Down sampled versions of the reference regressors are also displayed. Axes are frequency range in Hertz (abscissa) versus log-power spectral density (ordinate). Additional peaks identified via *hc* are visible even as they move in the frequency domain as aliasing changes.





Locations of noise voxels, for two decimation rates, for *hc*(red yellow) and *cc*(blue - light blue) in three sample slices overlaid on the raw EPI data. Values represent the percentage of repetitions in which a voxel was identified as a noisy source, with more conserved voxels having a higher score. *Top row:* Effective TR 0.45s (decimation factor of 3). *Bottom row:* Effective TR 2.25s (decimation factor of 15). EPI image intensity is scaled down for better visualization of single voxels. At higher decimation factors, there was greater variability in the locations of highest magnitude-phase correlation, whereas regions of high tSTD are more consistent. suggesting imperfect filtering, most likely a result of signals existing at these frequencies that were out of phase.

Power spectra of regressors generated from the down-sampled data are displayed in Figure 3-4 alongside reference regressors. There were no statistically significant differences between the frequency content of the measured and reference regressors for any down sampling factors. In other words, both metrics (tSTD and magnitude-phase correlation) are capable of detecting confound signals under conditions of strong aliasing.

While the frequency content of the regressors was retained after down sampling, the physical locations of the noise voxels in the set were found to change. Noise voxel locations were much more highly conserved by *compcor* compared to *highcor*, where the noise voxels tended to vary over down sampling factors and repetitions, see Figure 3-5. Voxels that change from supra- to sub- threshold between decimation repetitions were still found to be close to threshold. High tSTD voxels were strongly linked with anatomical features – specifically large vasculature and ventricle regions. Locations of highest magnitude-phase correlation varied depending on decimation factor, with some conserved locations clustered near ventricles, edge voxels, cortical regions, and in and around large veins. Both techniques identified a large portion of voxels around the periphery of the brain.

#### fMRI Task Dataset

As with the fast TR data, some overlap was observed in the location of voxels selected via *compcor* and *highcor*. At the 2% threshold employed, a mean of  $3241 \pm 486$  (sd.) voxels were selected per dataset, averaged over all 36 runs. The percentage of common voxels between these two sets was  $23\% \pm 6\%$  (min: 8.6 %, max: 33 %). The 2% threshold corresponded to an average absolute value magnitude-phase temporal correlation cut-off of 0.632 (min 0.450, max 0.862). Datasets with higher levels of artifact tended to have a higher proportion of

overlapping voxels, and a larger correlation threshold. Averaged over the dataset, a mean of 11.9 PCs were required to explain 80% of the variance in the data for *compcor* (min: 4, max: 15). *Highcor* generated slightly more regressors on average for the same explained variance, with a mean of 13.5 (min: 3, max: 15).

Average tSTD values for all 36 sample runs showed reductions over untreated data after filtering: compared to the unfiltered time series, mean improvements over all scans of tSTD were measured at (percent change  $\pm$  95% CI) 19.0%  $\pm$  1.3, 21.1%  $\pm$  1.8 and 34.5%  $\pm$  1.8 for *cc*, *hc*, and sequential application of *hc* followed by *cc* (see Figure 3-7, left). Overall tSTD was significantly reduced with *hc* filtering compared to *cc*, (t = -3.4, p < 0.002), while *hc+cc* treatment resulted in significant reductions over both *cc* (t = -53, p << 1) and *hc* (t = -17.5, p << 1). As a result of these reductions in the temporal signal variance, the estimated temporal SNR averaged over the series was improved from an average baseline of 33.2  $\pm$  2.8 to 42.5  $\pm$  3.6, 43.6  $\pm$  3.0, and 51.2  $\pm$  3.5 for *cc*, *hc*, and *hc+cc*.

Table 3-1 displays the percent change in tSTD reductions measured within white matter, cortical, and ventricle regions, along with the resultant changes in the tSNR within these regions. Representative spatial maps of tSTD reduction from one run for each subject are displayed in Figure 3-6. Signal changes are greatest in ventricle and cortical regions, consistent with removal of physiological sources.

Method	ROI		
	White Matter	Cortex	Ventricles
Temporal STD (% change)			
сс	16.1 ± 3.1	20.6 ± 4.5	23.5 ± 4.6
hc	18.1 ± 3.8	23.2 ± 5.8	26.9 ± 6.7
hc + cc	31.4 ± 3.8	36.9 ± 5.5	39.6 ± 6.2
Temporal SNR			
Unfiltered	35.4 ± 1.7	38.7 ± 3.4	44.8 ± 7.2
сс	41.3 ± 2.7	47.7 ± 3.7	55.6 ± 8.2
hc	42.4 ± 2.1	49.2 ± 2.2	58.0 ± 7.2
hc + cc	49.2 ± 2.7	57.8 ± 2.3	68.2 ± 8.0

**Table 3-1:** Filtering tSTD reduction (% change) and base measuredtSNR by ROI (± sd.), averaged over all runs in dataset 2.

Changes in task detection statistics were observed concomitant to the reductions in temporal standard deviation post filtering with *cc*, *hc*, and *hc+cc*, and are summarized in Figure 3-7 (centre and right). Mean z-scores over the measurement ROIs were increased by  $9.2\% \pm 4.2\%$ ,  $11.9\% \pm 4.1\%$ , and  $13.8\% \pm 5.2\%$  for *cc*, *hc*, and *hc+cc* (mean  $\pm 95\%$ C.I.). A small but significant improvement in mean-z scores was observed when comparing *hc* filtering to cc(t = -2.6, p < 0.01). Despite the significant extra reductions in tSTD from the *hc+cc* filtering process, activation statistics did not significantly improve over *cc* or *hc* (t = -1.6, p < 0.1, and t = -1.5, p < 0.13, respectively ). These mean performance values may be somewhat difficult to interpret, as there was a rather wide variability observed between subjects, as displayed in Figure 8. Subjects with significant extra confound signal or residual motion benefitted the most from the additional filtering.

The effects of filtering on counts of voxels passing threshold were highly variable as demonstrated in Figure 3-7 (right column). Investigation into this spread demonstrated a strong subject effect – some subjects datasets benefitted much more from filtering. Figure 3-8 demonstrates this effect, where it is apparent that one subject (subject 6) benefits much more from filtering on all runs. Data from subject 6 was initially of much poorer quality due to increased subject motion. Two subjects (subject 1 and subject 5) had very clean data, and while mean z-scores were seen to improve from the filtering, counts of voxels passing threshold were hardly affected, and actually were reduced in subject 5. Mean z scores were observed to fall for subject 4 under the additional filtering of hc+cc. Subsequent investigation revealed that small levels of residual task related motion that were picked up by the additional regressors. The implications of such imperfect paradigm filtering are discussed below.



Figure 3-6 Maps of spatial tSTD reduction post filtering

Figure 6: Maps of percent change reduction in temporal standard deviation (tSTD) of the residual (post-GLM) time series data for six subjects. Rows correspond to different filtering: *compcor, highcor*, and both. Consistent with the observations that the regressors are mostly physiological in nature, the majority of changes in the tSTD are localized in cortex and ventricles. See Table 3-1 for numerical values aggregated over subjects by tissue type. For additional visualization, Figure 3-9 displays additional signal standard deviation and z-statistic maps at a higher resolution (see methods) with a very small blurring kernel of 1mm.

# Discussion

In this work, confound regressors were generated from regions that had been automatically selected using the proposed *highcor* criteria, and were benchmarked against *compcor*. The content of these regressors and their filtering performance provide several interesting observations.

# **Detection of Physiological Signals**

As hypothesized, voxels with the largest correlations between magnitude and phase time-courses were shown to contain significant confound signal. Thanks to the very fast temporal sampling used in dataset 1, frequency peaks could be resolved and identified. Of course, if fMRI were performed at such rates, simple low-pass filtering would be sufficient for removal of significant cardio-respiratory fluctuations. By taking measurements of the critically sampled signals and down sampling to more typical acquisition rates, it was possible to predict the frequency distribution of the aliased confound signals. It was demonstrated that *highcor* and *compcor* operating on decimated data could still generate regressors containing accurate representations of the true frequency distributions over a wide range of down sampling factors (see Figure 3-4). When examining how the noise sets change after decimation, regions of large tSTD were found to be very spatially consistent, with prominent detection of large arteries where blood flow effects were directly visible in the time series. The spatial distribution of highest magnitude and phase correlations, on the other hand, showed increased variation when down sampling, which is not entirely surprising. While a core of voxels are retained near ventricles and large veins, correlation measures can be expected to change when different sets of data points are examined. Similarly to tSTD measures, the voxels



Figure 3-7 Group average filtering performance.

Filtering effects on dataset 2. All values are presented as percent change versus unfiltered data, mean  $\pm$  95% CI. Plots represent (left): tSNRof residual (post-GLM) whole brain datasets, (centre): mean z scores, and (right): counts of voxels passing threshold within the functionally defined ROIs (see methods). *cc*: *compcor*, *hc*: *highcor*, *hc+cc*: successive application of *compcor* to data filtered with *highcor* regressors.



#### Figure 3-8 Filtering performance by subject.

Filtering effects on dataset 2, grouped by subject. All values are presented as percent change versus unfiltered data, mean  $\pm$  95% CI. (left): mean z scores, and (right): counts of voxels passing threshold within the functionally defined ROIs (see methods). *cc*: *compcor*, *hc*: *highcor*, *hc+cc*: successive application of *compcor* to data filtered with *highcor* regressors. Mean z scores were observed to fall for subject 4 under the additional filtering of *hc+cc*, due to small levels of residual task related motion that were picked up by the additional regressors. that are more consistently selected exhibit the highest values of correlation between magnitude and phase signal changes.

#### Scaling of tSTD and Magnitude-Phase Correlation

Examination of the fast TR data by tSTD, magnitude-phase correlation, and frequency analysis provide visual aids for understanding the physiological-tothermal noise scaling issue. For the scan parameters used, the observed tSTD distribution (displayed in Figure 3-1) is very long-tailed. These tSTD scores can be best understood as a combination of multiple physical distributions: the high variance voxels containing mostly physiological signals are overlaid on the thermal noise background distribution. In the aggregated frequency spectra in Figure 3-3, the baseline background signal is the thermal noise floor, and the physiological and BOLD signal power is high above this baseline. As image SNR decreases, the detection of these signals is lowered as the relative noise floor rises, resulting in a shift in the distribution of tSTD scores towards a thermal-noise-dominated distribution. The job of any data driven regressor method is to accurately identify these strong confound peaks while leaving the BOLD signals unaffected, a task which becomes more difficult as the overall SNR is lowered. The question of how this type of SNR scaling will affect the metrics used by *compcor* and *highcor* is interesting. In the limit of totally thermally noise dominated signals, tSTD will be unable to differentiate physiological sources, and correlation values will approach zero. We expect the relative scaling of these metrics to differ especially as key imaging parameters change like image resolution and echo time. This hypothesis is based on the results reported in (24), measurements of physiological signal in the phase time-courses are demonstrated to be better spatially localized as resolution increases (and intra-voxel averaging of phase changes decreases) despite the lower overall SNR.



Figure 3-9 Filtering of high resolution sample data.

Filtering effects on high resolution example data. Top to bottom: temporal standard deviation of residuals (tSTD), percent reduction in tSTD over baseline, and z-statistic maps overlaid on mean EPI volume.

### Filtering Performance

An additional frequency peak is identified by *hc* in Figure 3-2 at 1.2 Hz. Crossexamination of Figure 3-3 indicates that this signal is present in the dataset at large, yet is relatively small in amplitude compared to other fluctuations. The small magnitude of the signal fluctuation means that the tSTD metric of *compcor* doesn't specifically select for it. Investigations showed that this nearly pure frequency is scanner noise, driven from the mechanical vibrations associated with the compressor. While small in amplitude, and perhaps unlikely to greatly affect time course variance, it will certainly affect noise autocorrelations. As an aside, it is important to recall that the plotted scale of the principle components demonstrated in Figure 3-2 are not directly comparable to the measured overall spectra in Figure 3-3, since Figure 3-3 is a summation of the power spectra of all voxels.

Despite *highcor* frequency spectra seeming to identify additional signals, there was no significant advantage in filtering performance versus the regressor sets generated via *compcor*, when measured on a group level. The interpretation of this result is that these additional signal sources present a relatively minor contribution to the total signal (as is visible in Figure 3-3), and the metrics used were coarse – averaging signal changes from huge numbers of voxels. Differences between *hc* and *cc* post filtering can be visualized in the maps of tSTD changes (Figure 3-6), where small localized changes are visible.

There appears to be a complimentary effect from applying *highcor* and *compcor* serially, as demonstrated by the power spectral analysis and the resultant changes in tSTD. After a single filtering step, signals at frequencies suggestive of respiratory noise is almost entirely removed from the fast-TR dataset, whereas only a portion of the low frequency noise and higher frequency (likely cardiac) fluctuations were affected. A second pass appeared to mostly remove these outstanding features (Figure 3-3).

We hypothesize that this behaviour at cardiac related frequencies is partially a result of timing: cardiac pulsitility can create out-of-phase signals across and within slices (from different slice timings, and from different sampling along the arterial/venous tree). Regressor generation then identifies the most prominent of these, yet any slightly out of phase signals cannot always be fully removed by least-squares regression. This is a known issue that is accounted for in external monitoring techniques like RETROICOR by generating orthogonal regressors (sin and cos pairs) at the detected nuisance frequencies. This interpretation is supported by the observation that *hc* identified voxels more concentrated in cortex and around ventricles, whereas *cc* tended to very prominently select large veins and arteries – regions with potentially different cardiac phase offsets. Future work is required to investigate this behaviour.

On dataset 2, a somewhat different effect is observed from the combined application of *hc* and *cc*: tSTD is improved, but with nearly no change in activation statistics. This is likely a result of two effects. First, these different metrics are measured over different volumes: tSTD was averaged over the entire brain volume (and/or over the segmented regions as in Table 1), whereas the z-statistics are measured over the pre-defined ROIs. This means if additional signals are removed that don't appear in the ROIs, little extra signal variance will be removed, leaving the z-statistics unaffected. A competing effect is the even further reduction in degrees of freedom associated with these extra regressors from a second filtering pass, which will lower the effective z scores.

Perhaps most importantly for end-users looking to apply such physiological noise reduction methods is the observation that *highcor* and *compcor* can identify similar confound signals from quite different metrics. The frequency contents of the regressors generated by both methods were very similar even under imposed aliasing conditions. This is due to the disturbing fact that physiological confound signals are very strong and pervasive in typical BOLD fMRI datasets, especially at high field strengths and moderate image resolutions.

Due to the prevalence of these physiological signals, their removal by any regressor method has important implications on resulting GLM or resting state analyses. In the sample data described in this paper, image-series temporal standard deviations in grey matter were reduced by twenty to nearly forty percent (and greater in some regions) just by the application of such simple, data-driven post-processing methods. Such an improvement cannot be overstated, especially when considering that such processing has the extra benefit of concurrently whitening the data. This type of effect from physiological noise reduction is not unexpected especially at high field strengths, as demonstrated by Hutton *et. al.*(7) who measure significant gains in tSNR at 7T.

While the performance observations herein are by no means exhaustive and are difficult to generalize to different imaging studies, they can perhaps add some confidence for use of such data-driven methods.

#### Paradigm Filtering

As with many other data driven techniques, the filtering of the functional paradigm is required because there is a potential to identify task related signal changes thanks to the strong BOLD response in macroscopic veins. In our experience, large regions of coherent activation are needed in order for task evoked BOLD response to be detected as an outlying signal, such as with large block design visual or motor tasks. More worrisome than the actual activation is task related motion, which can create more widespread signals with a larger likelihood of identification via PCA. The approach taken in this work (and used by others (16,31)) was simple masking of voxels that had even low levels of correlation with the task. More sophisticated techniques could be implemented: mirroring the process used for correction factors for noise auto-correlation, a preliminary GLM can be run and regressors generated from the residuals (4).

#### Related work

Utilizing the strong physiological signals in the phase data to correct magnitude time series is not a new concept, as other studies have demonstrated. Cheng and Li (32) employ a Weiner filtering technique on a per-voxel basis that removes some frequency contributions in the magnitude time-course based on the contents of the phase time-course. This is conceptually similar to the phase regressor technique introduced by Menon (23) which was originally proposed as a method to identify and remove macroscopic veins, where the voxel phase time-course is regressed out of the magnitude signal. It was recognized that this process could also remove any coupled signal changes potentially including physiological noise and motion. A single voxel time series can be relatively noisy, reducing the robustness of methods that operate on individual voxels. Boosting available SNR for regressor selection via pooling many hundreds or thousands of voxels is an attractive alternative, albeit with the potential drawback of missing unique, localized variations. Here, we err on the side of robustness and look to find a small set of regressors that capture confound signals.

### Requirement for phase data

In this work, regressors were generated and used to suppress physiological confound signals from the magnitude time-courses of all voxels. While this is the primary endpoint of filtering for most users, there is a growing interest in the phase data for uses such as vein suppression (23), fitting complex-valued GLMs (33), and thermometry (34). These applications are plagued by the typically low temporal stability of the phase, mainly due to the sensitivity to physiological processes (19,20,35). *Highcor* provides a natural way to identify voxels from which to extract references of the confounds as they appear in the phase time-course itself.

# Conclusion

In BOLD fMRI, confound signals can greatly impact the effective BOLD contrast-to noise. While often described as simply noise, these confounds, mostly physiological in origin, are real signals that are indistinguishable from brain activity evoked BOLD responses at typical imaging TRs. Importantly, improving base image SNR does nothing to alleviate these confounds. Data driven regressor methods are an attractive way to address physiological confounds thanks to their ease of implementation, model free nature, and promising behaviors with respect to aliased confound signals. This paper described *highcor*, a novel selection criteria for noise voxels used in the generation of such regressors, utilizing the often discarded phase component of the MRI signal. *Highcor* is based upon the physical expectation that physiological confounds can generate detectable signals in magnitude and the phase time-course that are highly temporally correlated with one another. These voxel sets were used for subsequent regressor generation, and were benchmarked against regressors from *compcor*, a robust method that selects noise voxels on the basis of high temporal standard deviation.

By examining the regressor frequency content, it was observed that *highcor* identified many prominent physiological signals including cardio-respiratory effects as well as low frequency fluctuations. *Highcor* was able to identify additional confound components consisting of signals with strong magnitude-phase correlation but lower overall peak-to-peak amplitude changes. These types of signals may have little influence on overall image tSNR, but important implications for time series whitening and GLM statistics. Despite the differences in regressors, *highcor* and *compcor* displayed comparable performance in the reduction of confound signals measured over a set of sample task-based fMRI data. Image-series temporal standard deviations were reduced by roughly twenty percent, just by this simple post-processing.

In closing, we encourage other researchers with access to phase data to try both approaches. For the majority of groups working solely with magnitude BOLD timecourses, we believe that the observed similarities between *highcor* and *compcor* provide some additional evidence to encourage the use of *compcor* in routine studies: that tSTD measures can reliably detect physiological signals, even under aliased conditions for typical imaging prescriptions.

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# 4. Phase-based Venous Suppression for Resting State fMRI

# Introduction

The point spread function (PSF) in BOLD fMRI is ultimately limited by the spatial specificity of neurovascular coupling mechanisms ((1-5)). Further reducing the accuracy of signal localization are the downstream BOLD effects in the venous architecture. Localized changes in blood oxygenation propagate downstream to draining venuoles and cortical and pial veins, leading to 'signal' spread and an additional anisotropic 'venous PSF' (6-10). These confounding effects have been mostly of interest in high resolution, single-subject studies that seek to measure fine-scale features such as layer specific activation differences (11, 12), or columnar organization (13-15). Increased PSF is often overlooked or ignored in studies owing to the lower resolution acquisitions and spatial blurring that are typically employed in acquiring and processing BOLD fMRI. However, venous effects should still be considered for studies at typical imaging resolutions since larger brain regions can generate BOLD fluctuations that propagate far downstream, and are sometimes detectable in even the largest of veins.

The confounding effects of vascular drainage are not exclusive to task-based fMRI studies and will similarly bias resting-state (RS) investigations. In RS data analysis, the statistical interdependence of low frequency BOLD signals between brain regions is captured (16) and has been used to reveal multiple distributed patterns of connectivity (17-19). Venous effects can potentially impact the spatial distribution of measured correlations of the networks, biasing both location and spatial extent. It has been shown that the low frequency fluctuations can often exhibit amplitudes of a similar magnitude as observed in response to tasks or stimuli (20, 21), suggesting that downstream BOLD effects can be as much as a problem as they are for task

driven paradigms. However, another mechanism is important to consider when measuring resting-state correlations: the effect of non-activity-related susceptibility fluctuations from large veins influencing surrounding tissue. This will result in spurious, spatially distributed correlations driven only by the common (confounding) venous source, leading to overstated signal correlations within or between highly vascularized areas. The spread of such spurious signal also has the potential to mask the detection of activity related signal correlations. All of these venous effects can be exacerbated by data blurring from both spatial smoothing as well as re-sampling during motion correction and group space alignment. For these reasons, veins should be understood to be a potential source of error especially when mapping structures (22), or defining networks based on seed regions that are along the cortical midline (e.g., the default mode network is typically defined based on seeds in the posterior cingulate cortex, see (23)).

If venous contamination is a contributing factor in typical RS-fMRI scans, methods to suppress such signals should result in a reduction of overall voxel correlation measures, and changes in the spatial characteristics of resting-state connectivity maps. To test this hypothesis, the phase regressor method is employed (24). The approach uses a post-processing method for informed suppression of macrovascular signals using information in the phase component of the fMRI time series data. The phase regressor and various other strategies for venous suppression in fMRI are introduced below.

# **Reducing Venous Contributions**

Functional MR imaging methods like ASL or CBV-fMRI can be less sensitive to macro-vascular effects and demonstrate improved spatial specificity versus gradient echo BOLD (GE-BOLD) (25-27). Despite the advantages of these methods for avoiding vascular related confounds, GE-BOLD remains a highly popular and widely used technique, especially for investigations of intrinsic functional connectivity using RS-fMRI due to its speed and simplicity of acquisition.

One strategy for combating these venous confounds is to perform the MRI experiment at a higher magnetic field strength. Signal biasing from intra-vascular effects is somewhat mitigated at high field strengths (typically  $\geq$  7T) in gradient echo based BOLD fMRI thanks to the shorter blood T<sub>2</sub> (6, 28). In addition to moving to higher fields, several techniques exist that can be used to further reduce detection of intra-vascular BOLD signals, including masking, temporal approaches, and the use of the spin-echo signal. On a coarse level, anatomically-driven venous measurement and masking is a possibility, but is limited to large veins, fails to address any extravascular signal except by region growing, and can be affected by partial volume effects and misalignment/distortions between a vessel reference map and the functional dataset. Temporal methods can be applied to differentiate micro and macro-vascular signal changes and to avoid localization issues arising from venous spread (12, 14, 29). Given appropriately high sampling rates, it is possible to measure BOLD signal onset times and apply differential processing accordingly. These methods are quite effective but are not generally applicable for resting-state imaging because of the lack of an onset event from which to reference BOLD signal changes.

Spin-echo (SE) based sequences are another method known to mitigate venous effects (6, 26, 30). By altering the measurement of the BOLD signal, the signals generated from veins differ from typical gradient echo (GE) fMRI. In SE-fMRI, signals from macro-vasculature (here, considered any vessels larger than the smallest of oriented intra cortical- veins, >25  $\mu$ m diameter (31)) produce approximately static perturbations in the local magnetic field, allowing for near complete signal refocusing from the spin echo and resulting in insignificant signal changes with BOLD. The effects on microvasculature (vessels <25  $\mu$ m diameter) differs, in that the smaller and more randomly oriented venuoles generate field perturbations that are incoherent on the diffusion length scale. Thus nearby diffusing spins cannot be refocused, leading to a modulation of the apparent T<sub>2</sub> and signal loss in the spin echo. Signal detected by spin-echo BOLD fMRI is thereby biased towards the microvasculature, and by implication, the active neuronal sites.

In GE based imaging, all of the field perturbations listed above still exist, but since no spin echoes are present, signal changes are measured from both the micro- and macro- vascular components. The macroscopic veins that give rise to the coherent intra-voxel T<sub>2</sub>\* de-phasing also generate detectable phase changes in the data. In the case of the randomly oriented microscopic veins, little to no coherent phase changes should be measurable, because of the incoherent manner in which the field perturbations will average within a voxel. This concept was used to develop the phase regressor, a post processing method for suppression of extra-vascular BOLD signal from macroscopic veins (24). Through high-resolution task-based experiments, it was demonstrated that the temporal magnitude and phase signal changes from larger veins in response to task have an approximately linear relationship. Such phase changes were identified and filtered from the magnitude time course, resulting in suppression of macroscopic venous effects.

Here, we investigate the applicability of the phase regressor method on whole-brain resting-state data sets, under the assumption that BOLD effects are a main contributor to the resting state signal flucations. In the following sections, the phase regressor technique is briefly reviewed and a modification proposed for application to resting-state data. Metrics are introduced for assessing its performance on resting-state data, and the technique is tested on a small set of subjects as a proofof-concept.

#### Phase Regressor

The phase regressor, as introduced by Menon (24), is a technique used to reduce the vascular signal contributions generated in GE-fMRI. The concept is reproduced here,

using notation from the original paper. For an fMRI acquisition of *n* time points, a magnitude signal time-course  $S_i$ ,  $i = 1 \dots n$ , and a phase time-course  $\phi_i$ ,  $i = 1 \dots n$  are measured for each voxel. The phase regressor *estimates* the signal in the magnitude that is explainable by the phase data,  $S_{est}$ , by finding linear fit parameters A and B,  $S_{est} = A\phi + B$ . Filtering is performed by subtracting out the estimate from the original data:  $S_{filt} = S - S_{est}$ . The process reduces the influence of macroscopic veins, because they are the predominant source of signal changes in *both* the phase and the magnitude time series. Other sources of correlated magnitude-phase signal change, such as motion artifacts, are also reduced on a per-voxel basis.

# Methods

### **Regressor Implementation**

Magnitude and phase time series in MRI tend to have different signal-to-noise characteristics due to the underlying noise distributions as well as varying contamination by physiological sources. From a data-fitting viewpoint, this results in different measurement uncertainties in magnitude and phase. It is therefore important to condition the fit of the phase regressor with knowledge of the relative error levels in the measurements. As a coarse measure, one can estimate the standard deviations  $\sigma_S$  and  $\sigma_\phi$  of the magnitude and phase time series respectively, if the signal changes of interest can be factored out. In its original implementation, the phase regressor was applied to task datasets with periodic paradigms. By filtering at the paradigm frequency (and harmonics),  $\sigma_S$  and  $\sigma_{\phi}$  could be estimated from the residual data, which included measurement noise, as well as all remaining physiological effects and uncorrected motion. RS-fMRI, by definition, does not have a well-defined paradigm to filter. Instead, the method can be modified to utilize the inherent frequency filtering that takes places in typical RS analysis: since most resting-state analyses rely on band-passed, low frequency data (23), the normally unused high frequency part of the spectrum is employed to estimate the residual

signal standard deviation in the magnitude and phase time series. Even though the noise statistics in the magnitude and phase differ and are typically not normally distributed (32, 33), this has been found to be a robust approach that improves on filtering without any heed for the relative measurement uncertainties. This is demonstrated in Figure 4-1, which depicts the time series and spectral components of a sample voxel, where is it evident that the background phase noise is nearly an order of magnitude worse than in the magnitude data in this specific case. This measure is fairly consistent between the high-and-low-bandpassed frequency bands. Significant physiological confound in a voxel could worsen the phase variance by this measure, for instance, the peak at 0.2 Hz in the phase component in Figure 4-1 that is likely related to respiration. For implementation, fitting a linear model with errors in both variables is straightforward and software is readily available. Data fitting was performed in python using the scipy.odr (34) interface to the Fortran ODRPACK library (35).

#### MRI Data

Data from seven healthy volunteers (age range = 22-31y, mean = 27y, 5 male and 2 female) were collected and analyzed with a typical RS pipeline (see below), with and without the addition of the phase regressor filtering. All volunteers provided informed consent for the study in accordance with the research ethics board guidelines at the University of Western Ontario. Scanning was performed on a 7 T head-only MRI scanner (Agilent – Direct Drive) with an AC84 head gradient coil (Siemens), using a conformal 23-channel whole head receive array coil. A tenminute resting-state BOLD fMRI scan was acquired on each volunteer. While the phase regressor based venous suppression was originally demonstrated on high-resolution data sets, for this study the RS-fMRI data were acquired at a more moderate resolution (2 mm isotropic). This was chosen to observe the effects of the phase regressor at a resolution more closely matched to those employed in the RS literature. EPI acquisition parameters were as follows: 2x2mm in-plane resolution,



Figure 4-1 Variance estimation from high frequency band.

Sample magnitude and phase time courses. Original resting-state data is filtered into two data sets; data destined for correlation analysis is band passed at 0.01 - 0.1 Hz (blue trace and shading), while the remainder is high-passed for use in variance estimation (green trace and shading). Left: Power spectrum of magnitude data (*top*), and phase data (*bottom*). Right: band-pass and high-pass signal timecourses of magnitude (*top*) and phase (*bottom*). Important is the relative difference in the signal variance between the magnitude and the phase data (see methods).
20 degree axial-oblique slice orientation, 2mm slice thickness, 110x90 matrix size, ramp sampling, 300 kHz readout bandwidth, GRAPPA factor: 3, TR: 2 s, TE: 23 ms, 44 slices, 300 volumes, and a 60° excitation flip angle. EPI data were reconstructed and resulted in separate complex time series for each coil. Coil sensitivities were estimated in the EPI space by taking a mean of the first ten volumes after basic detrending and temporal phase unwrapping. Each mean magnitude image is divided by the root sum of squares of all channels to generated the magnitude coil sensitivity maps. Relative phases are also calculated between these mean complex volumes, to generate the N approximate complex receiver maps. An anatomical reference  $T_1$ -weighted MPRAGE was also acquired with acquisition parameters: TR: 8 ms, TE: 3 ms, TI: 1.35 s, BW: 50 kHz, matrix size: 220x220x150, 1mm-isotropic resolution, GRAPPA acceleration of 2x2 (phase x phase2), with 64 x 44 additional reference lines.

#### Data Processing

FSL tools (36) were employed for brain masking and motion correction (BET and MCFLIRT (37)). Automated brain segmentations were utilized (see below), generated from the anatomical data using Freesurfer tools (38, 39). Surface-driven boundary based registration was performed to align anatomical and functional datasets. White matter and ventricle ROIs were generated from the Freesurfer segmentation and mean time courses from these regions were extracted for confound signal estimation. Six *compcor* regressors (40) were also generated and applied to reduce physiological artifact. AFNI tools (3dBandpass) (41) were used to bandpass the functional data between 0.01 and 0.1 Hz while regressing the six motion parameters (translation and rotation in x, y, and z) and mean WM and CSF signals, and *compcor* regressors.

Because few tools exist that properly handle the complex valued datasets, the phase data were processed separately from the magnitude data. The phase time-courses

underwent similar processing as the magnitude, with the additional steps of temporally unwrapping the phase (on a per voxel basis) and subtracting off the value of the first volume, resulting in delta-phase time-courses. At the echo times used in this study, this produced phase data without any spatial  $2\pi$  jumps (in the case these types of jumps existed, further spatial phase unwrapping would be required). Linear de-trending was performed to remove any residual effects of B<sub>0</sub> drifts. Motion correction parameters (as calculated from the magnitude data) were applied to the phase time-courses, followed by bandpass filtering and confound regression, as above.

All resting-state analyses and performance metrics were measured on the magnitude data with and without the application of the phase regressor based filtering. Importantly, the phase regressor was applied on the low frequency bandpassed EPI data, within each subject's native data space, *before* any spatial smoothing or transformations.

Intra-voxel resting-state signal correlation levels were measured with and without the phase regressor, performed as follows: Pairwise Pearson product-moment correlation coefficients, r, were computed between all brain voxels within each scan. A binning procedure was used to obtain counts of voxels passing pre-determined correlation thresholds (low:  $0.2 \le |r| < 0.4$ , medium:  $0.4 \le |r| < 0.6$ , and high:  $|r| \ge 0.6$ ). For each voxel pair, the source and destination tissue type (grey matter (GM), white matter (WM)) was recorded, and correlation values binned accordingly (WM - to - WM, WM - to - GM, GM - to - GM), allowing for comparison of aggregate correlation level changes within and between tissue types. Label maps of cortical grey matter, white matter, and ventricles were generated from Freesurfer segmentations, binarized and transformed into the EPI space. Any regions with label overlap that resulted from partial volume effects were masked out.

## **Resting-state Network Identification**

Group level seed-based correlation maps were computed using AFNI and 3dGroupInstacorr (41) for several common networks, with and without phase regressor filtering. Subject data were transformed into the MNI space for group analysis, and data were spatially smoothed using a 5mm full-width-half-max (FWHM) gaussian kernel prior to seed-based analysis. Spherical seed points (1 mm radius) were placed in several brain regions, chosen for associated RSNs that exhibit either a) connectivity over a mix of midline areas (with significant problematic large venous structures nearby), and b) networks with distributed, bilateral patterns lacking common venous connections. Seed points were placed in the posterior cingulate (MNI co-ordinates: 0, -52, 26), revealing the default mode network, in the left superior parietal area (28, -62, 50), secondary visual area (28, -94, -2), right frontal eye field (34 26 48), and precuneus (2, -62, 58). Differences in the statistical spatial correlation maps with and without phase regressor application were calculated and recorded. To investigate the spatial characteristics of the phase regressor signal estimates (S<sub>est</sub>, the macro vascular component), correlation maps were generated on this phase estimate using the same seed points.

# Results

Figure 4-2 demonstrates the application of the phase regressor for filtering on two representative grey matter voxels from the primary visual area of one subject, one voxel immediately next to a vein and one distant (~4 voxels) from any visible veins, as identified via signal nulls in the MPRAGE. The low frequency band-pass time series are displayed (0.01 - 0.1 Hz). In the voxel with no apparent vein, it can be observed that the phase signal is quite different from the magnitude, and little signal is removed after application of the phase regressor, resulting in only small differences in the filtered time course. In contrast, the voxel near a vein exhibits similar features in both the magnitude and phase time-courses. These combined features are almost totally eliminated after regression.



Figure 4-2 Sample time series for regressors.

Sample time series from two grey matter voxels, one close to (top), and away from (bottom) visible cortical veins, band-pass filtered between 0.01 and 0.1 Hz. Traces represent magnitude (blue), phase (red), and filtered magnitude data (green). In the voxel near a vein (top), large signal features common to both magnitude and phase time courses are reduced after filtering. In the voxel away from detectable veins (bottom), the magnitude and phase time series are uncorrelated, and the filtering has nearly no effect on the magnitude data. Magnitude/phase correlation coefficients in these two voxels were 0.72 (top) and -0.06 (bottom). The ratio of magnitude and phase signal standard deviations used in the weighted fit  $(\sigma_S/\sigma_{\phi})$  was observed to be fairly constant over most brain regions for each subject, with the exception of areas of low signal (e.g. from regions falling outside of the receive or transmit coils, such as the inferior hippocampus and the anterior portions of the temporal lobes). Changes in  $\sigma_S/\sigma_{\phi}$  were also observed when subtle phase errors from the EPI reconstruction were present. In both cases,  $\sigma_{\phi}$  was found to increase faster than  $\sigma_S$ . This is an expected behaviour as signal levels drop because the noise statistics in magnitude and phase are only approximately Gaussian for signal-to-noise ratios larger than ~2 and ~3 respectively(32). In areas with lower signal levels, noise distribution in the phase quickly widens, tending towards a uniform distribution over all angles (see (32)), and yielding very large estimates of  $\sigma_{\phi}$ . Regions where the phase signal is noisier are appropriately down weighted by the fitting procedure used, avoiding the potential mixing of phase noise into the magnitude data.

For each subject, measurements were taken of the phase regressor fit parameters. Maps of the voxel-wise magnitude-phase correlation and the linear fit explained variance ( $R^2$ ) are displayed in Figure 4-3. The fitting was performed only on the band-passed (low frequency) data. The regions where the model fits best are expected to match closely with the underlying magnitude-phase correlation values, scaled by the local estimates of  $\sigma_s$  and  $\sigma_{\phi}$ . Correlation values and  $R^2$  were observed to be largest near midline and in the periphery of the brain, and are lowest in white matter areas where negligible venous BOLD contributions (and little other confound, like edge effects and motion) are expected. These values and spatial patterns are similar across subjects, as demonstrated in a group average map of  $R^2$  (Figure 4-3, bottom row). In the group average, fine spatial features are no longer visible after spatial blurring and group-space alignment.



Figure 4-3 Whole brain regressor fit data

*(top row)* Per-voxel correlation coefficient between magnitude and phase time courses, *(middle)* R<sup>2</sup> estimate of phase regressor fit to the magnitude, and *(bottom)* Group average R<sup>2</sup>.

To examine the effects of the phase regressor filtering, inter-voxel (resting-state) correlation levels were measured for all subjects, and found to decrease after phase regressor filtering. Total counts of voxel pairs passing correlation thresholds, averaged over the subject group are summarized in Table 4-1. Significant reductions were observed in the total number of moderately- and highly- correlated voxels following phase regression. The reduced counts at higher correlation levels were balanced by increased counts in the very low correlation regime, around |r| < 0.14 -- a narrowing of the histogram of total voxel-voxel correlation values. Such behaviour is observed when applying other common 'global' confound regressors (such as motion parameters and CSF signal). Unlike the global regressors, the actual signals removed by the phase regressor technique vary in space on a voxel by voxel basis.

Examining these overall reductions in more depth, Figure 4-4 displays the changes in counts of voxel-voxel correlations binned by source and destination tissue type. In line with overall measures (Table 1), filtering resulted in paired correlation values that were decreased within and between all tissue classes at the correlation thresholds used. Since true activity-related correlations are not expected between voxels within white matter, this set provides a good baseline for comparisons. At the highest correlation threshold, there was significantly greater reduction in voxelvoxel correlation counts (50 % to 90 %) within areas identified as GM and between GM and WM, when compared to correlations between voxels in WM.

Qualitative examination of filtering performance on common resting-state networks (RSNs) revealed some notable behaviors (Figure 4-5). In many RSNs, correlation changes near midline are visible. Away from midline, changes in correlation levels are evident both within and peripheral to main network clusters. It appears that while finer structures are detectable in the phase regressor fit map in a single subject (as seen in Figure 4-3), only the largest regions persist as observable

## Table 4-1: Counts of voxel pairs passing threshold.

Counts of voxel pairs passing threshold for all voxels in the white matter, cortical grey matter, and ventricle regions,  $\pm$  standard deviation. Significant reductions at higher correlation levels were observed: (\*): p<0.02, (\*\*): p<0.002. Reference processing includes all pre-processing and confound regression other than the phase regressor.

	0.2 <  r  < 0.4	0.4 <   <i>r</i>   <0.6	<i>r</i>   > 0.6
Reference	2.8e8 ± 5.9e7	1.2e7 $\pm$ 5.8e6 $$ *	5.8e5 ± 2.1e5 **
Phase Regressor	2.2e8 ± 3.6e7	5.3e6 ± 2.2e6 *	1.9e5 ± 4.5e4 **



#### Figure 4-4 Group average correlation changes after phase regression.

Group averaged changes in counts of voxel pairs passing correlation thresholds after phase-regressor application, binned by tissue type, as percent difference from the unfiltered data, ± standard deviation. Significant differences *within* correlation threshold levels are indicated (pairs of \*, \*\*, and o), calculated via Tukey range test (HSD) with a family-wise error rate (FWER) = 1e-3. For display purposes, correlation threshold labels (x-axis) are condensed, and refer to: 0.2  $\leq |r| < 0.4, 0.4 \leq |r| < 0.6$ , and  $|r| \geq 0.6$ , see methods section. correlation changes at the group level, likely because of differences in venous anatomy between subjects combined with group level blurring effects.

When investigating the content and spatial characteristics of the phase regressor time-courses themselves (S<sub>est</sub> -- the estimated macro-vascular fraction that is subsequently removed), seed based analysis revealed remarkable patterns of resting state connectivity closely matching those observed in the magnitude data. This was observed both in core regions about the seed point, and in some bilateral network areas as seen in Figure 4-6. Also visible in these correlation maps from the phase data are regions of presumably large-scale vascular artifacts, as observed in the large correlation of the precuneus seed with the superior regions of the sagittal sinus. Note that the use of lower correlation thresholds was required in order to produce similar network extents as found in the magnitude data.

# Discussion

## Spatial Characteristics of RS-Correlation Changes

Processing resting-state GE-EPI fMRI data with the phase regressor leads to measurable spatial changes in resting-state correlation metrics, owing to the removal of signals present in both magnitude and phase time series. Importantly, spatial differences in voxel-voxel correlation levels persisted at the group level. Despite the phase regressor fitting revealing some finer scale spatial features on single subjects, at the group level only the largest veins appear to be well conserved, likely because of the intra subject variation in anatomy of smaller vessels combined with registration imperfections and blurring effects. An example of this is the attenuation of correlation scores along the sagittal sinus from the precuneus seed region (Figure 4-5, b). In this situation, strong venous signal that blurred into the seed region became part of the seed time-course, and correlations along the whole sagittal sinus are seen at lower thresholds. By removing the venous signals before blurring, this is avoided. Correlation *increases* after venous suppression are measured in "core" network areas from the reduction of the spurious signal that was previously mixed into the seed region, resulting in a potentially more accurate measurement of the local underlying activity-related signal changes. Other regions of correlation *reduction* are visible in the other investigated networks in Figure 4-5, especially near areas of known confound (sagittal sinus and brain midline, and cortical surfaces where motion and other artifacts can be more prominent).

Smaller-scale effects in the resting-state correlation maps were also observed, especially in the periphery of main network regions (Figure 4-5). In resting-state network maps that primarily show changes outside of what would typically be considered the core network regions/voxels (and eliminated by increasing the lower bound threshold) there is still value in phase based vessel suppression. Differences in correlation levels in voxels outside of the core network regions may not play a large role in visual identification, but they could be critical for group level comparisons (especially in clinical comparisons), graph metrics that rely on binary thresholding, and voxels that otherwise may be close to threshold and would increase false positives.

An interesting effect of the phase regressor filtering is the greater reduction of pairwise correlated voxels between white and grey matter, and within grey matter, as compared to counts between voxels within white matter (as shown in Figure 4-4). If one accepts that coherent and meaningful resting-state activity should not be observable in WM, correlation changes between these areas are likely due to the removal of residual physiological variations, given that there are few large venous structures traversing WM to be regressed out. When comparing these WM changes to correlation changes between GM and WM, and within GM, it is tempting to hypothesize that the residual physiological signals account for a similar percentage reduction in correlation levels (and RS-BOLD the remainder). This would be incorrect, because the strong percent change in WM disguises the fact that the total count of medium- and highly-correlated voxel pairs within WM are nearly an order



## Figure 4-5 Seed based group RS-correlation maps.

Seed based group RS-correlation maps (red-yellow) for exemplar networks (a- e, see methods section for seed co-ordinates). Changes in z-scores after phase regressor application are indicated, where green values denote reductions after filtering, and blue/purple denotes increased values. While some correlation changes exist within contiguous correlated regions, more interesting are the localized reductions on the periphery, where the extent of connectivity estimates might be affected.

of magnitude lower than the other categories. This means that while a significant *percentage* of highly correlated areas within WM are suppressed, they represent only a small fraction of all highly-correlated pairs.

In the context of resting-state correlations, reductions between voxels in GM and WM are particularly important. Any confounding correlations or mis-localization due to venous spread can be worsened by subsequent data blurring and group alignment procedures. The demonstrated reductions in correlation levels in this set of voxels can imply a possibility for improved localization of resting-state signals by removing these correlations *before* they are blurred into surrounding areas.

## Spatial Characteristics of Magnitude-Phase Correlation Changes

The underlying magnitude-phase signal correlations that are identified and used by the phase regressor are interesting to examine. As noted in the results, and depicted in Figure 4-3, the magnitude-phase correlations and concomitant regressor goodness-of-fit broadly follow patterns of known vascular density in the brain. Interestingly, there is a noticeable reduction in these values in the posterior sagittal sinus as compared to the more superior sagittal sinus areas, detectable in the group average images. This difference is worth discussing, given the presumably similar levels of deoxygenated blood in both regions. We believe the major contributor to this effect is the venous alignment with respect to the main magnetic field. The alignment affects the susceptibility shift experienced by the spins, and thus the phase response as oxygenation changes. This is a physical effect of cylindrical susceptibility perturbers oriented in an external magnetic field -- we don't detect such signals, but they in fact do not exist in the first place (or rather, are attenuated as the vein orientation approaches the magic angle cone). Secondary factors are also likely at play contributing to regional signal differences, such as imperfect group alignment and blurring, and differences in brain masking, averaged over the small number of subjects.

# Venous Signal at High Field

The data herein demonstrate that measureable magnitude-phase signal correlations exist in gradient echo EPI fMRI data in patterns that follow known vascular density (31, 42), as well as patterns that match known RSNs (Figure 4-5 and Figure 4-6). This raises the question: what is the source of such signals? Simulations and measurements of GE-EPI at 7 T suggest that the intra-vascular (IV) venous blood signal is greatly attenuated via the short T<sub>2</sub>, resulting in signal levels of less than 10% as compared to tissue at the echo times used (43). This is in contrast to low field strengths where nearly all of the detectable BOLD signal changes are venous in origin. While the blood T<sub>2</sub> at 7 T results in a lower absolute level of IV signal, the relative frequency shift experienced by intra and extra-vascular spins grows, resulting in larger detectible phase shifts and still allowing for measurement of correlated magnitude-phase signal changes from blood. At very long echo times or field strengths well beyond 7 T, this method will not be applicable for differentiating IV signal, although arguably IV signal is not a significant problem under such conditions. However, extra-vascular tissue spins are also candidates for detectable phase changes. The static de-phasing regime around large vessels will not only induce T<sub>2</sub><sup>\*</sup> decay in the tissue (leading to signal change in the magnitude and the familiar vein blooming effect seen in susceptibility weighted imaging), but also has the potential to generate coherent phase offsets, depending on the local geometry of veins within and in close proximity to a given voxel. Prior to this study, the phase regressor technique was validated at matched resolution and echo times at 7 T using a visual task, to ensure activity related BOLD phase changes were indeed detectable.

In theory, the phase regressor should be able to identify temporal changes in blood susceptibility via the BOLD effect, regardless of the source (activity-induced or residual physiological fluctuation), given sufficient magnitude and phase signal-tonoise ratio. It can equally well identify artifacts that generate coupled magnitude and phase signals. In task based studies, differentiating the activity-related signal from other confound sources is simpler owing to knowledge of the estimated response to paradigm, and the fact that task signal is detectable in the phase data itself (see (24)). In fact, phase changes have recently been shown to be detectable even from the more transient BOLD changes elicited in event related paradigms (44). This finding is important because of the potentially greater contributions of physiological contamination in the phase time-course – the ability to detect block and event related BOLD signals suggests that there are situations where the phase data may have sufficient SNR to be sensitive to RS signal changes. Most resting state fMRI shows correlations that are expressed in z-scores and r-values, without any heed paid to the actual amplitude of the fluctuations. Recent work (45, 46) has demonstrated that the amplitude of the BOLD signal during the resting sate is in some cases quite comparable to the amplitude of the BOLD signal in task based studies, and furthermore, the amplitude of these fluctuations can be positive or negative over "baseline". It stands to reason that the venous signals would follow, and thus be detectable through their phase perturbations.

Estimates of the macrovascular signal component (the phase regressor -- that is, the per voxel linear fit of the phase signal to the magnitude signal) proved interesting to directly visualize. As described in the results and seen in Figure 4-6, RSNs were remarkably well visualized from this (weighted) phase data. In the datasets tested, these signal correlations are absent from the raw phase data at the group level, for two reasons. First, by fitting the phase to the magnitude, a re-scaling of the phase time course occurs on a per voxel basis. Regions where the time series do not correlate well are basically down-weighted, leaving only the phase time-courses that exhibit signal from susceptibility perturbations that are also detected in the magnitude. It is important to remember that the *temporal* signal behaviour is *not* changed, as the only parameters in the fit are the zero offset and linear scaling for

each voxel. This means any temporal correlations measured between voxels in group level raw phase dataset are signal changes in the phase data itself.

A second effect also occurs from the fitting procedure that serves to additionally transform the phase data into a format more amenable for correlation measurements and group averaging: flipping of the sign of the phase during rescaling. Consider the situation of two voxels on either side of a susceptibility perturber like a large vein with a time varying susceptibility. These neighboring voxels will experience T<sub>2</sub>\* effects as the local magnetic field changes, resulting in a temporal intensity change in the magnitude component. Depending on the relative orientation of the vein and voxels in space, there is the potential for the phase timecourse to appear correlated or anti-correlated with the magnitude. Through the linear fit, the sign of this phase offset is taken into account, resulting in all anticorrelated phase time-courses being "flipped" in the phase regressor dataset. From this operation, the phase signals become more spatially coherent and amenable to blurring operations. Whereas nearby voxels with large relative offsets in the phase time-courses would have previously cancelled, this coarse type of alignment allows for some benefit from spatial filtering and group averaging as the phase changes due to a vessel are now coherent everywhere near that vessel. To summarize, we propose that the resting state signal activity is visible in these phase regressor maps because of the inherent filtering that suppresses non-BOLD related phase signals while improving the spatial coherence of the voxel phase offsets.

## Versus Spin Echo

The efficacy of this approach can, in the future, be compared to spin echo sequences that intrinsically suppress macroscopic venous effects. Different performance characteristics are expected since the localized extra-vascular phase changes are only detectable in the gradient echo phase data given sufficient SNR and voxel sizes with respect to underlying venous structure. In contrast, the spin echo refocusing



## Figure 4-6 Seed based group RS-correlation maps (phase data)

Seed based group RS-correlation maps (red-yellow) calculated from the phase fit data itself (S<sub>est</sub>). The maps are generated from the same seed points as in Figure 4-5, but calculated from this phase data contain both expected network connectivity, as well as additional conspicuous regions that are likely artifact. This is especially visible in (b and c) where portions of the sagittal sinus show correlation with the seed region: signal from the sagittal sinus that is blurred into the tissue induces these correlations that are then detected upon seed region analysis. will intrinsically occur independent of acquisition resolution and signal-to-noise levels. From these considerations, it is likely that spin echo sequences will provide superior venous suppression performance, but are limited by many factors that scale with MRI field strength and make their use a difficult trade-off for resting-state applications. High RF power requirements and lengthy repetition times (especially at high image resolutions) are hard problems to address. Recent technological developments including multiplexed acquisitions promise improvements in the utility of spin echo fMRI in high field, high-resolution regimes, but are still an area of active research (e.g., see (47, 48)). Until such advanced techniques become more commonplace, phase-based techniques in gradient echo fMRI can fill an important role in artifact detection and venous suppression.

#### Caveats and Confounds

The treatment of noise statistics in this work is a confound worth discussion, as the relative signal variances  $(\sigma_S/\sigma_{\phi})$  are used to weight the phase regressor fit at each voxel. As identified in the methods and results section, the noise statistics in magnitude and phase images are known to be non gaussian. When underlying activity and/or physiological signals are also included in a given voxel time series, it becomes clear that estimation of the signal variance is not a measure of the underlying noise in the time course. The purpose of the variance estimation is to provide a rough scaling on a per-voxel basis to inform the phase regressor fit in order to improve robustness and avoid introducing excessive phase noise into the "filtered" data. This measure of signal variances captures not only noisy voxels, but also voxels with significant phase fluctuations driven by physiological sources like respiration and motion. We are primarily concerned with situations where the phase variance is order-of-magnitude worse than the magnitude, and presumably not terribly trustworthy. While the estimation of variance in magnitude and phase can contain biases because of the noise statistics, especially when the SNR is low, we have found approximation to be quite robust in practice. We should note that this is

an overly conservative approach (if the phase variance is very high compared to magnitude signal variance, nothing gets removed from the magnitude signal in regression), and certainly better modeling of the noise statistics could be done to improve the weight estimates for the regression and thereby potentially improve performance of the method.

The correlation analysis as performed is admittedly a coarse approach, but it indicates that measureable differences in overall correlation levels across a set of subjects can be found. Regression of typical confound sources (WM, CSF, RVT, etc) has a similar effect on *global* correlations (49), and is accepted as an important preprocessing step. Preliminary data (not shown) demonstrated that the phase regressor does *not* replace the need for these other regressors, instead functioning in a complimentary manner. Importantly, and unlike the aforementioned regressor techniques, the phase regressor selectively alters signals in a spatially localized manner, meaning the correlation changes measured are not part of a single "widespread" effect, as is the case with e.g. cardiorespiratory effects or overall blood oxygenation level modulations (RVT).

It should be noted that the limited spatial resolution of the RS-fMRI data herein precludes more sophisticated investigation into the localization of the phase regressor signal, and should be addressed in future, higher resolution investigations. These low resolutions can also bias metrics that rely on segmentations like the reported global correlation changes between tissue types (Table 4-1 and Figure 4-4), as significant partial voluming between tissues occurs at these low resolutions, coupled with the limited ability to wholly resolve the cortical ribbon.

While the datasets used in this work were designed to be comparable in resolution with common resting-state protocols, the use of a 7 T MRI system might limit the transferability of this technique to lower field strengths like 3 T. Phase based techniques are typically less sensitive at lower field strengths, due to the smaller relative susceptibility shifts and therefore lower phase accrual for a given echo time. On the other hand, at lower fields a larger fraction of the observable signal is macrovascular in nature because of the lower susceptibility influence of microvasculature, and the relatively longer T<sub>2</sub> times of venous blood. This is especially true at 1.5 T and there is some evidence at 3 T, as reported in a recent comparison of spin echo and gradient echo for pattern analysis at 3 T (50). This would suggest that methods that suppress signal from large veins could remove much of the signal of interest, adversely affecting the ability to detect resting state activity. Nonetheless, the veracity of magnitude RSNs under conditions where the phase regressor eliminates most of the signal needs to be critically considered.

Access to phase data is an important consideration for studies planning to implement a similar protocol as described here. While the EPI data typically used for fMRI is acquired and reconstructed as a complex valued time series, the phase data is typically discarded and effort must be taken at scan time to ensure it is retained.

# Conclusions

Use of the phase regressor technique as modified for RS-fMRI has the potential to reduce contamination from venous signal contribution and residual artifacts. Phase regressor filtering applied to resting-state data acquired at 7 T demonstrated reductions in measured total correlation scores, reduced correlations between cortex and white matter voxels, and changes in spatial correlation maps of common RSNs at a group level. Given the differences in overall correlation levels that were measured after phase-regressor application, venous effects need to be seriously considered in resting-state studies, particularly of midline networks or when the seed region is selected along the midline or cortical surface where the greatest changes are evident.

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# 5. Summary and Conclusion

This thesis presented new methods to address three core confounds of performing functional neuroimaging at 7 Tesla. While such a high magnetic field strength promises improved signal- and contrast-to-noise for functional imaging, significant additional challenges arise. Herein, three of the myriad challenges were addressed, presenting methods to (a) combat the RF image inhomogeneity (center-brightening) artifact, (b) address the heightened physiological noise contribution in BOLD fMRI time series, and (c) to examine and reduce the confounding effects of the venous anatomy in resting state BOLD fMRI. Results of these investigations were published in major peer-reviewed journals in the field. The core developments and contributions of the work leading to each paper in this thesis are described below.

# B<sub>1</sub>+ Shimming

Imaging inhomogeneity due to non-uniform radiofrequency excitation was addressed in work detailed in Chapter 2.

As background for this research, pulse sequences and reconstruction code to perform mapping of the transmit RF fields were developed, tested, and benchmarked. These sequences were used to assess the performance of multichannel RF transmit coils developed by our lab, resulting in several co-authored papers. System runtime code (Agilent PSG) was modified and pulse sequences were developed that enabled modulation of the individual transmit channels for each excitation pulse in the sequence. Different formulations of the shimming optimization problem were tested and compared. Combining these developments, a new shimming technique was described and tested -- slice-by-slice shimming. It was demonstrated that significant performance gains could be achieved when restricting the shim region to individual slices. Shim solutions with lower overall transmit powers and more uniform excitations were robustly demonstrated. The performance benefits were explained by several factors. First, multi-slice shimming reduced the effective spatial extent over which uniformity of the RF transmit field is required, simplifying the problem. Secondly, additional degrees of freedom are made available in the multi-slice paradigm, enabling more control of the fields. Third, efficiencies in coil geometry are better utilized when slice locations align well with coil spatial profiles. e.g. if a slice is near to only one coil element, little contribution from other elements is expected, and the optimal powers reflect this, reducing SAR deposited in regions far from the slice of interest.

The advantages of such slice-by-slice shimming are many-fold. It is conceptually simple and fairly straightforward to implement, as there is no additional gradient activity required. It is applicable to nearly any multi-slice sequence, and was demonstrated with both low flip angle gradient echo and high flip angle fast spin echo imaging. The proposed method was found to robustly achieve quality, SAR-efficient shim solutions over a variety of volunteer head shapes and sizes. Critically, the solution speed is excellent, as even when scripted in MATLAB solutions are generated quickly enough for use on-line during the sequence preparation phase.

#### Physiological Noise

The use of the 7T for neuroimaging would not be complete without application to BOLD fMRI, a workhorse of neuroimaging research. Unfortunately, the signal to noise (SNR) benefits of high field imaging are not directly realized in BOLD fMRI, as the imaging becomes more susceptible to physiological noise which can limit the

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effective temporal SNR, and thus statistical power of the method. Chapter three addresses this idea by suggesting a new method to automatically identify corrupting signals in a data driven manner for subsequent removal.

While debugging artifacts in our in-house EPI reconstruction software, we observed the great dynamism of the phase signal in fMRI time series in motion-corrupted areas. Further investigation revealed that the time series of voxels with large magnitude and phase signal standard deviations contained significant physiological contamination from cardiac pulsatility, respiration, and other subject motion. The idea of *Highcor* arose from these observations -- finding the voxels with the highest magnitude and phase correlations (which are generated by only a small number of processes, most of which are confounding in nature) and using these as a "noise reference." Many voxels are identified (the top 1-2%), and dimensionality reduction is performed via principal component analysis (PCA) to find a small set of highfidelity reference signals for filtering.

There are many advantages of *Highcor* when compared to other data de-noising methods in the literature. By using a physically motivated criteria, the reference voxel set can identify a significant percentage of the physiological confounds in a very robust fashion, requiring no user intervention nor training data. It is conceptually simple to implement, requiring minimal processing aside from a phase coherent coil combination from the multiple-receiver data.

# Venous Biasing of BOLD Signal in the Resting State

Chapter four continues the theme of chapter three, utilizing the phase component of the BOLD fMRI data. However, instead of global confounding signals, we instead look to the very localized effects of the venous anatomy. As described in the introduction of chapter four, the susceptibility perturbations from the deoxygenated blood in small veins are the driving source of the BOLD signal we measure in gradient echo fMRI. It was previously shown by Menon (2002) that these veins also generate phase perturbations that are detectable and correlated with the magnitude signal (indeed, the same phenomenon drives both signals). By regressing the phase against the magnitude, an estimate of micro-vs-macro vascular contributions of the BOLD signal can be generated, and used to remove the macro-vascular portion. This is of interest because the macro-vascular components are inherently less localized to sites of brain activity. This was demonstrated in task based MRI, where the task signal can be directly visualized (quite remarkably) in the phase data itself.

In chapter four, the phase regressor was extended to investigations of the resting state, where venous biasing effects are typically ignored due to the low data resolutions and significant blurring and averaging of group level data. The phase regressor approach was modified to estimate signal variances using the band-passed frequencies that are typically discarded in resting state analysis. Through application of the modified phase regressor to resting state datasets, it was demonstrated that removal of macro-vascular signal contributions has measurable effects on the spatial distributions of resting state signal correlations in individual datasets and at a group level. Two distinct changes were observed: one from reduction of confounding venous signal sources (e.g. signal change in and around large veins like the sagittal sinus), and second from the attenuation of small macro-vascular signals (as in the task-fMRI case) where localized changes in network connectivity were detectable.

## **Recommendations for Future Work**

Using the same sections described above, several avenues for continuing research have become apparent.

#### **B<sub>1</sub>+ Shimming**

**Extend slice-by-slice methodology to other pulses.** Several other commonly used pulse sequence elements occur as spatially localized excitations separate from the slice. Examples are spatial saturation bands (outer volume suppression), localized fat saturation, and various magnetization preparation elements like ASL tagging. Modulating the B<sub>1</sub>+ shims for each such pulse is a fairly straight forward extension. We have already demonstrated promising results with outer volume suppression in the brain, where shimming quality of saturation bands can benefit greatly from their localized nature with respect to transmit array coil elements. Preliminary results suggest a near doubling in saturation uniformity with almost halving in SAR, making saturation somewhat more tractable for high field applications.

**Concurrent optimization of B<sub>1</sub>+ and B<sub>0</sub> shims.** The well-known sensitivity of EPI to variations in B<sub>0</sub> is worsened at high field strengths. Moving to modulate the B<sub>0</sub> shims on a per slice basis provides the same additional degrees of freedom demonstrated in the B<sub>1</sub>+ shimming. An initial implementation suggests that this approach is promising, with control of the linear B<sub>0</sub> shims easily achievable in real time, reducing off-resonance within each slice (especially in slices near the periphery of the brain). However, significant addition research work is required, as changes in the B<sub>0</sub> shims result in spatial distortions that change from slice to slice that are not trivial to correct.

**Application to the Siemens pTX platform.** Development and proof of concept occurred on the Varian/Agilent platform. While not precisely a research goal, integration with the Siemens environment could help the adoption of these techniques by a wider user-base, as pTX technology is further adopted in the future.

#### **Physiological Noise**

Physiological noise contamination in BOLD fMRI is a complex issue. When performing this research, it became abundantly clear that good criteria were lacking for assessing the overall quality of fMRI datasets, making benchmarking of filtering techniques especially difficult. Several avenues might help generate a better understanding of the physiological contamination present in the data:

**Improved modeling of physiological noise sources.** The well known Glover model describing the temporal-SNR to image-SNR relationship (see Chapter 3) assumes the "noise" sources are normal, modeling physiological and thermal noise components by simple signal standard deviations. As there is clearly a strong frequency dependence of physiological signal sources in the data (respiration and cardiac cycles, for instance), one can hypothesize that a frequency aware model may provide additional insight into the noise processes and performance of any filtering. This is a difficult problem, as any such model must also consider frequency aliasing effects from the relatively long imaging TRs compared to the fast physiological signals.

**Base image SNR assessment by frequency baseline**. One key metric for assessing quality of image data is the base signal-to-noise ratio (SNR). For a variety of reasons, assessing base image SNR is very difficult in BOLD EPI, especially when parallel imaging is utilized. As visible in Figure 3-3, power spectra of voxel time-courses

acquired at high temporal resolution exhibit a flat baseline noise power that corresponds to the background white noise in the data set. Given appropriate scaling, this baseline should be usable as a robust estimate for the overall noise level in the dataset (and therefore as a reference for image SNR), abstracting out effects of spatial signal variation and physiological noise.

#### Venous Biasing of BOLD Signal in the Resting State

Improved understanding of the localization properties of BOLD signal changes is important as scientists move to ever higher resolution investigations of the brain. The phase regressor method is a robust method of improving signal localization by eliminating macro-vascular signal biasing. Several avenues should be pursued to further validate this technique, to understand its limitations, and to improve robustness.

**Comparison to spin echo.** As suggested in Chapter 4, an important experiment to perform in the future is a comparison to spin-echo (SE) based fMRI. This test is an important validation, as the different physics of the SE-BOLD (specifically the biasing of the BOLD effect to micro-vasculature) are the exact situation that the phase regressor filtering aims to emulate -- if the phase regressor does indeed remove a large fraction of the macro-vascular signal, we should measure similar resting state signal correlations as in spin echo sequences. This is, however, a challenging task, as spin echo EPI sequences are difficult to perform at 7 T due to the duty cycle and SAR limitations. The delay requirement for signal regrowth also limits the effective temporal resolution of SE-EPI. Differences in spatial SNR deriving from the inhomogeneous RF (and therefore imperfect signal refocusing) also make direct comparisons of resting state correlation levels between SE and GE -EPI more difficult.

**Phase stability improvements.** One limitation of the phase regressor method is the requirement for high fidelity phase data. The phase data in MRI can be significantly less robust than the magnitude data, due to a variety of artifacts (effects of motion, off-resonance, and physiological noise) and signal processing issues like phase wrapping. Phase representations of the complex data also perform quite poorly in low SNR regimes. Low quality phase data reduces the efficacy of the phase regressor, as the correlation between magnitude and phase within a voxel will be attenuated. Improvements to phase stability should only benefit this method. Technologies exist that could help but typically their integration is not trivial, such as two-dimensional EPI navigators and the use of preprocessing tools that correctly support complex-valued data (e.g. in the motion correction stage).
## Appendix A: Ethics Approval



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#### Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. J.S. Gati

Review Number: 15018

Revision Number: 1 Review Level: Expedited

Protocol Title: 7 Tesla MRI Hardware and Software Development

Department and Institution: Imaging, Robarts Research Institute

Review Date: August 21, 2008

Sponsor:

Ethics Approval Date: October 02, 2008

Expiry Date: July 31, 2018 Documents Reviewed and Approved: Revised study methodology, revised sample size, revised poster and revised Letter of Information and Consent Form version 1.2

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

"he ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the ..SREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

investigators must promptly also report to the HSREB:

- a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
- b) all adverse and unexpected experiences or events that are both serious and unexpected;
- c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

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Chair of HSREB: Dr. Joseph Gilbert

Ethics Officer to Contact for Further Information					
.] Janice Sutherland	D Elizabeth Wambolt	Grace Kelly	Denise Grafton		
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## Curriculum Vitae - Andrew Curtis

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Awarus:	Western Graduate Research Scholarship	
	ISMRM Student Stipend recipient 2012, 2013	
	Poster Prize, Imaging Network Ontario, 1st Place - 2012 3rd Place - 2013	

### **Selected Related Publications:**

### **Journal articles**

Curtis AT, Hutchison RM, Menon RS (2014) Phase based venous suppression in resting state BOLD GE-MRI. *NeuroImage*.

Curtis AT, Menon RS (2014) HighCor: A novel data driven regressor identification method for BOLD fMRI . *NeuroImage*.

Curtis AT, Gilbert KM, Klassen LM, Gati JS, Menon RS. (2012) Slice-by-slice B1+ shimming at 7 T. Magn Reson Med 68 (4) 1109-1116

Gilbert KM, Belliveau JG, Curtis AT, Gati JS, Klassen LM, Menon RS. (2012) A conformal transcieve array for 7 T neuroimaging. Magn Reson Med 67 (5) 1487-1496

Gilbert KM, Curtis AT, Gati JS, Klassen LM, Menon RS. (2010) A Radiofrequency Coil to Facilitate B1 + Shimming and Parallel Imaging Acceleration in Three Dimensions at 7 Tesla. NMR in Biomedicine 24 (7), 815-823

Gilbert KM, Curtis AT, Gati JS, Klassen LM, Villemaire LE, Menon RS. (2010) Transmit/receive radiofrequency coil with individually shielded elements. Magn Reson Med 64 (6), 1640-1651 J. Near, C. Romagnoli, A. T. Curtis, L. M. Klassen, J. Izawa, J. Chin, R. Bartha (2009) High-field MRSI of the Prostate using a Transmit/Receive Endorectal Coil and Gradient Modulated Adiabatic Localization. Journal of Magnetic Resonance Imaging. 30:335-343.

### Other refereed contributions (international conferences)

A.T. Curtis, R.M. Hutchison, R.S. Menon. (2013) Venous suppression in resting state fMRI: Implications for correlation analysis. ISMRM 2013 Annual Meeting , # 2231.

A.T. Curtis, R.S. Menon. (2013) Automatic selection of artifact components via residual k0 phase ISMRM 2013 Annual Meeting , # 3349.

J. Penner, A.T. Curtis, L.M. Klassen, J.S. Gati, M.J. Borrie, R. Bartha. (2013) 7 Tesla In-Vivo Short-Echo-Time Single-Voxel 1H SemiLASER Spectroscopy: A Test/Retest Reproducibility Study. ISMRM 2013 Annual Meeting, # 3987.

A.T. Curtis, K.M. Gilbert, J.S. Gati, L.M. Klassen, R.S. Menon (2011) Multi-Slice B1+ Shimming for 7T MRI. (Finalist) ISMRM 2011 Annual Meeting # 4430.

J. Penner, A. Lim, A. Curtis, M. Klassen, J. Gati, M. Smith, M.J. Borrie, R. Bartha. (2011) In-vivo Short-Echo-Time Single-Voxel Proton LASER Spectroscopy at 7 Tesla Incorporating Macromolecule Subtraction. ISMRM Annual Meeting, #3436.

A.T. Curtis, L.E. Villemaire, K.M. Gilbert, J.S. Gati, L.M. Klassen, R.S. Menon (2010) A Head Mimicking Phantom for 7T, Matched for Tissue Parameters, B1 + Behavior, and Coil Loading Effects. Intl. Soc. Mag. Reson. Med. (ISMRM) Annual Meeting, #2318. (International, Poster, PhD work).

J. Penner, A. Curtis, M. Klassen, J. Gati, M. Smith, M.J. Borrie, R. Bartha (2010) Metabolite Nulling to Measure the Macromolecule Baseline for Quantitative <sup>1</sup>H Magnetic Resonance Spectroscopy at 7 Tesla. ISMRM Annual Meeting, #2207.

A.T. Curtis, K.M. Gilbert, J.S. Gati, L. M. Klassen, R.S. Menon (2009) 12 Channel Transceive Array for B1+ shimming and receive acceleration at 7T. ISMRM Parallel MRI workshop.

A.T. Curtis, R.S. Menon (2009) Calibration of Transceive-array RF power using Lanthanide Shift Agents. ISMRM Annual Meeting, #4216.

A.T. Curtis, C. Jones, L.M. Klassen, C.K. Anand, R.S. Menon (2009) Numerical Optimization of Minimum Phase RF Pulses for UTE Imaging. ISMRM Annual Meeting, #6453.